Chapter 9
Pharmacological Alterations of Peritoneal Transport Rates and Pharmacokinetics in Peritoneal Dialysis

N. Lameire and W. Van Biesen

In the first part of this chapter, the effects of pharmacological manipulations on peritoneal transport will be discussed. Increased understanding of peritoneal transport mechanisms may lead to the development of clinically useful methods to augment peritoneal transport efficiency. In this chapter, only pharmacological tools for influencing peritoneal transport will be discussed. A detailed discussion of the physiology of peritoneal transport is provided in other chapters of this book. In the second part of this chapter, the pharmacokinetic concepts underlying transperitoneal drug transport and their implications for rational and safe use of drugs in patients treated with peritoneal dialysis (PD) will be discussed. Basic concepts of pharmacokinetics will be briefly reviewed as a starting point to elaborate further on general pharmacokinetic principles in patients with decreased renal function and in patients on PD. Tables with data and guidelines for prescription of specific drugs will be presented. An update on the most recent pharmacokinetic studies in PD will be provided.

Peritoneal Membrane Transport

(For details on peritoneal membrane transport, see Chapter 6.) Peritoneal transport comprises three processes that occur simultaneously: 1) diffusion, 2) ultrafiltration, and 3) fluid reabsorption. Transport of low-molecular-weight solutes during PD is primarily diffusive, whereas convective solute transport becomes more important with their increasing molecular weight. The absorption of intraperitoneally administered macromolecules is linear in time, irrespective of molecular size or concentration. Total removal of a solute is dependent not only on the peritoneal transport rate but also on the total drained dialysate volume. The latter is determined by the instilled volume and the net ultrafiltration. The effective peritoneal surface area used for transport of solutes is determined both by the number of perfused capillaries (and thus by splanchnic blood flow) and by the contact of the dialysate with the peritoneal surface.

It should be noted that diffusion in general does not depend on peritoneal blood flow, which at 50–100 mL/min, is already more than adequate relative to the mass transfer area coefficient (MTAC) values of even the smallest solutes. The ability of vasoactive substances to influence peritoneal transport is thus not related to their ability to increase peritoneal blood flow, but to the associated recruitment of larger numbers of perfused peritoneal capillaries that increase the effective peritoneal surface area. It should be realized that the proportion of peritoneal blood flow involved in peritoneal transport is unknown, and it is possible that in some areas of the peritoneum blood flow may limit diffusion.

Ultrafiltration occurs because of the osmotic gradient between the hypertonic dialysate and the isotonic capillary blood. Ultrafiltration is determined by a number of factors such as the hydraulic conductance of the peritoneal membrane, perhaps reflecting the density of small and ultrasmall pores in the capillaries as well as the distribution of the capillaries in the interstitium. A recent review on the mechanisms of peritoneal ultrafiltration has been published [1].

Recent experiments using knockout mice for aquaporin [2] provide direct evidence for the role of AQP1 during PD. The results validated essential predictions of the three-pore model: i) the ultrasmall pores account for the sodium sieving, and ii) they mediate 50% of ultrafiltration (UF) during a hypertonic dwell. Other factors are the reflection coefficient of the osmotic agent, the hydrostatic and osmotic pressure gradients, and the sieving process (for detailed review see other chapters in this book). Fluid absorption occurs via the peritoneal lymphatics at a relatively constant rate. This absorption occurs partly directly via the subdiaphragmatic lymphatics or, more importantly, through absorption into the tissues of the parietal wall where it is subsequently taken up by local lymphatics and perhaps by

N. Lameire (✉)
University Hospital Ghent, De Pintelaan 185, Ghent, Belgium
e-mail: Norbert.lameire@ugent.be

R. Khanna, R.T. Krediet (eds.), *Nolph and Gokal's Textbook of Peritoneal Dialysis*,
DOI 10.1007/978-0-387-78939-2_9,

peritoneal capillaries. The determinants of peritoneal absorption are the intraperitoneal (IP) hydrostatic pressure and the effectiveness of the lymphatic system.

Role of Electric Charges on the Transport Across the Peritoneal Membrane

Anionic sites predominantly composed of heparan sulfate and chondroitin sulfate are a constant feature of basement membranes of the microvasculature [3–5]. They are particularly abundant in fenestrated capillaries, some of which have been identified in human parietal and diaphragmatic peritoneum [6]. These anionic charges could, at least theoretically, restrict the diffusive and convective passage of charged solutes across the membrane. There is a paucity of data concerning the influence of the peritoneal membrane anionic sites on transport of charged macromolecules across the peritoneum. It is well established that an increased peritoneal permeability to albumin in diabetic animals is observed like in many other capillary beds. Shostak and Gotloib [7] could attribute this phenomenon to a reduced density of microvascular and submesothelial negative charges, equivalent to that induced by diabetes in other capillary beds. More recently, administration of aminoguanidine preserved both submesothelial and subendothelial electronegative charges in diabetic rats and restored the hyperpermeability for albumin [8].

Leypoldt and Henderson [5] demonstrated that peritoneal transport rates for cationic dextrans were less than for either neutral or anionic dextrans. These results differ from what one should expect. On the other hand, negatively charged amino acids such as glutamic acids show a slower transperitoneal mobility compared to neutral or positively charged amino acids [9]. In contrast, based on the determination of peritoneal clearances of ten different proteins and their isoforms, Buis et al. [10] concluded that the peritoneal membrane was not a charge-selective barrier for the transport of macromolecules between blood and dialysate. The effect of electrically charged drugs on peritoneal transport will be discussed later.

Part I. Pharmacological Alterations of Peritoneal Transport

Better knowledge of the pharmacological alterations of peritoneal transport that occur in PD patients may be useful for several reasons:

1. Co-morbidity is high in renal failure and these patients are exposed to a multitude of drugs that may affect the peritoneal transport of solutes and water. Knowledge of the effects of such agents on transport parameters can influence the appropriate selection of a drug.
2. There may be need for augmenting the peritoneal diffusive capacity. A redefinition of adequacy targets of PD has emerged over recent years. Many studies have focused attention on optimizing the quantity of solute clearance in an attempt to improve clinical outcome. Dialysis dose is currently quantified in terms of small solute clearances, fractional urea (Kt/V), and creatinine clearance rates. The target small solute clearances have been a source of some controversy and in many studies the amount of the residual renal function (RRF) has been a major confounding factor in the correct interpretation of the results. Where the magnitude of the RRF has a direct influence on outcome, it has been more difficult to demonstrate a similar effect for peritoneal clearance, at least within the range of dose prescriptions in typical clinical use. In particular the ADEMEX (ADEquacy of PD in MEXico) study showed no difference in technique or patient survival, or quality of life between a standard dose and a higher peritoneal clearance regimen [11, 12].
3. A major cause of cardiovascular morbidity and mortality, and also of technique failure, in PD, is the inadequate removal of fluid across the peritoneal membrane. A better knowledge of fluid transport (filtration and transcapillary and lymphatic absorption) may open possibilities for pharmacological manipulation of the peritoneal ultrafiltration capacity, or chemical modification of the dialysate, in order to prevent excessive fluid reabsorption from the peritoneal cavity.
4. Although to date the biocompatibility of the PD fluids has greatly improved, still adverse interactions of both the "classical" and the "new" solutions with the peritoneal membrane may provoke structural and functional alterations in the membrane which may end in peritoneal fibrosis [13–16]. Treatment with vasoactive and/or anti-inflammatory agents could be attempted in order to decrease these adverse effects.
5. When PD is used to remove exogenous toxins, it is usually mandatory that removal rates be maximal. Conversely, when protein loss is excessive it may be judicious to decrease the transport rates, at least of larger solutes.
6. Finally, pharmacological manipulation of peritoneal transport has increased our understanding of peritoneal physiology.

This part of the chapter will describe the several pharmacological manipulations on peritoneal transport, seeking enhanced understanding of transport mechanisms and clinically useful methods to either augment transport or to preserve the structural and functional integrity of the membrane.

Drugs Acting on the Peritoneal Blood Flow and Their Impact on Solute Transport

Greatly improved mass transport must depend on augmentation of blood flow or peritoneal permeability or area, just as hemodialyzer efficiency increases with larger surface area dialyzers, more permeable membranes, and higher blood flow rates. As stated above, the ability of vasoactive substances to influence peritoneal transport is not directly related to their ability to increase peritoneal blood flow, but rather to the associated recruitment of larger numbers of perfused peritoneal capillaries that increase the effective peritoneal surface area.

A detailed overview of the anatomy and physiology of the peritoneal circulation is discussed in Chapter 4 of this book.

Despite several lines of evidence suggesting that peritoneal blood flow should be high enough to avoid any limitation in solute clearances and ultrafiltration, the real impact of effective peritoneal blood flow on the efficiency of PD is still controversial [17]. Recent experimental work has suggested that, at least in some circumstances, peritoneal ultrafiltration and solute clearances may be blood-flow limited [18].Values of the peritoneal capillary blood flow vary between 50 and 100 mL/min, based on peritoneal gas clearances in animals [19]; others have found lower values [20]. In uremic humans, an indirect estimation of effective peritoneal capillary blood flow found values between 100 and 200 mL/min [21]. The impact of the application of the distributed model of peritoneal circulation and the hypothesis of the "nearest capillary" have recently been discussed and the reader of this chapter is referred to that paper [22]. In stable continuous ambulatory peritoneal dialysis (CAPD) patients, values ranging from 20 to 151 mL/min with a median value of 66 mL/min were found [23–25]. All these values assume that gas clearances represent the "effective" peritoneal blood flow. When mesenteric blood flow is doubled, the clearances of small solutes such as urea increase by 30–50% [26], consistent with a resting blood flow that exceeds the maximal rate at which the capillary diffusion capacity can completely clear the perfusing blood [27]. This is compatible with the results obtained by Douma et al. [24], finding an increase in MTAC of small molecules without a change in peritoneal "effective" blood flow as measured by the MTAC of CO_2.

The splanchnic vascular bed can sequester blood, excluding it from, or releasing it into, the circulation as systemic volume changes. Thus, hemodynamic effects of drugs can influence splanchnic blood volume and flow rate considerably. Because drugs usually affect the splanchnic blood flow and volume pari passu, changes in peritoneal transport that result from the altered volume can be misinterpreted as flow rate mediated. There is also evidence to suggest that splanchnic blood volume, rather than flow rate, determines the degree of peritoneal mass transfer [28]. For example, the volume contraction induced by the systemic administration of dihydroergotamine results in lower peritoneal clearances of potassium, urea, and phosphate [29], and this effect is due to a reduction in blood volume. On the other hand, both volume expansion by dextrose infusion [30] and sodium chromate-induced hepatic venous stasis increase these parameters. Current opinion prevails that, under physiological conditions, peritoneal blood flow does not limit the transfer of solutes. However, the effective blood flow available for transport will only be a fraction of the total blood flow through the tissues surrounding the peritoneal cavity, because most of the exchange capillaries are too far from the cavity to be active in the exchange process [31], or they are contained in tissues not in contact with the solution in the cavity [32]. In contrast, in the "nearest capillary" theory of Ronco [33], it is hypothesized that the capillaries positioned closest to the mesothelium are dilated and have a low blood flow, while the most distal capillaries have a higher blood flow, but with a less effective diffusion due to interstitial resistances. The resulting "effective" peritoneal blood flow in this hypothesis would be a limiting factor for solute clearance.

As outlined in Chapter 6, most data obtained in experimental animals, as well as in humans, suggest that the effects of small peritoneal blood flow changes on solute transport are probably limited.

The regulation of the mesenteric circulation is very complex (for further details, see Chapter 6). It is sufficient here to remind that both extrinsic and intrinsic autoregulatory control mechanisms exist. In the latter, the venous pressure and the ingestion of meals also have an effect. Food ingestion increases intestinal blood flow and this functional hyperemia is mediated by certain gastrointestinal hormones such as gastrin and cholecystokinin. Autoregulation of blood flow, i.e., the maintenance of a constant blood flow over a range of perfusion pressures, is not as well developed in the intestinal circulation as in other vascular beds, such as those in the brain and kidney. The principal mechanism responsible for mesenteric autoregulation is metabolic, i.e., any intervention that results in an oxygen supply that is inadequate for the requirements of the tissue prompts the formation of vasodilator metabolites. However, a myogenic

mechanism probably also participates. Adenosine is a potent vasodilator in the mesenteric vascular bed and may be the principal metabolic mediator of autoregulation.

Influence of Drugs Reducing Peritoneal Blood Flow

Drugs Decreasing Peritoneal Blood Flow

Catecholamines

To explore vasoactive effects on peritoneal transport, catecholamines have been studied in animals undergoing PD. Gutman et al. [34] noted lower increments in dialysate urea with large IP doses of dopamine in anephric dogs, but did not measure dialysate volume. Because blood pressure increased, the lower urea accumulation in the dialysate was attributed to splanchnic vasoconstriction. To offset vasoconstriction, Parker et al. [35] added an α-adrenergic blocker to the dialysis fluid. With IP phentolamine and IV dopamine, peritoneal clearances increased in dogs. In human patients, however, Chan et al. [36] observed no effect of low (4 mg/L) or high doses (20–160 mg/L) of IP dopamine on dialysate urea, creatinine, or phosphate.

In rabbits, IP dopamine caused dose-related (0.6–1.8 mg/kg) increases in peritoneal urea clearance [37]. The increments occurred with lower doses than those used by Gutman et al. [34] and drug concentrations (10–30 mg/L) within the range studied by Chan et al. [36].

IV 1-norepinephrine significantly decreased peritoneal clearances of urea and creatinine in unanesthetized rabbits [36, 37]. Dose-dependent decrements of the peritoneal clearances correlated with the pressor response [38]. Comparable pressor doses of IV dopamine increased clearances of urea and creatinine to 145% of control values, whereas low doses had minimal and inconsistent effects [38]. Osmotic water flux increased only slightly (from 0.18 to 0.24 mL/kg/min) but significantly. Because dopamine vasoconstricts venules relatively more than arterioles as compared to norepinephrine [39], augmented water flux could be mediated by increased hydrostatic pressure rather than a change in hydraulic permeability. The augmented transport is attributed to dopamine receptor-mediated mesenteric vasodilation and, in part, by general α-adrenergic vasoconstriction increasing blood pressure, while mesenteric blood flow is maintained. Although dopamine may not be suitable for augmenting efficiency of routine PD, these data strongly suggest that dopamine should be preferable to 1-norephinephrine when vasopressor therapy is required during PD.

Only minimal increments in fluid and solute flux occurred with ibopamine, an oral dopamine analogue, whether given by mouth, IV, or IP to normal rabbits [40]. Interestingly, the dialysate to plasma ratio for norepinephrine was 1.17 in CAPD patients, suggesting local production in the peritoneal cavity [41]. An unexpected correlation was found between the dialysate levels of norepinephrine and the effective peritoneal surface area, represented by the MTAC for creatinine.

Recent in vitro studies have investigated the effects of epinephrine on the electrical transmesothelial resistance (R(TM)) of the isolated parietal sheep peritoneum by means of Ussing-type chamber experiments [42]. A parietal peritoneal planar sheet was mounted in a Ussing-type chamber and epinephrine (10^{-7} Mol) was added to the apical and the basolateral side. The R(TM) was measured before and serially after the addition of epinephrine for 30 min. As active ion transport is temperature-dependent, all measurements were performed at 37°C. The addition of epinephrine to the basolateral side within 1 min induced a dramatic increase of R(TM) which decreased thereafter progressively to reach control values again after 15 min. A similar effect of epinephrine on the apical side was apparent with a rapid rise and a subsequent decrease of R(TM). A clear association between the R(TM) and active ion transport was established from previous studies. The results of this study indicate a rapid action of epinephrine on the parietal peritoneum permeability. Similar results were obtained with visceral peritoneum [43].

Vasopressin and Angiotensin

Vasopressin and angiotensin cause a generalized vasoconstriction with a disproportionate reduction in mesenteric blood flow [44]. Parenteral administration of vasopressin to anesthetized dogs decreased peritoneal clearances of small solutes, consistent with a hormonally mediated reduction in mesenteric blood flow [45, 46]. Since inulin clearance increased slightly under these circumstances, a concurrent increase in membrane permeability has been postulated [47], in accord with the accelerated transport that occurs in isolated membrane preparations [48].

Angiotensin II is probably mainly involved in the control of mesenteric blood flow during volume depletion. The effect of angiotensin II (AII) on peritoneal permeability and lymphatic absorption in the rat was studied by Go et al. [49]. AII was added to the dialysate and it decreased the transcapillary ultrafiltration rate from 15.7 ± 2.8 mL/4 h dwell

in control to 5.7 ± 1.5 mL/4 h dwell. Lymphatic absorption was increased in a dose-dependent fashion with no change in clearances of urea nitrogen or inorganic phosphate.

Drugs Increasing Peritoneal Blood Flow

Although the mechanisms of a decrease in solute transport by a reduction in peritoneal blood flow are important, much more attention has been paid to the study of the possibilities for augmenting peritoneal transport by systemic or IP administration of vasodilating drugs. Many studies suggest that peritoneal clearances will increase only if a vasodilator selectively affects the splanchnic vasculature or is applied locally, e.g., by IP instillation. When administered IV such drugs may cause widespread vasodilation, decreasing blood pressure, splanchnic perfusion, and splanchnic volume, thereby lowering peritoneal transport rates. To date, membrane-active agents have augmented transport only when applied locally, i.e., instilled intraperitoneally.

Increased splanchnic perfusion augments peritoneal clearances of larger solutes at least as much as the transport of smaller solutes. This suggests an increase in peritoneal surface area or permeability resulting from vasodilation, attributed to dilation of the functional peritoneal capillaries combined with perfusion of more capillaries. Spreading the same wall mass over a larger circumference decreases the wall thickness and stretches pores. Intercellular junctions widen, accelerating mass transport [50]. Raising blood flow by local application of vasodilators also opens previously closed capillaries, increasing the surface area available for transport [51, 52]. In the resting state, blood may circulate predominantly through metarterioles. Enhanced perfusion opens more capillaries, exposing blood to a more permeable surface. Furthermore, vasodilators with a predominant venular site of action may cause greater increases in diffusion rates, but arteriolar dilators may increase the ultrafiltration rate. By increasing blood flow, diffusion and ultrafiltration may occur throughout a greater length of the capillaries than occurs under resting conditions.

Depending on the nature of the vasodilating agent there may be an increase (arteriolar relaxation), decrease (lowered venular tone), or no change (balanced effects) in capillary hydrostatic pressure. This hydrostatic pressure may affect capillary diameter, volume, and permeability and is a major determinant of the filtration rate through the capillary. The solute transfer of small molecules, measured by their MTAC, is usually markedly increased during the first 15 min of PD dwells. Besides being caused by initial arteriolar vasodilation and. hence, recruitment of capillary surface area, other explanations for this rapid increase are possible. These include an initial discharge (or saturation) of solutes from (in) the interstitium or an increased mixing, i.e., "macrostirring" caused by the exchange procedure per se [53].

These possibilities have been investigated during acute PD in rats, by assessing the mass transfer coefficient for 51Cr-EDTA as a function of time [53]. The discharge effect was studied by saturating the peritoneal interstitium with 51Cr-EDTA by IV tracer infusion prior to each dwell. The potential effect of initial vasodilation was studied by adding isoproterenol to the dialysis fluid. Finally, the potential influence of an increased interstitial "macrostirring," induced by high glucose concentrations, was investigated by comparing 1.36% glucose with 3.86% glucose dialysate. The conclusion of these experiments was that vasodilation, but not interstitial discharge (or loading), may explain the sharp rise in mass transfer occurring during the initial part of PD dwells. In addition, "macrostirring," induced by the exchange procedure per se, may also be important.

Specific drugs may directly affect the permeability of the capillary or the mesothelium [54]. Drugs that influence membrane charge, cell volume, cell metabolism, or intercellular junction may directly influence peritoneal permeability without affecting flow rates.

Isoproterenol

Isoproterenol, a β-adrenergic agonist, relaxes the mesenteric vascular bed. In patients with reduced peritoneal clearance, Nolph et al. improved transport rates by adding isoproterenol (0.06 mg/L) to the dialysis solution [55, 56]. Mean clearances increased to the lower range of normal but only transiently, and improved significantly, though not in all patients [57]. No systemic effects of IP isoproterenol were detected even with cardiac monitoring. Such use of isoproterenol has been explored in greater detail in animals. In acute studies in anesthetized dogs, IP isoproterenol increased urea and creatinine clearance by 45 and 30%, respectively, but subpressor IV doses did not augment transport [34]. In unanesthetized rabbits, 0.04 mol/kg of IP isoproterenol raised urea and creatinine clearance by 50%, but osmotically induced water flux was unaffected [58]. No systemic effects were observed. Despite raising mesenteric blood flow to 188% of control by IV isoproterenol, Felt et al. [26] found no increase in clearances. With IP isoproterenol a comparable flow increase raised peritoneal inulin and creatinine clearances by 27 and 18%,

respectively. The disparity in blood flow and clearance changes suggests that capillary blood volume may be as important as blood flow in mediating changes in permeability.

Vasodilator Gastrointestinal Hormones

Secretin is a polypeptide gastrointestinal hormone that increases mesenteric blood flow by as much as 100% above baseline when given in pharmacological doses [59]. Secretin, like cholecystokinin, increases predominantly hepatic blood flow. Slight increments in urea and creatinine clearances occurred with IV secretin and cholecystokinin [60]. IV, but not IP secretin (10 U/kg) increased osmotic water flux in rabbits [60]. The endogenous release of cholecystokinin or secretin or their intra-arterial infusion relaxes precapillary sphincters and increases the capillary filtration coefficient [61]. Gastrin, structurally similar to cholecystokinin, also increases mesenteric blood flow [59]. The effects of secretin and cholecystokinin on mesenteric blood flow are additive and potentiated by theophylline [62]. This hormonal mesenteric vasodilation is attributed to direct relaxation of vascular tone, presumably mediated by cyclic AMP.

Glucagon is structurally similar to secretin, but has a more potent effect on the mesenteric circulation. When administered IV, immediately before dialysis, glucagon significantly increased peritoneal clearances of urea and creatinine in nonanesthetized rabbits [60, 63]. The same dose given IP did not affect clearances. Since this large molecule should traverse the peritoneum slowly, hormonal activity presumably occurs at the endothelial rather than at the mesothelial surface. In dogs, IV infusion of about 30 μg/kg/h glucagon increased mesenteric arterial blood flow and peritoneal inulin but not creatinine clearance, unlike IP [26]. Glucagon did not affect peritoneal water flux during dialysis in rabbits [60]. The separation of the effects of all these gastrointestinal hormones on diffusive and on convective transport, suggests the possible use of different pharmacological agents acting additively.

Prostaglandins

Arachidonic acid (AA) was recently, investigated for its vascular permeabilizing potential in the rat peritoneal cavity and for its mechanism of action [64]. The antagonistic potential of antioxidants (vitamin E, vitamin C, and troxerutin) was also evaluated. Vascular permeability was equated to the rate of extravasation of Evans blue dye from plasma into the peritoneal cavity. IV arachidonate induced an immediate, dose-related, and significant increase in permeability, which was comparable to the effect induced by similar doses of serotonin. Aspirin reduced the arachidonate-induced permeability by 75%, but, interestingly, neither the stable thromboxane A(2) receptor agonist U46619 (prostaglandin H(2) endoperoxide epoxymethane) nor prostacyclin were able to increase peritoneal vascular permeability. In contrast, the permeabilizing action of arachidonic acid was very sensitive to antioxidant agents. Thus, vitamin C and the flavonoid compound troxerutin fully abolished arachidonate-induced permeability, whereas vitamin E had only a partial effect. In conclusion, IV administration of AA strongly enhanced peritoneal vascular permeability in the rat, apparently via free radical generation.

There is evidence that the mesothelial cells, when exposed to cytokines, show a time-dependent increase in the levels of both COX-1 and COX-2 mRNA, with the greatest increase being seen for COX-2. These data demonstrate specific stimulation of eicosanoid metabolism in human peritoneal mesothelial cells (HPMC) by peritoneal macrophage-derived cytokines, indicating the possible importance of these mediators in the activation of IP prostaglandin synthesis [65].

Depending on the local concentration of the specific terminal enzymes, e.g., endoperoxide reductase leading to placental growth factor (PGF) 2α or endoperoxide isomerase leading to prostaglandin E2 (PGE2), a given product predominates in a given tissue. Regional blood flow is one determinant of enzyme activity. In the circulation, the prostaglandins are degraded during a single passage through the lung, thereby acting only locally with the exception of prostacyclin and thromboxanes, which have half-lives of a few minutes. Prostaglandins of the PGA, PGE, or PGI series are vasodilators, whereas PGF2α and thromboxanes are potent vasoconstrictors [66, 67]. These prostaglandins act locally in arterial walls to influence vascular tone and modulate the response of vascular smooth muscle to other vasoactive agents [68], for example, by modifying vasoconstrictor responses [66].

IP instillation of PGA1 or PGE1 moderately increased peritoneal clearances of urea and creatinine in nonanesthetized rabbits, whereas PGE2 significantly raised creatinine clearance to 132% and urea clearance to 180% of control values [69]. In contrast, IP administration of the vasoconstrictor PGF2α decreased peritoneal clearances to 80% (urea) and 82% (creatinine) of control [69]. These prostaglandins did not affect fluid flux and were ineffective when given IV. Neither IV nor IP administration of prostacyclin affected peritoneal solute or water transport significantly, nor did prostacyclin show pronounced effects on peritoneal transport under baseline conditions. Oral pretreatment with sulfinpyrazone, a potent stimulator of prostaglandin synthetase, did not alter peritoneal clearances significantly [70]. When mefenamic acid, a prostaglandin synthetase inhibitor, was administered either IV or IP to unanesthetized

rabbits in doses sufficient to inhibit platelet function, neither the peritoneal clearances of creatinine or urea nor water flux changed [70].

Oral pretreatment of rabbits with indomethacin blocked platelet aggregation but did not change clearance or ultrafiltration rates significantly [70]. IP indomethacin increases the size of pinocytotic vesicles and narrows intercellular spaces in the rabbit [71]. Alteration of prostaglandin synthetase affects both vasoconstrictor and vasodilator prostaglandins. Hence, regional blood flow may remain unchanged. Yet, when vasodilator prostaglandin activity predominates to compensate for increased renin-angiotensin activity or ischemic vascular disease, aspirin and indomethacin decrease regional blood flow. However, the reduction of clearances induced by IV 1-norepinephrine, which should be accompanied by vasodilator prostaglandin stimulation, is exaggerated by pretreatment with indomethacin in only half of the animals so studied. These results suggest that endogenous prostaglandins do not play a major role in regulating peritoneal blood flow under ordinary circumstances. However, in patients who depend on vasodilator prostaglandins to maintain organ perfusion, blockade of prostaglandin synthetase could impair transport, and a history of exposure to such drugs should be sought if clearances are low. Intraperitoneally, the prostaglandin precursor AA (1.5–5.6 mg/kg) increased creatinine clearance and urea clearance, suggesting an effect of endogenous prostaglandins, but systemic use of indomethacin did not block this increase [70, 72].

In patients with peritonitis, the increased solute transport rates are accompanied by augmented prostaglandin release, abnormalities that can be blocked by indomethacin [73]. However, this effect was not confirmed in a longitudinal study in peritonitis [74].

The effects of nitroprusside on the peritoneal circulation and transport have been detailed in Chapter 4.

Other Vasodilators

No consistent change in peritoneal clearance of urea or creatinine was observed in patients given IP hydralazine, which decreased blood pressure slightly [57]. Theophylline acts as a nonselective antagonist of two types of adenosine receptors that mediate opposite effects on vascular tone [75]. In rabbits, changes in solute and water fluxes were inconsistent after IP or IV aminophylline in doses exceeding the therapeutic range [76]. Presumably widespread vasodilation blunted any potential gain in peritoneal blood flow.

Diazoxide caused a modest increase in peritoneal clearances of urea and creatinine and a significant decrement in blood pressure when IP administered to patients [57]. An increase in ultrafiltration rate approaching 50% of control values was found inconsistently. The IP administration of 5 mg of phentolamine to patients did not influence peritoneal solute transport rates, nor did it affect osmotic water flux [57].

In anesthetized rats, histamine raised only modestly the clearances of urea and inulin, whereas bradykinin augmented these clearances more substantially [77]. Histamine causes overt capillary dilation and increases permeability with protein exudation, which can be blocked in rabbits by both H1 and H2 receptor antagonists [78]. Minimal effects of histamine on small solute transport may reflect decreased plasma volume due to protein loss. In isolated rat mesentery, viewed by television microscopy after fluorescein labeling, protein exudation is also demonstrable with histamine [50]. Dilation is most prominent in the venous end of the capillary and similar changes are noted with nitroprusside.

The effects of calcium channel blockers on peritoneal mass transport have been studied by several investigators. In the anesthetized rat model, verapamil and diltiazem, given locally, modestly but significantly increased peritoneal clearances of urea without enhancing protein losses [79]. Kumano et al. [80] explored the effects of the IP administration of nicardipine, diltiazem, and verapamil in rats. All three vasodilators caused a decrease in blood pressure, which was associated with a decrease in net ultrafiltration rate. The drugs increased peritoneal net fluid absorption rate in a dose-dependent way. Nicardipine and verapamil increased the permeability to urea and glucose but not to protein. Diltiazem caused no change in permeability. Significant augmentation of small solute clearances and ultrafiltration associated with diminished glucose reabsorption were reported with IP verapamil and nifedipine in CAPD patients [81, 82]. In hypertensive CAPD patients, oral nifedipine administered in blood pressure-controlling doses significantly increased peritoneal clearances of creatinine and β2-microglobulin, associated with higher glucose reabsorption, while the rate of ultrafiltration remained unaffected [83]. These studies suggest that calcium channel blockers act on the arteriolar end of peritoneal capillaries without a consistent effect on venular permeability.

A recent clinical study evaluated the effects of oral losartan, prazosin, and verapamil on peritoneal membrane transport during a peritoneal equilibration test (PET), as well as the effects on creatinine clearance (CrCl), Kt/V urea, 24-h protein in drained dialysate, and drained volume [84]. None of the studied drugs significantly modified the peritoneal transport of creatinine, glucose, urea, sodium, potassium, or total protein as evaluated by PET. Verapamil significantly increased peritoneal CrCl, weekly Kt/V urea, and drained dialysate volume. It was concluded that oral administration of losartan, prazosin, and verapamil did not modify the peritoneal transport of solutes during a 4-h

PET, but oral small solute clearances and 24-h drained dialysate volume. Verapamil could thus be considered as an alternative in patients requiring increased dialysis dose and/or ultrafiltration.

In rats, modest increases in urea clearance and glucose absorption and a marked exaggeration of protein loss was seen following IP instillation of very large doses of captopril, an angiotensin-converting enzyme inhibitor [85]. These increments, despite drug-induced systemic hypotension, may reflect increased blood flow, surface area, or permeability. In the above-mentioned study by Kumano et al. [80], captopril was also investigated after IP administration. Captopril increased membrane permeability to small and large molecular solutes, with a consequent decrease in ultrafiltration rate. In a clinical study [86], six hypertensive CAPD patients received IP enalaprilat and five of them also received oral enalapril. After IP enalaprilat, blood pressure declined significantly, and plasma angiotensin-converting enzyme (ACE) activity was suppressed below detectable limits. There were no changes in peritoneal transport characteristics. In contrast, in another study in CAPD patients, glucose, creatinine, and β2-microglobulin transport rates were increased after oral administration of hypotensive doses of enalapril [83]. Smaller doses of oral captopril significantly reduced peritoneal protein loss in diabetic CAPD patients, with only a small decrease in their mean blood pressure [87].

Coronel et al. [88] evaluated the action of irbesartan, an angiotensin receptor blocker (ARB) with a long half life, on proteinuria, peritoneal protein losses, and peritoneal transport. After 30 days of treatment with irbesartan (145 ± 72 mg/day), and no changes in blood pressure level as compared with baseline, a reduction in proteinuria, decreased peritoneal protein losses at 4 h and 24 h dwell time, decreased peritoneal Kt/V urea, and increased peritoneal creatinine clearance were observed. Levels of serum albumin, prealbumin, and transferrin increased after treatment with irbesartan. Treatment with irbesartan in PD patients apparently modifies peritoneal transport and reduces peritoneal and urinary protein loss. This effect probably has a positive impact on nutritional parameters.

Using a sophisticated intra-abdominal camera, Ishida et al. [89] tested several antihypertensive drugs on the peritoneal capillaries in renovascular hypertensive dogs with mild renal insufficiency. The diameters of the small arteries of the peritoneum were measured after 3 days' oral administration of placebo, a selective ARB, or benazepril, an ACE inhibitor, or amlodipine, a calcium antagonist. A similar decrease in blood pressure was observed with all drugs. The diameter of the small vessels increased by 28% in dogs receiving the ARB and by 24% in dogs receiving benazepril, as compared with only 3% in dogs receiving the calcium antagonist.

Besides the hemodynamic effects that blockers of the angiotensin pathway may exert on the peritoneal structure and function, angiotensin is also thought to contribute to peritoneal fibrosis when the membrane is exposed to high glucose concentrations in PD [90], and ARBs may have a key role in preventing fibrosis as they may inhibit the TGF-beta1-Smad pathway [91]. However, another recent study found no differences in the protective effect on the membrane of either an ACE inhibitor or an ARB [92], but the expression of AQP-1 and AQP-4 in the mesothelium was significantly suppressed, accompanied by loss of peritoneal ultrafiltration in ACEI- and ARB-treated compared with control rats [93]. These results suggest that the renin-angiotensin system plays an important role in the regulation of water transport in the peritoneum and that administration of ACEI or ARB in patients CAPD should be carried out with caution.

The influences of a variety of other agents on peritoneal mass transport have been explored.

Statins have anti-inflammatory properties that may be of value in modulating responses to injury. The capacity of atorvastatin to modify peritoneal alterations secondary to hypertonic glucose were recently explored [94]. Administration of atorvastatin resulted in preserved ultrafiltration, protein loss, and peritoneal thickness.

Atrial natriuretic peptide (ANP) is a hormone with well-known diuretic and vasodilating properties. It has recently been reported that ANP could increase peritoneal fluid formation and increase peritoneal solute clearance. Recent studies in rats [95] suggest that ANP may decrease peritoneal fluid absorption by 51%, partially because of decreasing the direct lymphatic absorption, resulting in a significant increase in peritoneal fluid removal and small solute clearances. While the basic diffusive permeability of the peritoneal membrane was not changed, the peritoneal glucose absorption was retarded by adding ANP to peritoneal dialysate, perhaps through interaction of ANP with glucose metabolism.

The peritoneal transport rates of potassium and iodide-131 increased when streptokinase or serotonin was administered systemically to anesthetized dogs [45]. Whether these agents affect peritoneal permeability directly, or augment blood flow, remains to be determined.

In sedated rabbits dialyzed with a hypertonic dialysis solution, 0.25% procaine hydrochloride increased peritoneal urea and inulin clearances by more than 60% [96]. The effect persisted for at least 1 h after procaine was discontinued. Procaine may augment transport by vasodilation. However, the addition of procaine to either side of the isolated mesothelium increased transport, after a transient decrease. This effect may be due to disruption of the microfilaments of tight junctions between cells.

Using direct videomicroscopy of the peritoneal vasculature in rats, Mortier et al. [97] found that local application of acetylcholine, nitroglycerin, verapamil, and papaverine caused significant vasodilation of mesenteric arteries in the absence of any effects on systemic BP. Nitroglycerin 10^{-4} Mol induced a maximal and rapidly reversible vasodilation and acts independently of the endothelium.

The nitric oxide system and the peritoneal circulation and transport (see also Chapter 4).

Nitric oxide (NO) is the final common pathway for many of the vasodilating processes, including nitroprusside. Besides the expression of aquaporins (see below), Devuyst et al. [98] investigated the expression of endothelial nitric oxide synthase (eNOS) in 19 peritoneal samples from normal subjects, from uremic patients treated by hemodialysis (HD) or PD, and from nonuremic patients using Western blotting and immunostaining. eNOS was located in all types of endothelium and was up-regulated in the three patients with ascites and/or peritonitis. An adaptation of the L-citrulline assay to measure specific NOS activities within the peritoneum was more recently described; it appeared that the peritoneum lysate assayed for NOS activity can also be used for characterizing NOS isoform expression by immunoblot analysis [99].

Nitric oxide (NO) generation within the peritoneum could potentially affect peritoneal transport by increasing capillary vasodilatation, and increase peritoneal permeability during episodes of bacterial peritonitis. As peritoneal mesothelial cells have a common embryological derivation with endothelial cells, then mesothelial cells could potentially be a major source of locally produced NO. Davenport et al. [100] measured NO in fresh and spent dialysate effluent (SPDE) from uninfected CAPD patients, and from those during episodes of bacterial peritonitis. The results suggest that HPMC may be an important source of locally generated NO within the peritoneal cavity under basal conditions, but as they do not contain iNOS, the increased NO produced during episodes of acute bacterial peritonitis is more likely due to a combination of increased NO production by peritoneal endothelial cells and transmigrating macrophages. NO is very rapidly converted into nitrite and nitrate and the dialysate concentrations of both products have been used to estimate peritoneal NO production. In contrast to nitrite in plasma, which is rapidly converted to nitrate, nitrite in fresh and spent dialysis fluid is stable [101]. However, interpretation of such results should be made with caution. It is likely that the L-arginine–NO pathway is not the only route for generating nitrate, and that nitrate and nitrite are not acceptable measures of biologically active NO [102].

It is well known that different isoforms of NO synthase exist; the two most relevant ones in PD being eNOS and iNOS. The latter is induced whenever immunological stimulation is present. Peritoneal macrophages are an important source of iNOS [103–105]. Combet et al. [106] were able to demonstrate a strong increase in total NOS activity in an experimental model of peritonitis in the rat. This increase was inversely correlated with peritoneal free-water permeability. It is thus conceivable that the elevated levels of nitrate in peritonitis are derived from iNOS activity and not from the "hemodynamically active" pool of eNOS.

With these reservations in mind, nitrate in plasma and dialysate was measured [107] in stable CAPD patients and in patients with 11 peritonitis episodes in the acute phase and after recovery. The correlation between the MTAC of nitrate and the MTAC of creatinine indicated diffusion from the circulation and not local production of NO in the stable patients. From these studies it was suggested that D/P ratios of nitrate exceeding 1.0 during the acute phase of peritonitis are probably the result of local NO production, which may contribute to the marked vasodilation during peritonitis.

An important animal study showed that chronic uremia induces permeability and structural changes in the peritoneum, in parallel with AGE deposits and up-regulation of specific NOS isoforms and growth factors. These data suggest an independent contribution of uremia in the peritoneal changes during PD and offer a paradigm to better understand the modifications of serosal membranes in uremia [108]. Another study of the same research group demonstrated that long-term exposure of the human peritoneal membrane to dialysis solutions led to a significant increase in vascular density and endothelial area in the peritoneum in association with an up-regulation of NOS, vascular endothelial growth factor (VEGF), which co-localized with the advanced glycation end product pentosidine deposits. These data provide a morphologic (angiogenesis and increased endothelial area) and molecular (enhanced NOS activity and endothelial NOS upregulation) basis for explaining the permeability changes observed in long-term PD [109].

More recent studies have also suggested a major role for nitric oxide (NO) in the permeability changes and loss of ultrafiltration induced by acute peritonitis. Both in eNOS wild-type and knockout mice [110, 111] or with NOS blockade in wild-type mice the potential role of NO in peritonitis was explored. The results revealed that the permeability modifications and structural changes induced by acute peritonitis were significantly reversed in eNOS knockout mice, resulting in a net increase in ultrafiltration [110]. These results confirm that increased NO mediates permeability modifications during acute peritonitis. Breborowicz et al. [112] studied peritoneal transport of small and large solutes, and net ultrafiltration in rats during PD with glucose 3.86% solution, where L-NAME was used as an additive to dialysis fluid. In addition, the effect of IP L-NAME during acute peritonitis induced by lipopolysaccharides

was evaluated. L-NAME increased the peritoneal selectivity and net ultrafiltration. Lipopolysaccharides alone induced a significant decline in net ultrafiltration while, together with L-NAME, no changes in transperitoneal transport of small and large molecules was observed, nor a significant decline in net ultrafiltration. L-NAME given intraperitoneally reduced both local and systemic production of NO, which might explain its effects on peritoneal transport.

The effects of conventional and more biocompatible solutions on the peritoneal circulation will be discussed in Chapter 12.

Dipyridamole

Dipyridamole rapidly but transiently vasodilates [113] and has a sustained antiplatelet effect, which may explain the restoration of clearances towards normal in patients with intravascular platelet aggregations [114]. Peritoneal transport of urea and creatinine increased by 43 and 70%, respectively, in patients with normal vasculature given oral 300 mg/day of dipyridamole [115]. In rabbits, IV or IP dipyridamole increased urea and creatinine clearances by 39 and 16%, respectively [114]. The limited effectiveness and the transient vasodilator response of dipyridamole are reflected by two randomized control studies that did not demonstrate significant increases in peritoneal transport [47, 116]. Reduced peritoneal transport rates complicating some vascular diseases (vasculitis, diabetes mellitus, lupus, etc.) are improved by dipyridamole [117]. The augmentation of peritoneal transport rates persists after dipyridamole vasodilation abates, and is attributed to its antiplatelet effect. Peritoneal clearances of patients with normal vasculature improve only minimally and transiently with oral or IP dipyridamole [114]. Nevertheless, dipyridamole may be useful for selected patients when systemic disease with platelet thrombi affects mesenteric vessels, and an oral agent is preferred.

Alterations of the Electric Charges

Charged macromolecules may interact with peritoneal anionic sites, altering membrane ultrastructure and permeability. In rats, local administration of protamine, a polycation, markedly increases peritoneal permeability to inulin and, to a lesser extent, urea, associated with a partial disruption of the mesothelial junctions [118]. In rabbits, protamine-induced rise in peritoneal permeability to proteins can be reversed by heparin, which provides additional evidence for the physiological importance of negative electric charges on the membrane [119]. Also cationic poly-L-lysine augments peritoneal permeability for urea, inulin and albumin, while with the anionic poly-L-glutamic acid there was an opposite trend in rats [120]. These results were confirmed in a rabbit model by Pietrzak et al. [121]. Agents such as poly-L-lysine, polybrene, and procaine hydrochloride block the negative charges on the capillary walls and higher mass transports ensue, especially for charged solutes [122]. A poly-L-lysine -induced modest increase in the transfer rate of large uncharged molecules such as dextrans may be attributed to an effect on pore dimensions.

These findings contrast with those of Breborowicz et al. [123], who found decreased hydraulic permeability of the mesothelium in vitro when exposed to cationic ferritin or Alcian blue. In vitro studies of isolated mesothelium, however, may not relate closely to in vivo conditions, in which the capillary wall and interstitium are the more important transfer barriers. Further evaluation of polycations as transport accelerators, particularly for patients with impaired peritoneal transfer capacity, is undoubtedly warranted.

Influence of Pharmacological Substances on Peritoneal Convective Transport

As outlined in the chapter of peritoneal physiology, according to the three-pore model [124], the existence of a third, ultrasmall pore or aquaporin could explain the dissociation between water and sodium transport observed during PD, mainly when using hypertonic dialysis solutions. Aquaporin-1 has recently been recognized as the molecular correlate to such channels and positive staining for aquaporin-1 has recently been reported in the endothelial cells of the peritoneum of normal and uremic subjects [98, 125]. Aquaporins can be inhibited by mercurials, and in a study by Carlsson et al. [126], $HgCl_2$ was applied locally to the peritoneal cavity in rats, dialyzed with a hypertonic 3.86% glucose solution. $HgCl_2$ treatment reduced water flow and inhibited the sieving of $Na+$ without causing any untoward changes in microvascular permeability, compared with that of control rats. At least eight isoforms of aquaporins are now described, and besides aquaporin 1, aquaporins 3 and 4 are also present in the peritoneum [127].

Imai et al. [128] used a rat model of peritoneal sclerosis and could demonstrate that, in this model, the expression of AQP-1 and AQP-4 were significantly suppressed, and ultrafiltration volume was lost. The use of prednisolone in this

model completely restored the expression of AQP-1 and AQP-4, and peritoneal function improved. These findings were later confirmed by Stoenoiu et al. [129], who demonstrated that corticosteroids were able to induce an upregulation of aquaporin 1 in the peritoneal membrane with an associated increase in transcellular water transport across the peritoneal membrane.

Some drugs can also specifically affect the capillary filtration coefficient, i.e., the volume filtered per unit of pressure per unit of time (mL/mm Hg/min). The rate of ultrafiltration is largely determined, however, by the osmotic gradient across the peritoneum induced by dextrose. The gross ultrafiltration rate and solute mass transfer are offset by dialysate absorption; hence, lowering lymphatic flow rates raises net ultrafiltration and peritoneal clearance of solutes.

