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REVIEW ARTICLE

Clinical Pharmacokinetics of Drugs in Patients with Heart Failure: An Update (Part 2, Drugs Administered Orally)

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Abstract The purpose of the present review article is to update the information regarding pharmacokinetics of drugs in patients with heart failure that has accumulated since the last review article published in 1988 in *Clinical Pharmacokinetics.* Since this last review, our understanding of the pathophysiology of heart failure has changed from the cardio-renal model to the neuro-humoral model, and the pharmacologic approach to treatment of heart failure has been shifted from inotropic agents to those acting on the renin-angiotensin-aldosterone system. The pharmacologic agents now used for heart failure include many important classes of drugs, such as ACE inhibitors, angiotensin receptor blockers (antagonists) (ARBs), and mineralocorticoid receptor antagonists. In Part 1 of this review, we summarized the pharmacokinetic properties of relevant drugs administered intravenously. In Part 2, the present article, we describe pharmacokinetics of drugs following oral administration. For this purpose we conducted a systematic search of literature using MEDLINE, EMBASE, and Japan Centra Revuo Medicina (in Japanese). We retrieved a total of 110 relevant publications for 49 drugs and updated the information for ten drugs and provided new information for 31 drugs. We recognized that the pharmacokinetic data were obtained primarily from stable heart failure patients with moderate severity [New York Heart Association (NYHA) class II or III]. In addition, most patients were classified as heart failure with reduced ejection fraction. Furthermore, because most of the studies retrieved had no comparative groups of healthy subjects or patients without heart failure, historical controls from previous studies were used for comparisons. In Part 2, we also discuss the pharmacokinetics of active metabolites as well as parent drugs, because many drugs given by oral administration for the treatment of heart failure are prodrugs (e.g., ACE inhibitors and ARBs). The pharmacokinetic changes of drugs in patients with heart failure are discussed in the light of a physiologically based pharmacokinetic model. In addition, we discuss the effects of intestinal tissue heart failure-associated edema on drug absorption as it relates to the biopharmaceutical classification system, particularly for drugs demonstrating reduced systemic exposure as measured by the area under the plasma concentration–time curve after oral administration (AUC_{po}) in patients with heart failure as compared with healthy subjects. After review of the available data, it was seen that among patients with asymptomatic or compensated chronic heart failure there seemed to be no or minimal alterations in the maximum concentration (C_{max}) and AUC_{po} of the included drugs, unless there was concurrent liver and/or renal dysfunction. In contrast, the AUC_{po} of at least 14 drugs (captopril, cilazaprilat, enalapril/enalaprilat, perindopril, carvedilol, candesartan, pilsicainide, felodipine, furosemide, enoximone, milrinone, flosequinan, molsidomine, and ibopamine) were suspected or documented to increase after oral administration by 50 % or more in patients with symptomatic or decompensated heart failure.

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Key Points

In patients with compensated heart failure, only clinically insignificant changes were observed in the pharmacokinetics of orally administered drugs, unless they are complicated by liver and/or renal dysfunction.

In patients with decompensated heart failure, the oral pharmacokinetics of certain drugs may be altered, but the magnitude of changes would be at most a 50 % increase in the oral area under the plasma concentration–time curve as compared with those observed in patients without heart failure.

Since the pharmacokinetic data available in the literature were obtained mostly after a single oral administration and without appropriate control groups (e.g., healthy subjects or those with comparative clinical background except heart failure), further clinical trials conducted under long-term administration of drugs with relevant controls are needed.

1 Pathophysiological Changes in Heart Failure

Our understanding of the pathophysiology of heart failure has evolved from the traditional, cardio-renal model, for which cardiac glycosides and diuretics were the mainstay of pharmacotherapy, to the neuro-humoral model, where drugs acting on the renin-angiotensin-aldosterone system (RAAS) are the treatment of choice. As discussed in Part 1 of this review, heart failure may be defined as a complex clinical syndrome caused by the failure of the heart as a pump causing it to no longer meet the metabolic needs of the body, particularly during exercise and, in advanced stages, at rest [1]. Reduced cardiac output not only causes organ hypoxemia but diminishes delivery of drugs to the liver and the kidneys, the primary sites of drug elimination from the systemic circulation.

In response to reduced cardiac output, compensatory neuro-humoral reactions are triggered. These include the activation of the sympathetic nervous system, the RAAS, hypophyseal vasopressin secretion, and the proinflammatory cytokine system. It is now recognized that hypoxia and elevated proinflammatory cytokines may alter the expression of various drug-metabolizing enzymes and transporters [2–4]. These secondary pathophysiological reactions not only play important roles in the subsequent progression of heart failure but also in organ function, which may lead to alterations in the pharmacokinetics of therapeutic drugs. For example, the activation of the sympathetic nervous system may alter the distribution of blood supply to organs such that the perfusion of the splanchnic organs (e.g., the liver, gastrointestinal tract, and kidneys) is reduced to maintain blood supply to more vital organs, such as the brain and heart. As a result, the liver and kidneys are hypoperfused as compared with the brain and the heart.

Approximately one-half of patients with heart failure are known to have normal (preserved) ejection fraction (HF*p*EF), and the pathophysiological differences from those with reduced ejection fraction (HF*r*EF) have been the focus of intense discussion [5]. At present, most of the pharmacokinetic studies have been conducted with patients with HF*r*EF. In addition, the increased central venous pressure in patients with right-sided heart failure (RHF) leads to liver congestion and central vein dilation in the liver acinus, which may subsequently cause hepatocellular ischemia and necrosis [6]. While there is evidence showing that RHF causes hepatocellular necrosis, fibrosis, and microsomal enzyme reduction in animal experiments, the effects of RHF on the pharmacokinetics and disposition of drugs in humans remains largely to be studied [7].

According to a standard physiologically based pharmacokinetic (PBPK) model [8], the clearance of a drug by an organ is determined by blood flow (Q), the fraction of unbound drug in the blood (f_{ub}), and the intrinsic clearance (CL_{int}) of the drug by the organ. As a result, hepatic and renal clearance (CL_H and CL_R) of drugs may be altered in patients with newly developed or acutely exacerbated heart failure whose blood supply to the liver and the kidneys is substantially reduced. In addition, long-standing hypoperfusion and hypoxia may lead to structural damage to the liver and kidneys associated with diminished CL_{int} by these organs.

Intestinal absorption of drugs in patients with heart failure may be subject to changes associated with the reduced intestinal blood flow as well as from structural changes within the intestinal tissues. It has been long believed that patients with heart failure would have edematous changes in the intestinal wall as well as in peripheral tissues, and that this edema of intestinal tissue may impede the permeation of drugs from the gut lumen to epithelial cells and the transport of drugs from gut epithelial cells to portal blood flow. With use of transcutaneous ultrasonographic examination, a recent study [9] demonstrated that patients with heart failure have increased thickness of the bowel tissues from the terminal ileus to the colon compared with healthy subjects. In addition, it has been suggested that intestinal tissue damage secondary to chronic mucosal hypoperfusion and hypoxia may be associated with altered permeability to drugs. It was shown that intestinal wall tissue biopsied from patients with heart failure had significantly greater collagen content than

control subjects [10]. The permeability of the small and large intestine to hydrophilic sugar molecules was studied in patients with heart failure. Interestingly, it was shown that intestinal absorption of lactulose and mannitol (both by concentration-dependent passive diffusion) as well as D-xylose (via carrier-mediated transport) was increased compared with healthy subjects [9]. Drugs are transported from intestinal lumen to epithelial cells via transcellular and paracellular routes. The above data suggest that the integrity of the paracellular tight junction to sugar molecules may be damaged. In contrast, transcellular movement is the most common route of absorption for orally administered drugs, because most medicinal drugs are designed to be lipophilic enough to be transported via the transcellular route. Nevertheless, some drugs are hydrophilic and may be transported via the paracellular route. To determine whether the intestinal absorption of a drug in patients with heart failure is impeded compared with healthy subjects, a mass balance study with radio-labeled drugs may be required. However, it is practically impossible to conduct and, to our knowledge, no attempts have been made to answer this question.

Using the PBPK model and changes in the physiological parameters reported in the gastrointestinal tissues, the liver, and the kidneys, it may be possible to interpret, at least to some extent, reported changes in the pharmacokinetics of various drugs used in patients with heart failure. However, most patients with symptomatic heart failure often have comorbidities (e.g., diabetes mellitus, renal dysfunction) and are treated with various drugs, including ACE inhibitors [angiotensin II receptor blockers (ARBs)], β-adrenergic receptor antagonists (β-blockers), or diuretics. Theoretically, drug interactions with these drugs may alter physiological (e.g., organ perfusion) and/or pharmacokinetic parameters (e.g., alterations in f_{ub} and CL_{int} being attributable to inhibition of enzyme and transporter activities), and thus may further complicate the disposition of drugs administered orally in these patients.

2 Alterations in the Pharmacokinetics of Orally Administered Drugs

2.1 Absorption

The area under the plasma concentration–time curve (AUC) after oral administration (AUC_{po}) is defined by Eq. 1:

$$AUC_{po} = F_{oral} \cdot D/CL \quad (1)$$

where D is the oral dose and CL is the systemic clearance. F_{oral} is the absolute oral bioavailability; it may be considered as a product of F_a, F_{GI}, and F_H (i.e., $F_a \cdot F_{GI} \cdot F_H$), where F_a is the fraction of the orally administered drug entering the intestinal tissues, F_{GI} is the fraction of the drug escaping from the loss in the gastrointestinal wall due to metabolism or efflux to the intestinal lumen, and F_H is the fraction of the drug avoiding lost from the extraction in the liver during the hepatic first-pass. While the F_{oral} of a drug can be calculated by the ratio of AUC_{po} to the AUC after intravenous administration (AUC_{iv}), it is difficult to estimate the values of each component consisting of F_{oral} separately. Specifically, F_a may be estimated by a mass balance study using a radio-labeled drug conducted during an early developmental clinical study (phase I) in a small number of healthy subjects. Changes in F_a may be of concern in patients with heart failure, because they were shown to have thickened intestinal walls compared with healthy subjects, as described above [10]. For drugs with low permeability to the intestinal tissues, mucosal edema may impede their transport into the intestinal tissues.