Diuretics

The addition of 1 mg/kg of furosemide to hypertonic PD solution augmented sodium movement, accompanying osmotically induced water flux in rabbits [130]. Normally, electrolytes do not accompany water in the same concentration as exists in plasma water, suggesting that membrane charge impedes transport, a phenomenon that is interrupted by furosemide. IP furosemide also caused an increase in peritoneal urea clearance, but no demonstrable changes in transport rates occur in patients undergoing intermittent PD when treated systemically with this diuretic. Moreover, oral administration of furosemide did not affect sodium, potassium, or water transport in patients undergoing CAPD [131]. Furosemide, however, does increase the peritoneal transport of uric acid and of barbiturates [132]. Intraperitoneally, 1.25 mg/kg of ethacrynic acid did not affect sodium flux accompanying the bulk flow of water across the peritoneum, but augmented urea clearance to about 165% of baseline [130]. Patients treated by CAPD may experience a restoration of lost ultrafiltration capacity after treatment by furosemide or by hemofiltration [133]. A specific effect of furosemide has been postulated, but correction of an overexpanded splanchnic volume by decreasing glucose absorption was able to restore the ultrafiltration capacity.

Amphotericin B (AmB)

AmB increases the rate of ultrafiltration per osmotic gradient, i.e., the ultrafiltration coefficient [134]. Above 0.5 mg/kg there is no dose effect, and it is effective only from the serosal side [134, 135]. AmB creates channels in biological membranes for solute and water penetration. Increments in peritoneal solute clearances are only modest and can be accounted for by enhanced convection [134]. Peritoneal mass transport of sodium also increases. Because osmotic ultrafiltrate during PD is hyponatric, the sodium gradient so established is an impediment to water transport that is cancelled by AmB [135]. IP use of use of AmB has been reported to increase ultrafiltration during short peritoneal dwell in rabbits. However, IP AmB did not increase peritoneal fluid removal after 4 h of dwell in a rat model [136]. Although the basic membrane permeability may not be altered by this drug, the D/D0 ratio for glucose and dialysis-over-plasma concentration ratio (D/P) values for urea, sodium, and total protein, as well as the diffusive mass transport coefficient values for these solutes did not differ among the different experimental groups (with and without AmB). However, the D/P values as well as the diffusive mass transfer values for potassium were significantly higher in the drug-treated animals as compared to the control group, resulting in significantly higher potassium clearances in the AmB-treated animals as compared to the control group. These higher clearances for potassium in the AmB groups may suggest a local release of potassium due to the cytotoxic effect of AmB. The contribution of water release from local cells to the increase in IP volume in animals treated with a high dose of AmB cannot be ruled out. Based on these results, it was concluded that AmB is not useful for improvement of PD efficiency [136]. Another experimental study with IP administration of AmB in rabbits [137] found also that the drug acutely enhanced a change in IP volume during a 1-h dwell after 3-day IP treatment with a low dose but did not affect peritoneal solute permeability. This was likely mediated by transcellular water channels, but not by aquaporin-1. No beneficial effects on the ultrafiltration were found with prolonged treatment or with the higher dose. Also these investigators found that AmB has no major clinical relevance in treatment of ultrafiltration failure in PD patients.

Beta-Blockers (β-Blockers)

Use of β-blockers has been associated with peritoneal ultrafiltration failure [138]. Of 13 patients with ultrafiltration failure, 12 had used β-blockers, compared to 18 patients without these problems, where only two patients used these drugs. Possible mechanisms explaining this observation have been reviewed [139]. From a theoretical point of view, either a decrease in portal venous pressure or an increase in lymphatic absorption is a possible mechanism.

Increasing Ultrafiltration Rates by Miscellaneous Drugs

Secretin increases the hydraulic permeability of the peritoneal membrane [140]. This selective action on the splanchnic bed occurs from the vascular side only. The aminonucleoside puromycin also induces this effect on peritoneal capillaries [141]. Chlorpromazine (2 mg/L) IP increases the ultrafiltration rate and solute clearance, largely by increased convection and presumably by its surfactant effect [142]. This drug decreased surface tension of the dialysate.

Neostigmine decreases the rate of lymphatic flow and thereby increases net ultrafiltration in rats [143]. Anticholinesterase agents have complex hemodynamic effects that could influence peritoneal transport and increase gastrointestinal motility, which would enhance dialysate mixing.

Higher ultrafiltration rates due to diminished glucose reabsorption were reported with IP calcium channel blockers in CAPD patients [81, 82]. Ronco et al. [17] suggested that maximal rates of ultrafiltration are inhibited by the steep curvilinear rise in plasma protein oncotic pressure in the peritoneal capillaries, reflecting the limited blood flow rate. Maher et al. [144] demonstrated that the ultrafiltration coefficient decreases in rabbits as IP dwell is prolonged, suggesting some concentration polarization, which could be corrected by increasing turbulence at the membrane interfaces. Increased absorption of dextrose will accompany most manipulations that enhance solute permeability and hence dissipate the glucose osmotic gradient faster, reducing ultrafiltration. Insulin is required to maintain low plasma glucose levels and achieve the maximal gradient. Exogenous insulin added intraperitoneally does not increase the glucose mass transfer coefficient [145].

Lymphatic Absorption

Lymphatics are the primary route for absorption from the peritoneum of isotonic dialysate including macromolecules, particles, and formed blood elements [146]. Most absorption occurs via the subdiaphragmatic lymphatics, with lesser amounts via the mesenteric lymphatic vessels [147]. Yet before reaching lymphatic channels macromolecules are probably distributed in the large peritoneal tissue compartment [148] (see Chapters 5 and 6 in this book).

The rate of lymphatic flow from the peritoneum correlates positively with ventilation (diaphragmatic movement) and negatively with end-expiratory pressure; it decreases with erect posture and with dehydration [149].

In the rat PD model, neostigmine increased net ultrafiltration and solute transport by reducing the cumulative lymphatic absorption, without an increase in total transcapillary ultrafiltration [143]. Lower doses of IP failed to influence lymphatic absorption in CAPD patients [150], but the animal data were confirmed by a report of a CAPD patient suffering from myasthenia gravis who required high oral dosage of this drug [151]. In another animal study, phosphatidylcholine augmented net ultrafiltration and solute clearances without increasing flux of water and solutes into the peritoneal cavity, thus acting by reducing lymphatic reabsorption [152]. Similar results were reported in a clinical study [153]. It has been suggested that phosphatidylcholine affects peritoneal fluid kinetics through its cholinergic action [154]. These studies indicate that limiting lymphatic absorption is a potential mechanism for augmenting peritoneal clearances that should be explored further.

The Study of Different Additives to the Dialysate

Hyaluronan

Using the rat model it has been found that peritoneal absorption was significantly reduced and peritoneal small solute clearance substantially increased by adding to the peritoneal dialysate 0.01% hyaluronan, a long polysaccharide chain that consists of repeating disaccharide units of N-acetylglucosamine and glucuronic acid [155, 156]. It is speculated that the effect of hyaluronan is due to the accumulation of a restrictive filter "cake" of hyaluronan chains at the tissue–cavity interface [156].

Hyaluronan plays an important role in tissue hydraulic conductivity and has been shown to exhibit a high resistance against water flow. It can thus act in tissue as a barrier against rapid changes in tissue water content [157], impeding the efflux from the peritoneal cavity. This effect of hyaluronan is both size- and concentration-dependent [156].

It is also possible that exogenous high-molecular-weight hyaluronan stabilizes the endogenous hyaluronan, which forms a stagnant layer at the mesothelial cell surface [158]. Effluent dialysate from CAPD patients stimulates production of hyaluronic acid by human mesothelial cells and acts synergistically with cytokines, such as interleukin (IL)-1 [159]. It has been shown that normal human mesothelial cells in vitro surround themselves with a particular matrix, "coat," containing mainly hyaluronan [160]. In a prospective, randomized crossover study [161], PD patients

were submitted to three dialysis treatments using the following PD solutions: 1) a commercially available PD solution (Dianeal PD-4, 1.36% glucose), 2) Dianeal PD-4 containing 0.1 g/L hyaluronan (HA), and 3) Dianeal PD-4 containing 0.5 g/L HA. There were no significant differences in net UF or peritoneal volume profiles among the three treatments. Mean net UF calculated using residual volumes, estimated by RISA dilution, tended to be slightly higher during treatment with solution containing 0.1 and 0.5 g/L HA. These data support the acute safety of HA when administered IP to PD patients. Although not statistically significant, there was a trend toward decreased fluid reabsorption during treatment with HA.

N-acetylglucosamine

Related to the effects of hyaluronan, N-acetylglucosamine (NAG) has been used either as osmotic agent for PD [162, 163] or as an additive to classical dialysate. Chronic PD with dialysis solution supplemented with NAG (50 mmol/L) causes accumulation of glycosaminoglycans in the peritoneal interstitium, which results in a change of peritoneal permeability [164]. Supplementation of the dialysate with NAG could enhance the synthesis of hyaluronan by the mesothelial cells, since hyaluronan contains both glucuronic acid and NAG. In rats, equivalent concentrations of NAG and glucose were associated not only with a greater ultrafiltration with NAG [163], but also with a greater in vitro synthesis of hyaluronan [162].

Chronic PD in rats with a solution supplemented with NAG showed an accumulation of polyanionic glucosaminoglycans in the submesothelial interstitium that must be associated with a decreased hydraulic permeability of that tissue [165].

Glycosaminoglycans (GAGs)

Enhanced IP synthesis of GAGs increases the permselectivity of the peritoneum and preserves its function during chronic PD [166–168]. To verify whether the favorable effects of GAGs are purely functional or involve a morphological amelioration of the peritoneal membrane structure, a study was carried out in an animal model of plasticizer-induced peritoneal fibrosis [169]. Subtotally nephrectomized rats received either placebo, plasticizers (IP), or GAGs (SC), or plasticizers (IP) and GAGs (SC). In plasticizer-treated animals, peritoneal function tests and morphology were dramatically deranged. On the contrary, the SC administration of GAGs in plasticizer-treated rats maintained the peritoneal physiology and normal structure. The SC administration of GAGs apparently protects peritoneal functions by affecting the remodeling of the peritoneum, rather than by a purely functional or simple mechanical effect.

Heparin

In an animal model of chronic PD with repeated dwell studies it was shown that heparin may improve peritoneal fluid transport, possibly due to better healing and reduced peritoneal inflammation [170]. In a clinical study, Sjoland et al. [171] showed that IP tinzaparin reduces peritoneal permeability to small solutes and increases ultrafiltration in PD patients. In a recent experimental study [172], exposure to PD fluid induced activation of IP complement formation of C3a(desArg) and increase of C5a-dependent chemotactic activity, and coagulation (formation of thrombin–antithrombin complex) and recruitment of neutrophils. In the case of IP injection, neutrophil recruitment and complement activation were inhibited by low-molecular-weight heparin (LMWH). LMWH inhibited thrombin formation, reduced complement-dependent chemotactic activity, and increased the IP fluid volume, indicating an improved ultrafiltration.

Chondroitin Sulfate (CS)

CS, another naturally occurring polyanionic polymer GAG has been tested as an alternative osmotic agent or has been added to saline [173] or conventional dialysis solution to enhance peritoneal ultrafiltration [167]. In the presence of CS, net peritoneal ultrafiltration increased, while absorption of glucose and horseradish peroxidase from the peritoneal cavity decreased [173, 174]. It is postulated that the polyanionic CS molecules are trapped in the peritoneal interstitium, thus decreasing its hydraulic conductivity and permeability, which in turn increases net fluid removal during PD because of its slower absorption from the peritoneal cavity.

Phosphatidylcholine

In 1985, Grahame et al. detected the presence of surface-active material (phospholipids) in the peritoneal effluent of CAPD patients [175].The surface-active material, lining the peritoneal membrane, is mostly composed of phosphatidylcholine (lecithin). Peritoneal efficiency may be altered by the constant removal of phosphatidylcholine and other phospholipids in the dialysate effluent [175]. A decrease in dialysate phospholipids was reported in patients with a low ultrafiltration capacity and in those with peritonitis [176]. IP phosphatidylcholine promptly raised the ultrafiltration rate, while after oral administration about 30 days were required to achieve this effect. It was suggested that lecithin administration restored the normal peritoneal surfactant lining [176]. To explain augmentation of ultrafiltration after phosphatidylcholine, another group proposed that these phospholipid molecules bind to the anionic sites on the luminal side of the mesothelium, creating a water-repellent surface that diminishes the thickness of the unstirred dialysate. This would augment diffusion of solutes from blood to the peritoneum while the hydrophobic lecithin molecules would impede water absorption, favoring ultrafiltration [177].

In rabbits, phosphatidylcholine increases net ultrafiltrate volume [177], an effect that becomes significant only after hours of PD, and does not show up during hourly exchanges.

Clinical studies have shown that a phosphatidylcholine premixed dialysis solution significantly enhances ultrafiltration also in patients without ultrafiltration loss [153], but other results were controversial [178, 179]. Besides its surfactant effect, phosphatidylcholine may impede lymphatic absorption [152]. In rat experiments, administration of 50 mg/L phosphatidylcholine to a dialysate of 4.25% glucose leads to a reduction in lymphatic absorption without increased transperitoneal transport of water. However, in in vitro experiments, phosphatidylcholine was cytotoxic to human mesothelial cells, as indicated by the release of lactate dehydrogenase from their cytosol. These results suggest that the positive short-term effect of the addition of phosphatidylcholine to the dialysis solution (i.e., an increase in ultrafiltration) may be masked by its deleterious action on human mesothelial cell membrane [180].

Dioctyl Sodium Sulfosuccinate (DSS)

Dioctyl sodium sulfosuccinate (DSS) is a surfactant and has been shown to increase peritoneal small solute clearance. Penzotti and Mattocks [181, 182] accelerated peritoneal transport of labeled urea and creatinine in sedated rabbits by adding a variety of surface-acting agents including DSS and setyl trimethyl ammonium chloride. Dunham et al. [183] found a dose-dependent rise in creatinine and urea clearances when docusate sodium was given intraperitoneally to tranquilized rabbits. The effect persisted for 5 h. DSS was found to increase peritoneal fluid and small solute removal whereas the peritoneal solute transport rate did not change [184].

Cytochalasins

These molecules disrupt microfilaments of cellular junctions. IP cytochalasin D raises the clearances of creatinine and urea in the rabbit, consistent with augmented diffusion through intercellular gaps [185]. Similarly, cytochalasin B, D, and E increase permeability of the peritoneum to urea, inulin, and albumin in rats [186]. Only cytochalasin B effects were clearly reversible, which may relate to its unique ability to affect carrier proteins of the cell membrane.

Antioxidants and Free Radical Scavengers

Breborowicz et al. [187] tested the effect of L-2-oxothiazolidine-4-carboxylate (procysteine), a precursor of intracellular cysteine, on the function of human mesothelial cells in culture. Procysteine stimulated the proliferation of these cells and decreased their spontaneous death rate. The cells, when pretreated with procysteine, were resistant to injury by free radicals. Procysteine also reversed the cytotoxic effects of a mixture of essential and nonessential amino acids on the cells. The same drug was also studied in an in vivo model of lipopolysaccharide (LPS)-induced peritonitis in rats [188]. The addition of LPS to dialysis fluid increased the white blood cell count and the nitrite level (index of NO synthesis) in the dialysate. Simultaneous addition of procysteine to the dialysis fluid prevented an increase of while blood cells, but not of nitrites in the dialysate. The IP inflammation was accompanied by a decrease in net transperitoneal ultrafiltration, an increase in the absorption of glucose, and a loss of protein into the dialysate. Procysteine partially reversed the effect of peritonitis on net ultrafiltration.

Peritoneal leukocytes from rats exposed to LPS showed a reduced concentration of glutathione, an effect that was reversed in the presence of the drug. These results show that the addition of procysteine to dialysis fluid modified the peritoneal reaction to acute inflammation. The same group [189] showed that supplementation of IP infusion of saline with vitamin E decreased the peroxidation of peritoneum estimated as the malondialdehyde (MDA) level in rats'

omentum. However, the permeability of the peritoneum to glucose and protein in vitamin E-treated rats was increased. Vitamin E appeared to be cytotoxic to human mesothelial cells, as measured by inhibition of their proliferation, and this effect was irreversible.

Influence of Drugs on Peritoneal Mesothelial Cells

The short-term effects of antineoplastic agents such as methotrexate, doxorubicin, and mitoxantrone on the integrity of human peritoneal mesothelial cells (HPMC) membrane and mechanisms of intracellular potassium transport were assessed [190]. There was no evidence of significant cytotoxicity to either methotrexate, doxorubicin, or mitoxantrone. However, methotrexate diminished Na,K,ATPase activity and simultaneously enhanced 86Rb transport via a furosemide-sensitive pathway. Mitoxantrone reduced the furosemide-sensitive 86Rb influx in a dose-dependent manner. These data demonstrate that antineoplastic agents interfere with HPMC function, which might contribute to the oncostatic-induced peritoneal toxicity. The same group investigated the effects of insulin on the Na + /K(+)-ATPase expression and activity in human peritoneal mesothelial cells [191]. A time- and dose-dependent increase in the Na + /K(+)-ATPase activity was found. This effect appears to be mediated by an increase in [Na +]i and is not related to alterations in Na + /K(+)-ATPase subunit mRNA expression.

Transport Acceleration of Specific Solutes

Removal of barbiturates may be accelerated by increasing dialysate pH with Tris buffer, thereby influencing the rate of nonionic diffusion [192]. Alkalinization of peritoneal dialysate by THAM also raised uric acid transport [193]. Drugs that counteract the membrane anionic charge should enhance removal of charged solutes. Adding albumin to a PD solution enhances removal of barbiturates [194], ethchlorvynol [195], and salicylate [196], and is expected to augment the clearance of numerous other drugs that circulate bound to plasma proteins, such as quinine and phenytoin. For lipophilic drugs such as glutethimide and short-acting barbiturates, transport can be enhanced by adding lipid to the dialysate [197]. In general, for treating severe overdosage, the removal of drugs by PD is too slow. Specific effects such as chelation, however, may influence concentrations of drugs and certain uremic metabolites.

Peritoneal Protein Loss Attenuation

In a preliminary study, captopril significantly reduced protein loss into the peritoneum in diabetic CAPD patients, presumably by modulating vasoconstrictive responses of peritoneal capillaries [87]. In rabbits a marked increase in protein elimination into the peritoneum occurred after addition of histamine, an effect blocked by its antagonist [78]. Because histamine may be involved in the pathogenesis of hypersensitivity reactions to drugs, leachables or contaminants of the dialysis solution, antihistamine agents could be of value in such circumstances.

Several lines of evidence support the role of intact anionic sites on the peritoneal transport barrier in the restriction of the passage of charged macromolecules to the peritoneal cavity. Partial neutralization of anionic sites may account for the findings from an animal study in which dialysate pH adjustment from 5.6 up to 7.4 significantly increased peritoneal protein loss in the presence of nitroprusside [51]. Another group demonstrated that, in rabbits, transperitoneal protein loss was substantially enhanced by protamine. Neutralization of protamine with heparin prevented this effect [119]. In an animal study [5], blood to peritoneum transport rates of cationic DEAE dextran were less that those of both neutral dextran and dextran sulfate. The effects of chondroitin sulfate have been described above.

Conclusions of Part I

It is easy for clinicians as well as basic scientists to forget that the peritoneum, unlike synthetic hemodialysis membranes, is alive. The mesenteric circulation is remarkable for its size and complexity, and until recently not much was known about its physiology. The numerous drugs and hormones that affect mesenteric blood flow and membrane physiology have predictable effects on peritoneal transport parameters [198, 199]. Patients undergoing chronic dialysis often take several drugs, many of which have hemodynamic and membrane transport effects. The influences of these agents on the peritoneum must be ascertained. Patients treated for acute problems, for example, in

an intensive care unit, are exposed to an even greater abundance of drugs potentially altering transport. Rational use of drugs and other physiological manipulations in patients maintained by PD requires an understanding of their effects on peritoneal blood flow and permeability. It is naive to consider the peritoneum as an inert membrane with constant blood flow and transport characteristics. Further investigation of the interactions of drugs and the peritoneum may identify optimal methods for augmenting transport efficiency safely.

Part II: Pharmacokinetic Aspects of Peritoneal Transport of Drugs

This part of the chapter has been divided in two major sections: the first section covers some basic pharmacokinetic concepts in the presence of normal and abnormal renal function. More detailed information on this subject is available in standard textbooks and reviews on pharmacokinetics [200–202] and in chapters of textbooks in nephrology [203, 204]. Also in this first section a general discussion on the major factors determining the transperitoneal transport of drugs after systemic and IP administration will be provided.

In the second section the pharmacokinetic data obtained with drugs, commonly used in continuous ambulatory or automated PD (CAPD or APD) patients, have been listed in tables. Following each table, recommendations for possible dose adaptations in PD patients are provided.

Basic Pharmacokinetics

Drugs produce their therapeutic or toxic effects in biological systems by reacting with receptor sites or other sites of action located in target tissues. The intensity of these effects is, in most cases, determined by the concentration of the drug in the direct environment of the site of action (the "biophase"). It is not possible to determine drug concentrations in the biophase. However, all tissues are supplied by blood (or plasma). Although often a complex relationship exists between the drug concentration in the biophase and that in plasma water, the latter is an alternative and more accessible site to measure the drug concentration. Responses to a particular drug are therefore commonly related to the concentration of the drug (or in some cases of its metabolites), in plasma water. After administration of a drug, absorption from the site of administration to the plasma (in case of extravascular administration), distribution from the plasma to organs and tissues, and elimination by biotransformation (predominantly in the liver) or by excretion of the chemically unaltered parent drug (predominantly via the kidneys) take place. However, after biotransformation, the metabolites are often excreted by the kidneys, even when the parent drug is not. In the situation in which the metabolite(s) is pharmacologically active, dose adaptation in renal failure of drugs that are not primarily eliminated by the kidney may be necessary. As a consequence of these events, drug concentrations in plasma water, and in the biophase, change with time, as does the pharmacological effect.

In addition, drugs can be bound to proteins, and their effect may depend on the free/protein-bound ratio. With the usual methods, however, total plasma drug concentrations are measured, i.e., free drug and drug bound to plasma proteins together. If the protein binding of the drug is constant, total drug concentration in plasma water can be used as an index of free drug concentration. If, however, the protein binding of the drug has changed, e.g., because of renal failure or by interaction with other drugs, this relationship will change and the intensity of effect will be smaller or larger than expected for a particular total plasma drug concentration.

Compartmental Models

Pharmacokinetics involve the mathematical description of the time-course of the concentration of the drug (and, in some cases, its metabolites) in biological fluids after its administration. In most models, compartments are used; it is important to realize that a pharmacokinetic compartment does not necessarily correspond to a given anatomical body fluid compartment. The time-course of the plasma drug concentrations can usually be adequately described by a one-compartment model, in which the body is viewed as one space, in which the drug is distributed rapidly and homogeneously. Although this is an oversimplification, such a one-compartment model is often satisfactory for the study of the pharmacokinetics of a drug, e.g., in order to determine its optimal dosage.

A two-compartment model (Fig. 9.1) consists of a central and a peripheral compartment. The central compartment includes the plasma, but also the extracellular fluid of highly perfused organs such as heart, lung, liver, and kidney. The peripheral compartment involves the compartment in which the drug is distributed at a slower rate. Transfer between

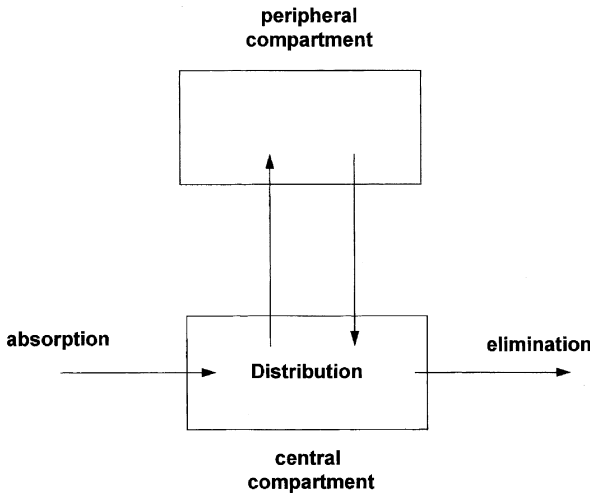


Fig. 9.1 Schematic representation of a two-compartment model

the two compartments is slow, and changes in concentration in one compartment will only be accompanied by changes in the other compartment with a certain delay. What parts of the organism belong to the central or to the peripheral compartment will depend upon the physicochemical characteristics of the drug, and of the general condition of the tissues involved. In a patient with sepsis, for example, the separation between central ("vascular") and peripheral ("interstitial tissue") compartments has greatly disappeared by the generalized hyperpermeability of the capillaries. Although three- and even more-compartmental models describe the situation more correctly, they are difficult to handle and their use is usually not needed.

Plasma Concentration–Time-Course

In Fig. 9.2 the time-course of the plasma concentrations of a drug after IV injection of a single dose is shown for both a one-compartmental and a two-compartmental model. Factors such as absorption, distribution, elimination, and excretion usually follow first-order kinetics. When first-order kinetics apply, the changes in concentration occurring are proportional to the drug concentration at that particular moment. After absorption and distribution are completed, the fall of the plasma concentration is only determined by elimination. As illustrated in Fig. 9.2, if elimination follows first-order kinetics, the log concentration versus time curve in a two-compartment model is a straight line. From the plasma concentration–time curve a number of pharmacokinetic parameters can be calculated. These are useful in the procedures for dose adaptation in different situations.

The elimination serum half-life of the drug ($t_{1/2}$), is the time taken for the plasma concentration as well as the amount of drug in the body to decrease by 50%. A closely related parameter is the elimination constant (K_e), where:

$$K_e = 0.693/t_{1/2} \tag{9.1}$$

The apparent volume of distribution (V_d) of a drug relates the total amount of drug in the body to the concentration of drug in plasma at the same moment.

The V_d can be calculated from:

$$V_d = D/C_0 \tag{9.2}$$

where D equals the dose given and C_0 equals the plasma concentration at the time 0, the time of administration. The V_d can be calculated only when the dose of the drug entering the body is known; that means when the drug is either given IV or if the exact amount absorbed is known.

The V_d provides an estimate of the extent of distribution of the drug throughout the body. If there is important uptake of the drug by the tissues, a V_d several times larger than the total body fluid volume (approximately 42 L for a body weight of 70 kg) can be found.

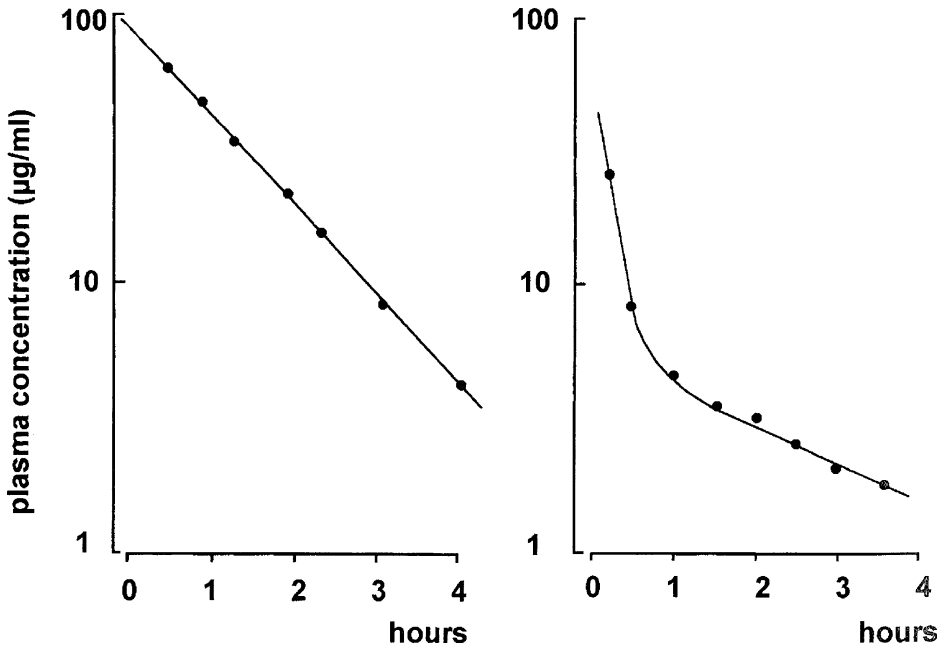


Fig. 9.2 Plasma concentrations as a function of time; in the left panel the logarithm of the plasma concentration is plotted for a drug for which a one-compartmental analysis is appropriate. In the right panel, log plasma concentrations are shown for a two-compartmental analysis. After the distribution phase there is a linear decay of the concentration, corresponding to the elimination phase

One of the important factors determining the size of the apparent V_d is the degree of plasma protein binding. The relationship between the apparent V_d of a drug and its protein binding is as follows:

$$V_d = V_B + V_T(F_B/F_T) \tag{9.3}$$

V_B and V_T are the volumes of water in blood and in tissues, respectively, and F_B and F_T are the fractions of free drug in blood and tissues, respectively. An increase in F_B without a proportional increase in F_T would produce an increase in the apparent V_d.

The apparent V_d can also be calculated from the area under the plasma concentration versus time-curve (AUC), and K_e:

$$V_d = D/AUC \times K_e \tag{9.4}$$

or

$$V_d = (D \times t_{1/2})(AUC \times 0.693)$$

Total body clearance or total plasma clearance is the volume of plasma that is cleared completely of the drug per unit time: it gives an estimate of the efficiency of the elimination of the drug by organs such as liver or kidney. Total body or plasma clearance is the sum of the clearances by the individual elimination routes, mainly biotransformation in the liver and excretion by the kidneys. For some substances elimination takes place only via the kidney, and then total body clearance equals renal clearance.

Total body clearance (Cl_{tot}) can be calculated by means of the equations:

$$Cl_{tot} = 0.693\ V_d/t_{1/2} \tag{9.5}$$

$$Cl_{tot} = D/AUC \tag{9.6}$$

Although clearance can be calculated from V_d and $t_{1/2}$, it does not depend on these parameters. On the other hand, $T_{1/2}$ of elimination is dependent not only upon the clearance, but also upon the V_d. Although gentamicin and digoxin are both cleared by the kidneys to approximately the same extent as creatinine (this means at a rate of approximately

120 mL/min in a normal situation), the elimination $T_{1/2}$ of digoxin is 36 h, while that of gentamicin is only 2 h. This is due to the fact that the V_d of digoxin is more than 500 L, while that of gentamicin is only about 15 L. When elimination in different situations is compared (for example, in patients with renal failure compared to healthy individuals, or in predialysis patients compared to those on dialysis), clearances and not only half-lives should be calculated whenever possible. Elimination $T_{1/2}$ should not be confused with duration of action. The latter is determined by the time during which drug concentrations are above a minimal effective concentration (MEC). For antibiotics, usually the minimal inhibitory concentration (MIC) of the susceptible antibiotic is considered.

The duration of drug action is dependent not only on the elimination $T_{1/2}$ of the drug but also on the dose given, bioavailability and of the drug distribution.

Total body clearance can be measured exactly only after IV drug administration or when the bioavailability, F, is known. Drugs are, however, often administered orally without knowing their exact bioavailability.

While the pharmacokinetic behavior of a drug is usually studied after single-dose administration, it is of utmost importance to know what happens after chronic administration of a drug. For some drugs at the moment of the second administration the amount still present in the body is negligible, so that after the second administration concentrations in the plasma will be similar to those after the first administration. This is, for example, the case when, in patients with normal renal function, gentamicin (with an elimination $T_{1/2}$ of 2 h) is administered three times a day. When, however, drugs are administered at dosing intervals shorter than four half-lives, an important fraction of what was introduced with the last administration is still present at the time of the second dosage. Consequently, the concentration after the second dose will be higher than that after the first dose, i.e., accumulation of the drug occurs. In that case, steady-state concentrations are obtained only after a number of administrations. The time to reach steady-state plasma concentrations depends only on the $T_{1/2}$, and is approximately four to five times the $T_{1/2}$ of the drug. For example, for digoxin, with its $T_{1/2}$ of 1.5 days, this works out at approximately 1 week. If the steady-state levels are to be achieved earlier, a loading dose of the drug must be given. The extent of accumulation (i.e., how much higher the steady-state levels will be than those after the first administration) depends on the $T_{1/2}$ and the dosing interval.

Pharmacokinetic Alterations in Patients with Decreased Renal Function

In patients with renal failure the fate of a drug can be altered profoundly. Gastrointestinal absorption after oral administration of a drug may be impaired in uremic patients because gastrointestinal pH or motility are altered. Biotransformation of drugs can be decreased or increased in uremic patients. There is also much interest in alterations in plasma protein binding of drugs in these patients. For a number of acidic drugs, which are mainly bound to plasma albumin, binding is often markedly decreased, due either to a decrease in albumin concentration in the plasma or to a decrease in the affinity at the binding sites; the decrease in affinity can be due to structural changes of the albumin molecules or to the presence of endogenous inhibitors. Some basic drugs bind mainly to α1-acid glycoprotein (α1-AGP). In renal failure the binding of these drugs may be increased due to the elevated α1-AGP concentrations in the plasma. These changes in protein binding can markedly affect the calculated pharmacokinetic parameters, and they can in some circumstances lead to changes in free drug concentration in plasma, to changes in efficacy and to side-effects.

Most important, of course, is the decrease in renal excretion of the drug. The renal clearance of a drug is usually decreased proportionally to the decrease in glomerular filtration rate. If renal excretion is the only elimination route of the drug, total body or plasma clearance will be reduced to the same extent. For substances that are only partly eliminated by the kidneys, the alteration in total body clearance will depend upon the relative importance of the renal versus the nonrenal elimination. It should, however, be re-emphasized that it is not because a drug is not eliminated via the kidney, that total body clearance is not altered in patients with renal failure. For example, hepatic clearance can also be affected by a change in protein binding or because of accumulation of other molecules. However, the V_d of drugs in these patients is often also different due to the changes in binding in plasma or in tissues. The plasma $T_{1/2}$, which depends on both V_d and Cl, is therefore not always a good parameter of the drug clearance in these patients. For example, digoxin is not bound to a significant extent to plasma proteins, but it is bound extensively to tissues of the kidneys, liver, and myocardium. This binding is decreased in patients with renal failure. As apparent from Eq. 9.3, a decrease in drug tissue binding without a corresponding decrease in drug plasma binding results in a decrease in the apparent V_d. In several studies it has been observed that the V_d of digoxin is significantly smaller in patients with chronic renal failure (230–280 L versus 500 L in normals).

The pharmacokinetic changes in chronic renal failure can, mainly after chronic administration of a drug, lead to important changes in total and free plasma concentrations, if the dose is not adjusted. Drug concentrations in the body can be much higher and the time to reach steady state (at a higher level) can be increased if the $T_{1/2}$ is prolonged. This

explains why, in patients with renal failure, a loading dose is often needed. Thus, for many drugs, dose adjustments will be necessary in chronic renal failure. The mean steady-state levels (Css) that will be achieved in a given situation can be calculated with the following equation:

$$\text{Css} = (F \times D)/(Cl_{\text{tot}} \times T) \tag{9.7}$$

where F = fraction absorbed, T = the dosing interval, and D the maintenance dose. This can also be expressed as:

$$\text{Css} = (F \times D)/Cl_{\text{tot}} \times T) \tag{9.8}$$

From these equations the maintenance dose needed for a given Css can be calculated. The many nomograms available for calculation of maintenance doses are based on these principles.

The loading dose (D*), i.e., the dose needed to obtain a given Css at once, can be calculated by the equation

$$D* = V_{\text{d}} \times \text{Css} \tag{9.9}$$

Pharmacokinetic Alterations in Patients on PD

PD can alter the pharmacokinetics of a drug, depending upon the route of administration of the drug and rate of removal via the dialysate. This can necessitate dose adaptations.

Pharmacokinetics of Drugs After Systemic Administration: Assessment

Plasma and dialysate concentrations can be measured as a function of time. To evaluate whether systemic kinetics are affected by dialysis, serum $T_{1/2}$, V_{d} and total body clearance (and in some cases residual renal clearance) can be calculated and compared to the values obtained in terminal chronic renal failure patients without dialysis. The amount recovered from the peritoneal dialysate over the period of time (Aper), can be used to assess the need for dose adaptation. This amount should be viewed in relation to that lost in the body over the same period of time by other routes, such as hepatic biotransformation or residual renal excretion.

The PD clearance (Clper) can be calculated from the equation:

$$\text{Clper} = (\text{Apert1} - \text{t2})/\text{AUC t1} - \text{t2} \tag{9.10}$$

where Aper t1 – t2 is the amount recovered in the dialysate over a given time period and AUC t1 – t2 is the area under the plasma concentration curve over the same time period. The peritoneal clearance should be compared to the total body clearance (Cl_{tot}). Indeed, the increased plasma clearance that can be found with dialysis is dependent of the peritoneal clearance of the drug, the residual renal clearance and the nonrenal clearance.

Factors Influencing Peritoneal Drug Clearance After Systemic Administration

The dialysis clearance of a systemically administered drug in the PD setting will depend upon factors that are summarized in Table 9.1. The peritoneal membrane characteristics have been described in the first part of this chapter. Only some of the other factors will be discussed below.

Dialysate Flow Rate

The most important factor in determining the magnitude of the peritoneal clearance of a drug is the dialysate flow rate, which is around 6–7 mL/min in CAPD. Small solute peritoneal clearances are largely dialysate flow-dependent. During the long dwells of CAPD, the transport rate of small solutes per unit of time is high at the beginning of the dwell and decreases with time because diffusion equilibrium is either obtained or approached. With increasing molecular weight of the solute the transport rate during the dwell becomes more homogeneous.

Table 9.1 Factors affecting peritoneal drug clearance after systemic administration

Dialysate properties
Flow rate
Temperature
pH
Osmotic content
Drug properties
Molecular weight
Ionic charge
Distribution volume (Vd)
Protein binding
Extrarenal clearance
Lipid or water solubility
Characteristics of the peritoneal membrane
Surface and charge
Permeability
Peritonitis
Sclerosis
Peritoneal blood flow
Stagnant layers
Ultrafiltration

The dialysate flow rate is greater during the rapid exchanges in some automated PD (APD) regimens. This explains why, during the rapid exchanges in APD programs, clearances of solutes with low molecular weight are increased. During the rapid exchanges of continuous cyclic PD (CCPD) (for example, four exchanges of 2.5 L over 8 h overnight, followed by a long diurnal dwell time of 10–12 h), the dialysate flow rate can be around 15–20 mL/min, values much greater than those for CAPD. Dialysis clearances during the short dwell times could be higher, because sink conditions tend to be maintained. It could be that during the rapid exchanges a significant fraction of a systemically given drug is removed through the peritoneum.

The first comprehensive reviews on the pharmacokinetic principles in the antibiotic treatment of peritonitis in APD have been published by Diaz-Buxo et al. [205] and Manley and Bailie [206]. Results from various APD and comparative CAPD pharmacokinetic studies were reviewed. In APD patients, antibiotic half-lives were shorter during the cycler exchanges. Antibiotic peritoneal clearance was greater in patients treated with APD than those treated with CAPD regimens. Antibiotic clearance depends upon RRF and dialysate flow rate.

Table 9.2 is taken from [206] and shows that the peritoneal clearances of different antibiotics are systematically higher in APD than in CAPD. To ensure that maximal antibiotic bioavailability occurs with intermittent IP dosing, it is recommended that the antibiotic-containing dialysate must dwell at least 4 h to ensure an adequate antibiotic depot in the body.

To determine the impact of dialysate flow rate (DFR) on cefazolin pharmacokinetics in PD patients, Manley et al. [207] performed a meta-analysis of published reports, and the data were analyzed based upon low DFR ($\leq$ 5.50 mL/min) or high DFR ($>$ 5.50 mL/min). Published literature provided data on 55 PD patients (12 high DFR, 43 low DFR). Regardless of data origin a prominent coefficient of determination ($p < 0.0001$) existed between DFR and all cefazolin pharmacokinetic data except peritoneal clearance. These findings demonstrate that an increased DFR leads to an increased rate of cefazolin clearance in APD patients. Clinicians dosing cefazolin in PD patients using a higher DFR than that used to determine cefazolin pharmacokinetics should use increased doses or prescribe lower/comparable DFRs. Data are not yet available for patients prescribed very high DFRs (e.g., continuous flow PD).

Table 9.2 Comparison of various antibiotic clearances in CAPD and APD patients (from [206])

	Dialysate flow (mL/h)		Peritoneal clearances (mL/min/1.73m^2)	
Antibiotic	APD	CAPD	APD	CAPD
Cefazolin	416.7	333.3	2.2 ± 0.7	1.0 ± 0.3
Tobramycin	416.7	333.3	4.2 ± 0.9	1.1 ± 0.8
Vancomycin	416.7	333.3	2.1 ± 0.7	1.2 ± 0.5
Piperacillin	416.7	333.3	5.3 ± 1.1	3.6
Fluconazole	500–687.5		11 ± 2.7	4.3–5.5

However, the concentration of most systemically administered drugs achieved in the drained dialysate after 2 h will be much lower than after long dwells so that the total amount of drug removed over 24 h in APD will be not much different from CAPD. We therefore suspect that the daily peritoneal removal of most drugs after systemic administration is also in the APD setting, as a rule, clinically unimportant.

The Molecular Weight of the Drug

The molecular weights of most drugs range between 100 and 700 Da, with some notable exceptions such as vancomycin (MW 1,450), insulin (MW 6,000), and Epo (MW 30,400). The diffusion of a solute from blood to dialysate is inversely proportional to the square root of the solute mass, both in HD and PD [208, 209].

Drug Protein Binding

Since only unbound, free drug is available for diffusion, a drug with a high plasma protein binding usually shows a low peritoneal clearance. The effect of plasma protein binding on the peritoneal transport of IV administered β-lactam antibiotics has been investigated in rats [210]. The antibiotic concentration–time profiles obtained in the dialysate were compatible with the concept that only unbound antibiotic is available for peritoneal transport. Although Flessner et al. [211] reported that bovine serum albumin is transferred through the peritoneal tissues from plasma to the peritoneal cavity in rats, the capillary membrane permeability of cephalosporins was 5–17-fold higher than that of albumin. Therefore, even if molecules bound to albumin can be transported through the peritoneal membrane, the contribution of this fraction is probably minor. For practical purposes this implies that the peritoneal membrane plays no important role in the transport of endogenous substances highly bound to proteins [212]. Dialysate concentrations of proteins are lower than serum concentrations and the protein binding of drug molecules in the peritoneal compartment is believed to be of minor clinical significance [213]. Based upon these considerations, a reasonably accurate formula for the prediction of the peritoneal clearance in CAPD after systemic administration of drugs has been proposed [214], where:

$$\mathrm{Clper(mL/min)} = 75\sqrt{(\mathrm{fU})}/\sqrt{(\mathrm{MW})} \tag{9.11}$$

In this formula, fU represents the free fraction in the serum and MW the molecular weight of the drug. This formula is valid for a 2 L dialysate and a 6 h dwell, in the absence of peritonitis. Erythromycin, for example, has a molecular weight of 730 and a free fraction of 0.30; therefore, the peritoneal clearance is estimated to be 1.52 mL/min. The validity of the formula was tested by comparing the predicted values with the observed clearances in 19 clinical studies. A linear regression analysis yielded a correlation coefficient of 0.958.

A drug with a low molecular weight (<500 kDa) and with a low plasma protein binding can have a clinically relevant PD clearance.

Need for Dose Adaptation After Systemic Drug Administration in PD

The dialyzability of a drug in any dialysis strategy is clinically relevant only when at least two conditions are fulfilled. First, the dialysis clearance should be at least 30% higher than the endogenous total plasma clearance; otherwise the additive effect of dialysis clearance on overall drug elimination is negligible [215]. Second, the V_d of the drug should be less than 1 L/kg body weight. If V_d is larger, only a small fraction of the drug is available in the plasma for elimination via dialysis, and the amount of drug removed is small, even for a high clearance. Since in terminal chronic renal failure for most drugs, the total endogenous drug plasma clearance is higher than 20–30 mL/min, and the V_d is more than 1 L/kg body weight, the peritoneal drug clearance rarely contributes significantly to drug removal in the CAPD setting. Therefore, additional dose adaptations for CAPD beyond the recommendations for terminal chronic renal failure are very rarely necessary. Notable exceptions are drugs with a small V_d, low protein binding and a small total plasma clearance in uremia.

The presence of peritonitis does not significantly influence the magnitude or rapidity of drug transport into the peritoneal cavity after systemic administration. For example, the peritoneal clearances of netilmicin and of ciprofloxacin in patients with or without peritonitis were not different [216, 217].

Studies after systemic administration of a drug are of interest not only to evaluate the need for dose adaptations to maintain adequate systemic concentrations, but also for knowing the dialysate drug concentrations. The low peritoneal drug clearance does not exclude that, for example, for an antibiotic, therapeutically effective concentrations

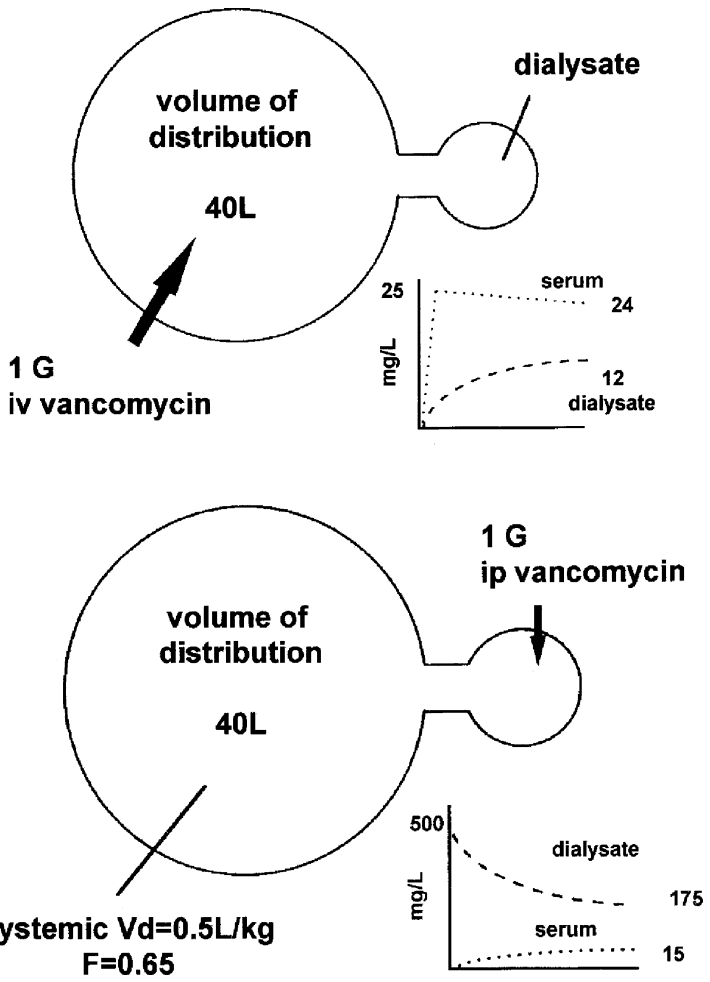
can be achieved in the dialysate after systemic administration, due to the low volume (2–3 L) in which the drug diffuses. The rapidity with which therapeutic concentrations are achieved in the dialysate may be influenced by the presence of peritonitis. For example, after IV administration, therapeutic vancomycin concentrations in the dialysate are reached after 30 min of dwell in peritonitis patients, vs. 2–4 h in a noninflamed peritoneum [218].

The concentrations of antibiotic drugs that are achieved in the dialysate after systemic as well as after IP administration must be viewed against their activities against the strains that are isolated from patients with peritonitis. As pointed out by several workers, used PD fluid is a better medium to test these activities than the classically used broth [219–221]. Furthermore, recent work has shown that culturing conditions, dialysate manipulations, and adherence capacity of germs are critical factors affecting antibiotic activity [222]. For drugs that are metabolized by equilibrium-rated reactions to metabolites that are removed by PD, a higher total clearance of the parent drug may also be present during PD, even if the drug itself is not found in the dialysate. Thus, the absence of the drug in drained dialysate does not mean that total clearance of that drug is not altered by CAPD. An example of this phenomenon has been described for mycophenolate acid and its metabolite mycophenolate glucuronide, where a significant amount of mycophenolate acid was removed in the dialysate, almost completely in its glucuronidated form [223].

Pharmacokinetics of Drugs After IP Administration

Peritoneal transport is also of interest with regard to IP administration of drugs. For example, the IP doses of insulin or Epo required to achieve adequate systemic concentrations, or of antibiotics for local treatment of peritonitis, need to be carefully calculated. There are two sources of blood supply to the organs of the peritoneal cavity, one to the parietal and the other to the visceral peritoneum; both layers are rich in lymphatic circulation. The venous blood of visceral peritoneum returns to the portal circulation, while the venous return from the parietal peritoneum drains into the systemic rather than into the portal circulation. Earlier pharmacokinetic studies have indicated that, after IP injection, drugs such as atropine, caffeine, glucose, glycine, and progesterone are absorbed predominantly via the visceral peritoneum [224]. Therefore, these drugs, when introduced IP, are subject to immediate handling by the liver and some of them might undergo a first-pass metabolism. After IP administration, drug concentrations can be measured as a function of time in both dialysate and plasma. In view of the low peritoneal clearance of drugs after systemic administration, the rapid drug disappearance out of the peritoneum when the drug is given via the IP route is at first sight surprising. It is, however, merely the consequence of pharmacokinetic factors, i.e., V_d and protein binding. The contrast between the small dialysate volume and the very large V_d of the drug in the body, leads to a high concentration gradient. This is illustrated for vancomycin in Fig. 9.3 (adapted from [225]).

Studies after IP administration of glycopeptides show that bioavailability increases with dwell time. The data in Fig. 9.4 (from [226]) show that bioavailability is highly variable at early dwell times so that, to ensure consistent absorption of an intraperitoneally administered drug, short dwell times are not recommended. This may be relevant for APD patients who receive antibiotics intraperitoneally during the rapid exchanges. It is likely that these patients may not be receiving their full dosages due to decreased dwell time in the peritoneal cavity. The bidirectional passage of a drug molecule across the peritoneum is influenced by the same factors that regulate the passage of creatinine, urea, and glucose, the molecules commonly used as markers of membrane transport status. Therefore, it is hypothesized that correlations exist between the pharmacokinetic variables used to describe and predict drug disposition in the PD patient and the transport parameters readily available for that patient. If so, these measures (peritoneal equilibration test (PET)), Kt/Vurea, and creatinine clearance (CCr)) could be used to individualize the PD patient's antibiotic regimen, drugs could be more accurately dosed, and better outcomes possibly achieved. Elwell et al. attempted to determine the correlations between pharmacokinetic variables and patient membrane transport characteristics [227]. This retrospective study re-evaluated data collected during previous pharmacokinetic studies for IP administered cefazolin, ceftazidime, and gentamicin in CAPD patients, and IV cefazolin and tobramycin in APD patients. Prominent correlations were found between renal CCr and renal Kt/V, with renal clearances of for CAPD cefazolin and ceftazidime, and for APD tobramycin and cefazolin. Correlations of total and renal CCr with drug CLtotal were found in the pooled cefazolin group. Total CCr also correlated well with cefazolin total clearance in the APD group, although the correlations between the PET classification and drug clearance were difficult to interpret due to few data in the APD cefazolin group. However, there was a trend observed between cefazolin CLp and the 4-h PET values for D/P creatinine. Future studies will be needed to establish a firm relationship between peritoneal membrane characteristics and peritoneal drug clearances. The high protein binding of some drugs in the plasma, versus a negligible protein binding in the dialysate, further promotes this apparent one-way diffusion from dialysate to blood.



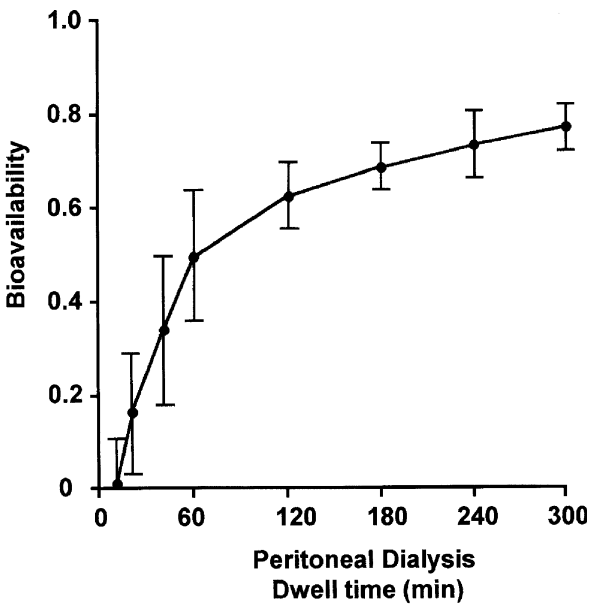


Fig. 9.3 Upper part: Model of pharmacokinetics in PD after IV administration of 1 g of vancomycin into a theoretical VD of 40 L (0.5 L/kg in an 80 kg patient). The inset shows the relationship of serum and dialysate concentrations over the duration of the 4-h dwell, which started at the same time as the IV administration. Lower part: Model of pharmacokinetics of vancomycin in PD after IP administration of 1 g of vancomycin into a 2 L exchange in a patient with a theoretical volume of 40 L. The inset shows the relationship of serum and dialysate concentrations over the 4-h duration of the vancomycin-containing exchange

Fig. 9.4 Relationship between systemic bioavailability and dwell time when teicoplanin is administered intraperitoneally. Bioavailability was calculated by comparison of AUC values following single IP and IV doses, as well as from the amount of drug remaining within the peritoneal cavity with time. From Brouard et al. [226], with permission

Factors Affecting Transperitoneal Drug Absorption After IP Administration

These factors are summarized in Table 9.3; only a few of them will be discussed here; some of them have been described in the first part of this chapter. An important factor influencing drug transport after IP administration is the electric charge of a drug. As outlined in the first part of this chapter, there exist anionic charges on the peritoneal basement membrane and capillaries subjacent to it [6, 228]. The presence or absence of these peritoneal anionic charges can influence transperitoneal absorption of cationic drug molecules such as aminoglycosides. We and others have, however, shown a much-enhanced transperitoneal absorption of gentamicin, netilmicin, and tobramycin during peritonitis [217, 229, 230] (see below). These observations are difficult to explain if electric charges are important in their transport. Similarly, conflicting effects on the transport of gentamicin with IP heparin, a negatively charged drug, have been reported. One earlier study reported lower blood gentamicin concentrations with IP heparin [231], while another study revealed that heparin caused an increase in transport of uncharged molecules such as urea and creatinine and of the positively charged gentamicin [232].

It is possible that incorporation of proteoglycans such as heparin, hyaluronic acid, or chondroitin sulfate in the peritoneal membrane alters peritoneal transport by mechanisms other than by electrical charge, as was shown by Hadler [233]. The effects of these molecules on peritoneal transport have been discussed separately in the first section of this chapter.

As the electrical charge of a molecule in solution depends upon the pH of the fluid, theoretically at least, drug transport characteristics could change when bicarbonate-containing dialysate solutions are used. It is, however, accepted that the conventional (acidic) glucose-containing dialysate solutions rapidly correct their pH to physiological values after instillation. Studies in rats have shown that a significant proportion of the transport of macromolecules from the peritoneal cavity to the plasma is via convective transport via peritoneal lymphatic absorption [234, 235].

As reviewed by a number of authors [212, 236–238], the systemic absorption of IP antibiotics varies from 50 to 80% within a dwell period of 6 h in CAPD. The amount absorbed can easily be measured by subtracting, from the amount of drug initially instilled, the amount of drug that is present in the first peritoneal outflow. This, however, assumes that there is no degradation of the drug over the time interval in the dialysate. Most commonly used antibiotics are stable in peritoneal dialysate, either alone or in combination, or in the presence of additives such as insulin or heparin [239–243]. However, for some cephalosporins a degradation of 12–6%, and for rifampicin a degradation of 6%, was found in CAPD solutions or in effluent over 6 h [239]. This may lead to an overestimation of the amount of drug absorbed after IP administration. Vancomycin is not stable at basic pH, and complex formation may occur after addition to bicarbonate-containing dialysate.

More recent studies have further explored the stability of antimicrobial chemical and bioactivity of antibiotics. Dooley et al. [244] evaluated the stability of gentamicin, vancomycin, and gentamicin and vancomycin in combination, and the stability of the bioactivity of ceftazidime, admixed in standard PD solutions and then maintained over a 14-day

Table 9.3 Factors affecting transperitoneal drug absorption after IP administration

Dialysate properties
Flow rate
Temperature
Volume
Chemical composition
pH
Drug properties
Molecular weight
Ionic charge
Distribution volume (Vd)
Binding to membrane
Lipid or water solubility
Characteristics of the peritoneal membrane
Surface and charge
Permeability
Peritonitis
Sclerosis
Peritoneal blood flow
Lymphatic absorbtion
Stagnant layers

period at room temperature or under refrigeration. Antibiotic concentration by immunoassay did not significantly deteriorate over 14 days for vancomycin or gentamicin when either room temperature or refrigerated samples were studied. By bioassay, gentamicin and ceftazidime, but not vancomycin, lost moderate but significant activity over 14 days when refrigerated bags were assayed (except for an insignificant decrement in gentamicin in the combined vancomycin and gentamicin bags). Bags stored at room temperature, in general, lost significant bioactivity over 14 days, but to levels where clinical efficacy would still be expected. The vancomycin bioassay performed on the combination bags demonstrated a remarkably enhanced bioactivity, presumably reflecting synergy with gentamicin. These data indicate thus that these antibiotics admixed with PD fluids retain a stable chemical activity, whether refrigerated or kept at room temperature, for at least 14 days.

Voges et al. [245] evaluated the stability of gentamicin, tobramycin, netilmicin, vancomycin, cefazolin, unfractionated heparin, and low-molecular-weight heparin when added to four different PD solutions (Extraneal® (Baxter Healthcare, Castlebar, Ireland); Physioneal®, Nutrinea®, and Dianeal® (Baxter Healthcare, Grosotto, Italy)) in new, non-PVC Clear-Flex containers. Netilmicin, vancomycin, cefazolin, and heparin in Physioneal®, Nutrineal®, Extraneal®, and Dianeal® were stable for at least 24 h at 25°C and for an additional 4 h at 37°C. Gentamicin in Nutrineal®, Extraneal®, and Dianeal® was stable for at least 24 h at 25°C and for an additional 4 h at 37°C; gentamicin in Physioneal® was stable for less than 24 h at 25°C. Tobramycin® in Nutrineal® and Extraneal was stable for at least 24 h at 25 °C and for an additional 4 h at 37°C; tobramycin in Physioneal® and Dianeal® was stable for less than 24 h at 25°C

Vancomycin stability in icodextrin has also been tested [246]. Premixed vancomycin-icodextrin PD solutions, whether stored refrigerated or at room temperature, were recently found to be stable for up to 7 days. However, it is recommended that these solutions be kept refrigerated whenever possible. Solutions stored at body temperature were stable for up to 24 h, permitting the practice of prewarming solutions prior to administration.

A faster and more important absorption of antibiotics such as aminoglycosides, vancomycin, piperacillin, and various β-lactam antibiotics in peritonitis patients has been frequently demonstrated[217, 229, 230, 247–249]. Figure 9.5, taken from the paper by De Paepe et al. [229], illustrates the difference between peritonitis and nonperitonitis. It is also apparent, that after IP administration of gentamicin, the decrease in dialysate concentration is much more pronounced than the increase in plasma concentrations. This is not surprising as the V_d of the body is much larger than the volume of the PD fluid. Equal concentrations of gentamicin in serum and dialysate were achieved at approximately 24 h. The clinical relevance of the higher systemic availability during peritonitis is questionable for drugs with a wide therapeutic toxic margin. However, if a drug with a narrow therapeutic index is only negligibly cleared after transport to the systemic circulation, systemic accumulation after repetitive IP administration of the drug could occur. After chronic administration of gentamicin into the PD fluid for 2–3 weeks, plasma concentrations approach the end of dwell-time dialysate concentrations [229]. This can lead to potentially toxic concentrations and necessitates dose reduction. After IP

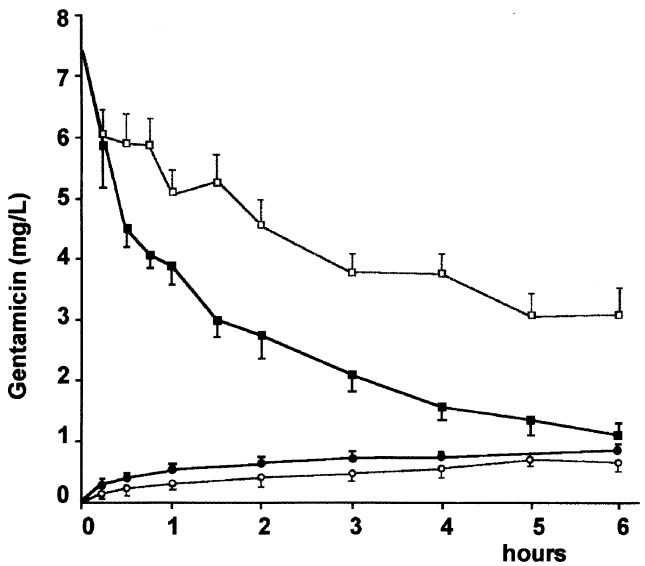


Fig. 9.5 Concentrations (mean ± SEM) of gentamicin in serum (○) and dialysate (□) in five patients without peritonitis and in serum (●) and dialysate (■) in five patients with peritonitis. Gentamicin was added in a concentration of 7.5 mg/L to the dialysate at time 0

administration of a single dose of 0.6 mg/kg of gentamicin, both total body clearance and the mean serum concentrations at 24 h were significantly lower in patients with, compared to patients without RRF [250].

Adverse Effects

Rapid transperitoneal drug absorption may cause adverse systemic effects. The "red man syndrome" has been described after rapid IP administration of 1 g of vancomycin diluted in 2 L of dialysate [251]. Drugs, when given intraperitoneally in therapeutic doses, may also cause peritoneal irritation. This has been described with a fixed combination of cilastatin/imipenem [212], AmB [252–255], certain brands of vancomycin [256], methylene blue [257], and angiotensin I [258].

Effect of PD on Drug Plasma Protein Binding

There are only a few studies in which the influence of PD, notably CAPD, on drug binding has been assessed. Drug protein binding of acid drugs in PD patients is expected to be lower than in undialyzed or HD patients. This may be secondary to the often poor nutritional status of these patients, as reflected by serum albumin concentrations in the lower normal range, the continuous peritoneal losses of proteins during the dialysis process, and accumulating endogenous compounds competing for occupation of binding sites. Changes in protein binding and total and free concentrations of digitoxin have been reported for CAPD and hemodialysis patients. The binding of digitoxin was $94.7 \pm 1.5\%$ in CAPD, significantly less than that observed in HD patients ($96.2 \pm 1.3\%$). Following a 0.1 mg oral dose of digitoxin, the mean free serum concentrations in CAPD and HD were 0.8 and 0.9 ng/mL, respectively, which is not significantly different [259]. One can also expect that in some malnourished PD patients the binding to serum albumin of several acid drugs may be lowered, possibly leading to elevated free drug concentrations. Protein binding of the antifungal drug ketoconazole was also lower in CAPD patients (98.5%) than in control subjects (99%) [260].

The influence of CAPD on the concentrations of α1-AGP in serum and dialysate and on the serum binding of two basic drugs (oxprenolol and propranolol) and of one acidic drug (phenytoin) has been reported [261]. Before starting CAPD treatment, the protein binding of oxprenolol and propranolol was higher, related to the elevated serum levels of α1-AGP concentrations in uremia [262], while the binding of phenytoin was lower than in healthy volunteers. During the first week after starting CAPD, the serum α1-AGP concentrations rose with a concomitant increase in the binding of oxprenolol and propranolol. Subsequently, however, the α1-AGP levels and the binding of oxprenolol and propranolol decreased to the values found before starting CAPD. The binding of phenytoin, which was lower than in normal healthy volunteers, did not show any change during CAPD. It must, however, be emphasized that, in general, changes in plasma protein binding of a drug only exceptionally lead to relevant changes in plasma drug concentrations. Changes in free drug concentration are immediately associated with changes in the V_d of the drug which "buffer" against major fluctuations in free drug plasma concentrations.

Peritoneal Pharmacokinetics of Common Drugs and Dose Recommendations

Description of the Tables

Since the tables in the previous edition of this book described the pharmacokinetics per class of drug studied during CAPD or CCPD, and most of the drug information on protein binding, elimination $T_{1/2}$, V_d and total plasma clearance in the presence of normal renal function, and on elimination $T_{1/2}$ and total plasma clearance in end-stage chronic renal disease (ESRD) have not changed, the tables of the previous edition have been reproduced in this chapter. However, the studies on pharmacokinetics of new drugs, not covered in the previous edition, or more recent pharmacokinetic data in PD of older drugs will be discussed under the respective drug classes. For a more general pharmacokinetic information on individual and more recent drugs outside the field of PD, the reader is referred to recent standard textbooks [263–265].

The pharmacokinetic data have been updated from reports published up to the beginning of 2007. Many papers contain results obtained in crossover studies after either IV, oral, or IP administration. Therefore, the data published per individual paper have been included in the tables. The dose/route column indicates the dose and the route of drug administration in each respective study. When available, the loading dose or maintenance dose is given. Data on serum $T_{1/2}$, maximal – or, occasionally, steady state (SS) – serum concentrations achieved, total plasma clearance and

peritoneal clearance are given. A comparison of these values with data obtained in normal renal function and in terminal renal failure shows the effect of PD on these parameters. Finally, the percentage of dose either removed from the body by PD (in case of systemic administration) or absorbed across the peritoneal membrane (after IP administration) is provided, whenever it has been calculated. Each table is accompanied by a brief discussion of the need for dose adjustment in PD, for drugs that are frequently used in these patients.

Pharmacokinetic Data in CAPD

Tables 9.4–9.14 summarize the pharmacokinetic data on systemic and IP drug administration in CAPD.

Cardiovascular Drugs (Table 9.4*)*

Based on the pharmacokinetic data, dose adaptation for digoxin is not necessary in CAPD patients beyond that for ESRD.

Data on pharmacokinetics of ACE inhibitors are scarce. In a study of five patients on CAPD, captopril was detectable in the dialysate after a single dose of 50 mg. However, the impact on total elimination varied widely between individuals [266]. After 24 h, only 0.5% of a dose of 2.5 mg quinaprilat was removed by PD. The elimination $T_{1/2}$ of quinaprilat is prolonged in patients with renal failure, and an inhibition of >90% of ACE was observed after administration of 2.5 mg of quinaprilat in CAPD patients. This dose can thus be recommended as starting dose in CAPD patients. Fosinoprilat was found to be cleared only to a limited extent by PD. Fosinoprilat, however, is also cleared by biliary secretion, that might compensate for the reduced renal clearance. In six CAPD patients, serum ACE activity remained significantly suppressed at 24 and 48 h after administration of 10 mg fosinoprilat [267]. The moderate pharmacokinetic alterations observed in these patients compared to those with normal renal function suggest that in most CAPD patients initial dose modifications are not necessary.

The pharmacokinetics and pharmacodynamics of ACE inhibitors and ARBs in ESRD have been extensively reviewed by Sica and Gehr in 2002 [268]. Table 9.5 is taken from this review, summarizing the protein binding, the hemodialysance, and the mode of systemic clearance of most of the currently used ARBs. The pharmacokinetics and pharmacodynamics of losartan and its active metabolite, E-3174, were studied in hypertensive CAPD patients [269]. Following a 1-week washout period, subjects received 100 mg of losartan orally for 7 days. On days 1 and 7, hemodynamic and hormonal responses were determined, as were pharmacokinetic parameters on day 7. The values of AUC0-24 and $T_{1/2}$ for losartan and E-3174 were 95 ± 49.9 μg/min/mL and 176 ± 82.1 μg/min/mL and 172.5 ± 86.7 min and 628 ± 575 min, respectively, and are similar to those of normal subjects and subjects on HD. Peritoneal clearance of losartan and E-3174 was negligible. In conclusion, the dose of losartan in CAPD patients should not be reduced compared with patients with normal renal function and the peritoneal elimination of the drug is negligible. Table 9.6, adapted from a review by Barbour and McKindley [270], provides some maintenance dose recommendations for various cardiovascular drugs in renal failure and during HD and PD treatment.

Table 9.7 summarizes the studies with β-lactam antibiotics and glycopeptides. In general, the amount of penicillin lost in the peritoneal cavity after systemic administration is negligible; on the other hand, the transperitoneal absorption can be as high as 90% in the presence of peritonitis. First-, second-, and third-generation cephalosporins have been extensively studied. Based on the adequate dialysate levels that are achieved after oral administration (cephadrine or cephalexin), some authors have used this group of antibiotics as first choice for initial treatment of peritonitis either as single drug or in combination with other drugs [271–275].

Cefazolin

CAPD patients without active peritonitis received a single IP dose of 1 g of cefazolin sodium for a 6-h dwell [276]. The bioavailability was found to be 77.9 ± 3.1%, V_d 0.20 ± 0.05 L/kg, and plasma $T_{1/2}$ 39.9 ± 25.4 h. Mean total, renal, and peritoneal clearances were 4.5 ± 2.3, 1. 4 ± 1.1, and 3.5 ± 1.8 mL/min, respectively. Mean plasma and dialysate concentrations at 24 h were 42.8 ± 14.3 and 31.8 ± 11. 7 μg/mL, respectively, well above the MIC of susceptible organisms. A once daily IP cefazolin dose of 500 mg/L gave desirable pharmacokinetic attributes for use as a suitable alternative to vancomycin for empiric treatment of CAPD-associated peritonitis.

In more recent years, cefazolin has been studied, either in combination with aminoglycosides and more in particular in APD. A study in Thailand [277], following the International Society for Peritoneal Dialysis (ISPD) 1996 recommendations for empiric treatment of peritonitis, studied the pharmacokinetics of a continuous IP cefazolin and

Table 9.4 Pharmacokinetic studies with cardiovascular drugs in CAPD

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
Digoxin	20–30	36	7.1 ESRD 4.2!	160	100	35	O 0.125 mg daily 5 days SS ($n = 1$)	97.9 at 2 h	3.2 ng/mL	12.6	2.0	<4/24 h	[437]
							O 0.50 mg	–	3.8 ± 2.3 ng/mL at 0.56 h	–	3.0 ± 1	1/24 h	[438]
							O 0.1 mg/day SS	–	–	–	3.9 ± 1.3	<2/24 h	[439]
							O 0.125 mg every 2–3 days	54–141	–	11–52	2.3–3.1	<10/4 days	[440]
							O 0.125 mg per day	–	–	–	3.6 ± 0.4	7.6 ± 0.9/24 h	[441]
Digitoxin	90 86–89 ESRD	145	0.5	3	200	2	0.1 mg/day SS	7.5 days	–	3.5	0.7 ± 0.3	<2/24 h	[439]
Quinidine	80–85	6	2	270	6	270	O 350 mg 4 × /day	5.4	–	154.2	0.79	0.6/24 h	[442]
Denopamine							O 10 mg SD	4.6 ± 2.5	0.0123 ± 0.0067	–	0.10 ± 0.05	<0.1/6 h	[443]
Labetalol	50	7	5.6	1,700	13	1,198	IV 0.7–1 mg/kg	13.05 ± 6.32	–	1,397.2 ± 272.3	1.94 ± 0.65	0.14/72 h	[444]
Propranolol	93	3.5	3	695	3.5	695	O 320 mg/day	–	–	–	–	3.3/24 h	[445]
							O 20 mg/day	–	–	–	–	5.2/24 h	
Atenolol	<5	5.5	0.7	176	73	13	IV 20 mg	27.6 ± 2.18	–	21 ± 1.4	2.53 ± 0.3	6/24 h	[446]
Esmolol	–	0.2	3.2	19,950	–	–	IV 150 mg/kg/min for 4 h	0.1 ± 0.06	0.8 (0.5) Css (80 kg)	20,504 ± 11,448	0	0	[447]
Betaxolol	55	14–22	6	327	30	200	–	27			–		[448]
Nifedipine	90–95	2	1.4	1,100	2.6	1,100	O 2 × 20 mg/day					<1/24 h	[449]
Isosorbide-5–nitrate	16–28	0.2–0.5	1.8	–	0.2–0.5	–	0.3 × 20 mg/day	4.2 ± 1.1	448 ± 118	–	4.3 ± 2.7	1–6/24 h	[450]
Diltiazem	80–85	4.0	5.3	1,400	3.4	1,400	O 60 mg	3.09 ± 1.15	95.8 ± 63.8 (3 h)	2,653 1,316 (70 kg)	1.5 ± 1.0	<0.1/24 h	[451]
Captopril	25–30	1.9	3	1,277	35	69	O 50 mg SD						
Free captopril								1 ± 0.3	0.387 ± 0.0075 2.77 ± 0.43			<1%/6 h	[452]

Table 9.4 (continued)

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
Total quinapril*	–	1*	–	–	0.9*	–	O 20 mg SD	1.0 ± 0.3	0.107 ± 0.067	2,207 ± 1,621	–	0	[199]
Quinaprilat	97*	–			12.5*			20.1 ± 0.124	0.689 ± 0.124	19 ± 8.3		2.6 ± 1.2/24 h	
Quinaprilat	90						O 2.5 mg	34.1	64.3	11.9	–	–	[453]
Iate	95	15	0.15	–	19–28	–	O 10 mg	19.5 ± 7.5	0.202 ± 0.071	70.6 ± 38.5	0.09 ± 0.07	2 ± 1.4/48 h	[267]
Guanfacine	30	17	4	–	14	–	–	–	–	–	1.5	–	[454]
Tocainide	10–15	11–14	3.2	182	17–43	100	O 400 mg SD	15 ± 5	3.2 ± 1	83 ± 36	<5 mL/min	2.2 ± 2/24 h	[455]
Flecainide	40	14–26	8.7	567	19–26	357	O 100 mg/day	40	–	30	2.2	1/24 h	[456]
Procainamide	14	3			14			34.1	64.3	11.9	–	–	[457]
	15	2	2	810	8	200	O 625 mg SD	26	1.9–4.8	143	0.28–5.55	<5/days	[458]
N-acetylprocainamide	10	6	1.5	200	4.2	29		42.8	–	29.8	1.74–7.20	<5	
Furosemide	95	0.5	0.12	162	1.4	105	O 500 mg						
							SD – perit	10.5 ± 1.2	12.8 ± 2.1	–	0.5 ± 0.1	0.9 ± 0.2/24 h	[459]
							+ perit	11.6 ± 3.3 O 500 mg	6.6 ± 0.4	–	0.5 ± 0.1	0.6 ± 0.1/24 h	
							SD – perit	12.5 ± 3.4	7.7 ± 0.6	–	0.4 ± 0.1	0.6 ± 0.1/24 h	[460]
							O 80 mg SD – perit	3.87 ± 1.26	3.2 ± 1.4	–	–	–	[461]
							IV 80 mg SD – perit	2.7 ± 0.83	–	60 ± 18	–	<1/24 h	
Theophylline	60	8.7	0.45	46	7.3	67		4.7	–	–	1.5	–	[462]
Mexiletine	64	5–9	5–6	846	22	200	IV 250 mg	10.5	–	25.6/kg	9.22/kg	<1%	[463]

*Data from [464].

Table 9.5 Important pharmacokinetic data for angiotensin receptor blockers (ARBs)

Compound	Protein binding (%)	Hemodialysance (mL/min)	Renal clearance	Hepatic clearance
Losartan	98.7	0	10	90
E-3174	99.8	0	50	50
Irbesartan	90	0	1	99
Valsartan	95	Not available	30	70
Eprosartan	98	11	30	70
Candesartan	99	0	60	40
Olmesartan	99	Not available	35–50	50–65
Telmisartan	99.5	0	1	99

Source: Adapted from Sica and Gehr [268].

Table 9.6 Maintenance dosage adjustment recommendations for various cardiovascular drugs in renal insufficieny and during hemo- and peritoneal dialysis

		Dosage adjustment based on Cr Cl (% of normal daily dose)		Significant dosage adjustment required	
	Drug	10–50 mL/min(%)	<10 mL/min(%)	HD	PD
Ace inhibitors	Benazepril	100	50	No	No
	Captopril	25–50	<25	Yes	No
	Enalapril	75–100	50	Yes	No
	Lisinopril	50–75	25–50	Yes	No
	Quinapril	50	25	No	No
	Ramipril	50–75	25–50	Yes	No
Antiarrhythmics	Bretylium	25–50	25	No	No
	Digoxin	25–50	<25	No	No
	Disopyramide	(based on TDM)	(based on TDM)	?	No
	Flecainide	25–50	25	No	No
	Procainamide	100	50–75	Yes	No
	Quinidine	Based on TDM	Based on TDM	Yes	No
	Tocainide	Based on TDM	Based on TDM	Yes	No
		100	50		
Beta-blockers	Atenolol	25–50	<25	Yes	No
	Metoprolol	100	100	Yes	No
	Nadolol	50	25	Yes	No
	Propranolol	100	75–100	No	No
	Sotalol	30	15–30	Yes	ND
Miscellaneous	Methyldopa	75–100	25–75	Yes	No
	Milrinone	100	50–75	ND	ND

Source: Adapted from Barbour and McKinley [270].

once-daily IP aminoglycoside administration. Cefazolin was administered as loading and continuous maintenance doses of 500 and 125 mg/L dialysate, respectively. Gentamicin, 0.6 mg/kg body weight, was given IP once daily. Duration of treatment was 120 h, serum cefazolin reached levels higher than the recommended levels (8 μg/mL) at 3.3 min after drug administration, and persisted through the 5-day duration of the study. Dialysate cefazolin levels during the studied period also were persistently higher than the recommended values. The peak serum gentamicin levels were lower than the suggested values of 4 μg/mL, whereas the trough serum gentamicin levels were higher than the minimal toxic concentrations (2 μg/mL). Dialysate gentamicin levels were higher than therapeutic concentrations for only 4.75 h in each day. It was difficult, using pharmacokinetic studies, to adjust the dosage regimen of gentamicin to achieve appropriately therapeutic levels in both serum and dialysate. It was concluded that the ISPD 1996 recommended dosage of continuous IP cefazolin was appropriate for the treatment of CAPD-related peritonitis, but once-daily IP gentamicin administration, had less therapeutic benefit.

The combination of cefazolin and tobramycin was also studied in APD patients [278] after a single IV dose of cefazolin (15 mg/kg) and tobramycin (0.6 mg/kg). Cefazolin and tobramycin half-lives were markedly shorter on cycler than off cycler. Mean serum and dialysate concentrations were above MIC of susceptible organisms throughout the

Table 9.7 Pharmacokinetic studies with β-lactams and glycopeptide antibiotics in CAPD

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
I. Beta-lactams													
Ampicillin	16–20	1.2	0.48	325	14	30	IV 2 g	9.5 ± 2.2	170.3 ± 56.6	25 ± 7.7	2.7 ± 0.5	11.3 ± 2.2/48 h	[465]
							IP 1 g/L	9.6 ± 2.6	48 ± 7.6	25 ± 7.7	-	60 ± 13/48 h	
Sulbactam	–	0.25	0.2	250	21	–	IV 1 g	9.7 ± 2.2	87.5 ± 29.9/5–6 h	22.6 ± 3.2	3.4 ± 0.4	152 ± 1.9/48 h	
							IV 1 g	9.4 ± 3.2	27.8 ± 4.1/5–6 h	22.6 ± 3.2	–	68 ± 13/48 h	
Imipenem	13–21	1	–	205	1	205	IV 500 mg SD	3.28 ± 0.59	29.3 ± 10.5	66.8 ± 18.1	–	3.2 ± 0.5	[466]
							IP 500 mg/L	–	–	–	–	79 ± 8	
Cilastatin	13–21	1	0.31	238	3.7–4.8	54	IV 500 mg SD	8.84 ± 3.8	34.8 ± 6.5	24 ± 14.9	–	5.2 ± 0.5	
Imipenem							IV 500 mg SD	6.2 ± 1.4	29.5 ± 12.2	76.3 ± 23.5	4.8 ± 0.6	–	[467]
							IV 1,000 mg SD	6.9 ± 1.1	69.5 ± 9.5	50.6 ± 15.6	5.4 ± 0	–	
							IV 500 mg	22.6 ± 6.4	51.9 ± 13.4	8.1 ± 1.8	5.4 ± 0.4		
							IV 1,000 mg	15.4 ± 5.0	110.8 ± 20.3	10.7 ± 1.4	5.4 ± 1.2		
Piperacillin	21	1	0.21	188	3.3	57	IV 2 g SD IP 500 mg/L	2.43 ± 0.84	104.4 ± 26.1	104 ± 37.7	3.17 ± 0.67	2.5 ± 0.7/6 h	[249]
							–petit	–	6.8 ± 2.9/2.6 h	–	–	67.8 ± 8.5/6 h	
							+perit	–	8.9 ± 2	–	–	83.4 ± 4.6/6 h	
							IV 1 g SD	2.41 ± 0.49	–	100.2 ± 13.8	2.7 ± 0.8	–	
							IP 1 g/L + perit	–	–	–	–	96.3/6 h	
							IV 3 g SD	2.12 ± 26.3	270 ± 31	65 ± 12.9	3.6	5.5/28 h	[288]
Tazobactam	–	0.89 ± 4.5	15.91 ± 1.9	219 ± 25	3.58 ± 46.5	49.5 ± 8	IV 0.375 g	6.36 ± 876.1	28.6 ± 5.7	36.9 ± 11.8	3.8	10.7/28 h	[288]
Temocillin	63–88	5–6	0.29	44	16–28	9	IV 15 mg/kg SD	13.4 ± 3.9	–	9.3 ± 1.8	–	8 ± 2.6/24 h	[468]
Cefamandole	67–80	0.7	0.16	109	15	9	IP 500 mg/L SD	10.4 ± 7.3	31.3 ± 4.7/6 h	20 ± 6.2	3.2 ± 1.6	71.7 ± 12.8/6 h	[469]
							IV 1 g SD	9.02 ± 1.0/1 h	65 ± 10	24.4 ± 6.4	1.48 ± 0.41	5 ± 2/24 h	[470]
							IP 500 mg	8.1 ± 1.2	33 ± 3/6 h	25.4 ± 6.6	2.5 ± 0.7	71 ± 10/6 h	
							IV 1 g	6.1 ± 1.7	–	21.9 ± 9.7	0.92 ± 0.25	5 ± 2.4/54 h	[471]
Cefazolin	70–85	1.8	0.14	60	27	5	IV 10 mg/kg	33.1 ± 1.0	–	5.7 ± 0.6	1.0 ± 0.4	–	[472]
							IP 10 mg/kg	–	30	5.85 ± 0.7	0.81 ± 0.14	73.7/4 h	
							IP 500 mg/L LD	–	54.8 ± 6.7	7.8	–	88/6 h	[473]
							250 mg/L MD perit +	–	110.9 ± 6.7	–	–	65/24 h	
							125 mg/L perit +	29.2 ± 16.2	141.3 ± 51.9	2.8 ± 1.5	–	–	[474]
Cefepime							IV 1 g SD	17.6 ± 2.9	62.9 ± 15.8	15.4 ± 4.9	3.86 ± 0.59	25/72 h	[285]
							IV 2 g SD	18.8 ± 1.6	124 ± 14	14 ± 1.3	4.35 ± 0.69	–	
Cefepime		1.3–2.3	20.5 ± 4.8	89–178	13.5 ± 2.6	18.7 ± 5.18	IV 1 g	17.6 ± 2.9	62.9 ± 15.8	15.4 ± 4.9	–		[284]
Cefodizime	88						IV 1 g SD	4.1–6.8	–	1.6–31.7	0.3–0.9	1.2–6.4/24 h	[475]
							IP 500 mg/L SD	4–9.8	–	19.7–39.2	–	41–100/24 h	
Cefoperazone	65–90	1.8	0.22	100	2.9	78	IV 1 g	–	104.2 ± 29.1	80 ± 20	–	–	[476]
							IP 1 g/L		33.2 ± 5.3/6 h	–	–	95 ± 12/10 h	

Table 9.7 (continued)

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
							IV 1 g day 1–3	2.65 ± 0.39	–	70.1 ± 19.2	6.9 ± 1.0	–	[477]
							IP 2 × 1 g/2 L 2 days	–	–	–	–	63.8 ± 4.8	
Cefoperazone Sulbactam							IV 2 g ± 0.82	2.08 ± 21.2	280.9 ± 33.4	71.9	0.55 ± 0.08	1.0/48 h	[478]
Cefoperazone							IV 1 g/L	2.33 ± 0.96	38.9 ± 12.42/2–4 h	71.9 ± 33.4	–	64 ± 14/6 h	
Sulbactam							IV 1 g	6.86 ± 1.67	82.2 ± 16.2	33.4 ± 5.3	3.6 ± 0.2	11.1 ± 1.4/48 h	
							IP 0.5 g/L	6.26 ± 1.45	82.2 ± 2.0	33.4 ± 5.3	–	70 ± 10/6 h	
Cefoperazone							IP 62.5 mg/L for 10 days + perit	–	10 at 24 h	–	–	–	[479]
Cefotaxime	36	1	0.28	322	2.5	135	IV 30 mg/kg	–	–	–	3.2	–	[480]
							IV 2 g	1.8 ± 1.2		65 ± 25	2.4 ± 0.8	–	[481]
							IP 1 g/L	2.6 ± 0.3	–	88 ± 39			
Cefotaxime (CFT)							1 g	3.1 ± 1.3		87.2 ± 34.3	1.93 ± 1.0	2.18/6 h	[482]
							IP 0.5 g/L	–	10–12/2–3 h	–	–	90/9 h	
						CFT	IV 1 g	2.31 ± 0.20	–	118.7 ± 12.3	6.7 ± 1.3	4.9 ± 0.7/24 h	[483]
						DAC*		11.4 ± 1.9	–	–	3.6 ± 0.9	2.6 ± 0.6/24 h	
						CFT	IP 0.5 g/L	2.3 ± 0.3	15 ± 1.5/2 h	–	–	58.7 ± 6.4/4 h	
						DAC		13.2 ± 4.3	9.7 ± 1.4/6 h	–	–	–	
						CFT	IV 2 g	2.24 ± 1.04	322.9 ± 105.2	81 ± 31	1.82 ± 0.43	–	[484]
						DAC		18.9 ± 21.7	37.8 ± 19.4	–	2.84 ± 0.7	–	
						CFT	IP 1 g/L	2.57 ± 1.03	29.7 ± 9.2/4–8 h	71.2 ± 29.3	11.5 ± 6.9	74.6 ± 21.3/6 h	
						DAC		25.3 ± 33.8	19.5 ± 12.6/7.1 h	–	3.46 ± 1.03		
						CFT	IV 1 g	1.59 ± 0.47	156/5 min	–	–	3.5/6 h	[485]
						DAC		–	17.4/2 h	–	–		
						CFT	IP 0.5 g/L	–	9.1/2 h	–	–	65/6 h	
						CFT	IP 250 mg/L						[486]
							+ perit	–	–	250.8 ± 59.5	–	90/24 h	
							– perit	–	–	94.8 ± 23.4		67/24 h	
						CFT	IV 1 g	2.3 ± 8.2		11–103	–	1.4–4.2/6 h	[487]
						DAC		–	10–60	–	–		
*Desacetyl Cefotaxime													
Cefotaxime						CFT	IP 500 mg/L (2 children)	1.83–2.49	11.9–13.1/4.08 and 2.22 h	79–62	1.14–2.81	56.6 and 64.8/5 h	[488]
						DAC		11–8.1	5.16–9.29/5.73–5.33		1.88–4.15		
						CFT	IP 500 mg/L + perit (children)	–	26.9 ± 7.8	–	–	–	[489]
Cefotetan	78–91	3.7	0.15	39	35	4	IV 1 g	15.5 ± 1.9	–	6.5–20	1.1–3.2	5–9/24 h	[490]
Cefotiam							IV 1 g	8.1 ± 2.4	–	20.9 ± 3.8	3.3 ± 0.2	6 ± 1.4/5 h	[491]
							IV 1 g	5.1	103	–	–	–	[248]
Cefoxitin	50–60	0.9	0.3	290	22	12	IV 2 g	7.8 ± 1.1	197	20.4 ± 1.45	1.44 ± 0.25	–	[492]

Table 9.7 (continued)