2.1.1 The Biopharmaceutical Classification System and Oral Absorption of Drugs

The Biopharmaceutics Classification System (BCS) was developed by Amidon and co-workers for predicting the oral absorption of drugs based upon their water solubility and intestinal permeability [11]. A drug is considered to be highly soluble when the highest available strength is soluble in 250 mL or less of aqueous media over a pH range of 1.0–7.5 at 37 °C. A drug is considered to be highly permeable to the intestinal tissue when the extent of intestinal absorption in humans is determined to be >90 % of an orally administered dose based on a mass balance study or in comparison to an intravenous reference dose. In a subsequent study [12], Amidon and colleagues proposed that a drug might be considered highly permeable to the intestinal tissue if its LogP value (i.e., *n*-octanol/water partition coefficient) is greater than that of metoprolol (1.72), having an F_a of 95 % by a clinical mass balance study. According to these two criteria, drugs are classified into one of the four categories of BCS. Drugs assigned to Class 1 are rapidly and completely absorbed after the oral administration. In 2000 the US Food and Drug Administration (FDA) adopted BCS as a tool for determining waiver of in vivo bioavailability and bioequivalence testing [13]. Since then, immediate-release solid dosage forms of Class 1 drugs have been granted a biowaiver based on these two clinical studies. We hypothesize that the absorption of Class 1 drugs may be unlikely to be altered by pathophysiological changes of the gut associated with heart failure. In contrast, the absorption of drugs assigned to Class 4 (low solubility and low permeability) may be more susceptible to alterations in intestinal absorption, because the absorption of these drugs are often erratic and

incomplete after oral administration in healthy subjects. For instance, it was shown earlier that the mean AUC_{po} of a Class 4 drug, furosemide, in patients with heart failure was much lower than that of healthy subjects [14, 15]. Another example of Class 4 drug is candesartan cilexetil. Its F_{oral} is low and variable, ranging from 15 to 42 % in patients with heart failure [16, 17]. This drug is discussed in more detail in this review. In this context, we describe BCS classes of each drug discussed in this review separately below. BCS classification of the drugs discussed in the present article was largely retrieved from previous reports by Amidon's group [11, 18]. If no information was available, it was estimated using the data obtained from the *Merck Index* [19] and other sources.

2.2 Oral Clearance

In the present article, alterations in AUC_{po} in patients with heart failure are discussed separately for those eliminated mainly by the liver and those eliminated mainly by the kidneys.

2.2.1 Drugs Eliminated Mainly by the Liver

According to one of the most widely used PBPK models (the well-stirred model), AUC_{po} of drugs that are eliminated mainly by the liver may be described as Eq. 2:

$$AUC_{po} = F_a \cdot F_{GI} \cdot D/\left(f_{ub} \cdot CL_{int,H}\right) \quad (2)$$

Where f_{ub} is the fraction of unbound drug in blood and $CL_{int,H}$ is the hepatic intrinsic clearance, representing the metabolic activity for the drug. Following intravenous administration, the AUC_{iv} of a drug eliminated mainly by the hepatic metabolism is dominated either by the hepatic blood flow (Q_H) for a drug having high CL_H (flow-dependent) or $f_{ub}{\cdot}CL_{int,H}$ for a drug having low CL_H (capacity-limited), depending on its drug-metabolizing enzyme activity ($f_{ub}{\cdot}CL_{int,H}$) as described in Part 1 of this review. However, after oral administration, the AUC_{po} of a drug is dominated by $f_{ub}{\cdot}CL_{int,H}$ irrespective of its CL_H.

As for possible mechanisms associated with altered drug-metabolizing activities ($CL_{int,H}$) in patients with heart failure, these remain largely to be investigated in humans. However, assuming that drugs assigned to BCS Class 1 (i.e., having high solubility and permeability) may be less susceptible to heart failure-associated changes in $F_a{\cdot}F_{GI}$, changes in AUC_{po} may be attributable to changes in $f_{ub}{\cdot}CL_{int,H}$.

2.2.2 Drugs Mainly Eliminated by the Kidney

For drugs that are eliminated mainly by the kidneys as unchanged form, F_H may be considered largely unity. For drugs that are not substrates of extrusion transporters expressed at epithelial cells of the intestinal wall, the F_{GI} would also be largely unity. As a result, the AUC_{po} for such a drug may be described as Eq. 3:

$$AUC_{po} = F_a \cdot D/CL_R \quad (3)$$

where CL_R is the renal plasma clearance of the drug. In healthy subjects the glomerular filtration rate (GFR) is approximately 120 mL/min (7.2 L/h). When a drug is low protein binding in plasma (i.e., $C_u = C_p$) and is eliminated by an active renal tubular excretion clearance of >450 mL/min, its renal extraction ratio [E_R, defined as CL_R/renal plasma flow (Q_R; 650 mL/min)], would be >0.7. For those drugs, CL_R will be described primarily by Eq. 4:

$$CL_R = Q_R \quad (4)$$

Therefore, the CL_R of such a drug would be considered flow dependent. A typical drug of this class is para-aminohippuric acid (PAH); it has an E_R of >0.80 [20]. Reviewing the literature, however, only a few medicinal drugs may be considered to be assigned to this class. For instance, metformin with a CL_R of 550 mL/min [21], some antiviral agents (e.g., peniciclovir, an active metabolite of famciclovir) with a CL_R of 450 mL/min [22], and captopril with a CL_R of 460 mL/min may be considered part of this group. At present, to our knowledge, no relevant literature has been reported regarding the changes in CL_R and systemic clearance of these drugs in patients with heart failure.

On the other hand, when the CL_R of a drug is small relative to Q_R (i.e., E_R <0.3 or 200 mL/min), its CL_R is described largely by Eq. 5:

$$CL_R = f_{ub} \cdot CL_{int,R} \quad (5)$$

where $CL_{int,R}$ is the intrinsic clearance of the kidneys. The $CL_{int,R}$ may consist of glomerular filtration, active tubular secretion, and tubular reabsorption. For these drugs, reduction in renal blood flow will not affect CL_R substantially, but reductions in GFR and tubular secretion associated with a reduction in the number of functional nephrons will affect the CL_R. There are many drugs in this class and their CL_R is considered capacity limited. The CL_R of these drugs may be reduced when renal damage secondary to heart failure or co-morbidities severely reduce glomerular filtration.

2.2.3 Drugs Whose Elimination Depends on the Liver and the Kidney to a Similar Extent

For drugs that are eliminated by the liver and the kidney to a similar extent (e.g., approximately 50 % each), their AUC_{po} will be described by Eq. 6:

$$\begin{aligned} AUC_{po} &= F_{oral} \cdot D/CL \\ &= F_a \cdot F_{GI} \cdot F_H \cdot D/(CL_H + CL_R) \\ &= F_a \cdot F_{GI} \cdot D/\left(f_{ub} \cdot CL_{int,H} + CL_R/F_H\right) \end{aligned} \quad (6)$$

For these drugs it would be difficult to attribute the observed changes in AUC_{po} to any of the parameters of the equation categorically. Taking the above discussion into account, we discuss the pharmacokinetic changes reported for specific drugs below.

2.3 Pharmacokinetics of Active Metabolites

Recently, a number of orally administered drugs are being formulated as prodrugs in order to improve their oral absorption, including many of the ACE inhibitors and ARBs on the market. For these drugs, active metabolites are generated during the first pass through the intestines and liver by enzymatic reactions (e.g., esterase). As a result, the clinical effects of these drugs should be interpreted in the light of the AUCs of the respective active metabolites rather than the parent drugs, particularly when the pharmacological activity of the active metabolite surpasses the parent drugs. When the activity of enzymes involved in the formation of active metabolites is high, the AUCs of active metabolites are largely dependent on the F_a of the parent drugs and the systemic clearance of active metabolites. In this context, in this review we describe the AUC and clearance, if available, of active metabolites.

3 Pharmacokinetics of Specific Drugs in Patients with Heart Failure

The latest review article on clinical pharmacokinetics in heart failure was published in 1988 by Shammas and Dickstein [23]. Since their article was published, additional data for new drugs have been obtained. The list of drugs for which pharmacokinetic data were either updated since their review or that are new is given in Table 1. For more detailed information on these drugs, please refer to Table 2.

3.1 β-Adrenergic Receptor Antagonists (β-Blockers)

3.1.1 Bisoprolol

Bisoprolol is a selective β_1-adrenoceptor antagonist that has been shown to improve cardiac function and reduce morbidity and mortality in patients with heart failure [24]. It has a high F_{oral} of 84–92 % in healthy subjects [25]. The drug is assigned to BCS Class 3. The clearance is 14.2–15.6 L/h (230–260 mL/min), to which CL_R and CL_H contribute equally [26, 27]. As a result, the CL_R and CL_H of the drug are capacity limited.

Nikolic and colleagues studied the pharmacokinetics of bisoprolol in 61 patients with heart failure [New York Heart Association (NYHA) class II or III] during the steady-state oral administration using non-linear mixed-effect modeling (NONMEM) [28]. They found that these patients had a mean oral clearance (CL_{po}) value (7.9 L/h or 131 mL/min) that was considered to be 25–35 % less than that reported for healthy subjects [26, 27]. However, it was unclear if the apparent difference would be statistically significant since no direct comparisons were made.

3.1.2 Carvedilol

Carvedilol is a non-selective β-blocker with α-adrenergic blocking actions [29, 30]. It is a racemic mixture, with the S(−) enantiomer possessing nonselective β_1- and β_2-blocking activity and the R(+) enantiomer having equal α- and β-adrenergic blocking activity. Carvedilol is assigned to BCS Class 2. The F_{oral} of carvedilol is low (about 25 %) due to the first-pass metabolism [31]. Carvedilol undergoes extensive hepatic metabolism via cytochrome P450 (CYP) enzymes, primarily CYP2D6 and CYP2C9; CL_{po} of the drug is decreased among patients with liver cirrhosis and those with genetic polymorphisms for poor metabolizers of *CYP2D6* [29, 31]. Increases in AUC_{po} for carvedilol have also been reported among patients with renal dysfunction and hypertension [32].