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
							IP4 × 50 mg/L 4 × 100 mg/L/24 h	20.2 ± 3.7	15 7	13 ± 3.3	4.1 ± 2.3	71.2/24 h	[493]
Cefpirome							IV 1 g	15.4 ± 1.9	–	15.4 ± 2.4	1.62 ± 1.5	12.4–96 h	[494]
Cefsulodin							IV 1 g SD	11.6 ± 4.7	–	14.7 ± 5.4	4.3 ± 1.7	8.7 ± 13/5 h	[491]
							IP 1 g						
							– perit	11.2 ± 1.9	–	26.5 ± 9	–	81 ± 3.6/5 h	
							+ perit	9.4 ± 1.3	–	23.9 ± 11.1	–	84 ± 6/5 h	
Ceftazidime	10–17	2	0.24	130	25	7	IP 4 × 125 mg/L						
							– perit	–	9.27–22.24 (6–24 h)	–	1.47–4.13		[495]
							+ perit	–	13.1–25.3 (6–24 h)	–	2.43–3.89	65–75/24 h	
							IV 1 g	–	–	–	3–4	4.3–7/4–6 h	[496]
							IV 1 g	1.9		8.7	–	–	[280]
Ceftazidime							IP 15 mg/kg single dwell	22 ± 5		14.1 ± 4.25	5.74 ± 1.6		[279]
Ceftazidime	10–17	2	0.24	130	25	7	IV 1 g	1.9		8.7	–	–	[280]
Ceftazidime							IP 15 mg/kg single dwell	22 ± 5		14.1 ± 4.25	5.74 ± 1.6		[279]
Ceftizoxime	31	1.4	0.4	190	35	6	IV 500 mg	10.2 ± 5.8	–	27.7	2.9	4.8 ± 2.1/6 h	[497]
							IV 1 g	12 ± 4.8	–	22.8	3.4	4.4/6 h	
							IP 250 mg/L	–	12.5/5 h	–	–	78 ± 4	
							IV 3 g	9.7 ± 5.1	411 ± 137/0.25 h	17.1 ± 7.4	2.8 ± 0.7	–	[498]
Ceftriaxone	85–95	6–9	0.09	15	12–57	8	IV 1 g	12.3 ± 4.4	412 ± 354	14 ± 5.6	0.6 ± 0.4	4.5 ± 2.9/72 h	[483]
							IP 1 g	13.7 ± 10.1/ 42 h	38.8 ± 11.6	–	–	44 ± 13/4 h	
Cefdinir							O 100 mg	10.8–21.9	1.64–4.43				[499]
Quinupristin–Dalfopristin	23–32	0.93 ± 0.15	1.07 ± 0.27	780 ± 120	–	–	IV 7.5 mg/kg	0.83 ± 0.13	2.89 ± 0.85	710 ± 200	–		[500]
Dalfopristin	50–56	0.71 ± 0.18	0.77 ± 0.34	770 ± 180	–	–		0.76 ± 0.29	8.52 ± 3.25	670 ± 360			
Ceftriaxone							IV 2 × 2 g at 24 h interval						
							– perit	9.8 ± 1.9	285 ± 69	13.3 ± 5	0.67 ± 0.5	–	[501]
							+ perit	14.8 ± 12.7	272 ± 54	15 ± 10	2.05 ± 1		
							IP 500 mg/L	10.5 ± 2.3	58.9	14.8	–	70.6 ± 7.9/4–6 h	[502]
							IP 1 g/L	–	71.1	–	–	–	
							IP 1 g/L	12.7 ± 2.9	–	10.1 ± 3.0 mL/ kg/h	0.69 ± 0.2 mL/ kg/h	71.4/5 h	[503]
							IV 1 g	12.2	–	7.4 (4–12.9)	–	–	[504]
Cefuroxime	33	1.3	0.2	140	20	15	IV 15 mg/kg	14.7 ± 1.1	–	–	3.59 ± 0.8	–	[505]
							IV 500 mg – perit	15.1 ± 1.9	24.2 ± 6.4	21.5 ± 1.2	4.2–2.9 ± 1.2–1.3	–	[506]
							IP 250 mg/L – perit						
							– perit	14.4 ± 2.1	12.1 ± 2.2	20.3 ± 1.4	2.3–6.5	70	

Table 9.7 (continued)

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
							IP 1 × 250 mg/L LD + 125 mg/L MD		43.2 ± 7.5 SS	–	9.9–12.4		
Cephalexin	18.537	0.8	0.26	263	20	10	O 500 mg SD	8.6 ± 0.9	–	18.4 ± 2.71	2.29 ± 0.63	–	[507]
							O 1–2 g/days for 3 days	–	97.8 ± 24.2/4 h	–	55 ± 19.4 in dialy sate day 1	16.5/day 1–25.5/day 2	[507]
Cephalothin	60–65	0.6	0.26	350	10	21	IP 100 mg/L 4 exch/24 h	–	5.6 ± 2.2/24 h	–	–	–	[508]
							IV 1 g + IP 250 mg/L	17.1 ± 6.0 ± 6.0	100.3 ± 39.2	11.1 ± 12.7	–	–	[474]
							IV 1 g	3.0	111.0	–	–	–	[248]
							IP 0.5 g/L	–	18.4/2 h	–	–	–	
Cephradine	7.519	1.0	0.31	323	12	20	O 500 mg SD	–	–	–	2.8–3.5	6.9/48 h	[509]
Moxalactam	50	2.5	0.3	97	20	12	IV 1 g	16.7 ± 2.9	123 ± 9	10.6 ± 2.0	2.7 ± 0.5	17.4 ± 3.1/24 h ± 60/4 h	[510]
							IP 0.5 g/L IV 1–2 g SD	13.2 ± 2.9	38.6 ± 12.7/4 h	11.5 ± 2.4	2.3 ± 0.5		[511]
							R MOX	17.3 ± 3.4	–	12.9 ± 6.9 (mL/h/kg)	1.1 ± 0.6		[287]
							S MOX	18 ± 3.3	–	13 ± 5.5 (mL/h/kg)	1.27 ± 0.62		
Moxalactam							IP 0.5–1 g/L SD						
							R MOX	–	–	–	–	71 ± 18	[483]
							S MOX	–	–	–	–	79 ± 18	
							IV 1 g SD	17.9 ± 4.2	171 ± 62/0.08 h	12.8 ± 7.7	2.1 ± 0.5	20.2 ± 8.3/48 h	
II. Glycopeptides Vancomycin							IP 0.5 g/L SD	15.4 ± 4.1	34.1 ± 8.5/4.3 h	–	–	57 ± 16/4 h	[52]
	10	7	0.47	55	240	2	IP 500 mg/L	–	23.7 ± 6.5	–	2.4 ± 0.08	53/6 h	[512]
							IP 10 mg/kg	81		9.4 ± 1.9	1.48 ± 3.6	–	
							IP 10 mg/kg 2 L	65.8 ± 10.7	6.3	15.1 ± 2.0	2.50 ± 0.33	65/4 h	
							IV 10 mg/kg	90.2 ± 24.2		6.45 ± 1.1	1.35 ± 0.35		[513]
							IP 500 mg/L LD	–	9.1/5 h	–	–	71.3/6 h	[514]
							IP 500 mg/L + perit	62.3	35.3 ± 19.1/6 h	–	–	–	[515]
							300 mg/kg per 2 L IP – perit	–	–	–	–	50.8/6 h	[247]
							300 mg/kg per 2 L IP – perit	–	–	–	–	73.9/6 h	
							IV 25 mg/kg + perit	115 ± 6	56.8 ± 4.7	7.2 ± 0.3	1.4 ± 1.05	–	[516]
							IV 15 mg/kg	111 ± 22	S57.1 ± 9.3	5.0 ± 1.4	1.2 ± 0.5		
							IP 30 mg/kg	91.7 ± 28	S30.4 ± 7.2	5.0 ± 1.3	1.7 ± 0.9	46/6 h	
							IP 1 g/2 L LD		15.5 ± 12.3/4 h	8.52	–	–	[517]
							IP 15 mg/kg LD		16.2 ± 1.75	–	–	–	
							IP 37.5 mg/L	–	13.3 ± 4.5	–	–	70 ± 15/3 h	[518]

Table 9.7 (continued)

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
							CAPD + perit						
Vancomycin							IP 37.5 mg/L	–	8.8 ± 2.5	–	–	39 ± 13/3 h	
							CAPD – perit						
							IP 15 mg/kg/2 L LD + MD 25 mg/L		17.8 ± 2.2/1–6 h			63 ± 10.1/4 h 71.9 ± 17.5/4 h	[225]
							IP 25 mg/L no LD		0.27 ± 0.42/6 h				
							IV 1 g perit +	103.9 ± 57.2	–	4.09 ± 0.45	3.84* ± 0.75 *max perit	–	[218]
Teicoplanin	95	41–62	0.84–1.13	36.438	124	<2	IV 3 mg/kg	162 ± 52	–	5.15 ± 1.34 mL/h/kg	0.34 ± 0.02 mL/h/kg	6.8 ± 1.2/6 days	[519]
							IV 6 mg/kg	242 (202–273)	–	5.7 ± 2.00.2	–0.4	–	[520]
							IV 3 mg/kg	135	4.84 ± 1.43/6 h	–	–	7.1 ± 1.2/6 h	[521]
							IP 6 mg/kg		8.0 ± 0.6			81.5 ± 10.7	[522]
							IV 3 mg/kg	377 ± 109	31.6 ± 5.2	2.76 ± 1.08	0.25 ± 0.21	3/5 h 9/2 weeks	[226]
							IV 6 mg/kg	266.4 ± 51.9	56.5 ± 7.0	0.007/kg	6.1 ± 0.7/46 h	357	
							IP 3 mg/kg	338 ± 60	6.6 ± 1.8/4 h	–	0.13 ± 0.07	77 ± 21	[226]
Teicoplanin	95	41–62	0.84–1.13	5–10	124	<2	IP 20 mg/L	508	9	2.5	–	–	[296]

Table 9.8 Pharmacokinetic studies with quinolones, aminoglycosides, trimethoprim-sulfamethoxazole, and miscellaneous antibiotics

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
Ciprofloxacin	40	3–4	2.8	652	16.8	300	O 750 mg ($n = 6$)	16.8 ± 5.1	3.61 ± 1.56	373.5 ± 213.4	–	0.4–1.6/48 h	[523]
							O 4 ×250 mg	8.44 ± 3.23	–	–	–	1/48 h	[216]
							– perit						
							+ perit	7.19 ± 1.75	–	–	–	1.5/48 h	
							O 4 × 250 mg every 12 h	11 ± 1	2.3 ± 0.2	256 ± 47	4.16 ± 0.33	2/48 h	[524]
Ciprofloxacin		4.6 ± 0.9	7.33 ± 5.67	86.3 ± 43.8	11.1 ± 2.8	19.6 ± 7.6	O 750 mg	8.9 ± 3.1	3.36 ± 1.12	33.0 ± 28.6	8.8 ± 6.5		[299]
Fleroxacin	18	8.6	1.5	168	24.7	63	IV 100 mg SD	28.6 ± 6.7	–	0.58 ± 0.13/kg	0.05 ± 0.01/kg	7.8 ± 3.6/96 h	[525]
							O 400 mg SD	–	4.9 ± 0.06	–	–		
Fleroxacin		8.9–13.5		122–168	13–21							<10	[301]
Ofloxacin	25–30	6* ± 1.2	1.23* ± 0.11	180.5* ± 12.1	18.4* ± 12.1	68.4* ± 35.1	O 300 mg	25.1 ± 2.54	–	3.55 ± 0.43	–	4.2/24 h ± 0.5	[300]
							O 200 mg	26.8 ± 2.5	–	35.2 ± 8.2	4.0 ± 0.5	5.8/24 h	[526]
							O 250 mg	–	–	–	–	5/24 h	[527]
							O 200 mg SD	35 ± 4.19	–	29.3 ± 11.2	4.5 ± 0.8	15/96 h	[528]
							IP 10 mg/L SD						
							– perit	–	–	–	–	81.9 ± 1.5/4 h	[529]
							4 × 20 mg/2 L MD	–	0.57 ± 0.07/24 h	–	–	–	
							IP 10 mg/L SD						
							– perit	–	–	–	–	84.7 ± 1.5/3 h	
							4 × 20 mg/2 L MD	–	17.8 ± 0.17	–	–	–	
Ofloxacin	25–30	6 ± 12	1.23	180.5	18.4 ± 12.1	68.4 ± 35.1	IP 200 mg	22.1	3.55	35.9	2.15	<10	[307]
Pefloxacin	25*	8*	1.9*	137*	12.1* ± 1.7	117*	O 400 mg SD	19.2 ± 3.3	–	1.0 ± 0.2 (mL/min/kg)	0.06 ± 0.01	–	[530]
							IV 400 mg SD	17.4 ± 2.3	6.4 ± 0.4	–	–	–	
Pefloxacin							IP 200 mg/L	–	3.5 ± 0.8/65 kg	1.3 ± 0.3 (mL/min/kg)	0.09 ± 0.02	–	
							O 400 mg SD	19 ± 5.8	5.6 ± 1.3	39.1 ± 11.1	2.7	2.3–3.7/24 h	[531]
Gentamicin	<10	2	0.24	95	60	2	IV 1 mg/kg	27.4 ± 11.7	4.5 ± 1.0	–	–	0 in 3/5 patients	[532]
							IP 1 mg/kg	27.9	3.64 (6 h)	–	–	84/6 h	
							IP 50 mg/L	36 ± 9	3.9 ± 1.5 (6 h)	–	2.94 ± 0.4	20.2 ± 9/24 h	[533]
							IP 7.5 mg/L	–	0.6 (6 h)	–	5.7 ± 0.4	64/6 h	[229]
							– perit				mass transfer		
							+ perit	–	0.8 (6 h)	–	16.4 ± 1.9	79.3/6 h	
							0.6 mg/kg	35.8	–	7.36 ± 1.49	5.74 ± 1.5	–	[250]
Tobramycin	<10	2.5	0.23	80	60	3	IV 1.1–15 mg/kg	34.6 ± 7.4	–	8.0 ± 1.0	3.8 ± 0.4	13–26/24 h	[534]
							IV 1.5 mg/kg	39.5 ± 18	–	7.6 ± 3.1	1.11 ± 0.8	–	[535]
							IP 1.5 mg/kg/2 L	35.1 ± 12	1.8	9.8 ± 4.0	1.96 ± 1.6	52/6 h	
							IV 2 mg/kg	25.7 ± 46.5	9.8 ± 3/0.3 h	7.3 ± 2 70 kg	3.4 ± 1 70 kg	30/48 h	[536]
							IP 2 mg/kg/2 L CCPD 2 L cycles/h	–	5.6 ± 2/6 h	–	–	73 ± 10.6 h	

Table 9.8 (continued)

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
							IP 160 mg/2 L						
							– perit	–	5.9 ± 1.4/40 h	–	12.8 ± 1.2	4.4 ± 4.4/48 h	[230]
							+ perit	–	6.5 ± 1.3/40 h	–	17.4 ± 1.1	5.5 ± 3.6/48 h	
							IP 5 mg/L	–	1.3–2.1 ± 0.12/24 h	6.8	–	48/48 h	[473]
Tobramycin							IP 50 mg/L LD	–	4.3/6 h	5.6	–	85/6 h	
							IP 7.5 mg/L MD	–	3.7	–	–	50 ss	
							IP 1.93 mg/kg/2 L LD	38.7 ± 10.6	6.6 ± 1.1	6.9 ± 1.2	–	–	[537]
							IP 0.96 mg/kg/2 L						
							IP 20 mg/2 L						
							– perit	–	–	–	6.5 ± 3.1 mass transfer	–	[538]
							+ perit	–	–	–	18.5 ± 8.2 mass transfer		
Streptomycin	35	2.5	0.26	85	80	3	IP 100 mg/L LD	–	5.5/5 h	–	7.3	75/6 h	[539]
							IP 30 mg/L MD	–	4.8	–	–	–	
Amikacin	<10	2.5	0.25	90	70	3	IV 7.5 mg/kg	42.2 ± 14.2	18.6–26.8/24 h	3.9 ± 1.0/1.73 m^2	2.0 ± 1.0/1.73 m^2	–	[540]
							IP 7.5 mg/kg/2 L	37.2 ± 13.2	19.6 ± 6.1/5.6 h	4.6 ± 1.2	2.7 ± 0.4	53 ± 14/5 h	
Netilmicin	<10	2.0	0.25	88	40	5	IV 100 mg						[217]
							– perit	18.1 ± 3.7	–	16.8 ± 2.3	3.38 ± 0.37	23 ± 2.7/48 h	
							+ perit	19.6 ± 2.0	–	18.5 ± 3.2	4.9 ± 1.1	27.9 ± 5.2/48 h	
Netilmicin							IP 1.5 mg/kg followed by IP 40 mg/day	–	1.9 ± 9.9	1.4 ± 9.0	–		[541]
Kanamycin	<10	2	0.23	95	80	2	IP 50 mg/L						
							– perit	–	3.1 ± 0.3	–	11.4 ± 0.9 mass transfer	67 ± 4/4 h	[542]
							+ perit	–	4.3 ± 0.4	–	17.2 ± 2.1 mass transfer	83 ± 2/4 h	
Trimethoprim	40–70	13	2	125	25	65	O 80 mg	24	–	–	2.32 ± 0.39 (night) 4.65 ± 1.25 (day)	–	[543]
Sulfamethoxazole	40–90	10	0.2	30	35	10	O 400 mg	15	–	–	1.64 ± 0.58 (night) 4.29 ± 0.95 (day)	–	
Trimethoprim							O 320 mg	27.7	–	31.1	0.88	2.75/24 h	[544]
							IV 320 mg	28.6 ± 10.6	–	29.3 ± 11	0.77 ± 0.36	2.7/24 h	
							IP 320 mg	27 ± 8.8		39.1 ± 20	0.77 ± 0.35	73	
Sulfamethoxazole							O 1,600 mg	12.8 ± 1.9		11.9 ± 3.2	0.62 ± 0.25	5.24/24 h	
							IV 1,600 mg	13.0		11.8 ± 3.1	0.62 ± 0.25	5.17/24 h	
							IP 1,600 mg	11.8 ± 2.2		15.3 ± 5.0	0.53 ± 0.08	65	
							IP	–	–	–	14 ± 2.5	60/3 h	[545]
Fosfomycin	<10%	1.5–2	–	–	4.88	–	IV 1 g	38.4 ± 8.7	32.6 ± 2.8/4 h	7.0 ± 1.4	3.2 ± 0.2	37.2 ± 3.6	[546]
							IP 0.5 g	– /5 h	34.7 ± 2.3	–	–	68.4 ± 6.0	

Table 9.8 (continued)

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
Roxithromycin		10–14	–	–			O 300 mg	20.6 ± 8.7	2.3–6.8	37–118	0.9–1.8	1.0–3.1	[315]
Aztreonam	50–60	1.8	0.2	80	7.2	22	IV 1 g	–	–	23.8 ± 2.5	2.1 ± 0.29	9/48 h	[547]
							IP 500 mg/L		30 ± 3.3/3 h	–	–	72.9 ± 2.4/6 h	
							IP 500 mg/L		42.5 ± 12.4/6 h	–	10.05 ± 3.7	90.8 ± 3/8 h	[548]
							IP 1.5 g/L single LD + pert	9.3 (6–14)	83 (61–92)/2 h	30.4	–	86–95	[310]
Metronidazole	20	7	0.7	82	7	82	IV 750 mg	10.93 ± 2.01	–	50.17 ± 18.6 (mL/kg/h)	4.49 ± 0.88	10/48 h	[322]
Metronidazole		6.0–8.8	0.53–1.1	68–87	6.1–9.5	55–183	IV 500–800 mg single dose	5.6				10	[324]
		6.1–14.7	0.52–0.96	68–81	7.0–2.1	–	O 250–2,000						
Ornidazole							IV 500 mg	11.8 ± 0.9		47.9 ± 6.3	3.0 ± 0.4	6.2 ± 1.1/48 h	[323]

Table 9.9 Pharmacokinetic data with antiviral and antifungal drugs in CAPD

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
Acyclovir	15	2–3	0.6	300	19.5	25	IV 200 mg/kg ($n = 1$)	14.7	–	48.6	3.6	7.3/24 h	[549]
							IV 5 mg/kg ($n = 1$) SD	17.1	7.7	48.3	4.4	5.7/24 h	[550]
							IV 1 g ($n = 2$) IV 0.5 g ($n = 2$)	13.2 ± 4.7	–	39.7 ± 10	3.4 ± 0.2	–	[551]
							IP 1 g/2L	10.8 ± 2.9	–	64.6 ± 7.5	–	61 ± 10	
Ganciclovir					6.3	35.5	5 mg/kg IV					Probably not relevant	[331]
Foscarnet		4.5						41.4–45.8		8.8–9.8	4.5–5.8	5–30	[336]
Zidovudine							O 200 mg SD				0	0	[552]
Zidovudine							O 200 mg ($n = 5$) SD	1.8 ± 0.5	5.3 ± 2.4	1,059 ± 511	5	<1/24 h	[552]
GZVD*								–	–	–	15	20/24 h	
Zidovudine	30	1.1	1.4	1,500	1.4	737	SD 200 mg						
							SD 200 mg O ($n = 1$)	7.9	1.36	856	4.2	0.5/14 h	[337]
							SD 100 mg O	26	0.2	2,079	5.8	0.14/14 h	
							SD 200 mg ZVD	19.9	9.06	–	3.6	8.5/14 h	
							100 mg ZVD	7.1	6.78	–	3.7	4/14 h	
Didanosine		1.56 ± 0.43		13.0 ± 1.6	3.6 ± 0.8	3.4 ± 1.2	300 mg IV	3.11 ± 0.88	9.17 ± 4.54	3.2 ± 1.2	?		[339]
		1.54 ± 0.38					300 mg per os	3.88 ± 1.26	2.16 ± 1.32				
Amphotericin B	90–95	24	0.46	15	40	9	50 mg IV/4 h	S: 10* D: 0.1–0.2*					[553]
							10 mg IV	S: 0.2 (1–12 h) D: 0.2					[554]
Fluconazole	11	33	0.71	–	98	–	O 100 mg	85	S:1,439 ± 246 D: 1,050 (6–24) 790 (24–48 h)	–	5.53 ± 1.03	18/48	[348]
							IP 150 mg/2 L	80	S: 2,123 ± 360	8.75 ± 22	4.3 ± 0.4		[555]
							IP 50 mg/2 L	72	S: 885 ± 136	7.63 ± 1.2	4.41 ± 0.49		
Fluorocytosine	4	5	0.7	113	85	7	LD 30–40 mg/kg 4 days		S ?				[556]
							MD 15 mg/kg O		D ?				

Table 9.9 (continued)

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
							LD 3.5 g 2 days 2.5 g 2 days		SSs: 24–86				[557]
							MD 1 g day IP 100 mg/L		SSs: 25–33				
							– perit	–	1.78	–	16.1 ± 2 Mass transfer	81 ± 2/4 h	[558]
							+ perit	–	–	–	19.0 Mass transfer	93/4 h	
							LD O 2 g + IP 100 mg/2 L		S: 25–33 D: 29–43				
Itraconazole	99.8	21–38	–	–	25		O 200 mg SD	–	S: 0.08	–	0	0	[351]
Ketoconazole	99	3	–	–	–	–	O 400 mg/day ($n = 1$)	3.51	–	–	–		[559]
							O 200 mg/day for 4 days		SC_{max} 2.0 ± 11.3 $DC_{max} < 0.1$				[560]
							O 400 mg/D for 4 days		SC_{max} 1.6 ± 0.5 $DC_{max} < 0.1$				
							O 200 mg SD – perit + perit		DC_{max} 0.021 (ND–0.073) DC_{max} 0.015 (0.010–0.019)				[561]
Ketoconazole	99	3	–	–	–	–	400 mg SD – perit + perit		C_{max} D: 0.029 (0.014–0.056) D: 0.074 (0.032–0.115)				
							O 400 mg SD	2.4 ± 0.8	C_{max} 2.3 ± 1.7		<1		[260]

Table 9.10 Pharmacokinetic data with H_2-antagonists, metoclopramide and cispramide

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
Cimetidine	13–25	1.5–2	0.8–1.2	313–808	3–5	193	IV 300 mg	6.9 ± 0.18	–	167.1 ± 8.06	3.01 ± 0.57	1.6 ± 0.23/24 h	[354]
							IV 300 mg	4.3	–	191 ± 55	4.2 ± 3.1	2.2 ± 1.4/24 h	[353]
Ranitidine	15	1.5–3	1.1–1.9	568–709	6–9	103–230	IV 50 mg	7.06 ± 0.96	–	126 ± 67.5	3.2 ± 0.7	1.3/24 h	[355]
							O 150 mg	10.02 ± 1.71	904 ± 529/4.2 h		2.6 ± 0.6	0.9/24 h	
Famotidine	15–20	2.5–3.5	1.1–1.4	412	9–18	40–60	IV 20 mg	15.5 ± 4.0	–	–	–	4.5 ± 1.1/24 h	[352]
Cisapride	98*	7–10*	2.4*	–	15*	385*	O 30 mg every 6 h	–	0.031–0.04 (serum)	–	–	–	[358]
							IV 10 mg every 6 h	–	0.007–0.008 (dialysate)	–	–	–	
							IP 5 mg/L every 6 h	–	0.028–0.053 (serum)	–	–	–	
Cisapride	98	36,440	2.4		9.6 ± 3.3	380 ± 161	O 20 mg		Probably not altered				[359]
Metoclopramide	–	3	3.4	916	14	196	O 15 mg (n = 1)	34.65	66.4	–	3.54	–	[562]
							IV 15 mg (n = 1)	30.13	329	61.6	1.47	3/6 h	
							IP 15 mg/2 L (n = 1)	30.13	146.2	–	–	97/6 h	
Lansoprazole	96	1.2–2.9					O 15–30 mg	1.6	Probably not altered				[356,357]
Pantoprazole	98	0.9–1.9	0.15–0.17	60–130	Not altered				Probably not altered				[563]
Omeprazole	95	0.7–2.1			0.7–2.1				Probably not altered				[356]

*Adapted from [495, 496].

Table 9.11 Pharmocokinetics of intravenously administered erythropoietin in peritoneal dialysis

PD regimen	Dose	C_{max} (U/L)	T_{max} (h)	$t_{1/2}$ (h)	AUC (U/1 h)	V_d (L)	Cl_{tot}	Percentage dose lost	References
6 CAPD	300	7,688 ± 1,103	0.5	11.2 ± 0.4	81,004 ± 9,523	5.0 ± 1.0/24 h	0.52 ± 0.008 mL/min/kg	2.63 ± 0.45/24 h	[564]
9 CAPD	100	1,595 ± 104 (11–145)	0.4 ± 0.1	8.7 ± 1.0	16,909 ± 1,217	4.9 ± 0.6	6.7 ± 0.5 mL/min	–	[565]
10 CAPD	100	2,000	–	5.1 ± 0.6	–	–	–	–	[566]
7 CAPD	100	1,440 (1,088–1,994)	–	8.3 (6.6–13)	14,623 (10,286–19,562)	4.5	6.0 (4.7–9.7) mL/min/1.73 m^2	–	[567]
12 IPD	100	1,923 ± 197	0.3	5.6 ± 0.3	–	3.7 ± 0.6	8.1 ± 1.4 mL/min	–	[361]
8 CAPD	120	3,959 ± 758	0.25	8 ± 2 (6.2 ± 10.2)	45,102 ± 11,405 (0–24 h)	0.033 ± 0.013 1/kg	0.047 ± 0.017 mL/min/kg	2.3/24 h (1.7–3)	[568]
6 CAPD	100	1,602	–	6.1	13 592	–	–	–	[569]

Table 9.12 Pharmocokinetics of subcutaneously administered erythropoietin in peritoneal dialysis

PD regimen	Dose	C_{max} (U/L)	T_{max} (h)	AUC (U/1 h)	Bioavailability (%)	References
6 CAPD	300	484 ± 75	24	8,230 ± 1,312 (0–24 h)	10.2 ± 1.0/24 h	[564]
9 CAPD	100	81 (11–145)	12	–	14/24 h; 31/72 h	[566]
12 IPD	100	32 ± 4	28 ± 5	–	14.9 ± 4.8	[361]
8 CAPD	120	176 ± 75	18	9,610 ± 4,862 (0–24 h)	21.5 (11.3–36)	[568]
6 CAPD	100	114	–	3,316	24.0	[569]
10 CAPD	50	81 ± 13 mU/L	24	1,492 ± 165 mU/1 h	-	[570]

Table 9.13 Pharmocokinetics of intraperitoneally administered erythropoietin in peritoneal dialysis

	Dose (U/kg)	Vol dialysate	Dwell (h)	C_{max} (U/L)	T_{max} (h)	AUC (U/1 h)	Bioavailability (%)	References
6 CAPD	300	2	4	108 ± 18	8–12	1,981 ± 271 (0–24 h)	2.5 ± 0.2	[564]
3 CAPD	300	2	12	170 ± 13	12	2,933 ± 413 (0–24 h)	3.6 ± 0.5	
9 CAPD	100		12	52 ± 14	12 ± 0.2	1,426 ± 366	8.5 ± 1.9	[565]
3 CAPD	100	2	10	80	12	56% of AUC after SC inj.	–	[566]
7 CAPD	100	2	12	23 (18–55)	14 (6.3–18)	808 (426–1,652)	6.8 (2.2–12)	[567]
12 IPD	100	dry cavity	–	213 ± 27	17 ± 2.3	–	41.4 ± 7.2	[361]
8 CAPD	50,000 U	1.5–2	8	375 ± 123	12	6,432 ± 2,150 (0–24 h)	2.9 (1.2–6.8)	[568]
10 CAPD	50	2	8	36 ± 4	12–24	803 ± 67 mU/1 h	–	[570]
6 CAPD	400	50 mL of (saline undiluted)	8	1,500 (estimated)	12	52,399 ± 6,865 mU/mL/h	>9-fold increase vs diluted	[360]
6 CAPD	400	2 diluted	8	300 (estimated)	12	5,739 ± 1,292 mU/m/h	–	

24-h period for both drugs. A model was developed to examine serum and dialysate concentrations after intermittent IP administration of 15 mg/kg cefazolin and 0.6 mg/kg tobramycin. The model-predicted IP cefazolin provides adequate serum and dialysate concentrations for 24 h. Intermittent IP tobramycin doses must be 1.5 mg/kg for one exchange during the first day and then given as 0.5 mg/kg thereafter. It was concluded that the current empiric dosing recommendations for PD-related peritonitis may be adequate for cefazolin (15–20 mg/kg); however, tobramycin doses must be changed to 1.5 mg/kg IP on day 1, then to 0.5 mg/kg IP thereafter in APD patients.

Ceftazidime

After IP administration of 1 g ceftazidime, serum concentrations reach therapeutic levels within 30 min and are maintained for more than 24 h. A V_d of 16 L was found. Overall, use of 1–1.5 g once daily or 15 mg/kg body weight has been recommended [279, 280]. The pharmacokinetics and dynamics of ceftazidime in CAPD peritonitis were recently explored in Thai patients [281]. In accordance with the ISPD 2000 recommendations, the antibiotic regimen comprised continuous IP cefazolin and once-daily IP ceftazidime. Cefazolin was administered as loading and continuous maintenance doses of 500 and 125 mg/L dialysate, respectively. Ceftazidime (20 mg/kg body weight) was given IP once daily. Duration of treatment was 96 h. Following ceftazidime administration, serum ceftazidime levels were above 8 μ/mL, the recommended MIC throughout 24 h. Dialysate ceftazidime levels were below the MIC for total periods of 4.19 and 6.26 h in day 1 and day 4, respectively. The clinical response rate to the empiric regimen was 90%. It was concluded that once-daily IP administration of ceftazidime according to the ISPD 2000 recommendation could not provide adequate therapeutic levels of ceftazidime in dialysate throughout 24 h. Despite this finding and the poor post-antibiotic property of ceftazidime, the empiric regimen including once-daily IP ceftazidime yielded good clinical outcome The objective of the recent study of Sisterhen et al. [282] was to determine whether a continuous maintenance

Table 9.14 Pharmocokinetics of miscellaneous drugs in CAPD

	Normal renal function				ESRD			PD					
	PB (%)	$t_{1/2}$ (h)	V_{dis} (L/kg)	Cl_{tot} (mL/min)	$t_{1/2}$ (h)	Cl_{tot} (mL/min)	Dosage/route	$t_{1/2}$ (h)	C_{max} (mg/mL)	Cl_{tot} (mL/min)	Cl_{per} (mL/min)	Percentage dose removed or absorbed	Refs
Ethosuximide	0	60	–	10	–	–	0.3 × 400 mg CCPD (child)	–	–	–	–	50/24 h	[373]
Phenobarbital	66	70	0.75	9	100	6	O 2 × 250 mg day 6 CCPD (child)	-	21	–	–	40/24 h	[373]
Phenytoin	87–93	18	0.57	25	9	125	O 3 × 100 mg	–	16.6 mm/L SS	–	1.77	–	[571]
							O 3 × 200 mg	–	22.6 mm/L SS	–	1.70	–	
							O 4 × 100 mg	–	26.1	–	1.60	–	
1.25 di–OH vit D								O 27.4	O 116	O 15.3	–	–	[572]
								IP 19.2	IP 121	IP 18.4	–	–	
1-alpha-OH-vit D							80 mg/kg	IV 109.4 ± 129.5	NM ?				[384]
Clodronate							300 mg IV	182 ± 138	26.0 ± 19.3	2.4 ± 0.6	7		[392]
Mycophenolate-Mofetil								O 2 × 1 g			14.6 ± 3.4	6.5 ± 1.6	[223]
Alprazolam	68.4	10–14.5	0.72–1.05	44–67	11.5	70	O 1 mg				–		[378]
Triazolam		2.56 ± 4.06	1.31 ± 0.1	330 ± 110	2.29	–	O 0.5 mg						[378]
Midazolam		1.36 ± 2.29	0.38–1.14	323–645		680	O 5–20 mg		680				[378]
	95–97.5				–	–	–						[573]
Loprazolam		6.3–14.8		230			O 0.5–2 mg						[378]
Zolpidem	92	1.5–2.4	0.54–0.68	15.7	3–4.8		O 5–20 mg		probably as in ESRD				[380]
Ethinyl estradiol		3.4 ± 1.6		1,007 ± 754				8.4 ± 4.1	9.3 ± 0.7	518 ± 3.7			[376]

dose of IP ceftazidime (125 mg/L) in the absence of a loading dose would maintain adequate serum and dialysate concentrations to be effective in the treatment of peritonitis. Mean serum concentrations at completion of the short rapid cycles and at 24 h were 28.92 ± 13.64 and 23.92 ± 11.93 μg/mL, respectively. Serum bioavailability at 24 h was 74 ± 6%. Mean dialysate concentrations at completion of the short rapid cycles and at 24 h were 87.43 ± 19.18 and 32.06 ± 6.27 μg/mL, respectively. All patients achieved serum and dialysate ceftazidime concentrations greater than the MIC within 4 h.

Cefotaxime

Cefotaxime is metabolized in the liver to an active metabolite, which is primarily excreted by glomerular filtration and tubular secretion. However, dose reduction is necessary only when the CrCl falls below 5 mL/min. Several studies explored the pharmacokinetics of cefotaxime in CAPD [283]: a high proportion of the IP administered cefotaxime is absorbed into the circulation and therapeutic serum levels can be obtained after IP administration; no further dose adaptation is needed for patients on CAPD.

Cefepime

The clearance of cefepime, a third-generation cephalosporin, is 15 mL/min in CAPD patients, with a peritoneal clearance of 4 mL/min [284]. For IV administration, 1–2 g every 48 h is recommended [285]. It has a low protein binding value, and a relatively low V_d; therefore, a once-daily IP administration is probably not recommended, and the IV route should be preferred. Elwell et al. [286] recently determined the pharmacokinetics of IP cefepime in six APD patients. All patients were administered a single IP dose of cefepime (15 mg/kg) over a 6-h dwell. Patients then underwent a fixed APD regimen consisting of the first 6-h dwell, followed by an 8-h dialysate-free period and a subsequent series of three overnight APD exchanges. One hour after IP administration, serum cefepime levels exceeded the MIC (8 mg/mL) for susceptible organisms. The mean serum and dialysate concentrations at 24 h were 15.8 ± 3.6 and 6.2 ± 2.3 mg/mL, respectively. Bioavailability was 84.3 ± 6.2%, V_d 0.34 ± 0.07 L/kg, and serum $t_{1/2}$ was 13.8 ± 3.2 h. Total, peritoneal, and renal clearances were 16.5 ± 4.4, 4.3 ± 0.7, and 3.5 ± 2.5 mL/min, respectively. It was concluded that IP cefepime dosed at 15 mg/kg resulted in adequate serum concentrations in APD patients at 24 h post dose. Pharmacokinetic predictions suggest that most APD and CAPD patients would achieve adequate serum cefepime concentrations if treated with standard doses of 1,000 mg given IP once daily.

Cefpirome can be administered both IP and IV. Dialysis clearance by PD is negligible.

Moxalactam is a semisynthetic β-lactam antibiotic with activity against a broad range of Gram-positive and Gram-negative aerobic and anaerobic bacteria. This antibiotic exists as two stereoisomers with different antimicrobial activities. Several pharmacokinetic studies in CAPD patients have shown that, after IV administration, dosage adjustment to account for loss of moxalactam via the peritoneal cavity is not necessary. It appears further that there are no significant differences between R-Mox and S-Mox kinetics in CAPD patients [287].

Piperacillin

For piperacillin, whether or not in combination with tazobactam, dose adaptations should be made according to RRF. During CAPD, 5.5% of piperacillin and 10.7% of tazobactam are removed by dialysis over 28 h [288]. Another study [289] assessed the pharmacokinetics of IP administration of the combination piperacillin/tazobactam (PIP/TAZ) to patients on CAPD with and without *Pseudomonas* peritonitis. All patients were given an IP loading dose of 4 g/0.5 g PIP/TAZ. Twenty-four hours after the initial dose, a maintenance dose of 0.5 g/0.0625 g PIP/TAZ was administered with each dialysate exchange for a period of 1 week. After the loading dose, the highest plasma Cmax was 51.6 ± 21.25 μg/mL and appeared at 1.5 ± 0.45 h. During the maintenance period plasma PIP concentration was 5.2 ± 4.75 μg/mL. Tazobactam was detected in the plasma of one patient only. The concentration of TAZ in the dialysate fluid during the maintenance period was 2.3 ± 0.5 μg/mL. It was concluded that piperacillin administered IP at 4 g reached plasma concentrations comparable to IV administration and were considered therapeutic (above the MIC90 for *Pseudomonas aeruginosa*) in CAPD patients with or without peritonitis. The maintenance dose, however, should be augmented. Tazobactam could not be detected in the plasma of most patients and the therapeutic implications of IP administration of TAZ cannot be directly correlated to IV administration.

The pharmacokinetics of IV piperacillin in APD patients were recently studied [290]. Eight patients received a single IV dose of piperacillin (35 mg/kg actual body weight). GFR and piperacillin clearance values were normalized to 1.73 m2. Dwell times used in the patients on APD were 2.25 ± 0.06 h on cycler and 7.26 ± 0.14 h off cycler. Piperacillin $T_{1/2}$ was not statistically different on or off the cycler (on cycler 1.99 ± 0.39 h, off cycler 4.39 ± 5.4 h) and remained

insignificant. Piperacillin total Cl was 31.29 ± 6.02 mL/min. Renal Cl and PD Cl accounted for 8.8 and 16.8% of total clearance. Mean piperacillin serum and dialysate end-of-dwell concentrations were above MIC of susceptible organisms (8 μg/mL) for the three cycler exchanges only. The predicted serum and dialysate concentrations, using a one-compartment model, suggest that IV piperacillin 4,000 mg would provide adequate concentrations for susceptible organisms over a 12-h period. Thus, the current IV piperacillin dosing recommendations of 4,000 mg every 12 h for PD-related peritonitis are appropriate for patients on automated PD, but intermittent IP piperacillin is not recommended.

Glycopeptide Antibiotics

The two major drugs in the class of glycopeptide antibiotics are vancomycin and teicoplanin. *Staphylococcus aureus* and *Staphylococcus epidermidis* are almost always susceptible to vancomycin. Concentrations of 5 μg/mL or less are inhibitory although some strains require 10–20 μg/mL. Vancomycin is a large molecule (around 1,500 Da) and has a low serum protein binding. In ESRD its $T_{1/2}$ is very prolonged [200–250 h]. Pharmacokinetic studies after IV administration in CAPD patients show a low peritoneal clearance, which, however, increases during peritonitis. Although it has been claimed that CAPD does not require dose adjustment, serum drug levels should be followed in patients with substantial RRF [291]. As the *V*d of vancomycin (0.5 L/kg) is large in comparison with the IP volume, there remains a high concentration gradient between dialysate and plasma after IP administration (Fig. 9.12 from [291]). Therefore, vancomycin is rapidly absorbed into the circulation. When the dialysate is drained, and new dialysate is instilled, it rapidly becomes saturated with vancomycin from the blood, and adequate IP levels of vancomycin are obtained. Because of this phenomenon, a single high dose (15 mg/kg) of vancomycin is sufficient to obtain adequate dialysate levels. Whether, from a microbiological point of view, vancomycin is still the antibiotic of first choice in the treatment of PD-related peritonitis, is a matter of debate. The growing concern on the emergence of vancomycin-resistant enterococci in the United States has forced the Ad Hoc Advisory Committee to classify vancomycin from agent of choice to agent to be avoided (see Chapter 19 in this book). Other centers, however, having a high incidence of methicillin-resistant staphylococci (MRSA), have recommended a center-tailored therapeutic approach of peritonitis where vancomycin is still regarded as the first choice [292].

There are few studies of the pharmacokinetics of vancomycin and gentamicin in PD patients and the influence of antibiotic concentrations on treatment outcome. Concerns about resistance to ceftazidime and potential of aminoglycoside toxicity make the choice of empiric antibiotics difficult. Blunden et al. [293] retrospectively collected data from 613 patients on PD between 1 June 2002 and 31 December 2005 and adopted a protocol that minimized aminoglycoside exposure to patients with RRF and carefully monitored serum antibiotic concentrations. There were no statistical differences in mean day-5 vancomycin concentrations for CAPD versus APD and for anuric versus not-anuric patients. However, low levels (<12 mg/L) were recorded for 12.8% CAPD and 15% APD patients. These remained low at day 10 in 16% patients (25% if not anuric), despite incremental dosing. Vancomycin concentration did not predict cure or relapse of Gram-positive or culture-negative peritonitis. Gentamicin concentration (>2 mg/L in >50% patients) did not predict outcome of Gram-negative and culture-negative peritonitis. Moreover, cure rates were the same irrespective of whether gentamicin was continued for 14 days or was switched to ceftazidime after 5 days.

This important study concluded that the International Society for PD (ISPD) dosing guideline for vancomycin in CAPD and APD patients produces adequate serum concentrations of the antibiotics in the vast majority, but that large incremental dosing of vancomycin is needed if day-5 levels are low; especially for not-anuric patients. While evidence of gentamicin toxicity in PD remains controversial, ISPD dosing regimen resulted in high levels for >50% patients. High gentamicin concentrations did not correlate with treatment success, but switching gentamicin to ceftazidime at day 5 appeared safe and limited aminoglycoside exposure. Increasing vancomycin and gentamicin concentrations do not appear to improve cure rates and alternative strategies (such as combination treatment) should be considered for future research.

The pharmacokinetics of a single dose of IV vancomycin (15 mg/kg total body weight) were recently studied in 10 APD patients [294]. Dwell times were 2.3 ± 0.1 h on cycler and 7.3 ± 0.1 h off cycler. Vancomycin $T_{1/2}$ was significantly different on-cycler than off-cycler (11.6 ± 5.2 h versus 62.8 ± 33.0 h). Vancomycin total Cl was 7.4 ± 2.0 mL/min. Renal Cl and PD Cl accounted for 23.6 and 28.0% of total Cl, respectively. Mean vancomycin serum and dialysate end-of-dwell concentrations were above MIC of susceptible organisms (5 mg/mL) for the first cycler and the second ambulatory exchanges only. This study suggests that, to provide adequate concentrations for susceptible organisms over a 24-h period, current intermittent vancomycin dosing recommendations for PD-related peritonitis need to be changed to 35 mg/kg IP on day 1, then 15 mg/kg IP thereafter (i.e., once daily) in APD patients.

Little information is available on the disposition of vancomycin during chronic PD in children. This problem was recently studied [295] following IP administration of vancomycin in children receiving short-dwell APD and long-

dwell CAPD. A 6-h exchange containing vancomycin 500 mg/L, using an exchange volume of 1,100 mL/m^2 body surface area (BSA), was followed by 4-, 6-, and 8-h antibiotic-free exchanges. The 8-h exchange was followed by three to four 90-min antibiotic-free exchanges. The bioavailability of vancomycin during a 6-h IP exchange was 70 ± 5%, resulting in a delivered dose of 12.0 ± 1.8 mg/kg, and a 6-h serum vancomycin concentration of 23.3 ± 7.2 μg/mL. Total body vancomycin clearance measured 10.72 ± 4.52 mL/min/1.73 m^2 BSA, while PD clearance measured 2.78 ± 1.08 mL/min/1.73 m^2 BSA and accounted for 29 ± 11% of total vancomycin clearance. Dialysis clearance during long-dwell (CAPD) and short-dwell (APD) regimens was similar accounting for 25 ± 13% and 32 ± 12% of total body clearance, respectively. It was concluded that IP absorption and dialysis clearance of vancomycin in children receiving PD are similar to those reported in adult dialysis patients. In contrast, total body clearance of vancomycin was increased and the $T_{1/2}$ decreased in children, due to increased elimination by nonrenal nondialysis routes. For intermittent IP vancomycin therapy in children with peritonitis, an IP load containing vancomycin 1,000 mg/L (or 30 mg/kg), followed by a single full-fill (1,100 mL/m^2 BSA) daily exchange, containing vancomycin 250 mg/L (or 7.5 mg/kg), from day 2 until the end of treatment will maintain a vancomycin dialysate concentration of >4 μg/mL.

Teicoplanin is a glycopeptide that is mainly excreted via the renal route and has a prolonged terminal $T_{1/2}$ in renal failure. In PD patients with peritonitis the serum $T_{1/2}$ was 508 ± 193 h, and the V_d was 0.48 L/kg [296]. A recent pharmacokinetic study with teicoplanin was performed in anuric CAPD patients [297]. One single IV dose of 10 mg/kg teicoplanin was administered and blood and dialysate were sampled at regular time intervals for 48 h post drug infusion. Teicoplanin serum levels above 10 μg/mL, the level desired to treat systemic infections, were detected for 24 h after administration. All dialysate concentrations were very low. Teicoplanin presented two phases of elimination: an early first phase and a late second phase. Mean Cmax was 75.56 μg/mL, mean $T_{1/2}$ of the early elimination was 3.34 h, mean $T_{1/2}$ of the late elimination was 61.68 h, mean AUC-time curve was 1,491.92 mg × h/L, mean clearance rate was 10.68 mL/min, mean apparent V_d was 0.80 L/kg, and mean V_d at steady state was 0.22 L/kg. The mean dialysate excretion was only 3.16% and the peritoneal clearance was 0.023 mL/min. Teicoplanin can thus be administered at 10 mg/kg every 24 h for the therapy of systemic infections in patients undergoing CAPD. However, its IV administration should be avoided in the treatment of peritonitis, because the achieved dialysate concentrations are very low.

Table 9.8 summarizes the data with quinolones, aminoglycosides, trimethoprim-sulphamethoxazole, and miscellaneous antibiotics. Pharmacokinetic data in CAPD of some of these antibiotics have been reviewed by us [217]. Fluoroquinolones have a large antibacterial spectrum, including Gram-negative bacteria and staphylococci. Most fluoroquinolones are well absorbed after oral administration and have a favorable pharmacokinetic profile. Janknegt [298] has summarized the pharmacokinetic and clinical studies with ciprofloxacin, ofloxacin, pefloxacin and fleroxacin in CAPD patients. Fractions of dose of quinolones removed by CAPD range between 1 and 2% at 24 h after dosing [299–301], probably due to the large V_d of these agents. As the IP levels of quinolones are reportedly low during the first 24 h of oral therapy, an IP loading dose is recommended [302]. It is of note that the concomitant administration of antacids significantly reduces the gastrointestinal absorption of the quinolones.

Although in CAPD therapy with quinolones requires dose adjustment as for patients with ESRD, high drug IP concentrations can be achieved after IV or oral administration, making these substances, at least theoretically, attractive alternatives to conventional treatment of CAPD peritonitis (for review and dose recommendations see refs [298, 302]. An additional study with oral ofloxacin in peritonitis was performed by McMullin et al. [303] in CAPD patients who received once-daily 400 mg oral ofloxacin for 7 days for the treatment of bacterial peritonitis. Ofloxacin, desmethyl ofloxacin, and ofloxacin-N-oxide accumulated over the course of therapy and could still be detected in serum and dialysate 5 days after the end of therapy. The mean elimination $T_{1/2}$ of ofloxacin in serum was 32 ± 7 h, desmethyl ofloxacin 45 ± 26 h, and for ofloxacin-N-oxide 44 ± 15 h. The total mean recovery of ofloxacin and its metabolites from the dialysate was 15.4%. This regimen results in serum and dialysate concentrations likely to be effective for the treatment of infection for at least 10 days.

Ciprofloxacin pharmacokinetic data in APD (CCPD) patients after administration of two doses of ciprofloxacin 750 mg orally every 12 h were recently studied by Yeung et al. [304]. The following results were obtained: serum $T_{1/2}$ 10.1 ± 1.2 h, Cmax 2.7 ± 0.5 mg/L, T_{max} 1.6 ± 0.1 h after the first dose, and peritoneal clearance 1.2 ± 0.1% of the total body clearance. While all patients achieved serum AUC-time curve above the MIC for *Escherichia coli* and *Klebsiella* species after the first dose, only two patients achieved this goal for *Pseudomonas aeruginosa*. End-of-dwell dialysate concentrations were above the MIC for *E. coli*, *Klebsiella* species, and *P. aeruginosa* after the second dose. Ciprofloxacin in an oral dose of 750 mg every 12 h in CCPD patients may thus be useful for empirical Gram-negative coverage of CCPD peritonitis and for treatment of documented peritonitis caused by sensitive *E. coli* or *Klebsiella* species.

A recent open-label, parallel-group study determined the pharmacokinetics after a single oral 600-mg dose of garenoxacin in subjects with severe renal impairment, including patients on CAPD [305]. Compared with healthy controls, garenoxacin, AUC, and Cmax were increased by 51% and lowered by 20%, respectively, in subjects with severe renal impairment. The terminal $T_{1/2}$ was prolonged in subjects with severe renal impairment compared with

healthy controls (26.5 ± 7 vs. 14.4 ± 3 h, respectively). In subjects receiving HD or CAPD, removal of garenoxacin from systemic circulation was relatively inefficient (HD, 1.5–11.5%; CAPD, 3%), suggesting no need for a supplemental dose of garenoxacin after dialysis.

The pharmacokinetics after IP administration in CAPD have been studied for ofloxacin, pefloxacin, and ciprofloxacin; the latter has also been studied in CCPD [306]. During CAPD, the half-lives of ciprofloxacin, pefloxacin, and ofloxacin are 10, 17–21, and 25 h, respectively. Adequate peritoneal ofloxacin levels were reported in the second and third exchanges after a single IP dose of 200 mg in the first exchange [307]. For fleroxacin, a mean dialysate to plasma concentration ratio of 0.5–0.6 can be expected after a short dwell of 4 h [301]. Therapeutic concentrations in the peritoneal fluid can be achieved in CAPD patients using an oral loading dose of 800 mg fleroxacin and a daily maintenance dose of 400 mg.

Aminoglycosides

After systemic administration of aminoglycosides a substantial fraction of the administered dose is removed over 24–48 h. The peritoneal clearance adds approximately 20–30% to the total removal from the body and clinically relevant concentrations in the dialysate are achieved after IV administration. This significant peritoneal clearance is due to the low protein binding and the small V_d of these drugs. It is recommended that plasma levels should be measured regularly, especially in repeated usage [250]. For all aminoglycosides tested, an important absorption has been observed after IP administration; there is a significantly higher systemic bioavailability in peritonitis compared to nonperitonitis patients. Continuous IP administration of aminoglycosides in patients with peritonitis leads to more or less constant plasma levels and carries the risk for ovotesticular toxicity and further decrease in RRF [308]. In order to decrease this potential ototoxicity and nephrotoxicity, once-daily administration seems to be preferable. Once-daily dosing with aminoglycosides is possible due to their important post-antibiotic effect. After IP administration of 0.6 mg/kg gentamicin, $T_{1/2}$ was 35.8 h, and V_d was 0.23 ± 0.08 L/kg [250]. A higher dose, 1 mg/kg, was recommended to obtain sufficient plasma and dialysate levels during 24 h.

Kim et al. [309] found that in peritonitis, the blood levels of netilmicin after a loading dose of 100 mg IP were the same irrespective whether the maintenance dose was either 0.6 mg/kg IP once daily, or 15 mg/2 L IP, four times daily. This study suggested thus that once-daily IP or continuous IP netilmicin may be empirically recommended to CAPD peritonitis patients but that the once-daily IP method may be the most convenient method. As mentioned earlier, aminoglycoside pharmacokinetics, in particular tobramycin, have in recent years been studied in association with cephalosporins (see above).

Aztreonam, a monobactam is effective against Gram-negative bacteria, with greater safety and a more predictable action in dialysate compared to aminoglycosides. The pharmacokinetics of aztreonam have been studied after both IV and IP administration in CAPD patients. Based on these data, several authors have described favorable results in Gram-negative peritonitis, including some *Pseudomonas* infections, with the IP route of aztreonam alone [310, 311], or in combination with cefuroxime [312] or vancomycin [313, 314].

The pharmacokinetics of roxithromycin were determined following a single oral dose to patients on PD. Serum elimination $T_{1/2}$ was doubled compared to healthy individuals. Less than 5% of the dose was recovered in dialysate over 48 h, and dialysate concentrations were low. Administration every 48 h is recommended [315].

It is of note that macrolides can inhibit metabolization, and thus affect the plasma levels of many other drugs. Serious adverse interactions are therefore possible, and dose adaptations for these medications (e.g., cyclosporin, oral contraceptives) are necessary when macrolides are administered.

Azithromycin is an azalide antibiotic with a similar antibacterial spectrum to erythromycin but with greater Gram-negative activity, a more favorable pharmacokinetic profile, and with improved absorption and higher sustained tissue concentrations compared with erythromycin. The pharmacokinetics and PD clearance of azithromycin were studied following a single 500-mg oral dose of azithromycin in eight CAPD patients without peritonitis [316]. Cmax concentrations occurred at 2–3 h with 0.35–1.35 μg/mL .The mean elimination $T_{1/2}$ was 84.55 h, and plasma clearance was 21.93 L/h. This compares with values of greater than 40 h and 40.8 L/h reported in healthy volunteers. After 8 h, the mean dialysate concentration was 0.07 μg/mL; the PD clearance was only 0.06 L/h. Azithromycin is thus not substantially removed by CAPD in the absence of peritonitis and cannot be recommended for widespread use in this setting at present.

Linezolid

Only rare case reports have described the use and limited pharmacokinetic data with linezolid, an antibiotic that is indicated in vancomycin-resistant enterococci (VRE) and vancomycin-intermediate-susceptible or -resistant

staphylococci (VISA and VRSA, respectively). After either IV [317] or oral [318] administration of 600 mg of linezolid, the $T_{1/2}$ ranged between 8.7 and 8.3 h, which is longer than given by the company information. A good penetration into the peritoneal cavity was observed.

Fusidic Acid

Because fusidic acid is metabolized and excreted by the liver, it is generally assumed that renal impairment has no effect on serum concentrations. Patients on CAPD were given the same dosage regimen for seven doses [319]. Accumulation was seen and, in the majority of patients, steady-state pharmacokinetics had not been achieved by the third day. The mean Cmax values for the first dose and for the seventh dose were 16.0 and 33.9 mg/L, respectively. Fusidic acid concentrations of 1.0–2.3 mg/L were detected in PD fluid in six of the seven CAPD patients. There was a tendency towards increased $T_{1/2}$ with repeated dosing. Protein-binding of fusidic acid in patient serum samples was 87.6–94.6%.

Anti-Tuberculosis Medication

An extensive in-depth review on anti-tubercular therapy in renal failure, including the pharmacokinetic aspects of these drugs in PD, has recently been published by Launay-Vacher et al. [320]. This review should be consulted for recommendations of dosing of the common and more recently developed antitubercular drugs.

Ahn et al. [321], administered nine patients on CAPD a conventional oral dose of antituberculosis medications and plasma and peritoneal fluid concentrations of isoniazid and rifampicin and pyrazinamide were measured. Average Cmax levels of isoniazid, rifampin, and pyrazinamide were 3.3, 6.5, and 30.9 mg/L, respectively, all of which much exceed the MIC for *Mycobacterium tuberculosis*. Peritoneal fluid concentrations of isoniazid and pyrazinamide were maintained well above the MICs for *M. tuberculosis*; however, the dialysate concentration of rifampicin was below the therapeutic range most of the time. Thus, for the treatment of systemic or pulmonary tuberculosis in CAPD patients, no dose adjustments are required for isoniazid, rifampicin, or pyrazinamide but for the treatment of tuberculous peritonitis, oral rifampin therapy is not expected to be effective because of its low peritoneal fluid concentration.

The two agents used in anaerobic infections, metronidazole and ornidazole, have a low peritoneal clearance and only 10 and 6% of the dose, respectively, are removed by the peritoneum [322, 323]. The dosage in CAPD patients is therefore the same as in undialyzed, uremic patients [324].

Table 9.9 summarizes the data for antiviral and antifungal drugs. An extensive recent review of antiviral drug therapy, including pharmacokinetic data in renal failure and dialysis is available [325].

Acyclovir has significant activity against HSV-1, HSV-2, and Varicella zoster virus (VZV). Acyclovir seems to have a three-compartment pharmacokinetic profile in CAPD patients [326]. Mean total plasma clearance was 46 mL/h/kg, 12% of which was due to PD. Acyclovir has an apparent V_d of 62.5 L, with a protein binding of less than 20%. It was found [327] that the doses recommended for ESRD patients (1,600 mg) led to supratherapeutic levels of acyclovir in CAPD patients, increasing the risk of neurotoxicity, which was reported in two patients [328]. Based on computer modelling, a daily oral dose of 600–800 mg is recommended [327].

As mentioned above, acyclovir-induced neurotoxicity is reported to be associated with high serum drug levels even when following the recommended reduced doses for this renal failure population. In view of the high oral bioavailability of valacyclovir (the L-valyl ester of acyclovir), the risk of neurotoxicity becomes more prominent [329]. In 12 CAPD patients who were administered a single oral dose of 500 mg valacyclovir, acyclovir was analyzed. High interpatient variations were observed with acyclovir apparent total clearance values of 7.238 ± 4 L/h and $T_{1/2}$ values of 22.27 ± 16.82 h. However, dosage simulations confirmed supratherapeutic acyclovir concentrations for all participants when following the recommended dose of 1,000 mg valacyclovir/24 h for varicella-zoster infections.

Ganciclovir is extensively used as an antiviral agent for cytomegalovirus (CMV) infections in immunocompromised patients. Sommadossi et al. [330] reported higher, although highly variable, values for V_d in patients with renal failure (V_d 0.41 ± 1.5 L/kg) compared to normal volunteers. Ganciclovir has a low molecular weight and a low protein binding (1–2%) and is thus effectively cleared by HD. However, due to the large V_d compared to the dialysate volume, removal of ganciclovir by PD is negligible, and the doses should be adapted as for patients with renal failure. It is of note that, due to an important tubular secretion, CAPD patients with RRF have a ganciclovir clearance higher than the creatinine clearance [331].

Izzedine et al. described the pharmacokinetics of ritonavir and nevirapine in a CAPD patient suffering from HIV infection [332]. Ritonavir does not appear in the peritoneal dialysate, but like in the study by Taylor et al. [333], the dialysate concentration of nevirapine was almost 50% of the plasma concentration so that monitoring of plasma levels during therapy with this drug in CAPD patients with HIV is recommended. In the study by Taylor et al. [333] the

pharmacokinetics of nelfinavir (1,250 mg bid) were also described. Nelfinavir, like ritonavir, does not cross the peritoneal membrane due to its large size and high protein binding.

Cidofovir

Brody et al. [334] found that in patients receiving cidofovir that the mean cidofovir clearance in subjects with normal renal function was 1.7 ± 0.1 mL/min/kg, which decreased with declining renal function as indicated by the regression equation. The mean V_d at steady state did not change significantly in subjects with kidney disease and cidofovir serum elimination $T_{1/2}$ was significantly increased in subjects with severe renal impairment. Cidofovir was not significantly cleared during CAPD. It was concluded that in patients with varying degrees of renal insufficiency aggressive dosage reduction of cidofovir is necessary.

Oseltamivir is an antiviral drug used in prophylaxis and therapy for influenza and its dose reduction is recommended for patients with ESRD. However, dosing recommendations are not available for treatment or prophylaxis of influenza in these patients. Robson et al. [335] assessed the pharmacokinetics and tolerability of oseltamivir in patients undergoing HD and CAPD. In this open-label, multiple-dose study, patients received 30 mg oral oseltamivir suspension over 6.5 weeks. This dose was predicted to be suitable for ESRD patients based on a two-compartment model. CAPD patients received six doses given once weekly after a dialysate exchange. In CAPD patients, mean Cmax after the first and sixth doses were 885 and 849 ng/mL, respectively. The mean AUC values for days 1–6 and days 36–43 were 33,400 and 32,400 ng h/mL, respectively. Oseltamivir was well-tolerated. In conclusion, a 30-mg dose of oseltamivir given once weekly in CAPD provides sufficient exposure to oseltamivir carboxylate to allow safe and effective anti-influenza treatment and prophylaxis.

No pharmacokinetic data for PD patients are available for foscarnet, and dose adaptations are recommended as in ESRD. One case report described a serum $T_{1/2}$ of 45.8 h for a patient on CAPD (normal renal function 4.5 h). CAPD clearance of foscarnet was calculated to be 4.5 mL/min with a total clearance of 8.8 mL/min [336].

Studies in a limited number of CAPD patients treated with zidovudine suggest that no further modification from the renal failure dosage regimen is necessary [337, 338]; however, great interpatient variability in its pharmacokinetics was noted [338].

Didanosine is an antiretroviral agent used for treatment of HIV infections. In patients with renal failure, elimination $T_{1/2}$ was reported to be prolonged to 3.6 ± 0.8 h as compared to 1.5 ± 0.5 h in normal renal function. CAPD has little effect on the removal of didanosine; dose reduction to one-fourth of the daily dose is thus recommended (a single administration), in patients on CAPD as well as in nondialyzed end-stage renal failure patients [339].

Antifungal Drugs

Information on the pharmacokinetics of antifungal drugs in PD patients is disappointingly scarce. Most studies are limited to occasional measurements of serum and/or dialysate levels during treatment for fungal peritonitis.

Amphotericin (AmB) is highly protein-bound and circulates in the blood in a complex of high molecular weight (200,000–300,000). It penetrates very poorly in the peritoneal fluid after systemic administration. The data are, however, conflicting [340–342]. Chemical peritonitis causing abdominal pain after IP administration of AmB B has been observed [252–255]. It has been proposed that for IP use the dialysate should be adjusted to a neutral pH to prevent aggregation [343]. AmB has been used in an IV dose of 0.5 to 1 mg/kg body weight, combined with an IP dose of 2–3 mg/L dialysate [344]. AmB induces the formation of pores and channels in the cell membrane, causing leakage of potassium and magnesium. This is probably the reason why the drug increases transcapillary ultrafiltration (see Part I, above); however, the chemical drug-induced peritonitis may also play a role in this phenomenon [345]. Studies of the absorption of AmB B after IP instillation are lacking, although the large V_d and the high protein binding are expected to favor its transfer to the blood stream.

Systemically administered fluorocytosine penetrates well into the peritoneal fluid [341]. The usual loading dose of 20–30 mg/kg in uremic patients is followed by a maintenance doses of 15 mg/kg. Serum levels of fluorocytosine should be monitored since toxicity is expected when serum levels exceed 100–125 μg/mL. This has mainly been tried with IP administration of 100–200 mg/2 L, together with IV AmB B [255, 346] or in a dose of 150 mg/L in combination with oral ketoconazole 400 mg daily [347].

Fluconazole is effective for both superficial and systemic fungal infections. The pharmacokinetic profile of orally administered fluconazole shows a low plasma protein binding, and a long plasma $T_{1/2}$, allowing once-daily dosing. The bioavailability is excellent. A good penetration of fluconazole into the dialysate after a single oral dose of 100 mg in

CAPD patients has been found [348]. When given systemically the dose should be the same as in undialyzed patients [349]. With IP administration the recommended dose is 150 mg in a single 2 L dwell, every 48 h.

Dahl et al. [350] investigated the pharmacokinetic characteristics of IP fluconazole in APD (CCPD). Five patients received a single dose of IP fluconazole 200 mg during their long daytime dwell. The bioavailability of IP fluconazole was $96 \pm 2\%$ over a 12-h dwell, absorption $T_{1/2}$ was 2.5 ± 1.2 h, serum elimination $T_{1/2}$ was 71.65 ± 12.76 h, and V_d was 0.66 ± 0.13 L/kg. Peritoneal clearance was 5.96 ± 0.93 mL/min and proportional to the total dialysate volume. Renal clearance was proportional to renal creatinine clearance. Current treatment guidelines for fungal peritonitis suggest fluconazole 200 mg intraperitoneally every 24 h. These data suggest that this dose, administered every 48 h, is more than sufficient to maintain serum and peritoneal concentrations above the MIC for most *Candida* species.

A single-dose pharmacokinetic study of itraconazole has been performed in patients with ESRD, including five CAPD patients [351]. The systemic pharmacokinetics of itraconazole were not affected by CAPD and the drug could not be detected in the dialysate. Oral administration of ketoconazole in CAPD patients revealed extremely low peritoneal clearances [253, 260]. After oral administration of 400 mg ketoconazole, Johnson et al. reported mean serum concentrations of 2.3 μg/mL, while the D/P ratio was only 0.03 after 5 h.

Table 9.10 covers the drugs used in gastroenterology. H2 antagonists are frequently described in dialysis patients. Studies have been performed with cimetidine, ranitidine, and famotidine [352–355]. Dosage reduction necessary for undialyzed patients, should be applied for patients on PD. No pharmacokinetic data on nizatidine or roxatidine in CAPD are available and it can be presumed that these drugs have a negligible peritoneal clearance.

To our knowledge omeprazole, a proton-pump inhibitor, has not been studied in CAPD patients. In patients with ESRD its pharmacokinetics are not significantly different from those in healthy subjects and the drug is not detected in dialysis fluid during HD [356]. One can therefore expect that omeprazole could be administered in uremic and CAPD patients at the usual dose of 20 mg/day. Lansoprazole and pantoprazole are also completely metabolized. The elimination $T_{1/2}$ of lansoprazole seemed to be prolonged in patients with moderate, but not in those with severe renal dysfunction. HD did not seem to influence the plasma concentrations of lansoprazole, probably due to a very high protein binding (97–99%) [357]. Lansoprazole also has some renally cleared active metabolites. The data with pantoprazole in patients with renal impairment are difficult to interpret, and further studies are required to clarify the controversial observations made until now [356].

With cisapride, a gastrokinetic drug, in a dose of 5 mg/L dialysate four times per day, excellent results were obtained in two diabetic CAPD patients suffering from gastroparesis. The IP dose produced the same plasma levels as the oral or IV doses of 30 and 10 mg, respectively [358]. In HD patients the terminal $T_{1/2}$ of cisapride was 9.6 ± 3.3 h and the V_d was 4.8 ± 3.3 L/kg. Cisapride was not found in the dialysate, in contrast with its metabolite norcisapride. The authors conclude that dose adaptation is not necessary [359].

Table 9.11 summarizes the data of IV erythropoietin (Epo)(11a), subcutaneous Epo(11b), and IP Epo(11c). A number of interesting pharmacokinetic studies have been performed with Epo in PD. With subcutaneous (SC) administration, Epo is slowly absorbed with a Tmax around 20–24 h. The SC bioavailability compared to IV dosing ranges between 10 and 36%. PD itself has no significant effect on the removal of Epo.

Human pharmacokinetic studies on IP administration of Epo show a very low bioavailability (ranging from 2.5 to 8.5%) when diluted in 2 L of dialysate, but this increased to $41.4 \pm 7.2\%$, when administered into a dry abdomen [360, 361]. The problem of low bioavailability of IP Epo when diluted in dialysate, can be overcome by using high dosages of Epo or low volumes of dialysate. Frenken et al. [362] utilized 100 U/kg intraperitoneally, diluted in 1 L of dialysate over a 9 h dwell thrice weekly and observed a slow but significant increase in hematocrit; Nasu et al. [363] reported an excellent hematocrit response when Epo in a high dose of 300 U/kg, diluted in 2 L dialysate, was given.

Bioavailability is further improved by instilling the dose into a dry peritoneum [364]. The pharmacokinetics of a single 100-U/kg IP Epo alfa in eight CAPD patients was studied after the instillation into a dry peritoneum and allowing a dwell for 8 h. CAPD was then resumed. A 14-h effluent dialysate sample was collected to determine Epo alfa recovery. The extent of Epo alfa absorption was significantly greater than previously reported for a 4-h dry dwell. The mean dose-normalized AUC using the 8-h dry dwell dosing technique was $6{,}331 \pm 2{,}536$ mIU · h/mL which was significantly greater than the value of $2{,}589 \pm 1{,}450$ mIU · h/mL from a previous study using a 4-h dry dwell. The absorption of Epo alfa administered by IP route is thus improved by extending the time the dose resides in a dry peritoneum.

To establish the effectivity of administration of IP Epo in a small amount of fluid in children with renal anemia on CAPD, it was found [365] that administration of Epo in a specially designed bag containing 50 mL NaCl 0.9%. leads to a decrease in the required dose from 262 to 194 U/kg/week while hemoglobin levels remained stable.

To compare the efficacy of IP and SC administration of Epo alfa, a 32-week prospective, randomized, crossover study was designed [366]. Twenty adult PD patients receiving stable doses of SC Epo alfa were enrolled in the study and were randomly assigned to receive either SC or IP Epo at the start of the study. Dose adjustments were made to

maintain baseline hematocrit ± 3%. Following 16 weeks of treatment, patients crossed over to the other route for an additional 16 weeks. IP Epo alfa was administered into an empty peritoneal cavity for approximately 8 h before resuming dialysis. End-of-study IP Epo alfa doses required to maintain target hematocrit were given twice weekly ($n = 1$), once weekly ($n = 11$), or once every other week ($n = 1$). The AUC for IP Epo alfa was larger than for SC administration and the slope of the 16-week dose-requirement curve was greater for IP administration, suggesting greater dose stability for SC administration. Paired analysis indicated greater IP intrapatient dose requirements. The mean difference in SC versus IP doses was 5,000 ± 1,510 U/week. It was concluded that IP Epo alfa may be a suitable alternative for some patients for whom SC dosing is undesirable. Darbepoetin (DarbEpo) is a hyperglycosylated analogue of recombinant human Epo which has an increased terminal $T_{1/2}$ in animal models. Macdougall et al. [367] extended these observations to humans. The single-dose pharmacokinetics of Epo alfa (100 U/kg) and an equivalent peptide mass of DarbEpo were compared following IV bolus in 11 stable PD patients. This was followed by an open-label study to determine the single-dose pharmacokinetics of an equivalent peptide mass of DarbEpo by SC injection in six of these patients. The mean terminal $T_{1/2}$ for IV DarbEpo was threefold longer than for IV Epo (25.3 versus 8.5 h), a difference of 16.8 h. The AUC-time curve was significantly greater for DarbEpo and the clearance was significantly lower (1.6 ± 0.3 versus 4.0 ± 0.3 mL/h/kg). The V_d was similar for both preparations. The mean terminal $T_{1/2}$ for SC DarbEpo was 48.8 h. The Cmax of SC DarbEpo was approximately 10% of that following IV administration, and bioavailability was approximately 37% by the SC route.

To characterize the pharmacokinetics of DarbEpo alfa and covariate relationships in HD and PD patients, Takama et al. [368] recently collected data from 63 HD and 68 PD patients who received IV DarbEpo alfa and applied pharmacokinetic modelling to them. The results of this analysis suggest no dosage regimen change is warranted for DarbEpo alfa in HD and PD patients over the range of distribution of covariates included in this study.

IP administration of iron dextran leads to an efficient absorption of iron. However, severe toxicity to the peritoneal membrane was found, precluding the use of concentrations higher than 2 mg/L [369]. Until now, intraperitoneal administration of iron dextran seems not to be recommendable.

Recombinant Human Growth Hormone (GH)

GH therapy is effective in the treatment of growth failure related to GH resistance among children with chronic renal failure. Recombinant human GH (MW 21,000) was intraperitoneally instilled and showed an immediate absorption with peak serum GH levels obtained between 4 and 8 h following administration [370]. It is highly probable that this drug is, at least partly, transported via the lymphatics. However, the traditional route of administration of GH is SC injection. A study [371] explored the effectiveness and tolerability of IP administration of GH in prepubertal PD patients. Peak serum GH was achieved 4 h after administration and serum $T_{1/2}$ was 4.6 h. The mean height velocity increased from a baseline of 4.6 to 8.5 cm/yr in year 1 and 6.1 cm/yr in year 2. This study suggests, thus, that the IP route of administration of GH can be utilized in the treatment of short stature among children requiring PD therapy.

Relevant to IP therapy with Epo and growth hormone is the study by Schroder et al. [372] who performed an in vitro study in which radiolabeled Epo and recombinant human growth hormone were added to small-volume (50- and 250-mL) dialysis bags. Recovery was measured after 15-min dwells. It was found that the adsorption of Epo and growth hormone was minimal (less than 7%). This finding provides another argument in favor of IP therapy in pediatric PD.

Table 9.12 summarizes data for miscellaneous drugs. An interesting observation was made on the removal of ethosuximide and phenobarbital in an epileptic child by PD [373]. During a peritonitis episode, the daily dialysis time of 8 h (CCPD) was increased to 24 h and the patient developed convulsions. Apparently, a substantial amount of both anticonvulsant medications was removed via the peritoneal dialysate and supplementary doses of both drugs were needed to stabilize the patient.

Leakey et al. [374] described a 3-year-old asthmatic boy who developed acute renal failure, necessitating acute PD. His plasma theophylline concentrations remained therapeutic; yet the child developed the symptoms of theophylline toxicity while undergoing PD. Excessively high plasma concentrations of the principal theophylline metabolite, 1,3-dimethyluric acid, were found. The high concentrations decreased only when renal function recovered. Apparently PD is not able to remove this theophylline metabolite.

In a pharmacokinetic study of flurbiprofen, CAPD patients were used as representative patients with ESRD. Neither flurbiprofen nor its metabolites were detected in the dialysate [375].

PD patients have a decreased clearance of ethinyl oestradiol, leading to slightly higher serum concentrations compared to women with normal renal function [376]. Serum $T_{1/2}$ was 8.4 ± 4.1 versus 3.4 ± 1.6 h in PD patients and normal individuals, respectively, after a single oral dose, and 15.7 ± 3.3 vs. 14.3 ± 2.3 after multiple dosing.

Data on the pharmacokinetics of benzodiazepines in PD are scarce but CAPD patients had longer serum half-lives than controls and HD patients [377]. There were also higher free fractions of the drug. CAPD patients should thus be monitored for side-effects and the dose should be adjusted accordingly. Dose modification may not be necessary in renal failure for midazolam [378], but some reports of sustained activity of midazolam due to accumulation of metabolites in renal failure were reported in ICU patients with renal failure [379]. Zolpidem is an imidazopyridine that differs in structure from benzodiazepines and is approximately 92% protein bound. The free fraction increases to 14.9% in uremic patients, while the V_d increases, and elimination $T_{1/2}$ doubles [380]. Although exact data are not available, dose reduction in CAPD patients seems to be prudent.

Morphine

Conjugation with glucuronic acid represents the major route of biotransformation of morphine and the glucuronides, morphine-3-glucuronide (M3G) and morphine-6-glucuronide (M6G), are eliminated via the kidneys. Chronic renal failure should thus affect the disposition of M3G and M6G. Some patients undergoing long-term PD require pain treatment with morphine and the pharmacokinetics of morphine and its metabolites in CAPD patients after a single IV dose of 10 mg morphine-hydrochloride were investigated [381]. While the systemic clearance of morphine (1,246 $\pm$ 240 mL/min) was in the range observed in patients with normal kidney function, both M3G and M6G showed substantial accumulation. The AUC ratio of M3G:morphine and of M6G:morphine was 5.5 and 13.5 times higher than in patients with normal kidney function. Renal clearances of morphine, M3G, and M6G and dialysate clearances were extremely low. Therefore the accumulation of M6G and M3G in kidney failure is not compensated by CAPD.

Mycophenolate Mofetil (MMF)

Mycophenolate mofetil is a prodrug of the immunosuppressive agent mycophenolic acid (MPA). It is rapidly converted to MPA following oral ingestion. MPA is metabolized to MPA glucuronide (MPAG), which is renally excreted. After initiation of PD in patients with a GFR $<$ 10 mL/min, the AUC substantially decreased. The calculated clearance increased from 8.1 mL/min/kg in nondialyzed patients to 14.6 mL/min/kg in CAPD patients. MPA itself was found in only trace amounts in the dialysate. However, MPAG was found to be removed by PD for up to 2 g/12 h, representing removal of 1.2 g of MPA [223]. MacPhee et al. [382] examined the pharmacokinetics of MMF after an overnight fast of a single oral dose of 1 g in patients on HD or on PD. Plasma concentrations of MPA and MPAG were measured from 0 (predose) to 36 h after administration. The mean AUC for MPA was 55.7 $\pm$ 32.6 mg/L/h for HD patients and 44.7 $\pm$ 14.7 mg/L/h for PD patients, which is similar to the expected values for subjects with normal renal function. The mean Cmax for MPA was lower than would be expected for subjects with normal renal function (16.01 $\pm$ 10.61 mg/L for HD, 11.48 $\pm$ 4.98 mg/L for PD). MPAG clearance was prolonged with AUC approximately five times what would be expected in subjects with normal renal function. No MPA was detectable in HD or PD fluid, but small amounts of MPAG were detected in PD fluid in 3 out of 10 subjects. The accumulation of MPAG may be responsible for the poor gastrointestinal tolerance of this drug in dialysis patients and probably limits the maximum dose of MMF that can be tolerated.

Vitamin D Analogues, Bisphosphonates, and Cinacalcet

A recent excellent comparative review on the pharmacokinetics of vitamin D analogues in patients treated with HD and PD was published by Bailie and Johnson [383]. This review summarizes also the studies performed with the vitamin D analogues in CAPD patients, discussed in the previous edition of this book.

CAPD treatment is associated with peritoneal losses of vitamin D metabolites, contributing to the low serum levels of 25-OH-D3 and 25-OH-D binding capacity; losses of 1,25(OH)2D3 and 24,25(OH)2D3 in the dialysate average 6–8% of the plasma pool per day [384, 385].

IP calcitriol (CT) raises serum calcium and depresses serum PTH more effectively than increasing dialysis fluid calcium [386]. The CT and alfacalcidol should, however, be injected directly through the catheter port and not into the dialysate, as a substantial amount is otherwise adsorbed to the PVC bags [387, 388]. Salusky et al. [388] have studied the pharmacokinetics of CT after IV, oral, and IP administration of 60 ng/kg in CAPD and CCPD patients. The serum CT levels were similar after 24 h for the different routes of administration. The bioavailability of CT (AUC 0–24 h) was 50–60% greater after IV than after oral or IP administration. Comparable results were obtained by Joffe et al. [384], who determined appearance of 1,25-OH vitamin D3 after oral, IV, and IP administration of alfacalcidol [384].

Murakami et al. [389] recently investigated whether transperitoneal absorption of maxacalcitol (22-oxacalcitriol ; OCT) inhibited intact parathyroid hormone (i-PTH) in CAPD patients when the OCT was added to the PD fluid.

After injection of 20 μg of OCT into the peritoneal cavity of CAPD patients, the mean concentration of OCT in PD fluid rapidly decreased, from 25,268 pg/mL at 0 h to 1,694 pg/mL at 2 h and 44.9 pg/mL at 4 h. In contrast, the mean serum OCT level increased from the pretreatment level, which was below the detection limit of the assay, to 656 pg/mL at 0.5 h and a peak of 759 pg/mL at 1 h, and thereafter gradually decreased, to 713.8 pg/mL at 2 h and 555.8 pg/mL at 4 h. Mean i-PTH significantly decreased, to 83.9% of the baseline level at 1 h and thereafter stayed at around 90%. No consistent trends in calcium and phosphate levels were observed in these patients. Injecting OCT into the peritoneal cavity can thus significantly decrease i-PTH levels. Hamada et al. [390] evaluated the stability of physiological activities of CT and OCT in PD bags and to determine the CT or OCT dosage for IP administration: CT 1.5 μg or OCT 10 μg were added to different PD solutions, contained in different containers. Although the levels of CT and OCT in PD bags made of polyvinyl resins decreased by 70–75% immediately after injection, levels in PD bags made of polypropylene resins decreased only slightly. The concentration of CT mixed into the acidic solution in glass containers was stable; the decreased concentration of CT in the PD solution might be due to adsorption onto polyvinyl resins. The results showed good peritoneal transport of OCT but not rapid disappearance, unlike after IV administration. If peritoneal administration of vitamin D derivatives is contemplated, it is important to select the composition of the PD bag resins, the type of vitamin D analog, and time lag to use when deciding the dosage of injectable vitamin D preparations, such as OCT or CT. It appears that IP administration in overnight dwells might be useful for PD patients as a complementary vitamin D preparation.

Biphosphonates are becoming increasingly popular for treatment of osteoporosis, morbus Paget, and hypercalcemia. An excellent review on the use of these drugs including PD patients has been published by Rodd [391]. In general it must be remembered that these drugs are poorly eliminated across the peritoneal membrane after IV administration and that the doses should be reduced as in patients with ESRD without PD.

The major route of elimination of clodronate is renal excretion. Hence, the dose of clodronate should be reduced in renal failure. In one study [392], CAPD removed clodronate poorly from the circulation (7% of administered dose over 24 h), and most of the clearance was attributed to skeletal deposition of the drug. This uptake was related to parathormone levels. Clearance of clodronate after a single IV injection was 2.4 ± 0.6 mL/min. The V_d was 0.49 ± 0.34 L/kg, and elimination $T_{1/2}$ was 16.9 ± 4.7 h. D/P for clodronate was approximately 0.4 after a 6-h dwell. Data on pamidronate in PD are not available, but most probably the same recommendations as for clodronate can be made, and dose adaptations as in patients with severe renal failure should be made.

The pharmacokinetics and dynamics of cinacalcet in ten CAPD patients were recently studied [393]. Following single-dose administration of cinacalcet, there was no evidence of increasing exposure with increasing degree of renal impairment, and the pharmacokinetic profile was similar for all subjects regardless of whether they were receiving HD or PD. Protein binding of cinacalcet was similar in all groups and the level of renal function did not affect the pharmacodynamics (as determined by intact parathyroid hormone and calcium levels). No serious adverse events occurred during either study. Therefore, the dose of cinacalcet does not need to be altered for degree of renal impairment or dialysis modality.

Insulin

Insulin is one of the most commonly administered IP drugs in PD patients. Earlier studies demonstrated that IP insulin is absorbed into the portal venous circulation [394] and that IP insulin leads to a persistent positive portal–systemic difference [395]. A substantial portion (50%) of the portal venous insulin is degraded during first passage through the liver. Such IP treatment appears to improve glucose control and glucose stability without increasing the risk of hypoglycemia [396–400]. The intrapatient variation of the plasma-free insulin was markedly lower with continuous IP than with continuous SC or intramuscular insulin administration [401, 402]. This could be attributed to the considerably smaller insulin depot after IP administration. IP insulin administration is most effective in patients on PD if it is given into an empty peritoneal cavity, at least 30 min before the dialysate is instilled [403]; this creates a high peritoneum to plasma concentration gradient and avoids the adsorption of insulin to the peritoneal fluid bags. When radiolabeled insulin was added to the 2-L dialysate bags only 35% of the dose entered the peritoneal cavity [404]. In contrast, about 84% of 16 U of unlabeled insulin added per bag reached the peritoneal cavity when administrated directly through a port on the Tenckhoff catheter [405]. IP insulin is rapidly absorbed and is detected in the peripheral blood within 15 min of administration, and peak serum insulin levels are observed 30–45 min after administration into an empty peritoneal cavity [235]. These peak values are delayed until 90–120 min when insulin is added to the dialysate [406]. However, due to the partial hepatic inactivation of IP insulin, absorption kinetics and efficacy of IP and systemic insulin are difficult to compare by measurement of peripheral blood insulin levels. Wideroe et al. [235] found that fluid volume and osmolality of the solution in the peritoneal cavity decrease the transport rate of insulin, but not its bioavailability. A better blood glucose regulation after 120 min was found with IP administration in

dialysate as compared to administration into an empty abdomen [235]. A recent review [407] has covered the most important aspects of insulin administration to PD patients.

Peroxisome Proliferator-Activated Receptor (PPAR)γ Agonists

Pharmacokinetic profiles of PPARγ agonists make these drugs potentially suitable for their use in patients with type 2 diabetes and patients with chronic renal failure with and without dialysis (for review see [408]). Furthermore, the available glitazones have an adequate oral bioavailability and are extensively metabolized by the liver. Rosiglitazone is mainly metabolized by cytochrome P450 (CYP) 2C8 into inactive metabolites. Less than 1% of the parent drug appears in the urine in unchanged form [408, 409]. Both total and unbound plasma concentrations of rosiglitazone after a single 8-mg oral dose were not affected by the presence of mild, moderate, and severe renal insufficiency, thus indicating that the starting dose of rosiglitazone needs not be adjusted in patients with renal impairment [410]. Moreover, similar values of AUC–time curve, maximum Cmax concentrations, and $T_{1/2}$ were observed in a group of ten HD patients (nondialysis day) in comparison with a group of healthy individuals after a single 8 mg oral dose of rosiglitazone. Metabolites of pioglitazone are more active and are excreted predominantly in the bile. Both pioglitazone as its metabolites do not accumulate in chronic renal failure. The pharmacokinetic profile of pioglitazone was similar in healthy subjects and in patients with moderate and severe renal failure [411].

PPARγ agonists therapy in dialysis patients has shown adequate safety and tolerance profiles. In the study of Manley and Allcock [412], there were three hospitalizations for new or worsening congestive heart failure (CHF) in a group of 40 HD patients with type 2 diabetes treated with glitazones. Interdialytic weight gain significantly increased, 0.3 kg in rosiglitazone-treated patients. Rosiglitazone therapy has been well tolerated in both diabetic and nondiabetic uremic patients on CAPD. Edema in lower extremities and weight gain in approximately 2% of the patients have been reported [413, 414]. Altogether, these results suggest that PPARγ agonists might be an adequate alternative in the antihyperglycemic therapy of diabetic patients with CRF, regardless of the treatment used for renal failure. According to the American Heart Association and the American Diabetes Association recommendations, in patients without clinical data of CHF, but with one or more risk factors for its development, as it is the case in CRF patients, therapy with glitazones should be initiated at low doses, i.e, rosiglitazone 4 mg/day and pioglitazone 15 mg/day. The increases in dose should be gradual, with tight monitoring for signs of excessive weight gain, peripheral edema, and/or CHF [415].

Heparin

Heparin has an average MW of 15 kDa and consists of a heterogeneous group of anionic mucopolysaccharides, called GAGs (see Part I of this chapter). Heparin is the most frequently used drug in PD, for the purpose of preventing fibrin formation and catheter obstruction. Furman et al. [416] performed a pharmacokinetic study of IP heparin, assayed as the activated-partial-thromboplastin time (APTT) of dialysate added to control plasma. The $T_{1/2}$ of disappearance from the peritoneal cavity ranged between 8.26 and 12.77 h. Systemic blood coagulation was unaffected by a single IP dose of 10,000 U of heparin. Other investigators [417, 418] showed that heparin did transfer across the rabbit peritoneal membrane and, to a slight extent, in CAPD patients [419]. In a CAPD patient with deep-vein thrombosis, long-term IP application of low-molecular-weight (LMW) heparin in a dose of 8,000 antifactor Xa units/2 L, resulted in adequate and therapeutic plasma levels as measured by antifactor Xa units [420]. IP administration of heparin (1,000–2,500 U/L) without addition of ATIII is sufficient for prevention of IP fibrin formation in CAPD patients [419, 421].

Enoxaparin

Brophy et al. [422] studied the pharmacokinetics and pharmacodynamics of enoxaparin in healthy volunteers and HD and PD subjects. Antifactor Xa activity estimated the pharmacokinetics, whereas thrombin generation time (TGT) estimated the pharmacodynamics. Enoxaparin 1 mg/kg was given SC to all subjects. Antifactor Xa max and AUC(0-12) were similar between groups, but the TGTmax was significantly greater in the dialysis groups. The TGT remained significantly more prolonged throughout the 12-h study period, and there was a trend toward greater TGT AUC (0–12) for both dialysis groups. These results suggest that in dialysis patients, there may be accumulation of active heparin metabolites that are undetected by the antifactor Xa assay. Therefore, these subjects exhibit greater thrombin generation time prolongation despite similar antifactor Xa exposure.

Thrombin Inhibitors

Ximelagatran is an oral direct thrombin inhibitor and may be used as an anticoagulant for the prevention and treatment of thromboembolic disease. After oral administration, ximelagatran is rapidly absorbed and bioconverted to its active form, melagatran. Eriksson et al. [423] studied the pharmacokinetics of this drug in volunteers with norma and impaired renal function. All volunteers received, in a randomized sequence, a 3-mg SC injection of melagatran and a 24-mg immediate-release tablet of ximelagatran. In renal failure, the AUC and the $T_{1/2}$ of melagatran were significantly higher than in the group with normal renal function. This result was related to the decreased renal clearance: 12.5 and 81.3 mL/min after SC administration of melagatran and 14.3 and 107 mL/min after oral administration of ximelagatran, respectively. Ximelagatran and melagatran were well tolerated in both groups. It was concluded that after administration of SC melagatran and oral ximelagatran, subjects with severe renal impairment had significantly higher melagatran exposure and longer $T_{1/2}$ because of lower renal clearances of melagatran compared with the control group with normal renal function. These results suggest that a decrease in dose and/or an increase in the administration interval in patients with severe renal impairment would be appropriate. Pharmacokinetic studies in PD have not yet been performed with these drugs.

Desferrioxamine

A pharmacokinetic study of desferrioxamine and its iron and aluminium chelates has been performed in CAPD patients [424]. Desferrioxamine (10 mg/kg) was administered either intramuscularly or intraperitoneally. The AUC calculated from 0 to 12 h was about 20% lower after the IP than after the intramuscular administration. An advantage of the IP administration was, however, the progressive increase in plasma concentrations, without an unduly high peak. The fact that 8–12 h after administration the concentrations of desferrioxamine in plasma and peritoneal fluid were approximately the same, is consistent with the low binding of desferrioxamine to plasma proteins.

Desferrioxamine was given IV and IP in a CAPD patient in order to remove iron. Forty-five percent of the total amount instilled was recovered in the outflow dialysate [425]. An IP dose of 750 mg/day or 1,250 mg on alternate days led to removal of 73 and 39.6 mg iron, respectively, as compared with 75 mg removal per week after an IV dose of 1,500 mg thrice weekly. Several authors have used IP desferrioxamine successfully to remove aluminium in PD patients [426–428]. IP doses of 40 mg/kg were used over a 10-h dwell in one study [427] and 0.5 g into each 2 L dialysate to a total dose of 6 g was applied in another study [429]. In the latter study the aluminium clearance with desferrioxamine was 3.1 versus 2.5 mL/min without desferrioxamine. The enhanced removal of aluminium by PD persists for several days after a single administration of the chelator.