Tenero and colleagues investigated the pharmacokinetics of carvedilol in 22 male patients with NYHA class III or IV (or a history of class IV) heart failure in an open-label, non-comparative trial [33]. Carvedilol was given in escalating doses (6.25–50 mg) twice daily for 7 days at each dosage level. Results were reported for mean maximum concentration (C_{max}), AUC_{po}, and time to C_{max} (t_{max}) for each dosage level. For both AUC_{po} and C_{max}, values were higher for the same dose among patients with class IV heart failure than with class III. For the 6.25, 12.5, 25, and 50 mg dosages, the mean [standard deviation (SD)] values of C_{max} for class III patients were 22.1 (8.7), 40.9 (18.5), 96.2 (43.5), and 198 (84) ng/mL, respectively. The corresponding values among patients with class IV heart failure were 30.9 (33.9), 63.9 (39.3), 119 (88), and 212 (143) ng/mL, respectively. Similar results were reported for the AUC_{po}, with higher AUC_{po} reported for patients with class IV heart failure (at least 50 % higher) than for those with class III heart failure. A similar pattern of increase was seen for each of the enantiomers, with class IV heart failure patients having higher values for both C_{max} and AUC_{po}. The greatest increases were seen for the AUC_{po} of the R(+) enantiomer (50 % or more). t_{max} values were reported as

Table 1 Drugs retrieved in the literature search, grouped according to the status of their drug information: no update since the latest review [23], partially updated, and newly reviewed. Parentheses indicate Biopharmaceutics Classification System classes of the respective drug (see Sect. 2.1.1)

No updates	Updated	New
Amrinone (Class 3)	Bumetanide (Class 3)	Beta-methyldigoxin (Class 3)
Disopyramide (Class 1/3)	Captopril (Class 1/3)	Bisoprolol (Class 3)
Hydrochlorothiazide (Class 3)	Digoxin (Class 3)	Candesartan (Class 4)
Metolazone (Class 3)	Enalapril (Class 1)	Candesartan cilexetil (Class 4)
Prazosin (Class 1)	Flecainide (Class 1)	Carvedilol (Class 2)
Procainamide (Class 3)	Furosemide (Class 4)	Cibenzoline (Class 1)
Quinidine (Class 1)	Hydralazine (Class 1)	Cilazapril (Class 1)
Tocainide (Class 3)	Lisinopril (Class 3)	Enoximone (Class 2)
	Mexiletine (Class 1)	Felodipine (Class 2)
	Theophylline (Class 1)	Flosequinan (ND)
		Fluvoxamine (Class 1)
		Fosinopril (Class 2)
		Ibopamine (Class 2)
		Irbesartan (Class 2)
		Losartan (Class 2)
		Midazolam (Class 1)
		Molsidomine (Class 4)
		Nicorandil (Class 1)
		Nifedipine (Class 2)
		Omapatrilat (Class 2)
		Perindopril (Class 1)
		Pilsicainide (Class 1/3)
		Pimobendan (Class 2)
		Pindolol (Class 3)
		Prenalterol (ND)
		Quinapril (Class 2)
		Ramipril (Class 1)
		Rivaroxaban (Class 2)
		Tolvaptan (Class 2)
		Torsemide (Class 2)
		Xamoterol (Class 3)

ND no data were available for classifying the Biopharmaceutics Classification System

median differences between the regimens. Based on the 95 % confidence intervals (CIs), no significant differences were seen between the regimens for the t_{max}, with the exception of the 6.25 and 12.5 mg doses. The difference between these values (t_{max} of 6.25 mg group minus those of the 12.5 mg group) was −0.44 h (95 % CI −0.74 to −0.10). These data were not stratified by NYHA class.

No data are available for steady-state CL_{po} or AUC_{po} for healthy subjects or patients without heart failure under the same dosage regimens as the study of Tenero and colleagues [33]. Rather, the authors referred to their previous study [31] where the steady-state pharmacokinetics of carvedilol were studied in 13 hypertensive patients and 12 patients with chronic renal failure after oral administration of carvedilol 25 mg once daily. They described that the mean (SD) value for AUC_{po} from time zero to 12 h ($AUC_{po,12}$) obtained from patients with NYHA class IV given carvedilol 25 mg twice daily appeared to be approximately 60 % higher than the AUC_{po} from time zero to 24 h ($AUC_{po,24}$) obtained from patients with hypertension given carvedilol 25 mg once daily [667 (640) vs. 413 (247) ng·h/mL].

Nikolic and colleagues also studied the pharmacokinetics of carvedilol in 52 Caucasians with heart failure [NYHA class II (79 %) and III (21 %)] who received long-term oral administration of carvedilol [34]. They reported that the population mean value for CL_{po} of the drug would be 43.8 L/h and that body weight, co-administration of digoxin, and smoking were significant covariates for CL_{po}. The CL_{po} of R- and S-enantiomers of carvedilol were

Table 2 Summary of the effects of heart failure on pharmacokinetic parameters of retrieved drug after oral administration

Drugs	No. of patients (HF/control)	Ischemic HF (%)	NYHA class	LVEF (%)	Renal function	Liver function	Control data	ΔCL/F (%)	$\Delta V_d/F$ (%)	$\Delta t_{½}$ (%)	References
ACE inhibitors											
Captopril	7/0	0	II	NA	NA	NA	HTN patients	NA	NA	−60	[45, 161]
	5/0	0	III/IV	NA	NA	NA	HTN patients	NA	NA	−43	[45, 161]
	12/0	42	I/II	NA	CL_{CR} 76 mL/min	NA	HTN patients	−52	NA	+8	[161, 162]
Cilazaprilat[a]	11/0	100	II/III	NA	NA	NA	HTN patients	−36	NA	+82	[49, 163]
	10/0	NA	II/III	NA	NSD	NSD	HTN patients	−52	NA	+142	[47, 163]
Enalapril	8/4	13	III/IV	NA	SCr <1.5 mg/dL	LFT <1.5 × ULN	HTN patients	−78	NA	+70	[52]
	7/0	NA	III/IV	NA	NSD	NSD	HTN patients	+77	NA	NA	[52, 164]
Enalaprilat[b]	7/0	NA	III/IV	NA	NSD	NSD	HTN patients	−64	NA	+177	[52, 164]
	8/4	13	III/IV	NA	SCr <1.5 mg/dL	LFT <1.5 × ULN	HTN patients	−24	NA	+47	[52]
Fosinoprilat[c]	10/10	Mixed	II/III	32	SCr <1.8 mg/dL	LFT <2 × ULN	Age-, sex-, wt-matched	−14	NA	+29	[54]
Lisinopril	12/0	75	III/IV	NA	NA	NA	HTN patients	+20	NA	NA	[165, 166]
	5/6	NA	NA	NA	CL_{CR} 31 mL/min	NSD	Healthy elderly subjects	−27*	NA	NA	[57]
	6/0	NA	III/IV	NA	NSD	NSD	HTN patients	−49	NA	+116	[164, 166]
Omapatrilat	19/17	NA	II/III	23	NSD	NSD	Age-, sex-, race-, wt-matched	−30	NA	NA	[60]
Perindopril	10/6	70	III/IV	NA	SCr <2.0 mg/dL	NSD	Healthy volunteers	−75*	NA	+360*	[64, 167]
Perindoprilat[d]	10/6	70	III/IV	NA	SCr <2.0 mg/dL	NSD	Healthy volunteers	−16	NA	−92*	[64, 167]
Quinapril	11/0	36	II/III/IV	NA	SCr 1.3 mg/dL RD ($n = 4$)	LD ($n = 2$) NSD ($n = 9$)	Volunteers (CL_{CR} 30–60 mL/min)	−77	NA	NA	[168, 169]
Quinaprilat[e]	12/0	>58	II/III	NA	SCr 1.4 mg/dL	NSD	Volunteers (CL_{CR} 30–60 mL/min)	+111	NA	NA	[67, 169]
	12/0	NA	II/III	35–50 % ($n = 6$) <35 ($n = 6$)	CL_{CR} 72 mL/min	NSD	Volunteers (CL_{CR} 60–90 mL/min)	+69	NA	+29	[68, 169]
	11/0	36	II/III/IV	NA	SCr 1.3 mg/dL RD ($n = 4$)	LD ($n = 2$) NSD ($n = 9$)	Volunteers (CL_{CR} 30–60 mL/min)	+49	NA	NA	[168, 169]
Ramipril	12/0	100	II/III	NA	NA	NA	HTN patients (CL_{CR} 40–80 mL/min)	+3	NA	NA	[71, 170]
Ramiprilat[f]	12/0	100	II/III	NA	NA	NA	HTN patients (CL_{CR} 40–80 mL/min)	−1	NA	NA	[71, 170]

Table 2 continued

Drugs	No. of patients (HF/control)	Ischemic HF (%)	NYHA class	LVEF (%)	Renal function	Liver function	Control data	ΔCL/F (%)	$\Delta V_d/F$ (%)	$\Delta t_{½}$ (%)	References
β-Adrenergic receptor antagonists (β-blockers)											
Carvedilol (racemic)	10/0	NA	III	NA	NA	NA	HTN patients	−4	NA	NA	[32, 33]
	10/0	NA	IV	NA	NA	NA	HTN patients	−36	NA	NA	[32, 33]
	15/9[g]	0	II/III	36	NA	NA	Healthy adults	+10	NA	−44 %*	[38]
	173/0	52	NA	26	SCr <2.5 mg/dL	LFT <2 × ULN	HTN patients	−33	NA	NA	[32, 171]
	41/0[h]	0	NA	≥30 (n = 29) <30 (n = 12)	NA	NA	Healthy adults	−74	−94	NA	[39, 172]
	24/0	58	NA	NA	NA	NSD	Healthy Japanese volunteers	−32	NA	NA	[36, 173]
	58/0	<28	I/II/III/IV	29.4	NA	NA	Healthy Japanese volunteers	+3	+103	NA	[37, 173]
R-carvedilol	10/0	NA	III	NA	NA	NA	HTN patients	−1	NA	NA	[32, 33]
	10/0	NA	IV	NA	NA	NA	HTN patients	−34	NA	NA	[32, 33]
	173/0	52	NA	26	SCr <2.5 mg/dL	LFT <2 × ULN	HTN patients	−38	NA	NA	[32, 171]
	24/0	58	NA	NA	NA	NSD	Healthy Japanese volunteers	−21	NA	NA	[36, 173]
	58/0	<28	I/II/III/IV	29.4	NA	NA	Healthy Japanese volunteers	+15	+58	NA	[37, 173]
S-carvedilol	10/0	NA	III	NA	NA	NA	HTN patients	−25	NA	NA	[32, 33]
	10/0	NA	IV	NA	NA	NA	HTN patients	−40	NA	NA	[32, 33]
	173/0	52	NA	26	SCr <2.5 mg/dL	LFT <2 × ULN	HTN patients	−36	NA	NA	[32, 171]
	24/0	58	NA	NA	NA	NSD	Healthy Japanese volunteers	−37	NA	NA	[36, 173]
	58/0	<28	I/II/III/IV	29.4	NA	NA	Healthy Japanese volunteers	−3	+118	NA	[37, 173]
Pindolol	8/0	0	II/III	<45	NA	NA	HTN patients	+5	NA	+3	[174, 175]
Angiotensin II receptor blockers											
Candesartan[i]	5/0	40	II/III	NA	SCr <2.0 mg/dL	NA	HTN patients	−24	NA	+36	[79, 176]
	1/0[j]	NA	II	NA	NA	NA	HTN patients	−52	NA	NA	[79, 177]
Irbesartan	10/10	Mixed	II/III	26	NSD	NSD	Age-, sex-, race-, wt-matched	−14	NA	+3	[83]
Losartan	11/0	NA	II/III/IV	27	CL_{CR} >50 mL/min	NSD	Healthy volunteers	−18	NA	+57	[84, 86]
Antiarrhythmics, class Ia											
Cibenzoline	6/5	83	II/III	28	NSD	NSD	Healthy volunteers	−23	−26	±0	[94]