Anticancer Drugs

For cancers that have disseminated to the peritoneal surfaces, IP chemotherapy results in high drug concentrations locally with low systemic toxicity. Using a rat model, Mohamed et al. [430] compared the pharmacokinetics and tissue absorption of paclitaxel infused intraperitoneally in two isotonic carrier solutions: 1.5% dextrose PD solution and hetastarch (6% hydroxyethyl starch), a high-molecular-weight solution. The mean total quantity of drug remaining in the peritoneal cavity was significantly greater with hetastarch at 12 and 18 h. There was a 105% increase in the AUC ratio of peritoneal fluid to plasma paclitaxel concentrations with hetastarch versus PD. The use of IP paclitaxel with hetastarch carrier solution provides a pharmacologic advantage for a local-regional killing of residual tumor cells with decreased systemic toxicity. Similar results were obtained with docetaxel [431].

Melphalan

The use of heated intraoperative IP melphalan may provide a pharmacokinetic and clinical advantage in a group of gastrointestinal cancer patients who cannot be made cancer-free with cytoreductive surgery. Thirteen patients with residual disease following cytoreductive surgery for peritoneal carcinomatosis received IP melphalan (70 mg/m^2) in 3 l of 1.5% dextrose PD solution at 41–42°C for 90 min [432]. During the 90 min of treatment 87.2 ± 4.3% of the drug was absorbed from the perfusate/peritoneal fluid and 11.9 ± 2.1% was excreted in the urine. The AUC ratio of peritoneal fluid to plasma was 33.3 ± 11.8 with an average peak plasma concentration of 0.82 ± 0.24 μg/mL occurring at 28.5 ± 13.1 min. Concentrations of melphalan in tumor nodules on the peritoneal surface were approximately ten times higher than in plasma with an average peak concentration of 7.2 ± 4.2 μg/g. It was concluded that approximately 90% of the drug was absorbed during the 90-min procedure with a 30 times greater exposure of drug at the peritoneal

surfaces than in the blood. These data demonstrate that heated intraoperative IP melphalan could have a significant impact on the treatment of peritoneal surface malignancies.

PD and Removal of Contrast Media

To examine the elimination of iomeprol, its safety in clinical use, and its peritoneal permeability in CAPD patients with variable degrees of RRF, a nonrandomized comparative study was undertaken in CAPD and HD patients [433]. In all CAPD patients, plasma iomeprol clearance was markedly slow, with a biological $T_{1/2}$ of over 32 h. Over 80% of plasma iomeprol was eliminated during the 4-h HD. The plasma iomeprol elimination rate was significantly higher from 4 h after the iomeprol administration in CAPD patients with RRF (creatinine clearance of 3.8 mL/min), compared to those with a creatinine clearance of 0.6 mL/min. However, $T_{1/2}$ in patients with RRF was over 24 h. D/P creatinine was significantly correlated with D/P iomeprol. In view of the prolonged elimination rate of iomeprol in CAPD patients both with and without RRF, a HD procedure or intensive PD just after the use of iomeprol may be advisable to promptly remove circulating iomeprol.

Another contrast medium, gadodiamide was studied by Joffe et al. [434] in patients with severely reduced renal function (GFR, 2–10 mL/min), patients on HD, and patients on CAPD. Gadodiamide injection caused no changes in renal function. In patients with severely reduced renal function, the elimination $T_{1/2}$ of gadodiamide was prolonged (34.3 h $\pm$ 22.9) compared with data in healthy volunteers (1.3 h $\pm$ 0.25). An average of 65% of the gadodiamide injected was eliminated during a HD session, but only after 22 days of CAPD, 69% of the total amount of gadodiamide was excreted, reflecting the low peritoneal clearance. It was concluded that gadodiamide is dialyzable and can safely be used in patients with severely impaired renal function or those undergoing HD or CAPD.

Homocysteine and Vitamins

The amount of total homocysteine eliminated by PD and its relationship to peritoneal transport characteristics in CAPD have been explored by Vychytil et al. [435]. A significant influence of plasma total homocysteine concentrations, of the daily dialysate effluent volume and of the D/P creatinine on peritoneal elimination of total homocysteine was found. The daily peritoneal excretion of total homocysteine was 5.27 $\pm$ 2.81 mg. There was a positive linear association of the daily total homocysteine elimination with plasma total homocysteine concentrations. A significant linear correlation was observed between D/P creatinine and D/P total homocysteine, D/P free homocysteine, as well as D/P protein-bound homocysteine. The peritoneal elimination of total homocysteine primarily depends thus on the plasma total homocysteine concentration and elevated total homocysteine plasma levels cannot be reduced efficiently by PD.

Boeschoten et al. [436] have summarized earlier studies on vitamin status and vitamin losses in the dialysate in IPD and CAPD patients. They have performed a more complete analysis of plasma and 24 h dialysate losses of vitamin A, B1, B2, B6, B12, C, folic acid, E, and β-carotene in 44 CAPD patients. Vitamins B12, A, and E and carotenoids were not detectable in dialysate. In contrast, vitamins B2, B3, B6, C, and folic acid were excreted in the 24 h dialysate in amounts higher than in 24 h urine of individuals with normal renal function. The loss of vitamin B1 in dialysate was low. The authors recommend vitamin supplementations in CAPD patients for vitamins B1, B6, C, and folic acid.

References

1. Flessner MF: Peritoneal ultrafiltration: mechanisms and measures. Contrib Nephrol 2006; 150: 28–36.
2. Ni J, Verbavatz JM, Rippe A, Boisde I, Moulin P, Rippe B, Verkman AS, Devuyst O: Aquaporin-1 plays an essential role in water permeability and ultrafiltration during peritoneal dialysis. Kidney Int 2006; 69: 1518–1525.
3. Charonis AS, Tsilibary PC, Kramer RH, Wissig SL: Localization of heparan sulfate proteoglycan in the basement membrane of continuous capillaries. Microvasc Res 1983; 26: 108–115.
4. Charonis AS, Wissig SL: Anionic sites in basement membranes. Differences in their electrostatic properties in continuous and fenestrated capillaries. Microvasc Res 1983; 25: 265–285.
5. Leypoldt JK, Henderson LW: Molecular charge influences transperitoneal macromolecule transport. Kidney Int 1993; 43: 837–844.
6. Gotloib L, Shostack A, Jaichenko J: Ruthenium-red-stained anionic charges of rat and mice mesothelial cells and basal lamina: the peritoneum is a negatively charged dialyzing membrane. Nephron 1988; 48: 65–70.
7. Shostak A, Gotloib L: Increased peritoneal permeability to albumin in streptozotocin diabetic rats. Kidney Int 1996; 49: 705–714.
8. Shostak A, Wajsbrot V, Gotloib L: Protective effect of aminoguanidine upon capillary and submesothelial anionic sites. Microvasc Res 2001; 61: 166–178.
9. Nakao T, Ogura M, Takahashi H, Okada T: Charge-affected transperitoneal movement of amino acids in CAPD. Perit Dial Int 1996; 16 Suppl 1: S88–S90.

10. Buis B, Koomen GC, Imholz AL, Struijk DG, Reddingius RE, Arisz L, Krediet RT: Effect of electric charge on the transperitoneal transport of plasma proteins during CAPD. Nephrol Dial Transplant 1996; 11: 1113–1120.
11. Paniagua R, Amato D, Vonesh E, Correa-Rotter R, Ramos A, Moran J, Mujais S: Effects of increased peritoneal clearances on mortality rates in peritoneal dialysis: ADEMEX, a prospective, randomized, controlled trial. J Am Soc Nephrol 2002; 13: 1307–1320.
12. Paniagua R, Amato D, Vonesh E, Guo A, Mujais S: Health-related quality of life predicts outcomes but is not affected by peritoneal clearance: The ADEMEX trial. Kidney Int 2005; 67: 1093–1104.
13. Devuyst O, Topley N, Williams JD: Morphological and functional changes in the dialysed peritoneal cavity: impact of more biocompatible solutions. Nephrol Dial Transplant 2002; 17 (suppl 3): 12–15.
14. Mortier S, De Vriese AS, Lameire N: Recent concepts in the molecular biology of the peritoneal membrane – implications for more biocompatible dialysis solutions. Blood Purif 2003; 21: 14–23.
15. Margetts PJ, Bonniaud P: Basic mechanisms and clinical implications of peritoneal fibrosis. Perit Dial Int 2003; 23: 530–541.
16. Margetts PJ, Brimble KS: Peritoneal dialysis, membranes and beyond. Curr Opin Nephrol Hypertens 2006; 15: 571–576.
17. Ronco C, Feriani M, Chiaramonte S, Brendolan A, Milan M, La GG: Peritoneal blood flow: does it matter? Perit Dial Int 1996; 16 (suppl 1): S70–S75.
18. Ronco C, Brendolan A, Crepaldi C, Conz P, Bragantini L, Milan M, La GG: Ultrafiltration and clearance studies in human isolated peritoneal vascular loops. Blood Purif 1994; 12: 233–242.
19. Aune S: Transperitoneal exchange. II. Peritoneal blood flow estimated by hydrogen gas clearance. Scand J Gastroenterol 1970; 5: 99–104.
20. Ronco C, Feriani M, Chiaramonte S, LaGreca G: Pathophysiology of peritoneal ultrafiltration. Perit Dial Int 1990; 10: 119–126.
21. Grzegorzewska AE, Antoniewicz K: An indirect estimation of effective peritoneal capillary blood flow in peritoneally dialyzed uremic patients. Perit Dial Int 1993; 13 (suppl 2): S39–S40.
22. Ronco C: Factors affecting hemodialysis and peritoneal dialysis efficiency. Contrib Nephrol 2006; 150: 1–12.
23. Douma CE, de Waart DR, Struijk DG, Krediet RT: Effect of amino acid based dialysate on peritoneal blood flow and permeability in stable CAPD patients: a potential role for nitric oxide? Clin Nephrol 1996; 45: 295–302.
24. Douma CE, de Waart DR, Struijk DG, Krediet RT: The nitric oxide donor nitroprusside intraperitoneally affects peritoneal permeability in CAPD. Kidney Int 1997; 51: 1885–1892.
25. Douma CE, Hiralall JK, de Waart DR, Struijk DG, Krediet RT: Icodextrin with nitroprusside increases ultrafiltration and peritoneal transport during long CAPD dwells. Kidney Int 1998; 53: 1014–1021.
26. Felt J, Richard C, McCaffrey C, Levy M: Peritoneal clearance of creatinine and inulin during dialysis in dogs: effect of splanchnic vasodilators. Kidney Int 1979; 16: 459–469.
27. Renkin EM: Exchange of substances through capillary walls. In CIBA Foundation Symposium. Edited by Wolstenholme GEW. Boston: Little, Brown; 1969: 50–66.
28. Pietrzak I, Hirszel P, Shostak A, Welch PG, Lee RE, Maher JF: Splanchnic volume, not flow rate, determines peritoneal permeability. ASAIO Trans 1989; 35: 583–587.
29. Shostack A, Hirszel P, Chakrabarti E, Maher JF: Dihydroergotamine lowers peritoneal transfer rates; a hypovolemic transport decrease. In Ambulatory Peritoneal Dialysis. Edited by Avram MM, Giordano C. New York: Plenum; 1990: 79–82.
30. Maher JF, Bennett RR, Hirszel P, Chakrabarti E: The mechanism of dextrose-enhanced peritoneal mass transport rates. Kidney Int 1985; 28: 16–20.
31. White R, Korthuis R, Granger DN: The peritoneal microcirculation in peritoneal dialysis. In The Textbook of Peritoneal Dialysis. Edited by Gokal R, Nolph KD. Dordrecht: Kluwer; 1994: 45–68.
32. Flessner MF: Small-solute transport across specific peritoneal tissue surfaces in the rat. J Am Soc Nephrol 1996; 7: 225–233.
33. Ronco C: The "nearest capillary" hypothesis: a novel approach to peritoneal transport physiology. Perit Dial Int 1996; 16: 121–125.
34. Gutman RA, Nixon WP, McRae RL, Spencer HW: Effect of intraperitoneal and intravenous vasoactive amines on peritoneal dialysis: study in anephric dogs. Trans Am Soc Artif Intern Organs 1976; 22: 570–574.
35. Parker HR, Schroeder JP, Henderson LW: Influence of dopamine and regitine on peritoneal dialysisin unanesthetized dogs [abstract]. Trans Am Soc Artif Intern Organs 1978; 7: 43 (abstract).
36. Chan MK, Varghese Z, Baillod RA, Moorhead JF: Peritoneal dialysis: effect of intraperitoneal dopamine. Dial Transplant 1980; 9: 380–384.
37. Hirszel P, Lasrich M, Maher JF: Divergent effects of catecholamines on peritoneal mass transport. Trans Am Soc Artif Intern Organs 1979; 25: 110–113.
38. Hirszel P, Lasrich M, Maher JF: Augmentation of peritoneal mass transport by dopamine: comparison with norepinephrine and evaluation of pharmacologic mechanisms. J Lab Clin Med 1979; 94: 747–754.
39. Goldberg LI: Cardiovascular and renal actions of dopamine: potential clinical applications. Pharmacol Rev 1972; 24: 1–29.
40. Maher JF, DiPaolo N, Shostack A, Hirszel P: Pharmacology of peritoneal transport. In Advances in CAPD. Edited by Khanna R, Nolph KD, Prowant B, Twardowski Z, Oreopoulos D. Toronto: University of Toronto Press; 1987: 3–6.
41. Selgas R, Munos IM, Conesa Jea: Endogenous sympathetic activity in CAPD patients: its relationsip to peritoneal diffusion capacity. Perit Dial Bull 1986; 6: 205–208.
42. Stefanidis I, Zarogiannis S, Hatzoglou C, Liakopoulos V, Kourti P, Poultsidi A, Mertens PR, Gourgoulianis K, Molyvdas PA: Enhancement of the transmesothelial resistance of the parietal sheep peritoneum by epinephrine in vitro: ussing-type chamber experiments. Artif Organs 2005; 29: 919–922.
43. Zarogiannis S, Stefanidis I, Hatzoglou C, Liakopoulos V, Gourgoulianis K, Molyvdas PA: Effect of adrenaline on the electrophysiologic profile of isolated visceral sheep peritoneum. Adv Perit Dial 2004; 20: 23–26.
44. Rocha e Silva M, Rosenberg M: The release of vasopressin in response to haemorrhage and its role in the mechanism of blood pressure regulation. J Physiol 1969; 202: 535–557.
45. Hare HG, Valtin H, Gosselin RE: Effect of drugs on peritoneal dialysis in the dog. J Pharmacol Exp Ther 1964; 145: 122–129.
46. Henderson LW, Kintzel JE: Influence of antidiuretic hormone on peritoneal membrane area and permeability. J Clin Invest 1971; 50: 2437–2443.

47. Rubin J, Adair C, Bower J: A double blind trial of dipyridamole in CAPD. Am J Kidney Dis 1985; 5: 262–266.
48. Shear L, Harvey JD, Barry KG: Peritoneal sodium transport: enhancement by pharmacologic and physical agents. J Lab Clin Med 1966; 67: 181–188.
49. Go M, Kumano K, Sakai T: [Effect of angiotensin II(AII) on peritoneal transport during peritoneal dialysis in rat]. Nippon Jinzo Gakkai Shi 1992; 34: 921–929.
50. Wayland H: Transmural and interstitial molecular transport. In Proc Int Symp Continous Ambulatory Peritoneal Dialysis. 1980: 18–27.
51. Miller FN, Nolph KD, Harris PD, Rubin J, Wiegman DL, Joshua IG, Twardowski ZJ, Ghods AJ: Microvascular and clinical effects of altered peritoneal dialysis solutions. Kidney Int 1979; 15: 630–639.
52. Nolph KD: Peritoneal anatomy and transport physiology. In Replacement of Renal Funcion by Dialysis. Edited by Drukker W, Parsons FM, Maher JF. The Hague: Martinus Nijhoff; 1983: 440–456.
53. Carlsson O, Rippe B: Enhanced peritoneal diffusion capacity of 51Cr-EDTA during the initial phase of peritoneal dialysis dwells: role of vasodilatation, dialysate 'stirring', and of interstitial factors. Blood Purif 1998; 16: 162–170.
54. Breborowicz A, Knapowski J: Local anesthetic bupivicaine increases the transperitoneal trasport of solutes. Perit Dial Bull 1984; 4: 224–228.
55. Brown ST, Ahearn DJ, Nolph KD: Reduced peritoneal clearances in scleroderma increased by intraperitoneal isoproterenol. Ann Intern Med 1973; 78: 891–894.
56. Nolph KD, Miller L, Husted FC, Hirszel P: Peritoneal clearances in scleroderma and diabetes mellitus: effects of intraperitioneal isoproterenol. Int Urol Nephrol 1976; 8: 161–169.
57. Nolph KD, Ghods AJ, Van SJ, Brown PA: The effects of intraperitoneal vasodilators on peritoneal clearances. Trans Am Soc Artif Intern Organs 1976; 22: 586–594.
58. Maher JF, Shea C, Cassetta M, Hohnadel DC: Isoproterenol enhancement of peritoneal permeability. J Dial 1977; 1: 319-331.
59. Thulin L, Samnegard H: Circulatory effects of gastrointestinal hormones and related peptides. Acta Chir Scand Suppl 1978; 482: 73–74.
60. Maher JF, Hirszel P, Lasrich M: Effects of gastrointestinal hormones on transport by peritoneal dialysis. Kidney Int 1979; 16: 130–136.
61. Biber B, Fara J, Lundgren O: Vascular reactions in the small intestine during vasodilatation. Acta Physiol Scand 1973; 89: 449–456.
62. Fara JW: Effects of gastrointestinal hormones on vascular smooth muscle. Am J Dig Dis 1975; 20: 346–353.
63. Hirszel P, Maher JF, LeGrow W: Increased peritoneal mass transport with glucagon acting at the vascular surface. Trans Am Soc Artif Intern Organs 1978; 24: 136–138.
64. Alvarez-Guerra M, Hannaert P, Hider H, Chiavaroli C, Garay RP: Vascular permeabilization by intravenous arachidonate in the rat peritoneal cavity: antagonism by antioxidants. Eur J Pharmacol 2003; 466: 199–205.
65. Topley N, Petersen MM, Mackenzie R, Neubauer A, Stylianou E, Kaever V, Davies M, Coles GA, Jorres A, Williams JD: Human peritoneal mesothelial cell prostaglandin synthesis: induction of cyclooxygenase mRNA by peritoneal macrophage-derived cytokines. Kidney Int 1994; 46: 900–909.
66. Messina EJ, Kaley G: Microcirculatory responses to prostacyclin and PGE2 in the rat cremaster muscle. Adv Prostaglandin Thromboxane Res 1980; 7: 719–722.
67. Nakano J, McCurdy JR: Hemodynamic effects of prostaglandins E1, A1 and F2-alpha in dogs. Proc Soc Exp Biol Med 1968; 128: 39–42.
68. Vane JR, McGiff JC: Possible contributions of endogenous prostaglandins to the control of blood pressure. Circ Res 1975; 36: 68–75.
69. Maher JF, Hirszel P, Lasrich M: Modulation of peritoneal transport rates by prostaglandins. Adv Prostaglandin Thromboxane Res 1980; 7: 695–700.
70. Maher JF, Hirszel P, Lasrich M: Prostaglandin effects on peritoneal transport. In Proc 2nd Symp Perit Dial. 1981: 65–69.
71. Mileti M, Bufano G, Scaravonati P, Pecchini F, Carnevale G, Lanzarini P: Effect of indomethacin on the peritoneum of rabbits on peritoneal dialysis. Perit Dial Bull 1983; 3: 194–195.
72. Hirszel P, Lasrich M, Maher JF: Arachidonic acid increases peritoneal clearances. Trans Am Soc Artif Intern Organs 1981; 27: 61–63.
73. Steinhauer HB, Schollmeyer P: Prostaglandin-mediated loss of proteins during peritonitis in continuous ambulatory peritoneal dialysis. Kidney Int 1986; 29: 584–590.
74. Zemel D, Struijk DG, Dinkla C, Stolk LM, ten BI, Krediet RT: Effects of intraperitoneal cyclooxygenase inhibition on inflammatory mediators in dialysate and peritoneal membrane characteristics during peritonitis in continuous ambulatory peritoneal dialysis. J Lab Clin Med 1995; 126: 204–215.
75. Londos C, Cooper DM, Wolff J: Subclasses of external adenosine receptors. Proc Natl Acad Sci U S A 1980; 77: 2551–2554.
76. Maher JF, Cassetta M, Shea C, Hohnadel DC: Peritoneal dialysis in rabbits. A study of transperitoneal theophylline flux and peritoneal permeability. Nephron 1978; 20: 18–23.
77. Brown EA, Kliger AS, Goffinet J, Finkelstein FO: Effect of hypertonic dialysate and vasodilators on peritoneal dialysis clearances in the rat. Kidney Int 1978; 13: 271–277.
78. Shostak A, Chakrabarti E, Hirszel P, Maher JF: Effects of histamine and its receptor antagonists on peritoneal permeability. Kidney Int 1988; 34: 786–790.
79. Lal SM, Nolph KD, Moore HL, Khanna R: Effects of calcium channel blockers (verapamil, diltiazem) on peritoneal transport. ASAIO Trans 1986; 32: 564–566.
80. Kumano K, Go M, Ning H, Sakai T: Effects of vasodilators on peritoneal solute and fluid transport in rat peritoneal dialysis. Adv Perit Dial 1996; 12: 27–32.
81. Balaskas EV, Dombros N, Savidis N, Pidonia I, Laziridis A, Tourkantonis A: Nifedipine intraperitoneally increases ultrafiltrationin CAPD patients. In Current Concepts in Peritoneal Dialysis. Edited by Ota K, Maher JF, Winchester JF, Hirszel P. Amsterdam: Excerpta Medica; 1992: 427–432.
82. Vargemezis V, Pasadakis P, Thodis E: Effect of a calcium antagonist (verapamil) on the permeability of the peritoneal membrane in patients on continuous ambulatory peritoneal dialysis. Blood Purif 1989; 7: 309–313.
83. Favazza A, Motanaro D, Messa P, Antonucci F, Gropuzzo M, Mioni G: Peritoneal clearances in hypertensive CAPD patients after oral administration of clonidine, enalapril, and nifedipine. Perit Dial Int 1992; 12: 287–291.

84. Rojas-Campos E, Cortes-Sanabria L, Martinez-Ramirez HR, Gonzalez L, Martin-del-Campo F, Gonzalez-Ortiz M, Cueto-Manzano AM: Effect of oral administration of losartan, prazosin, and verapamil on peritoneal solute transport in continuous ambulatory peritoneal dialysis patients. Perit Dial Int 2005; 25: 576–582.
85. Lal SM, Moore HL, Nolph KD: Effects of intraperitoneal captopril on peritoneal transport in rats. Perit Dial Bull 1987; 7: 80–85.
86. Ripley EB, Gehr TW, Kish CW, Sica DA: Hormonal, blood pressure, and peritoneal trasport response to short-term ACE inhibition. Perit Dial Bull 1994; 14: 378–383.
87. Coronel F, Hortal L, Naranjo P, Cruceyra A, Barrientos A: Captopril, proteinuria and peritoneal protein leakage in diabetic patients. Nephron 1989; 51: 443.
88. Coronel F, Berni A, Cigarran S, Calvo N, Herrero JA: Effects of angiotensin II receptor blocker (irbesartan) on peritoneal membrane functions. Adv Perit Dial 2004; 20: 27–30.
89. Ishida Y, Tomori K, Nakamoto H, Imai H, Suzuki H: Effects of antihypertensive drugs on peritoneal vessels in hypertensive dogs with mild renal insufficiency. Adv Perit Dial 2003; 19: 10–14.
90. Duman S, Wieczorowska-Tobis K, Styszynski A, Kwiatkowska B, Breborowicz A, Oreopoulos DG: Intraperitoneal enalapril ameliorates morphologic changes induced by hypertonic peritoneal dialysis solutions in rat peritoneum. Adv Perit Dial 2004; 20: 31–36.
91. Kyuden Y, Ito T, Masaki T, Yorioka N, Kohno N: Tgf-beta1 induced by high glucose is controlled by angiotensin-converting enzyme inhibitor and angiotensin II receptor blocker on cultured human peritoneal mesothelial cells. Perit Dial Int 2005; 25: 483–491.
92. Duman S, Sen S, Duman C, Oreopoulos DG: Effect of valsartan versus lisinopril on peritoneal sclerosis in rats. Int J Artif Organs 2005; 28: 156–163.
93. Imai H, Nakamoto H, Ishida Y, Yamanouchi Y, Inoue T, Okada H, Suzuki H: Renin-angiotensin system plays an important role in the regulation of water transport in the peritoneum. Adv Perit Dial 2001; 17: 20–24.
94. Duman S, Sen S, Sozmen EY, Oreopoulos DG: Atorvastatin improves peritoneal sclerosis induced by hypertonic PD solution in rats. Int J Artif Organs 2005; 28: 170–176.
95. Wang T, Cheng HH, Heimburger O, Chen C, Bergstrom J, Lindholm B. : Intraperitoneal atrial natriuretic peptide increases peritoneal fluid and solute removal. Kidney Int 2001; 60: 513–519.
96. Breborowicz A, Knapowski J: Augmentation of peritoneal dialysis clearance with procaine. Kidney Int 1984; 26: 392–396.
97. Mortier S, De Vriese AS, Van de Voorde J, Schaub TP, Passlick-Deetjen J, Lameire NH: Hemodynamic effects of peritoneal dialysis solutions on the rat peritoneal membrane: role of acidity, buffer choice, glucose concentration, and glucose degradation products. J Am Soc Nephrol 2002; 13: 480–489.
98. Devuyst O, Nielsen S, Cosyns JP, Smith BL, Agre P, Squifflet JP, Pouthier D, Goffin E: Aquaporin-1 and endothelial nitric oxide synthase expression in capillary endothelia of human peritoneum. Am J Physiol 1998; 275: H234–H242.
99. Combet S, Balligand JL, Lameire N, Goffin E, Devuyst O: A specific method for measurement of nitric oxide synthase enzymatic activity in peritoneal biopsies. Kidney Int 2000; 57: 332–338.
100. Davenport A, Fernando RL, Varghese Z: Intraperitoneal nitric oxide production in patients treated by continuous ambulatory peritonal dialysis. Blood Purif 2004; 22: 216–223.
101. Douma CE, de Waart DR, Struijk DG, Krediet RT: Are phospholipase A2 and nitric oxide involved in the alterations in peritoneal transport during CAPD peritonitis? J Lab Clin Med 1998; 132: 329–340.
102. Baylis C, Vallance P: Measurement of nitrite and nitrate levels in plasma and urine–what does this measure tell us about the activity of the endogenous nitric oxide system? Curr Opin Nephrol Hypertens 1998; 7: 59–62.
103. Akubeu J, Stochs SJ: Endrin-induced production of nitric oxide by rat peritoneal macrophages. Toxicol Lett 1998; 62: 311–316.
104. McCall TB, Palmer RM, Moncada S: Induction of nitric oxide synthase in rat peritoneal neutrophils and its inhibition by dexamethasone. Eur J Immunol 1991; 21: 2523–2527.
105. Moncada S, Higgs EA: Endogenous nitric oxide: physiology, pathology and clinical relevance. Eur J Clin Invest 1991; 21: 361–374.
106. Combet S, Van LM, Moulin P, Piech A, Verbavatz JM, Goffin E, Balligand JL, Lameire N, Devuyst O: Regulation of aquaporin-1 and nitric oxide synthase isoforms in a rat model of acute peritonitis. J Am Soc Nephrol 1999; 10: 2185–2196.
107. Douma CE, de Waart DR, Zemel D, Imholz AL, Koomen GC, Struijk DG, Krediet RT: Nitrate in stable CAPD patients and during peritonitis. Adv Perit Dial 1995; 11: 36–40.
108. Combet S, Ferrier ML, Van LM, Stoenoiu M, Moulin P, Miyata T, Lameire N, Devuyst O: Chronic uremia induces permeability changes, increased nitric oxide synthase expression, and structural modifications in the peritoneum. J Am Soc Nephrol 2001; 12: 2146–2157.
109. Combet S, Miyata T, Moulin P, Pouthier D, Goffin E, Devuyst O: Vascular proliferation and enhanced expression of endothelial nitric oxide synthase in human peritoneum exposed to long-term peritoneal dialysis. J Am Soc Nephrol 2000; 11: 717–728.
110. Ni J, Moulin P, Gianello P, Feron O, Balligand JL, Devuyst O: Mice that lack endothelial nitric oxide synthase are protected against functional and structural modifications induced by acute peritonitis. J Am Soc Nephrol 2003; 14: 3205–3216.
111. Ni J, Cnops Y, McLoughlin RM, Topley N, Devuyst O: Inhibition of nitric oxide synthase reverses permeability changes in a mouse model of acute peritonitis. Perit Dial Int 2005; 25 (suppl 3): S11–S14.
112. Breborowicz A, Wieczorowska-Tobis K, Korybalska K, Polubinska A, Radkowski M, Oreopoulos DG: The effect of a nitric oxide inhibitor (L-NAME) on peritoneal transport during dialysis in rats. Perit Dial Int 1998; 18: 188–192.
113. Sano N, Sato S, Hashimoto K: Differences among dipyridamole, carbochromen and lidoflazine in responses of the coronary and the renal arteries. Jpn J Pharmacol 1972; 22: 857–865.
114. Maher JF, Hirszel P, Abraham JE, Galen MA, Chamberlin M, Hohnadel DC: The effect of dipyridamole on peritoneal mass transport. Trans Am Soc Artif Intern Organs 1977; 23: 219–224.
115. Ryckelynck JP, Pierre D, De MA, Rottembourg J: [Improvement of peritoneal clearance by dipyridamole]. Nouv Presse Med 1978; 7: 472.
116. Reams JP, Young M, Sorkin M, Twardowski ZJ, Gloor H, Nolph KD: Effects of dipyridamole on peritoneal clearances. Uremia Invest 1986; 9: 27–33.
117. Maher JF, Hirszel P: Augmentation of peritoneal clearances by drugs. In Proc Int Symp Cont Amb Perit Dial. Edited by Legrain M. Amsterdam: Excerpta Medica; 1980: 42–46.

118. Alavi N, Lianos E, Andres G, Bentzel CJ: Effect of protamine on the permeability and structure of rat peritoneum. Kidney Int 1982; 21: 44–53.
119. Galdi P, Shostak A, Jaichenko J, Fudin R, Gotloib L: Protamine sulfate induces enhanced peritoneal permeability to proteins. Nephron 1991; 57: 45–51.
120. Capodicasa G, Capasso G, Anastasio P, Lanzetti N, Giordano C: Changes on peritoneal permeability by charged poly-amino acids. Perit Dial Bull 1987; 7: S13.
121. Pietrzak I, Hirszel P, Maher JF: Poly-1-lysine, a cationic macromolecule, increases peritoneal hydraulic and solute permeability. In Current concepts in Peritoneal Dialysis. Edited by Ota K, Maher JF, Winchester JF, Hirszel P. Amsterdam: Excerpta Medica; 1992: 433–438.
122. Maher JF, Pietrzak I, Hirszel P: Role of anions in restricitng peritoneal transfer rates. Arq Med 1989; 2: 347–349.
123. Breborowicz A, Rodela H, Bargman JM, Oreopoulos D: Effect of cationic molecules on the permeability of the mesothelium in vitro. Perit Dial Bull 1987; 7: S9.
124. Rippe B: A three-pore model of peritoneal transport. Perit Dial Int 1993; 13 (suppl 2): S35–S38.
125. Pannekeet MM, Mulder JB, Weening JJ, Struijk DG, Zweers MM, Krediet RT: Demonstration of aquaporin-CHIP in peritoneal tissue of uremic and CAPD patients. Perit Dial Int 1996; 16 (suppl 1): S54–S57.
126. Carlsson O, Nielsen S, Zakaria e, Rippe B: In vivo inhibition of transcellular water channels (aquaporin-1) during acute peritoneal dialysis in rats. Am J Physiol 1996; 271: H2254–H2262.
127. Akiba T, Ota T, Fushimi K, Tamura H, Hata T, Sasaki S, Marumo F: Water channel AQP1, 3, and 4 in the human peritoneum and peritoneal dialysate. Adv Perit Dial 1997; 13: 3–6.
128. Imai H, Nakamoto H, Ishida Y, Inoue T, Kanno Y, Okada H, Suzuki S, Okano H, Suzuki H: Glucocorticoid restores the deterioration of water transport in the peritoneum through increment in aquaporin. Adv Perit Dial 2000; 16: 297–302.
129. Stoenoiu MS, Ni J, Verkaeren C, Debaix H, Jonas JC, Lameire N, Verbavatz JM, Devuyst O: Corticosteroids induce expression of aquaporin-1 and increase transcellular water transport in rat peritoneum. J Am Soc Nephrol 2003; 14: 555–565.
130. Maher JF, Hohnadel DC, Shea C, DiSanzo F, Cassetta M: Effect of intraperitoneal diuretics on solute transport during hypertonic dialysis. Clin Nephrol 1977; 7: 96–100.
131. Scarpioni L, Ballocchi S, Bergonzi G, Fontana F, Poisetti P, Zanazzi MA: High dose diuretics in CAPD. Perit Dial Bull 1982; 2: 177–178.
132. Grzegorzewska A, Baczyk K: Furosemide-induced increase in urinary and peritoneal excretion of uric acid during peritoneal dialysis in patients with chronic uremia. Artif Organs 1982; 6: 220–224.
133. Bazzato G, Coli U, Landini S, Lucatello S, Fracasso A, Righetto F, Scanferla F, Morachiello P: Restoration of ultrafiltration capacity of peritoneal membrane in patients on CAPD. Int J Artif Organs 1984; 7: 93–96.
134. Maher JF, Hirszel P, Bennett RR, Chakrabarti E: Amphotericin B selectively increases peritoneal ultrafiltration. Am J Kidney Dis 1984; 4: 285–288.
135. Maher JF, Hirszel B, Bennett RR, Chakrabarti E: Augmentation of peritoneal hydraulic permeability by amphotericin B: locus of action. Perit Dial Bull 1984; 4: 229–231.
136. Wang T, Heimburger O, Cheng HH, Bergstrom J, Lindholm B: Amphotericin B does not increase peritoneal fluid removal. Adv Perit Dial 1998; 14: 3–10.
137. Zweers MM, Douma CE, de Waart DR, Korevaar JC, Krediet RT, Struijk DG: Amphotericin B, mercury chloride and peritoneal transport in rabbits. Clin Nephrol 2001; 56: 60–68.
138. Stegmayr BG: Beta-blockers may cause ultrafiltration failure in peritoneal dialysis patients. Perit Dial Int 1997; 17: 541–545.
139. Krediet RT: Beta-blockers and ultrafiltration failure. Perit Dial Int 1997; 17: 528–531.
140. Maher JF: Acceleration of peritoneal mass transport by drugs and hormones. Artif Organs 1979; 3: 224–227.
141. Avasthi PS: Effects of aminonucleoside on rat blood-peritoneal barrier permeability. J Lab Clin Med 1979; 94: 295–302.
142. Indraprasit S, Sooksriwongse C: Effect of chlorpromazine on peritoneal clearances. Nephron 1985; 40: 341–343.
143. Mactier RA, Khanna R, Moore H, Twardowski ZJ, Nolph KD: Pharmacological reduction of lymphatic absorption from the peritoneal cavity increases net ultrafiltration and solute clearances in peritoneal dialysis. Nephron 1988; 50: 229–232.
144. Maher JF, Hirszel P, Shostak A, Di PB, Chakrabarti E: Prolonged intraperitoneal dwell decreases ultrafiltration coefficient in rabbits. Am J Kidney Dis 1988; 12: 62–65.
145. Rubin J, Reed V, Adair C, Bower J, Klein E: Effect of intraperitoneal insulin on solute kinetics in CAPD: insulin kinetics in CAPD. Am J Med Sci 1986; 291: 81–87.
146. Dumont AE, Robbins E, Martelli A, Iliescu H: Platelet blockade of particle absorption from the peritoneal surface of the diaphragm. Proc Soc Exp Biol Med 1981; 167: 137–142.
147. Dedrick RL, Fenstermacher JD, Blasberg RG, Sieber SM: Peritoneal absorption of macromolecules. In Frontiers in Peritoneal Dialysis. Edited by Maher JF, Winchester JF. New York: Field, Rich; 1986: 41–46.
148. Lindholm B, Werynski A, Bergstrom J: Fluid transport in peritoneal dialysis. Int J Artif Organs 1990, 13: 352–358.
149. Khanna R, Mactier R, Twardowski ZJ, Nolph KD: Peritoneal cavity lymphatics. Perit Dial Bull 1986; 6: 113–121.
150. Hasbargen JA, Hasbargen BJ, Fortenbery EJ: Effect of intraperitoneal neostigmine on peritoneal transport characteristics in CAPD. Kidney Int 1992; 42: 1398–1400.
151. Chan PCK, Tam SCF, Cheng IKP: Oral neostigmine and lymphatic absorption in a myasthenia gravis patient on continuous ambulatory peritoenal dialysis. Perit Dial Int 1990; 10: 93–96.
152. Mactier R, Khanna R, Twardowski ZJ, Moore H, Nolph KD: Influence of phosphatidylcholine on lymphatic absorption during peritoneal dialysis in the rat. Perit Dial Int 1988; 8: 179–186.
153. Krack G, Viglino G, Cavalli PL, Gandolfo C, Magliano G, Cantaluppi A, Peluso F: Intraperitoneal administration of phosphatidylcholine improves ultrafiltration in continuous ambulatory peritoneal dialysis patients. Perit Dial Int 1992; 12: 359–364.
154. Ersoy FF, Khanna R, Moore H: Effect of phosphatidylcholine on peritoneal fluid kinetics. Perit Dial Int 1992; 12 Suppl 2: S3.
155. Wang T, Heimburger O, Waniewski J, Bergstrom J, Lindholm B: Time dependence of solute removal during a single exchange. Adv Perit Dial 1997; 13: 23–28.

156. Wang T, Cheng HH, Heimburger O, Chen C, Waniewski J, Bergstrom J, Lindholm B: Hyaluronan decreases peritoneal fluid absorption: effect of molecular weight and concentration of hyaluronan. Kidney Int 1999; 55: 667–673.
157. Fraser JR, Laurent TC, Laurent UB: Hyaluronan: its nature, distribution, functions and turnover. J Intern Med 1997, 242: 27–33.
158. Dobbie JW, Anderson JD: Ultrastructure, distribution, and density of lamellar bodies in human peritoneum. Perit Dial Int 1996; 16: 488–496.
159. Breborowicz A, Korybalska K, Grzybowski A, Wieczorowska-Tobis K, Martis L, Oreopoulos DG: Synthesis of hyaluronic acid by human peritoneal mesothelial cells: effect of cytokines and dialysate. Perit Dial Int 1996; 16: 374–378.
160. Heldin P, Pertoft H: Synthesis and assembly of the hyaluronan-containing coats around normal human mesothelial cells. Exp Cell Res 1993; 208: 422–429.
161. Moberly JB, Sorkin M, Kucharski A, Ogle K, Mongoven J, Skoufos L, Lin L, Bailey S, Rodela H, Mupas L, Walele A, Ogrinc F, White D, Wolfson M, Martis L, Breborowicz A, Oreopoulos DG: Effects of intraperitoneal hyaluronan on peritoneal fluid and solute transport in peritoneal dialysis patients. Perit Dial Int 2003; 23: 63–73.
162. Breborowicz A, Wieczorowska-Tobis K, Kuzlan M, Kupsz J, Korybalska K, Polubinska A, Krzysztof P, French I, Tam P, Wu G: N-acetylglucosamine: a new osmotic solute in peritoneal dialysis solutions. Perit Dial Int 1997; 17 (suppl 2): S80–S83.
163. Wu G, Wieczorowska-Tobis K, Polubinska A, et al: Use of N-acetyglucosamine as osmotic agent for peritoneal dialysis. Perit Dial Int 1996; 16 Suppl 2): S16.
164. Wu G, Wieczorowska-Tobis K, Polubinska A, Korybalska K, Filas V, Tam P, French I, Breborowicz A: N-acetylglucosamine changes permeability of peritoneum during chronic peritoneal dialysis in rats. Perit Dial Int 1998; 18: 217–224.
165. Comper WD, Laurent TC: Physiological function of connective tissue polysaccharides. Physiol Rev 1978; 58: 255–315.
166. Bazzato G, Fracasso A, Gambaro G, Baggio B: Use of glycosaminoglycans to increase efficiency of long-term continuous peritoneal dialysis. Lancet 1995; 346: 740–741.
167. Breborowicz A, Wieczorowska K, Martis L, Oreopoulos DG: Glycosaminoglycan chondroitin sulphate prevents loss of ultrafiltration during peritoneal dialysis in rats. Nephron 1994; 67: 346–350.
168. Wieczorowska K, Breborowicz A, Martis L, Oreopoulos DG: Protective effect of hyaluronic acid against peritoneal injury. Perit Dial Int 1995; 15: 81–83.
169. Fracasso A, Baggio B, Ossi E, Del PD, Bonfante L, Bazzato G, Gambaro G: Glycosaminoglycans prevent the functional and morphological peritoneal derangement in an experimental model of peritoneal fibrosis. Am J Kidney Dis 1999; 33: 105–110.
170. Pawlaczyk K, Kuzlan-Pawlaczyk M, Anderstam B, Heimburger O, Bergstrom J, Waniewski J, Breborowicz A, Lindholm B: Effects of intraperitoneal heparin on peritoneal transport in a chronic animal model of peritoneal dialysis. Nephrol Dial Transplant 2001; 16: 669–671.
171. Sjoland JA, Smith PR, Jespersen J, Gram J: Intraperitoneal heparin reduces peritoneal permeability and increases ultrafiltration in peritoneal dialysis patients. Nephrol Dial Transplant 2004; 19: 1264–1268.
172. Bazargani F, Albrektsson A, Yahyapour N, Braide M: Low molecular weight heparin improves peritoneal ultrafiltration and blocks complement and coagulation. Perit Dial Int 2005; 25: 394–404.
173. Breborowicz A, Wieczorowska K, Knapowski J, Martis L, Serkes KD, Oreopoulos DG: Chondroitin sulphate and peritoneal permeability. Adv Perit Dial 1992; 8: 11–14.
174. Breborowicz A, Radkowski M, Knapowski J, Oreopoulos DG: Effects of chondroitin sulphate on fluid and solute transport during peritoneal dialysis in rats. Perit Dial Int 1991; 11: 351–354.
175. Grahame G, Torchia M, Dankewich K, Ferguson I: Surface active material in peritoneal effluent of CAPD patients. Perit Dial Bull 1985; 5: 109–111.
176. Di Paolo N, Buoncristiani U, Capotondo L, Gaggiotti E, De MM, Rossi P, Sansoni E, Bernini M: Phosphatidylcholine and peritoneal transport during peritoneal dialysis. Nephron 1986; 44: 365–370.
177. Breborowicz A, Sombolos K, Rodela H, Ogilvie R, Bargman JM, Oreopoulos D: Mechanism of phosphatidylcholine action during peritoneal dialysis. Perit Dial Bull 1987; 7: 9.
178. De Alvaro F, Selgas R: Oral phosphatidylcholine effects on peritoneal mass transfer coefficient in CAPD patients [abstract]. Proc 15th congress EDTA/ERA 1988: 93 (abstract).
179. De Vecchi A, Castelnovo C, Guerra L, Scalamogna A: Phosphatidylcholine administration in continuous ambulatory peritoneal dialysis (CAPD) patients with reduced ultrafiltration. Perit Dial Int 1989; 9: 207–210.
180. Breborowicz A, Witowski J, Knapowski J, Serkes KD, Martis L, Oreopoulos DG: Effect of phosphatidylcholine on the function of human mesothelial cells in vitro. Nephron 1993; 63: 15–20.
181. Penzotti SC, Mattocks AM: Acceleration of peritoneal dialysis by surface-active agents. J Pharm Sci 1968; 57: 1192–1195.
182. Penzotti SC, Mattocks AM: Effects of dwell time, volume of dialysis fluid and added accelerators on peritoneal dialysis of urea. J Pharm Sci 1975; 60: 1520–1522.
183. Dunham CB, Hak LJ, Hull JH, Mattocks AM: Enhancement of peritoneal dialysis clearance with docusate sodium. Kidney Int 1981; 20: 563–568.
184. Wang T, Qureshi AR, Heimburger O, Waniewski J, Chen C, Bergstrom J, Lindholm B: Dioctyl sodium sulphosuccinate increases net ultrafiltration in peritoneal dialysis. Nephrol Dial Transplant 1997; 12: 1218–1222.
185. Hirszel P, Dodge K, Maher JF: Acceleration of peritoneal solute transport by cytochalasin D. Uremia Invest 1984; 8: 85–88.
186. Alavi N, Lianos E, Van Liew JB, Mookerjee BK, Bentzel CJ: Peritoneal permeability in the rat: modulation by microfilament-active agents. Kidney Int 1985; 27: 411–419.
187. Breborowicz A, Witowski J, Martis L, Oreopoulos DG: Enhancement of viability of human peritoneal mesothelial cells with glutathione precursor: L-2-oxothiazolidine-4-carboxylate. Adv Perit Dial 1993; 9: 21–24.
188. Korybalska K, Breborowicz A, Wieczorowska-Tobis K, Polubinska A, Moberly J, Martis L, Oreopoulos DG: Alterations of intraperitoneal inflammation by the addition of L-2-oxothiazolidine-carboxylate. Adv Perit Dial 1997; 13: 197–200.
189. Wieczorowska-Tobis K, Breborowicz A, Witowski J, Martis L, Oreopoulos DG: Effect of vitamin E on peroxidation and permeability of the peritoneum. J Physiol Pharmacol 1996; 47: 535–543.
190. Witowski J, Breborowicz A, Knapowski J: Effect of methotrexate, doxorubicin and mitoxantrone on human peritoneal mesothelial cell function in vitro. Oncology 1995; 52: 60–65.