Table 2 continued

Drugs	No. of patients (HF/control)	Ischemic HF (%)	NYHA class	LVEF (%)	Renal function	Liver function	Control data	ΔCL/F (%)	$\Delta V_d/F$ (%)	$\Delta t_{½}$ (%)	References
Disopyramide	11/5	55	II/III/IV	25	SCr 1.3 mg/dL	NSD	Healthy volunteers	−6	+8	+19	[178]
	11/5	55	II/III/IV	25	SCr 1.3 mg/dL	NSD	Healthy volunteers	−25[k,*]	−8[k]	+26[k,*]	[178]
Quinidine	7/9	NA	NA	NA	NSD	NSD	Patients without HF, RD or LD	NA	NA	+14	[179]
Antiarrhythmics, class Ib											
Mexiletine	116/374	NA	I/II	NA	SCr 1.1 mg/dL	NSD	Patients without HF	−29*	NA	NA	[103]
	94/374	NA	III/IV	NA	SCr 1.2 mg/dL	NSD	Patients without HF	−48*	NA	NA	[103]
Antiarrhythmics, class Ic											
Flecainide	2/0	50	IV	NA	WNL	WNL	Patients without HF	NA	NA	+276	[98, 180]
Pilsicainide	3/14	33	II/III	29	NSD	NSD	PVC patients without HF	−50	NA	+123	[107]
Tocainide	7/7	71	II/III/IV	NA	NSD	NSD	VT patients without HF	−10	−11	+7	[181]
Digitalis											
Beta-methyldigoxin	4/0	NA	NA	NA	CL_{CR} 79 mL/min	NSD	Healthy volunteers	NA	NA	−12	[182, 183]
Digoxin	10/9	NA	NA	NA	CL_{CR} 65 mL/min	NA	AF patients without HF	−32	NA	NA	[184]
	8/0	75	NA	NA	CL_{CR} 46 mL/min	NA	Healthy volunteers	−17[l]	+97[l]	+114[l]	[116, 185]
	8/0	75	NA	NA	CL_{CR} 47 mL/min	NA	Healthy volunteers	−3[m]	+170[m]	+170[m]	[116, 185]
	30/0	NA	III/IV	<30	CL_{CR} 60 mL/min	NA	Healthy volunteers	−18	+32	NA	[118, 185]
	14/92	NA	NA	NA	CL_{CR} 11–131 mL/min[n]	NSD	Patients without HF	−6	NA	NA	[186]
	77/308	NA	NA	NA	SCr 1.0 mg/dL[n]	NSD	Patients without HF	−19*	NA	NA	[187]
	172[n]	NA	NA	NA	SCr 0.82 mg/dL[n]	NA	Patients without HF	−12*	NA	NA	[188]
	30/0[o]	0	NA	NA	CL_{CR} 48 mL/min	NA	Healthy adults	+32	+45	−3	[185, 189]
	10/2	50	NA	NA	NA	NA	Patients without HF	NA	NA	−20	[114]
	113/0	NA	NA	NA	SCr 1.43 mg/dL	WNL	Healthy volunteers	−9	+77	NA	[185, 190]
	117[n,p]	NA	NA	NA	SCr 0.31 mg/dL[n]	NA	Pediatric patients without HF	−10*	NA	NA	[191]
	147[n,q]	NA	NA	NA	NA	NA	Infant patients without HF	−12*	NA	NA	[192]
	9/0	44	II/III	36	SCr 0.86 mg/dL	NA	Healthy volunteers	−13	NA	NA	[185, 193]
	143[n]	NA	NA	NA	SCr 0.90 mg/dL[n]	NA	Patients without HF	−4*	NA	NA	[194]
	257/7[r]	NA	NA	NA	CL_{CR} 38 mL/min	NA	Pediatric patients without HF	−24	+75	NA	[195]
Dihydrophyridine calcium channel antagonists											
Felodipine	11/0	100	III	<40	NA	WNL	Healthy volunteers	−52	NA	+61	[110, 196]
	11/0	NA	II/III	NA	NA	NA	Healthy volunteers	−42	NA	–15	[196, 197]
Nifedipine	12/5	>42	III/IV	NA	NA	NA	Healthy volunteers	+7	NA	−10	[112]

Table 2 continued

Drugs	No. of patients (HF/control)	Ischemic HF (%)	NYHA class	LVEF (%)	Renal function	Liver function	Control data	ΔCL/F (%)	ΔV_d/F (%)	Δ$t_{½}$ (%)	References
Loop diuretics											
Bumetanide	6/4	NA	III/IV	20	CL_{CR} 45 mL/min	NSD	Healthy volunteers	−44[s]	NA	+66	[124]
	20/0	minor	I/II/III/IV	NA	CL_{CR} 89 mL/min	NA	Healthy volunteers	−36[s]	NA	+30	[14, 124]
Furosemide	20/0	minor	I/II/III/IV	NA	CL_{CR} 89 mL/min	NA	Healthy volunteers	NA	NA	+226	[14, 198]
	10/0	NA	NA	NA	WNL	WNL	Healthy volunteers	NA	NA	+317	[199]
	11/0	NA	III	NA	CL_{CR} 56 mL/min	NA	Healthy volunteers	+3,694 [l,t]	NA	+264 [l]	[125, 198]
	11/0	NA	III	NA	CL_{CR} 51 mL/min	NA	Healthy volunteers	+2,679[m,t]	NA	+245[m]	[125, 198]
	23/0	NA	III/IV	NA	CL_{CR} 60 mL/min	NA	Healthy volunteers	−74	+133	NA	[198, 200]
	19/0	NA	II/III	NA	CL_{CR} 73 mL/min	NA	Healthy volunteers	−47	NA	+152	[198, 201]
	18/0	NA	III/IV	≤40	SCr 1.4 mg/dL	NA	Healthy volunteers	−62	NA	+427	[128, 198]
	16/0	NA	II/III	≤40	CL_{CR} 80 mL/min	NSD	Healthy volunteers	−49	NA	+107	[126, 198]
Torsemide	19/0	NA	III/IV	≤40	SCr 1.4 mg/dL	NA	Healthy volunteers	−37	NA	+82	[128, 198]
	16/0	NA	II/III	≤40	CL_{CR} 80 mL/min	NSD	Healthy volunteers	−41	NA	+75	[126, 198]
Oral anticoagulants											
Rivaroxaban	6/0	33	III	22	CL_{CR} >80 mL/min ($n = 3$) CL_{CR} 50–80 mL/min ($n = 2$)	NA	Healthy volunteers	−50	NA	−15	[139, 141]
	12/0	33	III/IV	21	CL_{CR} >80 mL/min ($n = 7$) CL_{CR} 50–80 mL/min ($n = 2$) CL_{CR} 30 to <50 mL/min ($n = 3$)	NA	Healthy volunteers	−47	NA	−4	[139, 141]
Phosphodiesterase 3 inhibitors											
Amrinone	15/0	20	II/III/IV	NA	SCr 1.4 mg/dL	NA	Healthy volunteers	−22	NA	+33	[202, 203]
Enoximone	10/0	70	II/III/IV	NA	SCr 1.8 mg/dL	NA	Healthy volunteers	−72	NA	+166	[204, 205]
	7/2	NA	III/IV	≤45	NA	NA	Healthy volunteers	−58	NA	+26	[205]
Milrinone	26/0	NA	III/IV	NA	NA	NA	Healthy volunteers	−32	NA	+238	[206]
	22/13	58	NA	NA	NSD	NSD	Healthy volunteers	−70	−2	+164	[207]
Pimobendan (racemic)	8/0	0	III/IV	18	NA	NA	Healthy volunteers	+45	±0	+4	[208, 209]
(+)-Pimobendan	8/0	0	III/IV	18	NA	NA	Healthy volunteers	+52	±0	+19	[208, 209]
(−)-Pimobendan	8/0	0	III/IV	18	NA	NA	Healthy volunteers	+37	−5	−8	[208, 209]
Thiazide/thiazide-like diuretics											
Hydrochlorothiazide	7/0	0	NA	NA	CL_{CR} 51 mL/min	NA	Patients without HF	NA	NA	+46	[210, 211]
Metolazone	3/3	NA	NA	NA	CL_{CR} 101 mL/min	NA	Healthy volunteers	±0	NA	+41	[212]