191. Witowski J, Breborowicz A, Topley N, Martis L, Knapowski J, Oreopoulos DG: Insulin stimulates the activity of Na + /K(+)-ATPase in human peritoneal mesothelial cells. Perit Dial Int 1997; 17: 186–193.
192. Twardowski ZJ, Khanna R, Nolph KD: Osmotic agents and ultrafiltration in peritoneal dialysis. Nephron 1986; 42: 93–101.
193. Knochel JP, Clayton LE, Smith WL, Barry KG: Intraperitoneal THAM: an effective method to enhance phenobarbital removal during peritoneal dialysis. J Lab Clin Med 1964; 64: 257–268.
194. Campion DAS, North JDK: Effect of protein bining of barbiturates on their rate of removal during peritoneal dialysis. J Lab Clin Med 1965; 66: 549–563.
195. Schultz JC, Crouder DG, Medart WS: Excretion studies in ethchlorvynol (Pacidyl) intoxication. Arch Intern Med 1966; 117: 409–411.
196. Etteldorf JN, Dobbins WT, Summitt RL, Rainwater WT, Fischer RL: Intermittent peritoneal dialysis using 5 per cent albumin in the treatment of salicylate intoxication in children. J Pediatr 1961; 58: 226–236.
197. Shinaberger JH, Shear L, Clayton LE, Barry KG, Knowlton M, Goldbaum LR: Dialysis for intoxication with lipid-soluble drugs: enhancement of glutethimide extraction with lipid dialysate. Trans Am Soc Artif Intern Organs 1965; 11: 173–177.
198. Ho-Dac-Pannekeet MM, Krediet RT: Water channels in the peritoneum. Perit Dial Int 1996; 16: 255–259.
199. Swartz RD, Starmann B, Horvath AM, Olson SC, Posvar EL: Pharmacokinetics of quinapril and its active metabolite quinaprilat during continuous ambulatory peritoneal dialysis. J Clin Pharmacol 1990; 30: 1136–1141.
200. Benet LZ, Kroetz DL, Sheiner LB: Pharmacokinetics- The dynamics of drug absorption, distribution, and elimination. In Goodman & Gilman's The Pharmacological Basis of Therapeutics. Edited by Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Goodman Gilman A. New York: McGraw-Hill; 1996: 3–27.
201. Benet LZ, Obie S, Schwartz JB: Design and optimization of dosage regimens; pharmacokinetic data. In Goodman &Gilman's The Pharmacological Basis of Therapeutics. Edited by Hardman JG, Limbird LE, Molinoff PB, Ruddon RW, Goodman Gilman A. New York: McGraw- Hill; 1996: 1707–1792.
202. Rowland M, Tozer TN: Clinical Pharmacokinetics-Concepts and Applications. Baltimore: Williams, Wilkins; 1995.
203. Carmichael DJS: Handling of drugs in kidney disease. In Oxford Textbook of Clinical Nephrology, 3rd edn. Edited by Davison AM, Stewart Cameron J, Grünfeld J-P, Ponticelli C, Ritz E, Winearls CG, van Ypersele C. Oxford: Oxford University Press; 2005: 2599–2618.
204. Olyaei AJ, de Mattos AM, Bennett WM: Use of drugs in patients with renal failure. In Diseases of the Kidney and the Urinary Tract, 8th edn. Edited by Schrier RW. Philadelphia: Wolters Kluwer/Lippincott Williams, Wilkins; 2007: 2765–2807.
205. Diaz-Buxo JA, Crawford TL, Bailie GR: Peritonitis in automated peritoneal dialysis: antibiotic therapy and pharmacokinetics. Perit Dial Int 2001; 21 (suppl 3): S197–S201.
206. Manley HJ, Bailie GR: Treatment of peritonitis in APD: pharmacokinetic principles. Semin Dial 2002; 15: 418–421.
207. Manley HJ, Bridwell DL, Elwell RJ, Bailie GR: Influence of peritoneal dialysate flow rate on the pharmacokinetics of cefazolin. Perit Dial Int 2003; 23: 469–474.
208. Lasrich M, Maher JM, Hirszel P, Maher JF: Correlation of peritoneal transport rates with molecular weight: a method for predicitng clearances. ASAIO J 1979; 2: 107–113.
209. Maher JF: Peritoneal transport rates: mechanisms, limitations, and methods for augmentation. Kidney Int Suppl 1980; 10: S117–S120.
210. Deguchi Y, Nakashima E, Ishikawa F, Sato H, Tamai I, Matsushita R, Tofuku Y, Ichimura F, Tsuji A: Peritoneal transport of beta-lactam antibiotics: effects of plasma protein binding and the interspecies relationship. J Pharm Sci 1988; 77: 559–564.
211. Flessner MF, Dedrick RL, Schultz JS: Exchange of macromolecules between peritoneal cavity and plasma. Am J Physiol 1985; 248: H15–H25.
212. Keller E, Reetze P, Schollmeyer P: Drug therapy in patients undergoing continuous ambulatory peritoneal dialysis. Clinical pharmacokinetic considerations. Clin Pharmacokinet 1990; 18: 104–117.
213. Morse GD, Rowinski CA, Lieveld PE, Walshe JJ: Drug protein binding during continous ambulatory peritoneal dialysis. Perit Dial Int 1988; 6: 144–147.
214. Janknegt R, Nubé MJ: A simple method for predicitn drug clearances during CAPD. Perit Dial Bull 1985; 5: 254–255.
215. Lee CS, Marbury TC: Drug therapy in patients undergoing haemodialysis. Clinical pharmacokinetic considerations. Clin Pharmacokinet 1984; 9: 42–66.
216. Fleming LW, Moreland TA, Scott AC, Stewart WK, White LO: Ciprofloxacin in plasma and peritoneal dialysate after oral therapy in patients on continuous ambulatory peritoneal dialysis. J Antimicrob Chemother 1987; 19: 493–503.
217. Lameire N, Belpaire F: Pharmacokinetics of antibiotics against gram-negative infections in continuous ambulatory peritoneal dialysis patients. Perit Dial Int 1993; 13 (suppl 2): S371–S376.
218. Harford AM, Sica DA, Tartaglione T, Polk RE, Dalton HP, Poynor W: Vancomycin pharmacokinetics in continuous ambulatory peritoneal dialysis patients with peritonitis. Nephron 1986; 43: 217–222.
219. Halstead DC, Guzzo J, Giardina JA, Geshan AE: In vitro bactericidal activities of gentamicin, cefazolin, and imipenem in peritoneal dialysis fluids. Antimicrob Agents Chemother 1989; 33: 1553–1556.
220. Verbrugh HA, Keane WF, Conroy WE, Peterson PK: Bacterial growth and killing in chronic ambulatory peritoneal dialysis fluids. J Clin Microbiol 1984; 20: 199–203.
221. Weissauer-Condon C, Engels I, Daschner FD: In vitro activity of four new quinolones in Mueller-Hinton broth and peritoneal dialysis fluid. Eur J Clin Microbiol 1987; 6: 324–326.
222. Wilcox MH, Smith DG, Evans JA, Denyer SP, Finch RG, Williams P: Influence of carbon dioxide on growth and antibiotic susceptibility of coagulase-negative staphylococci cultured in human peritoneal dialysate. J Clin Microbiol 1990; 28: 2183–2186.
223. Morgera S, Neumayer HH, Fritsche L, Kuchinke S, Lampe D, Ahnert V, Bauer S, Mai I, Budde K: Pharmacokinetics of mycophenolate mofetil in renal transplant recipients on peritoneal dialysis. Int J Clin Pharmacol Ther 1998; 36: 159–163.
224. Lukas G, Brindle SD, Greengard P: The route of absorption of intraperitoneally administered compounds. J Pharmacol Exp Ther 1971; 178: 562–564.
225. Bailie GR, Eisele G, Venezia RA, Yocum D, Hollister A: Prediction of serum vancomycin concentrations following intraperitoneal loading doses in continuous ambulatory peritoneal dialysis patients with peritonitis. Clin Pharmacokinet 1992; 22: 298–307.

226. Brouard RJ, Kapusnik JE, Gambertoglio JG, Schoenfeld PY, Sachdeva M, Freel K, Tozer TN: Teicoplanin pharmacokinetics and bioavailability during peritoneal dialysis. Clin Pharmacol Ther 1989; 45: 674–681.
227. Elwell RJ, Bailie GR, Manley HJ: Correlation of intraperitoneal antibiotic pharmacokinetics and peritoneal membrane transport characteristics. Perit Dial Int 2000; 20: 694–698.
228. Gotloib L, Bar SP, Jaichenko J, Shustack A: Ruthenium-red-stained polyanionic fixed charges in peritoneal microvessels. Nephron 1987;, 47: 22–28.
229. De Paepe M, Lameire N, Belpaire F, Bogaert M: Peritoneal pharmacokinetics of gentamicin in man. Clin Nephrol 1983; 19: 107–109.
230. Rubin J, Deraps GD, Walsh D, Adair C, Bower J: Protein losses and tobramycin absorption in peritonitis treated by hourly peritoneal dialysis. Am J Kidney Dis 1986; 8: 124–127.
231. Regamey C, Schaberg D, Kirby WM: Inhibitory effect of heparin on gentamicin concentrations in blood. Antimicrob Agents Chemother 1972; 1: 329–332.
232. Ponce SP, Barata JD, Santos JR: Interference of heparin with peritoneal solute transport. Nephron 1985; 39: 47–49.
233. Hadler NM: Enhanced diffusivity of glucose in a matrix of hyaluronic acid. J Biol Chem 1980; 255: 3532–3535.
234. Mactier RA, Moore H, Khanna R, Shah J: Effect of peritonitis on insulin and glucose absorption during peritoneal dialysis in diabetic rats. Nephron 1990; 54: 240–244.
235. Wideroe TE, Dahl KJ, Smeby LC, Balstad T, Cruischank-Flakne S, Folling I, Simondsen O, Ahlmen J, Jorstad S: Pharmacokinetics of transperitoneal insulin transport. Nephron 1996; 74: 283–290.
236. Lameire N, Bogaert M: Peritoneal pharmacokinetics and pharmacological manipulation of peritoneal transport. In Continuous Ambulatory Peritoneal Dialysis. Edited by Gokal R. Edinburgh: Churchill Livingstone; 1986: 56–93.
237. Maher JF: Influence of continuous ambulatory peritoneal dialysis on elimination of drugs. Perit Dial Bull 1987; 7: 159–167.
238. Paton TW, Cornish WR, Manuel MA, Hardy BG: Drug therapy in patients undergoing peritoneal dialysis. Clinical pharmacokinetic considerations. Clin Pharmacokinet 1985; 10: 404–425.
239. Janknegt R, Koks CHW, Nubé MJ: Stability of antibiotics in CAPD fluid. Perit Dial Bull 1985; 5: 78.
240. Kehoe WH, Weber JN, Fries DS: The stability and comparability of clindamycin phosphate and gentamicin sulfate alone and in combination with peritoneal dialysis solution. Perit Dial Bull 1988; 8: 153–154.
241. Mason NA, Johnson CE, O'Brien MA: Stability of ceftazidime and tobramycin sulfate in peirotneal dialysis solution. Am J Hosp Pharm 1993; 49: 1139–1142.
242. Sewell DL, Golper TA: Stability of antimicrobial agents in peritoneal dialysate. Antimicrob Agents Chemother 1982; 21: 528–529.
243. Sewell DL, Golper TA, Brown SD, Nelson E, Knower M, Kimbrough RC: Stability of single and combination antimicrobial agents in various peritoneal dialysates in the presence of insulin and heparin. Am J Kidney Dis 1983; 3: 209–212.
244. Dooley DP, Tyler JR, Wortham WG, Harrison LS, Starnes WF, Jr., Collins GR, Ozuna IS, Violet PL, Ward JA: Prolonged stability of antimicrobial activity in peritoneal dialysis solutions. Perit Dial Int 2003; 23: 58–62.
245. Voges M, Faict D, Lechien G, Taminne M: Stability of drug additives in peritoneal dialysis solutions in a new container. Perit Dial Int 2004; 24: 590–595.
246. Nornoo AO, Elwell RJ: Stability of vancomycin in icodextrin peritoneal dialysis solution. Ann Pharmacother 2006; 40: 1950–1954.
247. Bastani B, Spijker DA, Westervelt FB: Peritoneal absorption of vancomycin during and after resolution of peritonitis in continuous ambulatory peritoneal dialysis patients. Perit Dial Bull 1988; 8: 135–136.
248. Imada A, Itagaki N, Hasegawa H, Horiuchi A: Comparative study of the pharmacokinetics of various beta-lactams after intravenous and intraperitoneal administration in patients undergoing continuous ambulatory peritoneal dialysis. Drugs 1988; 35 (suppl 2): 82–87.
249. Ryckelynck JP, Debruyne D, Hurault de LB, Moulin M: [Pharmacokinetics of piperacillin during continuous ambulatory peritoneal dialysis]. Pathol Biol (Paris) 1988; 36: 507–510.
250. Low CL, Bailie GR, Evans A, Eisele G, Venezia RA: Pharmacokinetics of once-daily IP gentamicin in CAPD patients. Perit Dial Int 1996; 16: 379–384.
251. Husserl F, Back S: Intraperitoneal vancomycin and the "red man" syndrome. Perit Dial Bull 1987; 7: 262 (letter to editor).
252. Benevent D, El Akoum N, Lagarde C: Danger de l'administration intrapéritonéale de l'amphotéricine B au cours de la dialyse péritonéale continue ambulatoire. La Presse Médicale 1984; 13: 1844.
253. Fabris A, Biasioli S, Borin D, Brendolan A: Fungal peritonitis in peritoneal dialysis: our experience and review of treatment. Perit Dial Bull 1984; 4: 75–77.
254. Mandell IN, Ahern MJ, Klier AS, Andriole VI: Candida peritonitis complicationg peritoneal dialysis: successful treatment with low dose of amphotericin B. Clin Nephrol 1976; 6: 192–196.
255. Struijk DG, Krediet RT, Boeschoten EW, Rietra PJ, Arisz L: Antifungal treatment of Candida peritonitis in continuous ambulatory peritoneal dialysis patients. Am J Kidney Dis 1987; 9: 66–70.
256. Piraino B, Bernardini J, Johnston JR, Sorkin M: Chemical peritonitis due to intraperitoneal vancomycin (Vancoled). Perit Dial Bull 1987; 7: 156–159.
257. Steiner RW: Adverse effects of intraperitoneal methylene blue. Perit Dial Bull 1983; 3: 43 (letter).
258. Bonner G, Lukowski K: Angiotensin I in peritoneal dialysis fluid improved hypotension: a case report. Clin Nephrol 1987; 27: 99–101.
259. Peters U, Risler T, Grabensee B: Pharmacokinetics of digoxin with end)stage)renal failure treated with continuous ambulatory peritoneal dialysis [abstract]. Kidney Int 1981; 20: 159.
260. Johnson RJ, Blair AD, Ahmad S: Ketoconazole kinetics in chronic peritoneal dialysis. Clin Pharmacol Ther 1985; 37: 325–329.
261. Belpaire FM, Van d V, Fraeyman NH, Bogaert MG, Lameire N: Influence of continuous ambulatory peritoneal dialysis on serum alpha 1-acid glycoprotein concentration and drug binding. Eur J Clin Pharmacol 1988; 35: 339–343.
262. Haughey DB, Kraft CJ, Matzke GR, Keane WF, Halstenson CE: Protein binding of disopyramide and elevated alpha-1-acid glycoprotein concentrations in serum obtained from dialysis patients and renal transplant recipients. Am J Nephrol 1985; 5: 35–39.
263. Buxton ILO: Pharmacokinetics and pharmacodynamics: the dynamics of drug absorption, distribution, action, and elimination. In Goodman, Gilman's The Pharmacological Basis of Therapeutics, 11th edn.; On-line Edition. Edited by Brunton LL, Parker KL, Buxton ILO, Blumenthal DK. Mc Graw-Hill; 2007.

264. Daugirdas JT, Blake P, Ing TS (eds): Handbook of Dialysis, 4th edn. Philadelphia: Wolters/Kluwer, Lippincott Williams Wilkins; : 2007.
265. Thummel KE, Shen DD, Isoherranen N, Smith HE: Design and optimization of dosage regimens: pharmacokinteic data. In Goodman, Gilman's The Pharmacological Basis of Therapeutics. Edited by Brunton LL, Parker KL, Buxton ILO, Blumenthal DK. McGraw-Hill; 2007.
266. Hoyer J, Schulte KL, Lenz T: Clinical pharmacokinetics of angiotensin converting enzyme (ACE) inhibitors in renal failure. Clin Pharmacokinet 1993; 24: 230–254.
267. Gehr TW, Sica DA, Grasela DM, Fakhry I, Davis J, Duchin KL: Fosinopril pharmacokinetics and pharmacodynamics in chronic ambulatory peritoneal dialysis patients. Eur J Clin Pharmacol 1991; 41: 165–169.
268. Sica DA, Gehr TW: The pharmacokinetics and pharmacodynamics of angiotensin-receptor blockers in end-stage renal disease. J Renin Angiotensin Aldosterone Syst 2002; 3: 247–254.
269. Pedro AA, Gehr TW, Brophy DF, Sica DA: The pharmacokinetics and pharmacodynamics of losartan in continuous ambulatory peritoneal dialysis. J Clin Pharmacol 2000; 40: 389–395.
270. Barbour MM, McKindley DS: Pharmacology and pharmacotherapy of cardiovascular drugs in patients with chronic renal disease. Semin Nephrol 2001; 21: 66–78.
271. Beaman M, Solaro L, McGonigle RJ, Michael J, Adu D: Vancomycin and ceftazidime in the treatment of CAPD peritonitis. Nephron 1989; 51: 51–55.
272. Boeschoten EW, Rietra PJ, Krediet RT, Visser MJ, Arisz L: CAPD peritonitis: a prospective randomized trial of oral versus intraperitoneal treatment with cephradine. J Antimicrob Chemother 1985; 16: 789–797.
273. Drew PJ, Casewell MW, Desai N, Houang ET, Simpson CN, Marsh FP: Cephalexin for the oral treatment of CAPD peritonitis. J Antimicrob Chemother 1984; 13: 153–159.
274. Knight KR, Polak A, Crump J, Maskell R: Laboratory diagnosis and oral treatment of CAPD peritonitis. Lancet 1982; 2: 1301–1304.
275. Ragnaud JM, Roche-Béziam MC, Marcau Ceal: Traitement des péritonites en dialyse péritonéale continue ambulatoire par une dose unique quotidienne de 1 g céfotiam par voie intrapéritonéale. Pathol Biol (Paris) 1986; 34: 512–516.
276. Low CL, Gopalakrishna K, Lye WC: Pharmacokinetics of once daily intraperitoneal cefazolin in continuous ambulatory peritoneal dialysis patients. J Am Soc Nephrol 2000; 11: 1117–1121.
277. Tosukhowong T, Eiam-Ong S, Thamutok K, Wittayalertpanya S, Na Ayudhya DP: Pharmacokinetics of intraperitoneal cefazolin and gentamicin in empiric therapy of peritonitis in continuous ambulatory peritoneal dialysis patients. Perit Dial Int 2001; 21: 587–594.
278. Manley HJ, Bailie GR, Frye R, Hess LD, McGoldrick MD: Pharmacokinetics of intermittent intravenous cefazolin and tobramycin in patients treated with automated peritoneal dialysis. J Am Soc Nephrol 2000; 11: 1310–1316.
279. Grabe DW, Bailie GR, Eisele G, Frye RF: Pharmacokinetics of intermittent intraperitoneal ceftazidime. Am J Kidney Dis 1999; 33: 111–117.
280. Stea S, Bachelor T, Cooper M, de SP, Koenig K, Bolton WK: Disposition and bioavailability of ceftazidime after intraperitoneal administration in patients receiving continuous ambulatory peritoneal dialysis. J Am Soc Nephrol 1996; 7: 2399–2402.
281. Booranalertpaisarn V, Eiam-Ong S, Wittayalertpanya S, Kanjanabutr T, Na Ayudhya DP: Pharmacokinetics of ceftazidime in CAPD-related peritonitis. Perit Dial Int 2003; 23: 574–579.
282. Sisterhen LL, Stowe CD, Farrar HC, Blaszak CK, Blaszak RT: Disposition of ceftazidime after intraperitoneal administration in adolescent patients receiving continuous cycling peritoneal dialysis. Am J Kidney Dis 2006; 47: 503–508.
283. Andrassy K: Pharmacokinetics of cefotaxime in dialysis patients. Diagn Microbiol Infect Dis 1995; 22: 85–87.
284. Okamoto MP, Nakahiro RK, Chin A, Bedikian A: Cefepime clinical pharmacokinetics. Clin Pharmacokinet 1993; 25: 88–102.
285. Barbhaiya RH, Knupp CA, Pfeffer M, Zaccardelli D, Dukes GM, Mattern W, Pittman KA, Hak LJ: Pharmacokinetics of cefepime in patients undergoing continuous ambulatory peritoneal dialysis. Antimicrob Agents Chemother 1992; 36: 1387–1391.
286. Elwell RJ, Frye RF, Bailie GR: Pharmacokinetics of intraperitoneal cefepime in automated peritoneal dialysis. Perit Dial Int 2005; 25: 380–386.
287. Morse G, Janicke D, Cafarell R, Piontek K, Apicella M, Jusko WJ, Walshe J: Moxalactam epimer disposition in patients undergoing continuous ambulatory peritoneal dialysis. Clin Pharmacol Ther 1985; 38: 150–156.
288. Johnson CA, Halstenson CE, Kelloway JS, Shapiro BE, Zimmerman SW, Tonelli A, Faulkner R, Dutta A, Haynes J, Greene DS: Single-dose pharmacokinetics of piperacillin and tazobactam in patients with renal disease. Clin Pharmacol Ther 1992; 51: 32–41.
289. Zaidenstein R, Weissgarten J, Dishi V, Koren M, Soback S, Gips M, Averbuch Z, Simantov R, Assulin E, Golik A: Pharmacokinetics of intraperitoneal piperacillin/tazobactam in patients on peritoneal dialysis with and without pseudomonas peritonitis. Perit Dial Int 2000; 20: 227–231.
290. Manley HJ, Bailie GR, Frye R, McGoldrick MD: Intermittent intravenous piperacillin pharmacokinetics in automated peritoneal dialysis patients. Perit Dial Int 2000; 20: 686–693.
291. Bailie GR, Eisele G: Vancomycin in peritoneal dialysis-associated peritonitis. Semin Dial 1996; 9: 417–423.
292. Van Biesen W, Vanholder R, Vogelaers D, Peleman R, Verschraegen G, Vijt D, Lameire N: The need for a center-tailored treatment protocol for peritonitis. Perit Dial Int 1998; 18: 274–281.
293. Blunden M, Zeitlin D, Ashman N, Fan SL: Single UK centre experience on the treatment of PD peritonitis–antibiotic levels and outcomes. Nephrol Dial Transplant 2007; 22: 1714–1719.
294. Manley HJ, Bailie GR, Frye RF, McGoldrick MD: Intravenous vancomycin pharmacokinetics in automated peritoneal dialysis patients. Perit Dial Int 2001; 21: 378–385.
295. Blowey DL, Warady BA, bdel-Rahman S, Frye RF, Manley HJ: Vancomycin disposition following intraperitoneal administration in children receiving peritoneal dialysis. Perit Dial Int 2007; 27: 79–85.
296. Finch RG, Holliday AP, Innes A: Pharmacokinetic behavior of intraperitoneal teicoplanin during treatment of peritonitis complicating continous ambulatory peritoneal dialysis. Antimicrob Agents Chemother 1996; 40: 1971–1972 (letter).
297. Stamatiadis D, Papaioannou MG, Giamarellos-Bourboulis EJ, Marinaki S, Giamarellou H, Stathakis CP: Pharmacokinetics of teicoplanin in patients undergoing continuous ambulatory peritoneal dialysis. Perit Dial Int 2003; 23: 127–131.
298. Janknegt R: CAPD peritonitis and fluoroquinolones: a review. Perit Dial Int 1991; 11: 48, 53–58.

299. Kowalsky SF, Echols M, Schwartz MT, Bailie GR, McCormick E: Pharmacokinetics of ciprofloxacin in subjects with varying degrees of renal function and undergoing hemodialysis or CAPD. Clin Nephrol 1993; 39: 53–58.
300. Lameire N, Rosenkranz B, Malerczyk V, Lehr KH, Veys N, Ringoir S: Ofloxacin pharmacokinetics in chronic renal failure and dialysis. Clin Pharmacokinet 1991; 21: 357–371.
301. Stuck AE, Kim DK, Frey FJ: Fleroxacin clinical pharmacokinetics. Clin Pharmacokinet 1992; 22: 116–131.
302. Nikolaidis PP: Quinolones: pharmacokinetics and pharmacodynamics. Perit Dial Int 1993; 13 (suppl 2): S377–S379.
303. McMullin CM, Brown NM, Brown IM, Tomson CR, White LO, Reeves DS, MacGown AP: The pharmacokinetics of once-daily oral 400 mg ofloxacin in patients with peritonitis complicating continuous ambulatory peritoneal dialysis. J Antimicrob Chemother 1997; 39: 829–831.
304. Yeung SM, Walker SE, Tailor SA, Awdishu L, Tobe S, Yassa T: Pharmacokinetics of oral ciprofloxacin in continuous cycling peritoneal dialysis. Perit Dial Int 2004; 24: 447–453.
305. Krishna G, Gajjar D, Swan S, Marbury T, Grasela DM, Wang Z: Garenoxacin pharmacokinetics in subjects with renal impairment. Curr Med Res Opin 2007; 23: 649–657.
306. de Fijter CW, Biemond A, Oe LP, Moesker HL, Verhoef J, Donker AJ, Verbrugh HA: Pharmacokinetics of ciprofloxacin after intraperitoneal administration in uninfected patients undergoing CCPD. Adv Perit Dial 1992; 8: 18–21.
307. Cheng IK, Chau PY, Kumana CR, Chan CY, Kou M, Siu LK: Single-dose pharmacokinetics of intraperitoneal ofloxacin in patients on continuous ambulatory peritoneal dialysis. Perit Dial Int 1993; 13 (suppl 2): S383–S385.
308. Chong TK, Piraino B, Bernardini J: Vestibular toxicity due to gentamicin in peritoneal dialysis patients. Perit Dial Int 1991; 11: 152–155.
309. Kim YW, Jang HJ, Kim YH, Yoon YR, Shin JG, Cha IJ: Comparative study of pharmacokinetics of once daily and continuous intraperitoneal netilmycin in continuous ambulatory peritoneal dialysis patients with peritonitis. Perit Dial Int 1999; 19 (suppl 2): S291–S293.
310. Brown J, Altmann P, Cunningham J, Shaw E, Marsh F: Pharmacokinetics of once daily intra-peritoneal aztreonam and vancomycin in the treatment of CAPD peritonitis. J Antimicrob Chemother 1990; 25: 141–147.
311. Dratwa M, Glupczynski Y, Lameire N, Matthys D, Verschraegen G, Vaneechoutte M, Boelaert J, Schurgers M, Van LH, Verbeelen D: Treatment of gram-negative peritonitis with aztreonam in patients undergoing continuous ambulatory peritoneal dialysis. Rev Infect Dis 1991; 13 (suppl 7): S645–S647.
312. Fuiano G, Sepe V, Viscione M, Nani E, Conte G: Effectiveness of single daily intraperitoneal administration of aztreonam and cefuroxime in the treatment of peritonitis in continuous ambulatory peritoneal dialysis (CAPD). Perit Dial Int 1989; 9: 273–275.
313. Cheng IK, Chan CY, Wong WT: A randomised prospective comparison of oral ofloxacin and intraperitoneal vancomycin plus aztreonam in the treatment of bacterial peritonitis complicating continuous ambulatory peritoneal dialysis (CAPD). Perit Dial Int 1991; 11: 27–30.
314. Dratwa M, Glupczynski Y, Lameire N, Matthys D, Verschraegen G, van EM, Boelaert J, Schurgers M, Van LH, Verbeelen D: Aztreonam in CAPD peritonitis. Lancet 1987; 2: 213–214.
315. Lam YW, Flaherty JF, Yumena L, Schoenfeld PY, Gambertoglio JG: Roxithromycin disposition in patients on continuous ambulatory peritoneal dialysis. J Antimicrob Chemother 1995; 36: 157–163.
316. Kent JR, Almond MK, Dhillon S: Azithromycin: an assessment of its pharmacokinetics and therapeutic potential in CAPD. Perit Dial Int 2001; 21: 372–377.
317. Allcock NM, Krueger TS, Manley HJ, Kumar VK, Abdallah J: Linezolid disposition during peritonitis: a case report. Perit Dial Int 2004; 24: 68–70.
318. Gendjar SR, Moriyama B, Bailey EM, Faber M, Shetty A, Borg DL, et al: Pharmacokinetics of oral linezolid in patients on peritoneal dialysis [abstract]. J Am Soc Nephrol 2001; 12: A2205.
319. Brown NM, Reeves DS, McMullin CM: The pharmacokinetics and protein-binding of fusidic acid in patients with severe renal failure requiring either haemodialysis or continuous ambulatory peritoneal dialysis. J Antimicrob Chemother 1997; 39: 803–809.
320. Launay-Vacher V, Izzedine H, Deray G: Pharmacokinetic considerations in the treatment of tuberculosis in patients with renal failure. Clin Pharmacokinet 2005; 44: 221–235.
321. Ahn C, Oh KH, Kim K, Lee KY, Lee JG, Oh MD, Kim Y, Han JS, Kim S, Lee JS, Jang IJ, Shin SG: Effect of peritoneal dialysis on plasma and peritoneal fluid concentrations of isoniazid, pyrazinamide, and rifampin. Perit Dial Int 2003; 23: 362–367.
322. Guay DR, Meatherall RC, Baxter H, Jacyk WR, Penner B: Pharmacokinetics of metronidazole in patients undergoing continuous ambulatory peritoneal dialysis. Antimicrob Agents Chemother 1984; 25: 306–310.
323. Merdjan H, Baumelou A, Diquet B, Chick O, Singlas E: Pharmacokinetics of ornidazole in patients with renal insufficiency; influence of haemodialysis and peritoneal dialysis. Br J Clin Pharmacol 1985; 19: 211–217.
324. Lau AH, Lam NP, Piscitelli SC, Wilkes L, Danziger LH: Clinical pharmacokinetics of metronidazole and other nitroimidazole anti-infectives. Clin Pharmacokinet 1992; 23: 328–364.
325. Izzedine H, Launay-Vacher V, Issad B, Deray G: Anti-viral drugs in continuous ambulatory peritoneal dialysis (CAPD). Minerva Urol Nefrol 2002; 54: 93–106.
326. Boelaert J, Schurgers M, Daneels R, Van Landuyt HW, Weatherley BC: Multiple dose pharmacokinetics of intravenous acyclovir in patients on continuous ambulatory peritoneal dialysis. J Antimicrob Chemother 1987; 20: 69–76.
327. Stathoulopoulou F, Almond MK, Dhillon S, Raftery MJ: Clinical pharmacokinetics of oral acyclovir in patients on continuous ambulatory peritoneal dialysis. Nephron 1996; 74: 337–341.
328. Davenport A, Goel S, Mackenzie JC: Neurotoxicity of acyclovir in patients with end-stage renal failure treated with continuous ambulatory peritoneal dialysis. Am J Kidney Dis 1992; 20: 647–649.
329. Stathoulopoulou F, Dhillon S, Thodis H, Stathakis C, Vargemezis V: Evaluation of valaciclovir dosage reduction in continuous ambulatory peritoneal dialysis patients. Nephron 2002; 91: 164–166.
330. Sommadossi JP, Bevan R, Ling T, Lee F, Mastre B, Chaplin MD, Nerenberg C, Koretz S, Buhles WC, Jr: Clinical pharmacokinetics of ganciclovir in patients with normal and impaired renal function. Rev Infect Dis 1988; 10 (suppl 3): S507–S514.

331. Swan SK, Munar MY, Wigger MA, Bennett WM: Pharmacokinetics of ganciclovir in a patient undergoing hemodialysis. Am J Kidney Dis 1991; 17: 69–72.
332. Izzedine H, Launay-Vacher V, Deray G: Pharmacokinetics of ritonavir and nevirapine in peritoneal dialysis. Nephrol Dial Transplant 2001; 16: 643.
333. Taylor S, Little J, Halifax K, Drake S, Back D: Pharmacokinetics of nelfinavir and nevirapine in a patient with end-stage renal failure on continuous ambulatory peritoneal dialysis. J Antimicrob Chemother 2000; 45: 716–717.
334. Brody SR, Humphreys MH, Gambertoglio JG, Schoenfeld P, Cundy KC, Aweeka FT: Pharmacokinetics of cidofovir in renal insufficiency and in continuous ambulatory peritoneal dialysis or high-flux hemodialysis. Clin Pharmacol Ther 1999; 65: 21–28.
335. Robson R, Buttimore A, Lynn K, Brewster M, Ward P: The pharmacokinetics and tolerability of oseltamivir suspension in patients on haemodialysis and continuous ambulatory peritoneal dialysis. Nephrol Dial Transplant 2006; 21: 2556–2562.
336. Alexander AC, Akers A, Matzke GR, Aweeka FT, Fraley DS: Disposition of foscarnet during peritoneal dialysis. Ann Pharmacother 1996; 30: 1106–1109.
337. Gallicano KD, Tobe S, Sahai J, McGilveray IJ, Cameron DW, Kriger F, Garber G: Pharmacokinetics of single and chronic dose zidovudine in two HIV positive patients undergoing continuous ambulatory peritoneal dialysis (CAPD). J Acquir Immune Defic Syndr 1992; 5: 242–250.
338. Kremer D, Munar MY, Kohlhepp SJ, Swan SK, Stinnett EA, Gilbert DN, Young EW, Bennett WM: Zidovudine pharmacokinetics in five HIV seronegative patients undergoing continuous ambulatory peritoneal dialysis. Pharmacotherapy 1992; 12: 56–60.
339. Knupp CA, Hak LJ, Coakley DF, Falk RJ, Wagner BE, Raasch RH, van der Horst CM, Kaul S, Barbhaiya RH, Dukes GE: Disposition of didanosine in HIV-seropositive patients with normal renal function or chronic renal failure: influence of hemodialysis and continuous ambulatory peritoneal dialysis. Clin Pharmacol Ther 1996; 60: 535–542.
340. Kravitz SP, Berry PL: Successful treatment of Aspergillus peritonitis in a child undergoing continuous cycling peritoneal dialysis. Arch Intern Med 1986; 146: 2061–2062.
341. Muther RS, Bennett WM: Peritoneal clearance of amphotericin B and 5-fluorocytosine. West J Med 1980; 133: 157–160.
342. Peterson LR, Kelty RH, Hall WH, Votava HJ: Therapy of Candida peritonitis: penetration of amphotericin B into peritoneal fluid. Postgrad Med J 1978; 54: 340–342.
343. Khanna R, Oreopoulos DG, Vas S, McCready W, Dombros N: Fungal peritonitis in patients undergoing chronic intermittent or continuous ambulatory peritoneal dialysis. Proc Eur Dial Transplant Assoc 1980; 17: 291–296.
344. Rault R: Candida peritonitis complicating chronic peritoneal dialysis: a report of five cases and review of the literature. Am J Kidney Dis 1983; 2: 544–547.
345. Imholz AL, Koomen GC, Struijk DG, Arisz L, Krediet RT: The effect of amphotericin B on fluid kinetics and solute transport in CAPD patients. Adv Perit Dial 1993; 9: 12–15.
346. Eisenberg ES: Intraperitoneal flucytosine in the management of fungal peritonitis in patients on continuous ambulatory peritoneal dialysis. Am J Kidney Dis 1988; 11: 465–467.
347. Slingeneyer A, Laroche B, Steel F, Canaud B, Beraud JJ, Mion C: Oral ketoconazole plus IP 5-fluorocytosine as a sole treatment of fungal peritonitis in CAPD [abstract]. Perit Dial Bull 1984; 4: S60 (abstract).
348. Debruyne D, Ryckelynck JP, Moulin M, Hurault de LB, Levaltier B, Bigot MC: Pharmacokinetics of fluconazole in patients undergoing continuous ambulatory peritoneal dialysis. Clin Pharmacokinet 1990; 18: 491–498.
349. Levine J, Bernard DB, Idelson BA, Farnham H, Saunders C, Sugar AM: Fungal peritonitis complicating continuous ambulatory peritoneal dialysis: successful treatment with fluconazole, a new orally active antifungal agent. Am J Med 1989; 86: 825–827.
350. Dahl NV, Foote EF, Searson KM, Fein JL, Kapoian T, Steward CA, Sherman RA: Pharmacokinetics of intraperitoneal fluconazole during continuous cycling peritoneal dialysis. Ann Pharmacother 1998; 32: 1284–1289.
351. Boelaert J, Schurgers M, Matthys E, Daneels R, van PA, De BK, Woestenborghs R, Heykants J: Itraconazole pharmacokinetics in patients with renal dysfunction. Antimicrob Agents Chemother 1988; 32: 1595–1597.
352. Gladziwa U, Wagner S, Dakshinamurty KV, el DE, Dreuw B, Klotz U: Pharmacokinetics and pharmacodynamics of famotidine in patients with reflux oesophagitis. Eur J Clin Pharmacol 1993; 44: 357–360.
353. Kogan FJ, Sampliner RE, Mayersohn M, Kazama RM, Perrier D, Jones W, Michael UF: Cimetidine disposition in patients undergoing continuous ambulatory peritoneal dialysis. J Clin Pharmacol 1983; 23: 252–256.
354. Paton TW, Manuel M, Walker SE: Cimetidine disposition in patients on continous ambulatory peirtoneal dialysis. Perit Dial Bull 1982; 2: 73–76.
355. Sica DA, Comstock T, Harford A, Eshelman F: Ranitidine pharmacokinetics in continuous ambulatory peritoneal dialysis. Eur J Clin Pharmacol 1987; 32: 587–591.
356. Andersson T: Pharmacokinetics, metabolism and interactions of acid pump inhibitors. Focus on omeprazole, lansoprazole and pantoprazole. Clin Pharmacokinet 1996; 31: 9–28.
357. Barradell LB, Faulds D, McTavish D: Lansoprazole. A review of its pharmacodynamic and pharmacokinetic properties and its therapeutic efficacy in acid-related disorders. Drugs 1992; 44: 225–250.
358. Lazarovits AI, Page D: Intraperitoneal cisapride for the treatment of diabetics with gastroparesis and end-stage renal disease. Nephron 1990; 56: 107–109.
359. Gladziwa U, Bares R, Klotz U, Dakshinamurty KV, Ittel TH, Seiler KU, Sieberth HG: Pharmacokinetics and pharmacodynamics of cisapride in patients undergoing hemodialysis. Clin Pharmacol Ther 1991; 50: 673–681.
360. Bargman JM, Jones JE, Petro JM: The pharmacokinetics of intraperitoneal erythropoietin administered undiluted or diluted in dialysate. Perit Dial Int 1992; 12: 369–372.
361. Kromer G, Solf A, Ehmer B, Kaufmann B, Quellhorst E: Single dose pharmacokinteics of recombinant human erythropoietin comparing intravenous, subcutaneous and intraperitoneal administration in IPD patients [abstract]. Kidney Int 1990; 37: 311.
362. Frenken LA, Struijk DG, Coppens PJ, Tiggeler RG, Krediet RT, Koene RA: Intraperitoneal administration of recombinant human erythropoietin. Perit Dial Int 1992; 12: 378–383.
363. Nasu T, Mitui H, Shinohara Y, Hayashida S, Ohtuka H: Effect of erythropoietin in continuous ambulatory peritoneal dialysis patients: comparison between intravenous and intraperitoneal administration. Perit Dial Int 1992; 12: 373–377.

364. Taylor CA, III, Kosorok MR, Zimmerman SW, Johnson CA: Pharmacokinetics of intraperitoneal epoetin alfa in patients on peritoneal dialysis using an 8-hour "dry dwell" dosing technique. Am J Kidney Dis 1999; 34: 657–662.
365. Reddingius RE, de Boer AW, Schroder CH, Willems JL, Monnens LA: Increase of the bioavailability of intraperitoneal erythropoietin in children on peritoneal dialysis by administration in small dialysis bags. Perit Dial Int 1997; 17: 467–470.
366. Johnson CA, Wakeen M, Taylor CA, III, Zimmerman SW, Burkart J, Bhattacharya A, Kosorok MR: Comparison of intraperitoneal and subcutaneous epoetin alfa in peritoneal dialysis patients. Perit Dial Int 1999; 19: 578–582.
367. Macdougall IC, Gray SJ, Elston O, Breen C, Jenkins B, Browne J, Egrie J: Pharmacokinetics of novel erythropoiesis stimulating protein compared with epoetin alfa in dialysis patients. J Am Soc Nephrol 1999; 10: 2392–2395.
368. Takama H, Tanaka H, Nakashima D, Ogata H, Uchida E, Akizawa T, Koshikawa S: Population pharmacokinetics of darbepoetin alfa in haemodialysis and peritoneal dialysis patients after intravenous administration. Br J Clin Pharmacol 2007; 63: 300–309.
369. Park SE, Twardowski ZJ, Moore HL, Khanna R, Nolph KD: Chronic administration of iron dextran into the peritoneal cavity of rats. Perit Dial Int 1997; 17: 179–185.
370. Fine RN, Fine SE, Sherman BM: Absorption of recombinant human growth hormone (rhGH) following intraperitoneal instillation. Perit Dial Int 1989; 9: 91–93.
371. Gipson DS, Kausz AT, Striegel JE, Melvin TR, Astrom LJ, Watkins SL: Intraperitoneal administration of recombinant human growth hormone in children with end-stage renal disease. Pediatr Nephrol 2001; 16: 29–34.
372. Schroder CH, Swinkels LM, Reddingius RE, Sweep FG, Willems HL, Monnens LA: Adsorption of erythropoietin and growth hormone to peritoneal dialysis bags and tubing. Perit Dial Int 2001; 21: 90–92.
373. Marquardt ED, Ishisaka DY, Batra KK, Chin B: Removal of ethosuximide and phenobarbital by peritoneal dialysis in a child. Clin Pharm 1992; 11: 1030–1031.
374. Leakey TE, Elias-Jones AC, Coates PE, Smith KJ: Pharmacokinetics of theophylline and its metabolites during acute renal failure. A case report. Clin Pharmacokinet 1991; 21: 400–408.
375. Cefali EA, Poynor WJ, Sica D, Cox S: Pharmacokinetic comparison of flurbiprofen in end-stage renal disease subjects and subjects with normal renal function. J Clin Pharmacol 1991; 31: 808–814.
376. Price TM, Dupuis RE, Carr BR, Stanczyk FZ, Lobo RA, Droegemueller W: Single- and multiple-dose pharmacokinetics of a low-dose oral contraceptive in women with chronic renal failure undergoing peritoneal dialysis. Am J Obstet Gynecol 1993; 168: 1400–1406.
377. Schmith VD, Piraino B, Smith RB, Kroboth PD: Alprazolam in end-stage renal disease: I. Pharmacokinetics. J Clin Pharmacol 1991; 31: 571–579.
378. Garzone PD, Kroboth PD: Pharmacokinetics of the newer benzodiazepines. Clin Pharmacokinet 1989, 16: 337–364.
379. Bauer TM, Ritz R, Haberthur C, Ha HR, Hunkeler W, Sleight AJ, Scollo-Lavizzari G, Haefeli WE: Prolonged sedation due to accumulation of conjugated metabolites of midazolam. Lancet 1995; 346: 145–147.
380. Salva P, Costa J: Clinical pharmacokinetics and pharmacodynamics of zolpidem. Therapeutic implications. Clin Pharmacokinet 1995; 29: 142–153.
381. Pauli-Magnus C, Hofmann U, Mikus G, Kuhlmann U, Mettang T: Pharmacokinetics of morphine and its glucuronides following intravenous administration of morphine in patients undergoing continuous ambulatory peritoneal dialysis. Nephrol Dial Transplant 1999; 14: 903–909.
382. MacPhee IA, Spreafico S, Bewick M, Davis C, Eastwood JB, Johnston A, Lee T, Holt DW: Pharmacokinetics of mycophenolate mofetil in patients with end-stage renal failure. Kidney Int 2000; 57: 1164–1168.
383. Bailie GR, Johnson CA: Comparative review of the pharmacokinetics of vitamin D analogues. Semin Dial 2002; 15: 352–357.
384. Joffe P, Cintin C, Ladefoged SD, Rasmussen SN: Pharmacokinetics of 1 alpha-hydroxycholecalciferol after intraperitoneal, intravenous and oral administration in patients undergoing peritoneal dialysis. Clin Nephrol 1994; 41: 364–369.
385. Shany S, Rapoport J, Goligorsky M, Yankowitz N, Zuili I, Chaimovitz C: Losses of 1,25- and 24,25-dihydroxycholecalciferol in the peritoneal fluid of patients treated with continuous ambulatory peritoneal dialysis. Nephron 1984; 36: 111–113.
386. Delmez JA, Dougan CS, Gearing BK, Rothstein M, Windus DW, Rapp N, Slatopolsky E: The effects of intraperitoneal calcitriol on calcium and parathyroid hormone. Kidney Int 1987; 31: 795–799.
387. Joffe P, Ladefoged SD, Cintin C, Lehmann H: 1 alpha-Hydroxycholecalciferol adsorption to peritoneal dialysis bags: influence of time, glucose concentration, temperature, and albumin. Nephrol Dial Transplant 1992; 7: 1249–1251.
388. Salusky IB, Goodman WG, Horst R, Segre GV, Kim L, Norris KC, Adams JS, Holloway M, Fine RN, Coburn JW: Pharmacokinetics of calcitriol in continuous ambulatory and cycling peritoneal dialysis patients. Am J Kidney Dis 1990; 16: 126–132.
389. Murakami K, Miyachi H, Watanabe A, Kawamura N, Fujii M, Koide S, Murase M, Kushimoto H, Hasegawa M, Tomita M, Hiki Y, Sugiyama S: Suppression of parathyroid hormone secretion in CAPD patients by intraperitoneal administration of Maxacalcitol. Clin Exp Nephrol 2004; 8: 134–138.
390. Hamada C, Hayashi K, Shou I, Inaba M, Ro Y, Io H, Maeda K, Fukui M, Tomino Y: Pharmacokinetics of calcitriol and maxacalcitol administered into peritoneal dialysate bags in peritoneal dialysis patients. Perit Dial Int 2005; 25: 570–575.
391. Rodd C: Bisphosphonates in dialysis and transplantation patients: efficacy and safety issues. Perit Dial Int 2001; 21 Suppl 3: S256–S260.
392. Saha HH, la-Houhala IO, Liukko-Sipi SH, Ylitalo P, Pasternack AI: Pharmacokinetics of clodronate in peritoneal dialysis patients. Perit Dial Int 1998; 18: 204–209.
393. Padhi D, Harris RZ, Salfi M, Sullivan JT: No effect of renal function or dialysis on pharmacokinetics of cinacalcet (Sensipar/Mimpara). Clin Pharmacokinet 2005; 44: 509–516.
394. Schade DS, Eaton RP, Davis T, Akiya F, Phinney E, Kubica R, Vaughn EA, Day PW: The kinetics of peritoneal insulin absorption. Metabolism 1981; 30: 149–155.
395. Nelson JA, Stephen R, Landau ST, Wilson DE, Tyler FH: Intraperitoneal insulin administration produces a positive portal-systemic blood insulin gradient in unanesthetized, unrestrained swine. Metabolism 1982; 31: 969–972.
396. Kritz H, Hagmuller G, Lovett R, Irsigler K: Implanted constant basal rate insulin infusion devices for Type 1 (insulin-dependent) diabetic patients. Diabetologia 1983; 25: 78–81.