Table 2 continued

Drugs	No. of patients (HF/control)	Ischemic HF (%)	NYHA class	LVEF (%)	Renal function	Liver function	Control data	ΔCL/F (%)	ΔV_d/F (%)	$\Delta t_{½}$ (%)	References
Vasodilators											
Flosequinan	8/0	NA	II/III	NA	CL_{CR} 32 mL/min	NA	Healthy volunteers	−87	NA	+231	[213, 214]
	18/0	89	II/III/IV	NA	SCr <3.4 mg/dL	LFT <2 × ULN	Healthy volunteers	−87	NA	+188	[214, 215]
Hydralazine	10/0	60	III	NA	SCr 0.8–2.7 mg/dL	NSD	Healthy volunteers	+311	NA	−35	[148, 216]
Molsidomine	9/0	NA	NA	NA	NA	decreased	Healthy volunteers	−67	NA	+163	[217, 218]
Nicorandil	25/0	48	II/III/IV	NA	NA	NA	Patients without HF	+28	NA	+53	[219, 220]
Others											
Fluvoxamine	10/10	30	III/IV	31	CL_{CR} 62 mL/min	WNL	Healthy elderly subjects	−21	−6	+19	[146]
Ibopamine	10/0	20	II/III/IV	NA	NA	NA	Healthy volunteers	−57[u]	NA	−84[u]	[221, 222]
	20/0	35	II	NA	SCr <1.5 mg/dL	LFT <1.5 × ULN	Healthy volunteers	−22[u]	NA	−18[u]	[222, 223]
	9/8	44	II	57	SCr ≤1.5 mg/dL	WNL	Healthy volunteers	−42[u]	NA	+26[u]	[222]
	9/8	67	III	44	SCr ≤1.5 mg/dL	WNL	Healthy volunteers	+28[u]	NA	+30[u]	[222]
	9/8	44	IV	23	SCr ≤1.5 mg/dL	WNL	Healthy volunteers	+16[u]	NA	+41[u]	[222]
Midazolam	6/6	NA	II/III	19	NA	NA	Age-, wt-matched healthy volunteers	−32	NA	+43	[155]
Prazosin	8/0	100	III/IV	NA	NA	NA	Healthy elderly subjects	−29	NA	+51	[224, 225]
Prenalterol	12/0	100	III/IV	NA	SCr 1.3 mg/dL	WNL	Healthy volunteers	−31	NA	NA	[226, 227]
Theophylline	11/15[v]	NA	II/III	NA	NA	NA	Geriatric subjects without HF	−48	+41	+124	[159]
	16/16[v]	NA	≥II	NA	NSD	NSD	Patients without HF	−43*	NA	NA	[160]

Table 2 continued

Drugs	No. of patients (HF/control)	Ischemic HF (%)	NYHA class	LVEF (%)	Renal function	Liver function	Control data	ΔCL/F (%)	ΔV_d/F (%)	$\Delta t_{½}$ (%)	References
Xamoterol	8/8	NA	II/III	NA	CL_{CR} 75 mL/min	NA	Age, sex-matched	−35	NA	−10	[228]

AF atrial fibrillation, CL_{CR} creatinine clearance, *CL/F* apparent oral clearance of the drug from plasma after oral administration, *CYP* cytochrome P450, *HF* heart failure, *HTN* hypertension, *LD* liver disease, *LFT* liver function test, *LVEF* left ventricular ejection fraction, *NA* no applicable data, *NSD* no significant disease, *NYHA* New York Heart Association, *PVC* premature ventricular contractions, *RD* renal disease, *SCr* serum creatinine, $t_{½}$ elimination half-life, *ULN* upper limit of normal, V_d/F apparent volume of distribution after non-intravenous administration, *VT* ventricular tachycardia, *WNL* within normal limits, *wt* bodyweight, + indicates increase compared with controls, − indicates decrease compared with controls

*Statistically significant ($p < 0.05$)

[a] Active metabolite of cilazapril

[b] Active metabolite of enalapril

[c] Active metabolite of fosinopril

[d] Active metabolite of perindopril

[e] Active metabolite of quinapril

[f] Active metabolite of ramipril

[g] Pediatric patients aged from 0.12 to 19.3 years old

[h] Pediatric patients aged from 0.07 to 19.3 years old

[i] Active metabolite of candesartan cilexetil

[j] A patient with *CYP2C9*1/*3* genotype

[k] Based on the free serum concentrations

[l] Data from decompensated state

[m] Data from compensated state

[n] Combined data from the all study participants (i.e., HF patients and controls)

[o] Pediatric patients aged from 2 to 14 years old

[p] Pediatric patients aged from 0.08 to 4.43 years old

[q] Infant patients aged from 31 to 362 days old

[r] Pediatric patients aged 7.3 ± 4.5 years old

[s] Renal clearance

[t] Vasko et al. [125] reported the area under the plasma concentration–time curve from time zero to infinity values, normalized to a 40 mg oral dose of furosemide, of 3.48 ± 0.72 and 4.75 ± 1.18 μg/min·mL for decompensated and compensated states, respectively. We considered that the unit was typographical error (i.e., the correct unit was μg·min/mL), but the reason why the values were so high was unclear

[u] As unbound blood epinine, the active metabolite of ibopamine

[v] Non-smokers

reported to be 107 and 146 L/h, respectively, in healthy subjects [35].

Horiuchi and colleagues measured peak and trough levels of the R(+) and S(−) enantiomers of carvedilol in blood samples drawn from 24 Japanese patients with heart failure treated long-term with carvedilol [36]. Doses of carvedilol ranged from 1.25 to 20 mg daily, with most patients ($n = 22$) receiving once-daily dosing. Genotyping for *CYP2D6* was also performed; patients were subsequently grouped based on the *CYP2D6* allele present. Peak blood concentrations of the R(+) enantiomer were higher than for the S(−) enantiomer. The etiology of heart failure and age had no significant effect on CL_{po} of either enantiomer. The presence of the *CYP2D6**10 allele also had no significant effect on CL_{po} of carvedilol enantiomers compared to other alleles. The authors suggested that heart failure itself reduced the metabolic activity of the CYP2D6 enzyme. Additionally, the authors compared the findings from this study to data on carvedilol from healthy volunteers and reported that the CL_{po} of both enantiomers of carvedilol was 25–29 % of that for healthy volunteers with *CYP2D6* alleles present. This suggested that all metabolic activity for carvedilol appeared to be reduced in the presence of heart failure.

In contrast to these findings, Saito and colleagues reported a reduction in CL_{po} of carvedilol among Japanese heart failure patients with certain *CYP2D6* genotypes [37]. Of 56 patients included in the trial, *CYP2D6* genotyping was available for 40 patients. For patients with *CYP2D6**1/*5, *5/*10, or *10/*10 alleles, CL_{po} of both enantiomers was lower than in those patients with *1/*1 or *1/*10 alleles. The reported mean (SD) CL_{po} values for the R(+) enantiomer were 0.23 (SD not reported), 0.33 (0.22), and 0.42 (0.08) L/h/kg in the former group versus 0.59 (0.29) and 0.64 (0.29) L/h/kg in the latter group, respectively. Corresponding values for the S(−) enantiomer were 0.40 (not reported), 0.51 (0.22), and 0.90 (0.13) L/h/kg vs. 1.07 (0.48) and 1.12 (0.45) L/h/kg, respectively. Both body weight and α_1-acid glycoprotein also influenced CL_{po} of carvedilol, increasing and decreasing CL_{po}, respectively.

The pharmacokinetics of carvedilol have also been investigated in pediatric patients with heart failure secondary to dilated cardiomyopathy or congenital heart disease [38]. Fifteen patients (aged 6 weeks to 19 years) were treated with carvedilol starting at a dose of 0.09 mg/kg twice daily and titrated to a maximum of 0.70 mg/kg/day (up to 50 mg/day). The pharmacokinetic parameters of carvedilol were determined at varying timepoints after the first dose of the drug in both patients and in nine healthy adult volunteers. Compared to adults, both the elimination half-life ($t_{½}$) and mean residence time (MRT) were shorter for pediatric patients—2.9 vs. 5.2 h for $t_{½}$ and 3.7 vs. 5.9 h for MRT ($p < 0.05$ for both comparisons). When patients were grouped by age (≤3.5 and >3.5 years), very young children had a significantly shorter $t_{½}$ [mean (SD); 2.24 (0.73) h] than adults [5.19 (1.90) h; $p < 0.05$]. Younger children also had a lower systemic exposure to carvedilol as shown by the AUC_{po} than older children [34.9 (18.8) vs. 53.9 (20.5) ng·h/mL; $p = 0.01$].

Albers and colleagues developed a pharmacokinetic model for carvedilol using data from 41 pediatric patients (aged 0.1–19.3 years) with heart failure [39]. Comparisons of model estimates to measured carvedilol plasma concentrations were done to evaluate the model, and the two were found to be in agreement [based on percentage of measured data (90 %) found to be within the 90th percentile of the model estimates]. Based on a model simulation of a 0.35 mg/kg dose given twice daily, the AUC_{po} was found to increase with age. The median (10th to 90th percentile) AUC_{po} for 1-, 7.5-, 14.5-, and 19.3-year-old patients were 113.2 (62.5–223.0), 153.9 (86.9–298.8), 300.1 (167.6–504.1), and 495.4 (260.3–903.3) µg·h/L, respectively. C_{max} also increased with age, with corresponding values for a 0.35 mg/kg dose of 37.6 (17.0–73.7), 43.7 (18.9–97.1), 87.0 (38.8–172.6), and 133.5 (66.4–285.6) µg/L. This trend was seen for all doses used in the simulations (0.5, 0.7, 1.0, and 1.5 mg/kg) for both AUC_{po} and C_{max}, suggesting that higher doses may be needed in very young children and adolescents to achieve an AUC_{po} comparable with that of an adult.

3.1.3 Metoprolol

Metoprolol is assigned to BCS Class 1. Its F_{oral} is low (50 %) due to an extensive first-pass effect. Metoprolol is eliminated mainly by hepatic metabolism and less than 5 % of the dose administered intravenously is recovered in the urine as unchanged drug [40].

Taguchi and colleagues performed a population pharmacokinetic analysis to investigate the effects of genetic polymorphisms of *CYP2D6* on the CL_{po} of metoprolol in 34 Japanese patients, of whom five had heart failure (four patients in NYHA class II and one patient in class III). The results showed that the presence of *CYP2D6**10 and age (>70 years) were significant covariates for $CL_{po,}$ but the presence of heart failure was not [41]. However, this study was underpowered for determining the effects of heart failure on the drug's pharmacokinetics, because only five patients with heart failure were enrolled in the study.

3.2 ACE Inhibitors

ACE inhibitors exert their effect by preventing the conversion of angiotensin I to angiotensin II, a potent vasoconstrictor [42]. The duration of action of most ACE inhibitors is about 24 h, with the exception of captopril and

benazepril, which have an action of about 6 h [43]. The onset of action is generally rapid (about 1 h). Routes of elimination are both renal and via the feces, with some agents, such as captopril, enalapril, lisinopril, perindopril, and quinapril, predominately excreted renally. Most ACE inhibitors are metabolized to active metabolites (e.g., enaraprilat for enalapril), except for captopril and lisinopril.