397. Micossi P, Bosi E, Cristallo M, Monti LD, Librenti MC, Petrella G, Galimberti G, Spotti D, Giudici G, Vergani C: Chronic continuous intraperitoneal insulin infusion (CIPII) in type I diabetic patients non-satisfactorily responsive to continuous subcutaneous insulin infusion (CSII). Acta Diabetol Lat 1986; 23: 155–164.
398. Saudek CD: Developing and assessing an implantable insulin infusion pump. Interactions of university, industry, and government. Int J Technol Assess Health Care 1986; 2: 471–482.
399. Schade DS, Eaton RP, Friedman N, Spencer W: The intravenous, intraperitoneal, and subcutaneous routes of insulin delivery in diabetic man. Diabetes 1979; 28: 1069–1072.
400. Selam JL, Slingeneyer A, Hedon B, Mares P, Beraud JJ, Mirouze J: Long-term ambulatory peritoneal insulin infusion of brittle diabetes with portable pumps: comparison with intravenous and subcutaneous routes. Diabetes Care 1983; 6: 105–111.
401. Vaag A, Handberg A, Lauritzen M, Henriksen JE, Pedersen KD, Beck-Nielsen H: Variation in absorption of NPH insulin due to intramuscular injection. Diabetes Care 1990; 13: 74–76.
402. Wredling R, Liu D, Lins PE, Adamson U: Variation of insulin absorption during subcutaneous and peritoneal infusion in insulin-dependent diabetic patients with unsatisfactory long-term glycaemic response to continuous subcutaneous insulin infusion. Diabete Metab 1991; 17: 456–459.
403. Balducci A, Slama G, Rottembourg J, Baumelou A, Delage A: Intraperitoneal insulin in uraemic diabetics undergoing continuous ambulatory peritoneal dialysis. Br Med J (Clin Res Ed) 1981; 283: 1021–1023.
404. Wideroe TE, Smeby LC, Berg KJ, Jorstad S, Svartas TM: Intraperitoneal (125I) insulin absorption during intermittent and continuous peritoneal dialysis. Kidney Int 1983; 23: 22–28.
405. Peetoom JJ, Willekens FL, Meinders AE: Absorption and biological effect of intraperitoneal insulin administration in patients with terminal renal failure treated by continuous ambulatory peritoneal dialysis (CAPD). Neth J Med 1985; 28: 435–441.
406. Shapiro DJ, Blumenkrantz MJ, Levin SR, Coburn JW: Absorption and action of insulin added to peritoneal dialysate in dogs. Nephron 1979; 23: 174–180.
407. Quellhorst E: Insulin therapy during peritoneal dialysis: pros and cons of various forms of administration. J Am Soc Nephrol 2002; 13 (suppl 1): S92–S96.
408. Iglesias P, Diez JJ: Peroxisome proliferator-activated receptor gamma agonists in renal disease. Eur J Endocrinol 2006; 154: 613–621.
409. Snyder RW, Berns JS: Use of insulin and oral hypoglycemic medications in patients with diabetes mellitus and advanced kidney disease. Semin Dial 2004; 17: 365–370.
410. Chapelsky MC, Thompson-Culkin K, Miller AK, Sack M, Blum R, Freed MI: Pharmacokinetics of rosiglitazone in patients with varying degrees of renal insufficiency. J Clin Pharmacol 2003; 43: 252–259.
411. Budde K, Neumayer HH, Fritsche L, Sulowicz W, Stompor T, Eckland D: The pharmacokinetics of pioglitazone in patients with impaired renal function. Br J Clin Pharmacol 2003; 55: 368–374.
412. Manley HJ, Allcock NM: Thiazolidinedione safety and efficacy in ambulatory patients receiving hemodialysis. Pharmacotherapy 2003; 23: 861–865.
413. Lin SH, Lin YF, Kuo SW, Hsu YJ, Hung YJ: Rosiglitazone improves glucose metabolism in nondiabetic uremic patients on CAPD. Am J Kidney Dis 2003; 42: 774–780.
414. Wong TY, Szeto CC, Chow KM, Leung CB, Lam CW, Li PK: Rosiglitazone reduces insulin requirement and C-reactive protein levels in type 2 diabetic patients receiving peritoneal dialysis. Am J Kidney Dis 2005; 46: 713–719.
415. A consensus statement from the American Heart Association and American Diabetes Association, Thiazolidinedione use, fluid retention, and congestive heart failure. Diabetes Care 2004; 27: 256–263.
416. Furman KI, Gomperts ED, Hockley J: Activity of intraperitoneal heparin during peritoneal dialysis. Clin Nephrol 1978; 9: 15–18.
417. Canavese C, Salomone M, Mangiarotti G, Pacitti A, Trucco S, Scaglia C, Assone F, Lunghi F, Vercellone A: Heparin transfer across the rabbit peritoneal membrane. Clin Nephrol 1986; 26: 116–120.
418. Gotloib L, Crassweller P, Rodella H, Oreopoulos DG, Zellerman G, Ogilvie R, Husdan H, Brandes L, Vas S: Experimental model for studies of continuous peritoneal'dialysis in uremic rabbits. Nephron 1982; 31: 254–259.
419. Takahashi S, Shimada A, Okada K, Kuno T, Nagura Y, Hatano M: Effect of intraperitoneal administration of heparin to patients on continuous ambulatory peritoneal dialysis (CAPD). Perit Dial Int 1991; 11: 81–83.
420. Schrader J, Tonnis HJ, Scheler F: Long-term intraperitoneal application of low molecular weight heparin in a continuous ambulatory peritoneal dialysis patient with deep vein thrombosis. Nephron 1986; 42: 83–84.
421. Tabata T, Shimada H, Emoto M, Morita A, Furumitsu Y, Fujita J, Inoue T, Miki T, Nishizawa Y, Morii H: Inhibitory effect of heparin and/or antithrombin III on intraperitoneal fibrin formation in continuous ambulatory peritoneal dialysis. Nephron 1990; 56: 391–395.
422. Brophy DF, Carr ME, Jr., Martin EJ, Venitz J, Gehr TW: The pharmacokinetics of enoxaparin do not correlate with its pharmacodynamic effect in patients receiving dialysis therapies. J Clin Pharmacol 2006; 46: 887–894.
423. Eriksson UG, Johansson S, Attman PO, Mulec H, Frison L, Fager G, Samuelsson O: Influence of severe renal impairment on the pharmacokinetics and pharmacodynamics of oral ximelagatran and subcutaneous melagatran. Clin Pharmacokinet 2003; 42: 743–753.
424. Allain P, Chaleil D, Mauras Y, Varin MC, Ang KS, Cam G, Simon P: Pharmacokinetics of desferrioxamine and of its iron and aluminum chelates in patients on peritoneal dialysis. Clin Chim Acta 1988; 173: 313–316.
425. Falk RJ, Mattern WD, Lamanna RW, Gitelman HJ, Parker NC, Cross RE, Rastall JR: Iron removal during continuous ambulatory peritoneal dialysis using deferoxamine. Kidney Int 1983; 24: 110–112.
426. Andreoli SP, Dunn D, DeMyer W, Sherrard DJ, Bergstein JM: Intraperitoneal deferoxamine therapy for aluminum intoxication in a child undergoing continuous ambulatory peritoneal dialysis. J Pediatr 1985; 107: 760–763.
427. Hercz G, Salusky IB, Norris KC, Fine RN, Coburn JW: Aluminum removal by peritoneal dialysis: intravenous vs. intraperitoneal deferoxamine. Kidney Int 1986; 30: 944–948.
428. Payton CD, Junor BJ, Fell GS: Successful treatment of aluminium encephalopathy by intraperitoneal desferrioxamine. Lancet 1984; 1: 1132–1133.
429. O'Brien AA, McParland C, Keogh JA: The use of intravenous and intraperitoneal desferrioxamine in aluminium osteomalacia. Nephrol Dial Transplant 1987; 2: 117–119.

430. Mohamed F, Marchettini P, Stuart OA, Sugarbaker PH: Pharmacokinetics and tissue distribution of intraperitoneal paclitaxel with different carrier solutions. Cancer Chemother Pharmacol 2003; 52: 405–410.
431. Mohamed F, Stuart OA, Sugarbaker PH: Pharmacokinetics and tissue distribution of intraperitoneal docetaxel with different carrier solutions. J Surg Res 2003; 113: 114–120.
432. Sugarbaker PH, Stuart OA: Pharmacokinetic and phase II study of heated intraoperative intraperitoneal melphalan. Cancer Chemother Pharmacol 2007; 59: 151–155.
433. Iwamoto M, Hiroshige K, Suda T, Ohta T, Ohtani A, Nakashima Y: Elimination of iomeprol in patients undergoing continuous ambulatory peritoneal dialysis. Perit Dial Int 1999; 19: 380–385.
434. Joffe P, Thomsen HS, Meusel M: Pharmacokinetics of gadodiamide injection in patients with severe renal insufficiency and patients undergoing hemodialysis or continuous ambulatory peritoneal dialysis. Acad Radiol 1998; 5: 491–502.
435. Vychytil A, Fodinger M, Papagiannopoulos M, Wolfl G, Horl WH, Sunder-Plassmann G: Peritoneal elimination of homocysteine moieties in continuous ambulatory peritoneal dialysis patients. Kidney Int 1999; 55: 2054–2061.
436. Boeschoten EW, Schrijver J, Krediet RT, Schreurs WH, Arisz L: Deficiencies of vitamins in CAPD patients: the effect of supplementation. Nephrol Dial Transplant 1988; 3: 187–193.
437. Pancorbo S, Comty C: Digoxin pharmacokinetics in continuous peritoneal dialysis. Ann Intern Med 1980; 93: 639.
438. De Paoli Vitali E, Casol D, Tessarin C, Tisone GF, Cavogna R: Pharmacokinetics of digoxin in CAPD. In Advances in Peritoneal Dialysis. Edited by Gahl GM, Kessel M, Nolph KD. Amsterdam: Excerpta Medica; 1981: 85–87.
439. Risler T, Peters U, Passlick J, Grabensee B, Krokou J: Pharmacokinetics of digoxin and digitoxine in patients on continuous ambulatory peritoneal dialysis. In Advances in Peritoneal dialysis. Edited by Gahl GM, Kessel M, Nolph KD. Amsterdam: Excerpta Medica; 1981: 88–89.
440. De Paepe M, Belpaire F, Bogaerts Y: Pharmacokinetics of digoxin in CAPD. Clin Exp Dial Apheresis 1982, 6: 65–73.
441. Gloor HJ, Moore H, Nolph KD: The peritoneal handling of digoxin during CAPD. Perit Dial Bull 1982; 2: 13–16.
442. Chin TW, Pancorbo S, Comty C: Quinidine pharmacokinetics in continuous ambulatory peritoneal dialysis. Clin Exp Dial Apheresis 1981; 5: 391–397.
443. Yamakado M, Umezu M, Nagano M, Tagawa H: Pharmacokinetics of denopamine in patients on contiuous ambulatory peritoneal dialysis. In Current Concepts in Peritoneal Dialysis. Edited by Ota K, Maher JF, Winchester JF. Amsterdam: Excepta Medica; 1992: 441–444.
444. Halstenson CE, Opsahl JA, Pence TV, Luke DR, Sirgo MA, Plachetka JR, Abraham PA, Matzke GR: The disposition and dynamics of labetalol in patients on dialysis. Clin Pharmacol Ther 1986; 40: 462–468.
445. Parrott KA, Alexander SE, Stennett DJ: Loss of propranolol via CAPD in two patients [abstract]. Perit Dial Bull 1984; 2: 110.
446. Salahudeen AK, Wilkinson R, McAinsh J, Bateman DN: Atenolol pharmacokinetics in patients on continuous ambulatory peritoneal dialysis. Br J Clin Pharmacol 1984; 18: 457–460.
447. Flaherty JF, Wong B, La FG, Warnock DG, Hulse JD, Gambertoglio JG: Pharmacokinetics of esmolol and ASL-8123 in renal failure. Clin Pharmacol Ther 1989; 45: 321–327.
448. Bianchetti G, Padovani P, Thenot JP, Thiercelin JF, Martin-Dupont C, Morselli L: Betaxolol disposition in chronic renal insufficiency, hemodialysis and ambulatory peritoneal dialysis[abstract]. Eur J Clin Invest 1982; 12S: 3A (abstract).
449. Spital A, Scandling JD: Nifedipine in continuous ambulatory peritoneal dialysis. Arch Intern Med 1983; 143: 2025 (letter).
450. Evers J, Bonn R, Boertz A, Cawello W, Luckow V, Fey M, Aboudan F, Dickmans HA: Pharmacokinetics of isosorbide-5-nitrate during haemodialysis and peritoneal dialysis. Eur J Clin Pharmacol 1987; 32: 503–505.
451. Grech-Belanger O, Langlois S, LeBoeuf E: Pharmacokinetics of diltiazem in patients undergoing continuous ambulatory peritoneal dialysis. J Clin Pharmacol 1988; 28: 477–480.
452. Fujimura A, Kajiyama H, Ebihara A, Iwashita K, Nomura Y, Kawahara Y: Pharmacokinetics and pharmacodynamics of captopril in patients undergoing continuous ambulatory peritoneal dialysis. Nephron 1986; 44: 324–328.
453. Wolter K, Fritschka E: Pharmacokinetics and pharmacodynamics of quinaprilat after low dose quinapril in patients with terminal renal failure. Eur J Clin Pharmacol 1993; 44 Suppl 1: S53–S56.
454. Rottembourg J, Issad B, Guerret M, Lavene D, Baumelou A, Kiechel JR: Particularités d'utilisation de la guanfacine chez l'insuffisant rénal traité par dialyse péritonéale continue ambulatoire. In Structures cérébrales et contrôle tensionnel Paris: Sandoz; 1983: 165–172.
455. Raehl CL, Beirne GJ, Moorthy AV, Patel AK: Tocainide pharmacokinetics during continuous ambulatory peritoneal dialysis. Am J Cardiol 1987; 60: 747–750.
456. Bailie GR, Waldek S: Pharmacokinetics of flecainide in a patient undergoing continuous ambulatory peritoneal dialysis. J Clin Pharm Ther 1988; 13: 121–124.
457. Low CL, Phelps KR, Bailie GR: Relative efficacy of haemoperfusion, haemodialysis and CAPD in the removal of procainamide and NAPA in a patient with severe procainamide toxicity. Nephrol Dial Transplant 1996; 11: 881–884.
458. Sica DA, Yonce C, Small R, Cefali E, Harford A, Poynor W: Pharmacokinetics of procainamide in continuous ambulatory peritoneal dialysis. Int J Clin Pharmacol Ther Toxicol 1988; 26: 59–64.
459. Bourtron H, Singlas E, Brocard JF, Charpentier B, Fries D: Pharmacocinétique clinique du furosémide au cours de la dialyse péritonéale continue ambulatoire. Thérapie 1985; 40: 155–159.
460. Baumelou A, Singlas E, Merdjan H, et al: Pharmacocinétique des médicaments administrés par voie générale chez les malades traités par dialyse péritonéale continue ambulatoire. Sém Urol Néphrol 1985; 11: 124–136.
461. Martin V, Winne R, Prescott LF: Frusemide disposition in patients on continous ambulatory peritoneal dialysis. Brit J Clin Pharmacol 1991; 31: 227–228.
462. Lee CS, Peterson JC, Marbury TC: Comparative pharmacokinetics of theophylline in peritoneal dialysis and hemodialysis. J Clin Pharmacol 1983; 23: 274–280.
463. Jones TE, Reece PA, Fisher GC: Mexiletine removal by peritoneal dialysis. Eur J Clin Pharmacol 1983; 25: 839–840.
464. Olson SC, Horvath AM, Michniewicz BM, Sedman AJ, Colburn WA, Welling PG: The clinical pharmacokinetics of quinapril. Angiology 1989; 40: 351–359.

465. Blackwell BG, Leggett JE, Johnson CA, Zimmerman SW, Craig WA: Ampicillin and sulbactam pharmacokinetics and pharmacodynamics in continuous ambulatory peritoneal dialysis (CAPD). Perit Dial Int 1990; 10: 221–226.
466. Somani P, Freimer EH, Gross ML, Higgins JT, Jr: Pharmacokinetics of imipenem-cilastatin in patients with renal insufficiency undergoing continuous ambulatory peritoneal dialysis. Antimicrob Agents Chemother 1988; 32: 530–534.
467. Chan CY, Lai KN, Lam AW, Li PK, Chung WW, French GL: Pharmacokinetics of parenteral imipenem/cilastatin in patients on continuous ambulatory peritoneal dialysis. J Antimicrob Chemother 1991; 27: 225–232.
468. Boelaert J, Daneels R, Schurgers M, Mellows G, Swaisland AJ, Lambert AM, Van Landuyt HW: Effect of renal function and dialysis on temocillin pharmacokinetics. Drugs 1985; 29 (suppl 5): 109–113.
469. Pancorbo S, Compty C: Pharmacokinetics of cefamandole in patients undergoing continuous ambulatory peritoneal dialysis. Perit Dial Bull 1983; 3: 135–137.
470. Janicke DM, Morse GD, Apicella MA, Jusko WJ, Walshe JJ: Pharmacokinetic modeling of bidirectional transfer during peritoneal dialysis. Clin Pharmacol Ther 1986; 40: 209–218.
471. Bliss M, Mayersohn M, Arnold T, Logan J, Michael UF, Jones W: Disposition kinetics of cefamandole during continuous ambulatory peritoneal dialysis. Antimicrob Agents Chemother 1986; 29: 649–653.
472. Bunke CM, Aronoff GR, Brier ME, Sloan RS, Luft FC: Cefazolin and cephalexin kinetics in continuous ambulatory peritoneal dialysis. Clin Pharmacol Ther 1983; 33: 66–72.
473. Paton TW, Manuel MA, Cohen LB, Walker SE: The disposition of cefazolin and tobramycin following intraperitoneal administration in patients on CAPD. Perit Dial Bull 1983; 3: 73–76.
474. Morrison G, Audet P, Peingold R, Murray T: Cefazolin: the cephalosporin antibiotic of choice in CAPD patients [abstract]. Kidney Int 1999; 21: 174 (abstract).
475. Mendes P, Lameire N, Rosenkranz B, Malerczyk V, Damm D: Pharmacokinetics of cefodizime during continuous ambulatory peritoneal dialysis. J Antimicrob Chemother 1990; 26 (suppl C): 89–93.
476. Keller E, Jansen A, Pelz K, Hoppe-Seyler G, Schollmeyer P: Intraperitoneal and intravenous cefoperazone kinetics during continuous ambulatory peritoneal dialysis. Clin Pharmacol Ther 1984; 35: 208–213.
477. Hodler JE, Galeazzi RL, Frey B, Rudhardt M, Seiler AJ: Pharmacokinetics of cefoperazone in patients undergoing chronic ambulatory peritoneal dialysis: clinical and pathophysiological implications. Eur J Clin Pharmacol 1984; 26: 609–612.
478. Johnson CA, Zimmerman SW, Reitberg DP, Whall TJ, Leggett JE, Craig WA: Pharmacokinetics and pharmacodynamics of cefoperazone-sulbactam in patients on continuous ambulatory peritoneal dialysis. Antimicrob Agents Chemother 1988; 32: 51–56.
479. Leehey DJ, Reid R, Chan AY, Ing TS: Cefoperazone in the treatment of peritonitis in continuous ambulatory peritoneal dialysis patients. Artif Organs 1988; 12: 482–483.
480. Schuring R, Kampf D, Spieber W, Weihermuller K, Becker H: Cefotaxime pharmacokinetics in peritoneal dialysis. In Advances in Peritoneal Dialysis. Edited by Gokal R, Kessel M, Nolph KD. Amsterdam: Excerpta Medica; 1981: 96–98.
481. Alexander D, Bamertoglio J, Barriere S, Warnock D, Schoenfeld P: Cefotaxime pharmacokinetics in peritoneal dialysis [abstract]. Clin Pharmacol Ther 1984; 35: 225.
482. Matouscovic K, Moravek J, Vitko S, Prat V, Horcickova M: Pharmacokinetics of intravenous and intraperitoneal cefotaxime in patients undergoing CAPD. Perit Dial Bull 1985; 5: 33–35.
483. Albin HC, motes-Mainard FM, Bouchet JL, Vincon GA, Martin-Dupont C: Pharmacokinetics of intravenous and intraperitoneal cefotaxime in chronic ambulatory peritoneal dialysis. Clin Pharmacol Ther 1985; 38: 285–289.
484. Heim KL, Halstenson CE, Comty CM, Affrime MB, Matzke GR: Disposition of cefotaxime and desacetyl cefotaxime during continuous ambulatory peritoneal dialysis. Antimicrob Agents Chemother 1986; 30: 15–19.
485. Hasegawa H, Imada A, Horiuchi A, Nishii Y, Fukushima M, Kurokawa E: Pharmacokinetics of cefotaxime in patients undergoing haemodialysis and continuous ambulatory peritoneal dialysis. J Antimicrob Chemother 1984; 14 (suppl B): 135–142.
486. Petersen J, Stewart RD, Catto GR, Edward N: Pharmacokinetics of intraperitoneal cefotaxime treatment of peritonitis in patients on continuous ambulatory peritoneal dialysis. Nephron 1985; 40: 79–82.
487. Overgaard S, Lokkegaard N, Scroder S, Fugleberg S, Nielsen-Kudsk F: Cefotaxime disposition pharmacokinetics during peritoneal dialysis. Pharmacol Toxicol 1987; 60: 321–324.
488. Paap CM, Nahata MC, Mentser MA, Mahan JD, Puri SK, Hubbard JA: Cefotaxime and metabolite disposition in two pediatric continuous ambulatory peritoneal dialysis patients. Ann Pharmacother 1992; 26: 341–343.
489. Bald M, Rascher W, Bonzel KE, Muller-Wiefel DE: Pharmacokinetics of intraperitoneal cefotaxime in children with peritonitis undergoing continuous ambulatory peritoneal dialysis. Perit Dial Int 1990; 10: 311–313.
490. Browning MJ, Holt HA, White LO, Chapman ST, Banks RA, Reeves DS, Yates RA: Pharmacokinetics of cefotetan in patients with end-stage renal failure on maintenance dialysis. J Antimicrob Chemother 1986; 18: 103–106.
491. Brouard R, Tozer TN, Merdjan H, Guillemin A, Baumelou A: Transperitoneal movement and pharmacokinetics of cefotiam and cefsulodin in patients on continuous ambulatory peritoneal dialysis. Clin Nephrol 1988; 30: 197–206.
492. Greaves WL, Kreeft JH, Ogilvie RI, Richards GK: Cefoxitin disposition during peritoneal dialysis. Antimicrob Agents Chemother 1981; 19: 253–255.
493. Arvidsson A, Alvan G, Tranaeus A, Malmborg AS: Pharmacokinetic studies of cefoxitin in continuous ambulatory peritoneal dialysis. Eur J Clin Pharmacol 1985; 28: 333–337.
494. Veys N, Lameire N, Malerczyk V, Lehr KH, Rosenkranz B, Ringoir S: Single-dose pharmacokinetics of cefpirome in patients receiving hemodialysis and in patients treated by continuous ambulatory peritoneal dialysis. Clin Pharmacol Ther 1993; 54: 395–401.
495. Ryckelynck JP, Vergnaud M, Hurault de LB, Allouche G, Malbruny B, Morel C: [Pharmacokinetics of ceftazidime injected peritoneally in continuous ambulatory peritoneal dialysis]. Pathol Biol (Paris) 1986; 34: 328–331.
496. Comstock TJ, Straughn B, Kraus AP, Meyer MC, Finn AL, Chubb JM: Ceftazidime pharmacokinetics during continuous peritoneal dialysis (CAPD) and intermittent peritoneal dialysis (IPD) [abstract]. Drug IntellClin Pharm 1983; 17: 453.
497. Gross ML, Somani P, Ribner BS, Raeader R, Freimer EH, Higgins JT, Jr: Ceftizoxime elimination kinetics in continuous ambulatory peritoneal dialysis. Clin Pharmacol Ther 1983; 34: 673–680.

498. Burgess ED, Blair AD: Pharmacokinetics of ceftizoxime in patients undergoing continuous ambulatory peritoneal dialysis. Antimicrob Agents Chemother 1983; 24: 237–239.
499. Tomino Y, Fukui M, Hamada C, Inoue S, Osada S: Pharmacokinetics of cefdinir and its transfer to dialysate in patients with chronic renal failure undergoing continuous ambulatory peritoneal dialysis. Arzneimittelforschung 1998; 48: 862–867.
500. Johnson CA, Taylor CA, III, Zimmerman SW, Bridson WE, Chevalier P, Pasquier O, Baybutt RI: Pharmacokinetics of quinupristin-dalfopristin in continuous ambulatory peritoneal dialysis patients. Antimicrob Agents Chemother 1999; 43: 152–156.
501. Favre H, Probst P: Pharmacokinetics of ceftriaxone in continuous ambulatory peritoneal dialysis patients after intravenous administration to CAPD patients with and without peritonitis. Chemotherapia 1987; 6 (suppl 2): 273–274.
502. Zaruba K, Rastorfer M, Probst P: Pharmacokinetics of ceftriaxone in contiunous ambulatory peritoneal dialysis patientsafter intraperitoneal administration. Chemotherapia 1987, 6 Suppl 2: 267–270.
503. Koup JR, Keller E, Neumann H, Stoeckel K: Ceftriaxone pharmacokinetics during peritoneal dialysis. Eur J Clin Pharmacol 1986; 30: 303–307.
504. Ti TY, Fortin L, Kreeft JH, East DS, Ogilvie RI, Somerville PJ: Kinetic disposition of intravenous ceftriaxone in normal subjects and patients with renal failure on hemodialysis or peritoneal dialysis. Antimicrob Agents Chemother 1984; 25: 83–87.
505. Chan MK, Browning AK, Poole CJ, Matheson LA, Li CS, Baillod RA, Moorhead JF: Cefuroxime pharmacokinetics in continuous and intermittent peritoneal dialysis. Nephron 1985; 41: 161–165.
506. Dahl K, Walstad RA, Wideroe TE: The effect of peritonitis on the transperitoneal transport of cefuroxime in patients on CAPD treatment. Nephrol Dial Transplant 1990; 5: 275–281.
507. Davis GM, Forland SC, Cutler RE: Serum and dialysate concentrations of cephalexin following repeated dosing in CAPD patients. Am J Kidney Dis 1985; 6: 177–180.
508. Munch R, Steurer J, Luthy R, Siegenthaler W, Kuhlmann U: Serum and dialyzate concentrations of intraperitoneal cephalothin in patients undergoing continuous ambulatory peritoneal dialysis. Clin Nephrol 1983; 20: 40–43.
509. Johnson CA, Welling PG, Zimmerman SW: Pharmacokinetics of oral cephradine in continuous ambulatory peritoneal dialysis patients. Nephron 1984; 38: 57–61.
510. Singlas E, Boutron HF, Merdjan H, Brocard JF, Pocheville M, Fries D: Moxalactam kinetics during chronic ambulatory peritoneal dialysis. Clin Pharmacol Ther 1983; 34: 403–407.
511. Jones TE, Milne RW, Mudaliar Y, Sansom LN: Moxalactam kinetics during continuous ambulatory peritoneal dialysis after intraperitoneal administration. Antimicrob Agents Chemother 1985; 28: 293–298.
512. Pancorbo S, Comty C: Peritoneal transport of vancomycin in 4 patients undergoing continuous ambulatory peritoneal dialysis. Nephron 1982; 31: 37–39.
513. Blevins RD, Halstenson CE, Salem NG, Matzke GR: Pharmacokinetics of vancomycin in patients undergoing continuous ambulatory peritoneal dialysis. Antimicrob Agents Chemother 1984; 25: 603–606.
514. Rogge MC, Johnson CA, Zimmerman SW, Welling PG: Vancomycin disposition during continuous ambulatory peritoneal dialysis: a pharmacokinetic analysis of peritoneal drug transport. Antimicrob Agents Chemother 1985; 27: 578–582.
515. Mounier M, Benevent D, Denis F: Pharmacocinétique de la vancomycine chez les patients insuffisants rénaux chroniques en dialyse péritonéale continue ambulatoire. Pathol Biol (Paris) 1985; 33: 542–544.
516. Whitby M, Edwards R, Aston E, Finch RG: Pharmacokinetics of single dose intravenous vancomycin in CAPD peritonitis. J Antimicrob Chemother 1987; 19: 351–357.
517. Neal D, Bailie GR: Clearance from dialysate and equilibration of intraperitoneal vancomycin in continuous ambulatory peritoneal dialysis. Clin Pharmacokinet 1990; 18: 485–490.
518. Rubin J: Vancomycin absorption from the peritoneal cavity during dialysis-related peritonitis. Perit Dial Int 1990; 10: 283–285.
519. Traina GL, Gentile MG, Fellin G, Rosina R, Cavenaghi L, Buniva G, Bonati M: Pharmacokinetics of teicoplanin in patients on continuous ambulatory peritoneal dialysis. Eur J Clin Pharmacol 1986; 31: 501–504.
520. Janknegt R, Koelman HH, Nube MJ: Pharmacokineitcs of rifampicin and teicoplanin during CAPD. Med Sci Res 1987; 15: 171–172.
521. Br J Clin M, Traina GL, Gentile MG, Fellin G, Rosina R, Cavenaghi L, Buniva G: Pharmacokinetics of intraperitoneal teicoplanin in patients with chronic renal failure on continuous ambulatory peritoneal dialysis. Br J Clin Pharmacol 1988; 25: 761–765.
522. Guay DR, Awni WM, Halstenson CE, Kenny MT, Keane WF, Matzke GR: Teicoplanin pharmacokinetics in patients undergoing continuous ambulatory peritoneal dialysis after intravenous and intraperitoneal dosing. Antimicrob Agents Chemother 1989; 33: 2012–2015.
523. Shalit I, Greenwood RB, Marks MI, Pederson JA, Frederick DL: Pharmacokinetics of single-dose oral ciprofloxacin in patients undergoing chronic ambulatory peritoneal dialysis. Antimicrob Agents Chemother 1986; 30: 152–156.
524. Golper TA, Hartstein AI, Morthland VH, Christensen JM: Effects of antacids and dialysate dwell times on multiple-dose pharmacokinetics of oral ciprofloxacin in patients on continuous ambulatory peritoneal dialysis. Antimicrob Agents Chemother 1987; 31: 1787–1790.
525. Stuck AE, Frey FJ, Heizmann P, Brandt R, Weidekamm E: Pharmacokinetics and metabolism of intravenous and oral fleroxacin in subjects with normal and impaired renal function and in patients on continuous ambulatory peritoneal dialysis. Antimicrob Agents Chemother 1989; 33: 373–381.
526. Passlick J, Wonner R, Keller E, Essers L, Grabensee B: Single- and multiple-dose kinetics of ofloxacin in patients on continuous ambulatory peritoneal dialysis (CAPD). Perit Dial Int 1989; 9: 267–272.
527. Flor S: Pharmacokinetics of ofloxacin. An overview. Am J Med 1989; 87: 24S–30S.
528. Rosenkranz B, Malerczyk V, Zamba K, Jungbluth H, Lameire N: Pharmacokinetics of ofloxacin in CAPD [abstract]. Kidney Int 1991; 39: 1239 (abstract).
529. Kampf D, Borner K, Hain H, Conrad W: Multiple-dose-kinetics of ofloxacin after intraperitoneal application in CAPD patients. Perit Dial Int 1991; 11: 317–321.
530. Schmit JL, Hary L, Bou P, Renaud H, Westeel PF, Andrejak M, Fournier A: Pharmacokinetics of single-dose intravenous, oral, and intraperitoneal pefloxacin in patients on chronic ambulatory peritoneal dialysis. Antimicrob Agents Chemother 1991; 35: 1492–1494.

531. Nikolaidis P, Walker SE, Dombros N, Tourkantonis A, Paton TW, Oreopoulos DG: Single-dose pefloxacin pharmacokinetics and metabolism in patients undergoing continuous ambulatory peritoneal dialysis (CAPD). Perit Dial Int 1991; 11: 59–63.
532. Somani P, Shapiro RS, Stockard H, Higgins JT: Unidirectional absorption of gentamicin from the peritoneum during continuous ambulatory peritoneal dialysis. Clin Pharmacol Ther 1982; 32: 113–121.
533. Pancorbo S, Comty C: Pharmacokinetics of gentamicin in patients undergoing continuous ambulatory peritoneal dialysis. Antimicrob Agents Chemother 1981; 19: 605–607.
534. Paton TW, Manuel M, Walker SE: Tobramycin disposition in patients on continuous ambulatory peritoneal dialysis [abstract]. Perit Dial Bull 1982; 2: 179–181.
535. Bunke CM, Aronoff GR, Brier ME, Sloan RS, Luft FC: Tobramycin kinetics during continuous ambulatory peritoneal dialysis. Clin Pharmacol Ther 1983; 34: 110–116.
536. Walshe JJ, Morse GD, Janicke DM, Apicella MA: Crossover pharmacokinetic analysis comparing intravenous and intraperitoneal administration of tobramycin. J Infect Dis 1986; 153: 796–799.
537. Halstenson C, Matzke GR, Comty C: Intraperitoneal administration of tobramycin during CAPD [abstract]. Kidney Int 1984; 25: 256 (abstract).
538. Rubin J: Tobramycin absorption from the peritoneal cavity. Perit Dial Int 1990; 10: 295–297.
539. Sennesael JJ, Maes VA, Pierard D, Debeukelaer SH, Verbeelen DL: Streptomycin pharmacokinetics in relapsing Mycobacterium xenopi peritonitis. Am J Nephrol 1990; 10: 422–425.
540. Smeltzer BD, Schwartzman MS, Bertino JS, Jr: Amikacin pharmacokinetics during continuous ambulatory peritoneal dialysis. Antimicrob Agents Chemother 1988; 32: 236–240.
541. Anding K, Krumme B, Pelz K, Bohler J, Schollmeyer P: Pharmacokinetics and bactericidal activity of a single daily dose of netilmicin in the treatment of CAPD-associated peritonitis. Int J Clin Pharmacol Ther 1996; 34: 465–469.
542. Krediet R, Boeschoten E, Arisz L: Kanamycin as marker for middle molecular solute transport in CAPD patients with and withour peritonitis [abstract]. Blood Purif 1987; 5: 291 (abstract).
543. Martea M, Hekster YA, Vree TB, Voets AJ, Berden JHM: Pharmacokinetics of cephradine, sulfamethoxazole and trimethoprim and thier metabolites in a patient with peritonitis undergoing continuous ambulatory peritoneal dialysis. Pharm Weekbl Sci 1987; 9: 110–116.
544. Walker SE, Paton TW, Churchill DN, Ojo B, Manuel MA, Wright N: Trimethoprim-sulfamethoxazole pharmacokinetics during continuous ambulatory peritoneal dialysis (CAPD). Perit Dial Int 1989; 9: 51–55.
545. Rubin J, Planch A: Absorption of sulfamethoxazole and albumin from the peritoneal cavity. ASAIO Trans 1990; 36: 834–837.
546. Bouchet JL, Albin H, Quentin C, de BB, Vincon G, Martin-Dupont P, Potaux L, Aparicio M: Pharmacokinetics of intravenous and intraperitoneal fosfomycin in continuous ambulatory peritoneal dialysis. Clin Nephrol 1988; 29: 35–40.
547. Gerig JS, Bolton ND, Swabb EA, Scheld WM, Bolton WK: Effect of hemodialysis and peritoneal dialysis on aztreonam pharmacokinetics. Kidney Int 1984; 26: 308–318.
548. Nikolaidis P, Dombros N, Alexiou P, Balaskas E, Tourkantonis A: Pharmacokinetics of aztreonam administered i.p. in continuous ambulatory peritoneal dialysis (CAPD) patients. Perit Dial Int 1989; 9: 57–59.
549. Seth SK, Visconti JA, Hebert LA, Krasny HC: Acyclovir pharmacokinetics in a patient on continuous ambulatory peritoneal dialysis. Clin Pharm 1985; 4: 320–322.
550. Shah GM, Winer RL, Krasny HC: Acyclovir pharmacokinetics in a patient on continuous ambulatory peritoneal dialysis. Am J Kidney Dis 1986; 7: 507–510.
551. Burgess ED, Gill MJ: Intraperitoneal administration of acyclovir in patients receiving continuous ambulatory peritoneal dialysis. J Clin Pharmacol 1990; 30: 997–1000.
552. Schwenk MH, Halstenson C, Simpson ML, Pence TV, Reynolds DJ: Pharmacokinetics of zidovudine in an AIDS patient durin continuous ambulatory peritoneal dialysis [abstract]. Am Coll Clin Pharm 1990 (abstract), 1127.
553. Kerr CM, Perfect JR, Craven PC, Jorgensen JH, Drutz DJ, Shelburne JD, Gallis HA, Gutman RA: Fungal peritonitis in patients on continuous ambulatory peritoneal dialysis. Ann Intern Med 1983; 99: 334–336.
554. Fraser AK, O'Connor JP: Peritoneal penetration of amphotericin B [abstract]. Perit Dial Bull 1984; 4: 265 (abstract).
555. Debruyne D, Ryckelynck JP: Fluconazole serum, urine, and dialysate levels in CAPD patients. Perit Dial Int 1992; 12: 328–329.
556. Cecchin E, Panarello G, de March IS: Fungal peritonitis in ambulatory peritoneal dialysis. Ann Intern Med 1984; 100: 321 (letter).
557. Jones JM, Greenfeld RA: Administration of flucytosine to a patient on CAPD. Perit Dial Bull 1982; 2: 46–47.
558. Krediet R, Boeschoten E, Struijk D, Arisz L: Pharmacokinetics of intraperitoneally administered 5-fluorocytosine in continuous ambulatory peritoneal dialysis [abstract]. Nephrol Dial Transplant 1987; 2: 453 (abstract).
559. Doherty D, Seth S, Bay W: Fungal peritonitis and ketoconazole levels in a CAPD patient [abstract]. Perit Dial Bull 1984; 4: S20 (abstract).
560. McGuire N, Port FK, Kauffman CA: Ketoconazole pharmacokinetics in continuous ambulatory peritoneal dialysis. Perit Dial Bull 1984; 4: 199–201.
561. Valainis GT, Morford DW: Ketoconazole levels in peritoneal fluid. Perit Dial Bull 1985; 5: 136 (letter).
562. Gora ML, Visconti JA, Seth S, Shields B, Bay W: Pharmacokinetics of intraperitoneal metoclopramide in a patient with renal failure. Clin Pharm 1992; 11: 174–176.
563. Fitton A, Wiseman L: Pantoprazole. A review of its pharmacological properties and therapeutic use in acid-related disorders. Drugs 1996; 51: 460–482.
564. Boelaert JR, Schurgers ML, Matthys EG, Belpaire FM, Daneels RF, De Cre MJ, Bogaert MG: Comparative pharmacokinetics of recombinant erythropoietin administered by the intravenous, subcutaneous, and intraperitoneal routes in continuous ambulatory peritoneal dialysis (CAPD) patients. Perit Dial Int 1989; 9: 95–98.
565. Gahl GM, Passlick J, Pustelnik A, Kampf D, Grabensee B: Intraperitoneal versus intravenous recombinant erythropoietin in stable CAPD patients [abstract]. Proc 6th Congress EDTA/ERA Gothenburg 1990: 199.
566. Hughes RT, Cotes PM, Oliver DO, Pippard MJ, Royston P, Stevens JM, Strong CA, Tam RC, Winearls CG: Correction of the anaemia of chronic renal failure with erythropoietin: pharmacokinetic studies in patients on haemodialysis and CAPD. Contrib Nephrol 1989; 76: 122–130.

567. Kampf D, Kahl A, Passlick J, Pustelnik A, Eckardt KU, Ehmer B, Jacobs C, Baumelou A, Grabensee B, Gahl GM: Single-dose kinetics of recombinant human erythropoietin after intravenous, subcutaneous and intraperitoneal administration. Preliminary results. Contrib Nephrol 1989; 76: 106–110.
568. Macdougall IC, Roberts DE, Neubert P, Dharmasena AD, Coles GA, Williams JD: Pharmacokinetics of recombinant human erythropoietin in patients on continuous ambulatory peritoneal dialysis. Lancet 1989; 1: 425–427.
569. Stockenhuber F, Loibl U, Gottsauner-Wolf M, Jahn C, Manker W, Meisl TF, Balcke P: Pharmacokinetics and dose response after intravenous and subcutaneous administration of recombinant erythropoietin in patients on regular haemodialysis treatment or continuous ambulatory peritoneal dialysis. Nephron 1991; 59: 399–402.
570. Lui SF, Chung WW, Leung CB, Chan K, Lai KN: Pharmacokinetics and pharmacodynamics of subcutaneous and intraperitoneal administration of recombinant human erythropoietin in patients on continuous ambulatory peritoneal dialysis. Clin Nephrol 1990; 33: 47–51.
571. Hess B, Keusch G, Fluckiger J, Binswanger U: [Pharmacokinetics of phenytoin in continuous ambulatory peritoneal dialysis. 2 cases and brief review of the literature]. Schweiz Med Wochenschr 1984; 114: 16–19.
572. Jones CL, Vieth R, Spino M, Ledermann S, Kooh SW, Balfe J, Balfe JW: Comparisons between oral and intraperitoneal 1,25-dihydroxyvitamin D3 therapy in children treated with peritoneal dialysis. Clin Nephrol 1994; 42: 44–49.
573. Calvo R, Suarez E, Rodriguez-Sasiain JM, Martinez I: The influence of renal failure on the kinetics of intravenous midazolam: an “in vitro” and “in vivo” study. Res Commun Chem Pathol Pharmacol 1992; 78: 311–320.