3.2.1 Captopril

Captopril is an active compound and does not need to be activated following systemic absorption. It is assigned to BCS Class 1/3, and its F_{oral} is reported to be 70–75 % [44]. Captopril is eliminated via the liver and the kidneys to a similar extent (50 % each), and its CL_R would be flow-dependent (460 mL/min). Nishida and colleagues evaluated the pharmacokinetics of captopril in 12 patients with heart failure; the cohort was grouped by NYHA heart failure class (I, II, and III) and given a single oral dose of 12.5 mg of captopril [45]. For all three groups, the mean t_{max} was 2 h. Mean (SD) values for C_{max} were 281 (116), 261 (151), and 274 (122) ng/mL for NYHA classes I, II, and III, respectively. Mean $t_{½}$ values for the three groups were 2.79, 4.00, and 3.16 h, respectively. The authors noted that both t_{max} and $t_{½}$ were prolonged compared with values reported for healthy volunteers or hypertensive patients, although the pharmacokinetics with AUC_{po} were not evaluated. The authors also performed additional analyses by dividing the patients into two groups by NYHA status: group I was comprised of seven patients with NYHA class II and group II included five patients with NYHA classes III and IV. A $t_{½}$ of 2.79 h was found for group I patients and 4.00 h for group II patients. Unfortunately, it is difficult to attribute the observed changes in the pharmacokinetic parameters to a single factor, because patients' liver and renal function were not reported.

3.2.2 Cilazapril

Cilazapril is assigned to BCS Class 1 and has an F_{oral} of 76 % [46]. Cilazapril is a prodrug and is rapidly hydrolysed by non-specific esterases to the active metabolite, cilazaprilat. The inhibition of ACE activity after the administration of cilazapril is largely attributable to cilazaprilat. Cilazaprilat is eliminated mainly in the urine as unchanged drug with a CL_R of 180 mL/min [46]. These data suggest the involvement of active secretion at least to some extent, and the CL_R of the drug is capacity limited.

After an oral administration, the plasma AUC_{po} of cilazapril was largely comparable with that of cilazaprilat. In one small trial, ten patients with NHYA class II or III heart failure received cilazapril 0.5 or 1 mg given once daily for 8 weeks [47]. In this study patients having renal or hepatic disease were excluded. The authors noted that, following a single dose, the pharmacokinetics of cilazaprilat in heart failure patients were similar those seen in healthy volunteers in a previous study [48]. However, accumulation of cilazaprilat was seen following multiple dosing with 0.5 mg—a 55 % increase in C_{max} (not statistically significant), a 57 % increase in trough (24-h) concentrations ($p < 0.05$), and a 77 % increase in AUC ($p < 0.05$). Similarly, plasma clearance was 46 % lower ($p < 0.05$). Accumulation was also seen with the 1 mg dose, but to a lesser extent.

Wiseman and colleagues reported similar results in a trial involving 21 patients with NYHA class II or III heart failure [49]. Cilazapril was given as 0.5, 1.25, or 2.5 mg single oral doses on three consecutive days followed by daily dosing for 6 weeks using the minimum effective dose. Again, the authors reported that plasma cilazaprilat concentrations after a single dose of cilazapril 0.5 mg were similar to those seen in healthy volunteers. The C_{max} and trough (24-h) concentrations and AUC_{po} with multiple dosing were 61, 94, and 101 % higher, respectively, than those seen with single-dose 0.5 mg in the same patients; these changes were greater than those seen in healthy volunteers given higher doses of cilazapril.

3.2.3 Enalapril

Enalapril is a prodrug and is metalized to its active metabolite (enalaprilat or MK422) during first-pass metabolism. The drug is assigned to BCS Class 1; its intestinal absorption is at least 61 % according to a mass balance study [50]. The renal elimination of enalaprilat is capacity limited ($CL_R = 222.4$ mL/min) [51]. Plasma concentrations of enalapril and enalaprilat were evaluated in eight patients with heart failure (NYHA class III or IV) and five patients with mild to moderate hypertension [52]. Patients with heart failure received sequential singe doses of enalapril of 2.5, 5, and 10 mg; patients with hypertension were given 20 mg twice daily or 40 mg once daily. Compared to hypertensive patients, those with heart failure showed prolonged $t_{½}$ for both enalapril and its metabolite. For the 5 and 10 mg doses, the mean (SD) $t_{½}$ for enalapril was 3.4 (1.5) and 5.8 (4.7) h, respectively. In contrast, the mean $t_{½}$ for the 20 and 40 mg doses was 2 h or less. For MK422, the mean $t_{½}$ for the 5 mg dose was 7.8 (5.0) h and for the 10 mg dose was 6.8 (2.5) h. Corresponding values for the 20 and 40 mg doses in hypertensive patients were 4.6 (2.0) and 5.3 (1.1) h, respectively. The mean CL_{po} of the drug was also lower among patients with heart failure (0.6–0.7 L/min) vs. hypertensive patients (2.5–2.7 L/min). In both groups, a disproportionate increase in the AUC_{po} of the parent compound enalapril was seen, with threefold or greater increases seen with a doubling of the dose. This

effect was not apparent for the metabolite, where increases in AUC were proportional to increases in dose.

3.2.4 Fosinopril

Fosinopril is assigned to BCS Class 2, and its F_{oral} is only 30 % [53]. According to data obtained from a mass balance study using ^{14}C-fosinopril, the low F_{oral} of the drug is due to incomplete absorption rather than a first-pass effect [53]. The F_{oral} of the drug obtained from patients with heart failure showed no significant difference from that obtained from healthy subjects [54]. Fosinopril is also a prodrug and is metabolized almost completely to its active metabolite, fosinoprilat. It is eliminated mainly by the liver via metabolism and to some extent via biliary excretion. The CL_R and non-CL_R of fosinoprilat are 17 and 28 mL/min, respectively; thus, its CL_R and CL_H are capacity limited [53]. In an open-label, crossover trial, Kostis and colleagues investigated the pharmacokinetics of both intravenous and oral fosinopril [54]. Ten patients with NYHA class II or III heart failure [left ventricular ejection fraction (LVEF) $\leq$ 40 %] and ten matched control subjects were given fosinopril 10 mg orally or 7.5 mg intravenously in a random sequence. Following oral administration of fosinopril, no statistically significant differences were seen in plasma fosinoprilat concentrations between patients and controls for any of the pharmacokinetic parameters measured. However, there were numeric differences between the groups. The mean (SD) $t_{½}$ was 14.2 (7.3) h for heart failure patients and 11.0 (5.2) h for controls. AUC_{po} [1,716 (808) vs. 1,489 (619) ng·h/mL] and C_{max} [196 (67) vs. 177 (64) ng/mL] were also higher among heart failure patients and CL_{po} was lower [452 (183) vs. 519 (153) mL/h], but again none of these differences reached statistical significance. Similar results were seen after intravenous administration of fosinopril.

3.2.5 Lisinopril

Lisinopril is assigned to BCS Class 2. Its mean F_{oral} is 25 % and shows a large inter-individual variability, ranging from 6 to 60 % [50, 55, 56]. Lisinopril is an active compound and does not undergo hepatic metabolism; it is eliminated via the urine unchanged. The F_{oral} of the drug was reported to be reduced to about 16 % in patients with stable NYHA class II to IV heart failure [55].

Gautam and colleagues compared the pharmacokinetics of lisinopril in three groups of patients: young healthy adults, elderly healthy adults, and patients with heart failure [57]. All participants were given lisinopril 5 mg daily for 7 days, and blood samples were obtained on days 1 and 7. The mean (standard error) CL_{po} of lisinopril was lower in heart failure patients [12.2 (3.7) mL/min] than in young and elderly adults [47.5 (8.3) and 20.8 (5.0) mL/min, respectively; $p < 0.05$]. The AUC_{po} from time zero to 96 h ($AUC_{po,96}$) was also highest among heart failure patients, followed by elderly adults then young adults [1195.9 (145.8) vs. 870.4 (139.2) vs. 526.2 (77.8) ng·h/mL]. The authors noted that creatinine clearance (CL_{CR}) (which was lower in elderly adults and heart failure patients than in young adults, $p < 0.05$) was significantly correlated with both lisinopril CL_{po} ($r = 0.63$, $p = 0.006$) and $AUC_{po,96}$ ($r = -0.67$, $p = 0.004$) [57]. The mean (SD) CL_{CR} values obtained for young healthy subjects, elderly healthy subjects, and elderly patients with heart failure were 111 (28), 67 (20), and 31 (30) mL/min, respectively. Collectively, the reduced CL_{po} of the drug in the elderly patients with heart failure was most likely due to reduced renal function rather than heart failure.

3.2.6 Omapatrilat

Omapatrilat is a BCS Class 2 drug with a low F_{oral} (20–30 %) [58]. Omapatrilat is an orally active compound. It is eliminated by hepatic metabolism but has no substantial concentrations of active metabolites in plasma [59]. An open-label, crossover trial was conducted with omapatrilat to determine the pharmacokinetics of the ACE inhibitor administered orally (25 mg) and intravenously (10 mg) [60]. The study included 19 patients with NYHA class II or III heart failure (LVEF <40 %) and 17 control subjects. For oral omapatrilat, the mean (SD) C_{max} was higher among heart failure patients than among controls [36.2 (20.2) vs. 22.9 (17.9) ng/mL] as was the AUC_{po} [59.7 (31.3) vs. 41.7 (25.4) ng·h/mL]. F_{oral} was also higher for heart failure patients [28.9 % (13.8) vs. 21.9 % (13.3)]. A similar trend of a higher C_{max} and AUC_{po} among heart failure patients was seen for the S-methyl omapatrilat metabolite, but not for S-methyl PMPA (where C_{max} and AUC were higher among controls).

3.2.7 Perindopril

Perindopril is in BCS Class 1. The F_{oral}, as perindopril erbumine, was demonstrated to be 75–95 % [61, 62]. Perindopril is an inactive prodrug and is converted extensively to its active metabolite, perindoprilat, by hydrolysis in the liver and subsequently to an inactive glucuronide form and others. The plasma $t_{½}$ of perindopril is short (0.8–1 h) and only 4–12 % of the oral dose is eliminated in the urine as an unchanged form. In contrast, perindoprilat is eliminated via the kidney with a CL_R of 170 mL/min (capacity limited) and $t_{½}$ of 3–10 h in healthy subjects [63].

Bellissant and Giudicelli compared the pharmacokinetics of perindopril between ten patients with NYHA class III

or IV heart failure and six healthy adults in two separate trials [64]. Patients with heart failure were given a single 4 mg dose of perindopril in an open-label trial; healthy adults were given single doses of 4, 8, and 16 mg in a crossover trial. Statistical analyses were done between the groups for the 4 mg dose of perindopril and its active metabolite, perindoprilat. For both the parent compound and its metabolite, mean (SD) C_{max} and AUC values were higher among patients with heart failure. For perindopril, C_{max} values for patients and healthy adults were 113 (40) vs. 87 (32) ng/mL ($p = 0.2036$). For AUC_{po}, the values were 544 (337) vs. 136 (33) ng·h/mL ($p = 0.0040$). t_{max} was also higher among patients, with values of 1.9 (1.2) vs. 0.8 (0.3) h ($p = 0.0224$), as were $t_{½}$ values [4.6 (1.9) vs. 1.0 (0.2) h, $p = 0.0002$] and MRT [6.9 (2.9) vs. 1.9 (0.4) h, $p = 0.0003$]. Because the F_{oral} of perindopril is high (75–95 %) and the magnitude of increases observed in the AUC_{po}, MRT, and $t_{½}$ (approximately fourfold increase) were much greater than that seen in C_{max} (approximately 30 % increase), it can be concluded that the metabolic conversion of perindopril to perindoprilat and possibly to other metabolites would be decreased in patients with severe heart failure as compared with healthy subjects.

As for perindoprilat, the C_{max} mean (SD) value was three times higher among heart failure patients [16 (8) ng/mL] than in healthy volunteers [5 (2) ng/mL, $p = 0.0023$]. The $t_{½}$ and MRT of perindoprilat in patients with heart failure were significantly reduced to approximately one-tenth of those in healthy subjects [3.5 (1.7) vs. 43.8 (13.2) h, $p = 0.0006$; and 6.1 (1.9) vs. 58.9 (19.4) h, $p = 0.0011$, respectively]. In contrast, the mean (SD) AUC from time zero to 72 h (AUC_{72}) of perindoprilat observed in the two groups was largely comparable: 109 (85) vs. 92 (30) for the patients with heart failure and healthy subjects, respectively. These findings appear to suggest that the elimination of perindoprilat would be augmented in the patients with heart failure. However, caution must be exercised for such an interpretation. First, $t_{½}$ values of perindoprilat reported by Bellissant and Giudicelli appeared to be much longer than those reported by others. Mean (SD) $t_{½}$ values of perindoprilat obtained from healthy subjects were much shorter than those of Bellissant and Giudicelli: 5 (0.8) h by Verpooten and colleagues [65] and 10.9 h by Lecocq et al. [63]. There is a description in the package labeling of perindopril that the apparent $t_{½}$ of perindopril is 3–10 h for the majority of the elimination; but there is a prolonged terminal $t_{½}$ of 30–120 h resulting from slow dissociation of perindoprilat from plasma and tissue angiotensin-converting enzyme binding sites. Collectively, it would be difficult to conclude that the clearance of perindoprilat is augmented substantially in patients with heart failure. It is also reported that the dose-interval AUC obtained from patients with heart failure was 40 % higher than that obtained from healthy subjects during repeated administration of perindopril. This finding indicates that the CL_{po} of perindopril would be reduced, and its formation clearance from perindopril is shown to be reduced.

3.2.8 *Quinapril*

Quinapril is in BCS Class 3, and its F_{oral} is reported to be 50 % [66]. Quinapril is a prodrug and is converted to its active metabolite, quinaprilat, after intestinal absorption. Squire and colleagues described the pharmacokinetics of quinapril and its metabolite following a 2.5 mg single oral dose given to 12 patients with NYHA class II or III heart failure [67]. The mean (SD) t_{max} for quinapril was 2.6 (1.2) h and 3.6 (0.8) h for its metabolite. The respective C_{max} values for quinapril and quinaprilat were 49.7 (30.9) and 51.0 (22.8) ng/mL, respectively. The AUC from time zero to 24 h (AUC_{24}) for quinaprilat was 422 (259) ng·h/mL. It is not clear if the patients with heart failure had altered pharmacokinetics, because no concurrent control subjects were included in the study. Nevertheless, it is interesting to compare these data with those obtained from healthy subjects. Elliott and colleagues performed a pharmacokinetic study of quinapril in ten young healthy volunteers after an oral dose of 2.5 mg and reported AUC_{72} of 288 ng·h/mL for quinaprilat, implying that patients with heart failure may have a greater AUC than healthy subjects.

The pharmacokinetics following multiple-dose administration of quinapril were evaluated by Begg and colleagues [68]. Quinapril 10 mg twice daily was given for up to 4 weeks to 12 patients with NYHA class II or III heart failure. The mean (SD) quinaprilat C_{max} was 362 (197) with a t_{max} of 1.88 (0.71) hours, a dose-interval AUC [AUC from time zero to 12 h (AUC_{12})] of 1,706 (533) μg·h/mL, and a $t_{½}$ of 3.7 (1.2) h. LVEF and $t_{½}$ were found to be significantly associated ($r^2 = 0.57$, $p = 0.005$).

3.2.9 *Ramipril*

Ramipril is assigned to BCS Class 1, and its F_{oral} is reported to be 50–60 % [69, 70]. A mass balance study using oral administration of ^{14}C-ramipril showed that 55 and 37 % of the radioactivity was recovered in urine and feces, respectively, in healthy subjects [69, 70]. Ramipril is a prodrug and is converted almost completely to its active metabolite, ramiprilat, in the liver [70]. Ramiprilat is eliminated mainly via the kidney with a mean (SD) CL_R of 40.3 (13.1) mL/min (capacity limited) [71]. However, Verho and colleagues reported that ramiprilat is also excreted into bile by as much as one-third the amount excreted in urine for 24 h after oral administration. This

was determined using a T-drain in eight patients who underwent cholecystectomy [72].

The pharmacokinetics of multiple-dose ramipril (5 mg once daily for 14 days) and its metabolite were evaluated in 13 patients with NYHA class II or III heart failure [71]. Based on data from 11 patients at day 14, the mean (SD) C_{max} of ramipril was 21.1 (14.8) ng/mL, with a t_{max} of 1.4 (0.9) h and an $AUC_{po,24}$ of 79.1 (57.6) ng·h/mL. The corresponding values for ramiprilat were 26.6 (10.0) ng/mL, 2.5 (1.4) h, and 238.3 (98.0) ng·h/mL. The C_{max} values for both ramipril and ramiprilat increased by 27 and 20 % from day 1 values, respectively, a non-significant increase. AUCs were also increased from day 1 to day 14, with greater increases seen for ramipril (a near twofold increase) than for ramiprilat (a 25 % increase), but neither difference was significant. There was, however, greater between-patient variability for ramipril AUC_{po} than for ramiprilat AUC. To our knowledge, no comparable data are available for healthy subjects except for those reported in a Japanese article. Kondo and colleagues [73] reported the plasma concentration of ramipril 5 mg given once daily for 15 days. The authors reported the mean (SD) C_{max} and the dose interval AUC on day 15 for ramipril and ramiprilat to be 18.8 (2.1) vs. 15.5 (2.2) ng/mL and 39.2 (6.0) vs. 102.8 (17.8) ng·h/mL, respectively. The C_{max} and AUC for ramiprilat obtained from the above-described patients with heart failure appeared to be greater than the corresponding values obtained from the healthy subjects. It remains to be confirmed if these differences are reproducible in a comparative study.

3.3 Angiotensin II Receptor Blockers

As their name implies, ARBs bind to the angiotensin II AT_1 receptor, blocking the action of angiotensin II [74]. Pharmacokinetic data in heart failure patients were available for four of the ARBs: candesartan, irbesartan, losartan, and valsartan. Both irbesartan and losartan undergo hepatic metabolism via CYP isoenzymes and are primarily eliminated via the biliary route (~70 %). About 14 % of a dose of losartan is metabolized by CYP3A4, CYP2C9, and CYP2C10 to an active metabolite (E3174) that has 10–40 times the potency of losartan [75]. Irbesartan also undergoes hepatic metabolism (via CYP2C9 and CYP3A4), but to inactive metabolites [74, 76]. Candesartan is available as an esterified prodrug (candesartan cilexetil) that undergoes conversion to the active candesartan in the gastrointestinal wall; it is 60 % renally eliminated [74, 77]. For valsartan, about 80 % of a dose is excreted unchanged in the feces, with about 25 % excreted renally [74, 78]. Losartan pharmacokinetics are affected by hepatic impairment, requiring lower doses; however, renal impairment does not have a significant effect [75]. No adjustments are needed for irbesartan in the presence of renal or hepatic impairment [76]. Renal impairment but not mild to moderate hepatic impairment may alter the pharmacokinetics of candesartan [77]. Valsartan pharmacokinetics are not affected by mild to moderate renal or hepatic dysfunction [78].

3.3.1 *Candesartan*

Candesartan cilexetil is assigned to BCS Class 4 and was reported to have low and variable F_{oral} ranging from 15 to 42 % [16, 17]. Candesartan cilexetil is a prodrug and is rapidly and completely metabolized to candesartan, an active moiety, during the first pass in the gastrointestinal tissues and the liver. Candesartan that reaches the systemic circulation is eliminated mainly via the kidneys. Its CL_R is considered capacity limited, because the average value obtained from hypertensive patients with normal renal function (CL_{CR} 70 mL/min/1.73 m^2) was 28 mL/min/1.73 m^2 [79]. Anpo and colleagues studied the pharmacokinetics of candesartan in five Japanese patients with NYHA class II or III heart failure after oral administration of candesartan cilexetil 4 mg. The patients were on average 68 years old and had moderate to severe renal dysfunction (the mean CL_{CR} was 32 mL/min). They had mean (SD) values for C_{max}, $AUC_{po,48}$ and $t_{½}$ of 57 (22) ng/mL, 825 (514) ng·h/mL, and 12.0 (2.9) h, respectively [80]. No direct comparisons were made with those patients without heart failure. However, these values appear largely comparable to those reported by Aoi [79]. They studied the pharmacokinetics of the drug in six elderly (mean age 67 years) hypertensive patients with normal renal function (the mean CL_{CR} was 70 mL/min/1.73 m^2) after an oral administration of the drug at the same dose; a C_{max} of 57 (12) ng/mL, $AUC_{po,48}$ of 577 (132) ng·h/mL, and $t_{½}$ of 11.7 (2.8) h were reported. Collectively, the pharmacokinetics of candesartan appear unaffected by mild to moderate heart failure, unless patients are complicated by concomitant renal dysfunction. Buter and colleagues [81] reported that there were negative correlations between AUC_{po} as well as $t_{½}$ of candesartan cilexetil and CL_{CR} in patients with normal to severely impaired renal function.

3.3.2 *Irbesartan*

Irbesartan is assigned to BCS Class 2. It is rapidly absorbed after oral administration, and its F_{oral} is reported to be 60–80 % [82]. Irbesartan is eliminated almost exclusively by either hepatic metabolism or by biliary excretion. The metabolites so far identified are pharmacologically inactive. Because its clearance is 157–176 mL/min in healthy subjects [82], its CL_H is considered capacity limited.

Kostis and colleagues compared the pharmacokinetics of irbesartan between heart failure patients and controls in

a crossover trial [83]. Ten patients with NYHA class II or III heart failure (LVEF <35 %) and ten matched controls were given 75 mg of irbesartan orally or as an intravenous infusion; the alternate treatment was given after a 7- to 10-day washout period. Blood samples were taken for up to 96 h after the dose for determination of pharmacokinetic parameters. The reported mean AUC_{po} for the heart failure patients was 8,308 vs. 7,182 ng·h/mL for controls (ratio 1.16, 95 % CI 0.93–1.44). For C_{max}, the corresponding values were 1,630 and 1,359 ng/mL, respectively (ratio 1.20, 95 % CI 0.85–1.70). The values for t_{max} (1.5 vs. 2.0 h) and $t_{½}$ (14.9 vs. 14.5 h) were similar between the groups. Overall, no significant differences were seen between the two groups.

3.3.3 Losartan

Losartan is assigned to BCS Class 2; it has a rather low F_{oral} (25–35 %) [84]. Because its clearance is 610 mL/min and the blood-to-plasma concentration ratio is 0.53, the low F_{oral} is most likely due to a first-pass effect. Losartan is extensively metabolized to its 5-carboxylic acid, E3174, with the metabolite eliminated by renal and non-renal routes equally. The CL_R of E3174 is capacity limited (25 mL/min). While both losartan and E3174 are considered to contribute to the pharmacologic action of losartan, E3174 may have a greater contribution to the prolonged hypotensive effects after oral administration because of its longer $t_{½}$ than losartan [85].

Lo and colleagues investigated the pharmacokinetics of losartan in 11 patients with heart failure (LVEF ≤45%) during an open-label crossover trial [86]. Patients received a 10 mg intravenous dose and a 50 mg oral dose of losartan for 7–8 days; each phase was separated by a 1-week washout period. For oral losartan, AUC_{po}, $t_{½}$, C_{max}, t_{max}, F_{oral}, and CL_{po} were determined; these parameters were also determined for the metabolite, E3174. Following repeated oral dosing of losartan, the mean (SD) AUC_{po} was reported as 577.2 (267.1) ng·h/mL, $t_{½}$ as 3.3 (1.4) h, C_{max} as 223.3 (199.4) ng/mL, t_{max} as 1.31 (0.93) h, F_{oral} as 35.5 % (95 % CI 29.3–43.0), and the CL_R as 42.6 (25.5) mL/min. For the metabolite, E3174, C_{max} was similar [222.9 (91.6) ng/mL], but both the t_{max} and $t_{½}$ were prolonged at 4.5 (1.1) and 7.6 (1.5) h, respectively, with a higher AUC [2,262.8 (1,225.4) ng·h/mL] and a lower clearance [18.1 (5.9) mL/min]. The authors compared these data with data from a previously published study in healthy adult volunteers. Mean CL_R values for losartan and E3174 in heart failure patients were lower than in healthy adults [72 (20.6) and 25.9 (6.9) mL/min, respectively] and AUC [476 (200) and 1,915 (538) ng·h/mL, respectively, in healthy adults] was higher, but no statistical analyses were done [84].

3.3.4 Valsartan

Valsartan is assigned to BCS Class 4 and has a low F_{oral} (25 %). It has no active metabolites and eliminated mainly (89 %) into the bile as unchanged drug [87]. Because the clearance [2.2 L/h (37 mL/min)] would be largely accounted for by hepatic elimination, its low F_{oral} is most likely due to incomplete intestinal absorption.

The pharmacokinetics of valsartan were investigated by Prasad and colleagues in an open-label trial enrolling 20 patients with NYHA class II or III heart failure (LVEF ≤40 %) [88]. Patients were given a 7-day treatment with 40, 80, and then 160 mg of valsartan administered every 12 h. Pharmacokinetic evaluations were done on the last day of the dosing period (i.e., days 7, 15, and 21). Values for C_{max}, t_{max}, minimum concentration (C_{min}), AUC_{po}, and $t_{½}$ increased proportional to the dose; approximately twofold between the dosages. For the 40 mg dose, mean (SD) C_{max}, t_{max} (median), C_{min}, AUC_{po}, and $t_{½}$ values were 1.94 (1.0) μg/mL, 3 h, 0.47 (0.3) μg/mL, 13.12 (7.2) μg·h/mL, and 5.2 (1.9) h, respectively. For valsartan 80 mg, the respective values were 3.95 (2.3) μg/mL, 2.5 h, 1.05 (0.8) μg/mL, 25.94 (15.7) μg·h/mL, and 6.5 (2.4) h. These values were increased for valsartan 160 mg: 6.40 (3.2) μg/mL, 3 h, 1.98 (1.6) μg/mL, 43.54 (25.9) μg·h/mL, and 6.6 (3.9) h, respectively. Age, NYHA class, and weight had no significant effects on the pharmacokinetics of valsartan.

Comparable pharmacokinetic data were obtained from six healthy Japanese subjects given 160 mg of valsartan orally once daily for 7 days [89]. The mean (SD) values for C_{max}, t_{max}, $AUC_{po,24}$, and $t_{½}$ obtained on day 7 were 3.72 (0.63) μg/mL, 3 h (as median), 21.6 (6.9) μg·h/mL, and 5.0 (0.9) h, respectively. These values appear to be similar to those obtained from patients with heart failure given valsartan 80 mg twice daily [88].

3.4 Antiarrhythmics

Antiarrhythmic agents are generally classified based on their pharmacologic actions [90]. Based on the Vaughn-Williams system, antiarrhythmics are categorized as class I (sodium channel antagonists), class II (β-blockers), class III (potassium channel antagonists), or class IV (calcium channel antagonists). However, some agents may exert multiple effects for control of heart rhythm and another classification system (i.e., Sicilian-Gambit) has been proposed and utilized.

3.4.1 Cibenzoline

Cibenzoline is a class I antiarrhythmic agent with some potassium and calcium channel blocking effects [91]. It is

used in the treatment of both supraventricular and ventricular arrhythmias. Cibenzoline is assigned to BCS Class 3. It has a high F_{oral} (92 %) and is eliminated mainly (86 %) into urine as unchanged drug [92]. Because the CL_R of cibenzoline (337–421 mL/min) far exceeds the CL_{CR}, active tubular secretion is involved in the renal elimination of the drug. The CL_R of the drug may be susceptible not only to the changes of CL_{CR} but also to changes in the Q_R [93]. Cibenzoline has a $t_{½}$ of about 7.5 h, which is prolonged in patients with renal failure.

Massarella and colleagues reported no significant differences in pharmacokinetic parameters evaluated between six patients with heart failure (NYHA class II or III) and five healthy controls [94]. Cibenzoline 80 mg was given as a single oral and intravenous dose simultaneously using a stable isotope technique. Mean (SD) values for oral cibenzoline for C_{max}, t_{max}, and AUC_{po} for heart failure patients were 327 (49) ng/mL, 1.4 (0.3) h, and 3,159 (1,290) ng·h/mL, respectively. Corresponding values for healthy controls were 313 (67) ng/mL, 1.5 (0.4) h, and 2,424 (1,165) ng·h/mL, respectively. Although not significantly different, apparent volume of distribution (V_d) was smaller in patients with heart failure than in controls [5.4 (1.0) vs. 7.3 (3.4) L/kg]. Values for clearance (total, renal, and non-renal) were also numerically smaller for heart failure patients than for healthy controls [488 (207), 289 (147), and 199 (120) mL/min vs. 636 (240), 385 (115), and 251 (167) mL/min, respectively]. Similar differences were seen for intravenous cibenzoline.

3.4.2 Flecainide

Flecainide is assigned to BCS Class 1; it is well-absorbed after oral administration and has good solubility. Flecainide is eliminated by both polymorphic hepatic metabolism (CYP2D6) and by renal elimination, largely to an equal extent, with a $t_{½}$ of 10–18 h [43, 95]. The $t_{½}$ is prolonged in poor metabolizers of CYP2D6 and in those with impaired renal function [96]. Both the CL_H and CL_R are capacity limited [95].

Franciosa and colleagues [97] reported in an abstract that patients with heart failure had a CL_{po} of the drug that was 20 % lower than that of the control group after oral administration of a single dose. However, the abstract has not been fully published as an original article. Cavalli and colleagues [98] reported that the $t_{½}$ of flecainide measured after discontinuation of the drug was prolonged to 41–45 h in patients with exacerbated NYHA class IV heart failure. The corresponding values for healthy subjects were 7–23 h. Unfortunately, no detailed information regarding the genotype of *CYP2D6*, renal function, and concomitantly administered drugs was available.

Nitsch and colleagues studied plasma trough concentrations of flecainide in 42 patients with heart failure (NYHA class III or IV) who were on a long-term flecainide therapy at a fixed oral dose of 100 mg twice daily [99]. They found that the mean (SD) plasma flecainide concentrations obtained from patients with NYHA class III or IV were in a toxic range, at 870 (150) ng/mL, and plasma drug concentrations showed a negative correlation with LVEF ($r = -0.60$). However, they did not report pharmacokinetic parameters and nor did they show comparisons with data obtained from patients with normal cardiac function. Therefore, no conclusions can be drawn regarding the effects of heart failure on flecainide disposition based on this study.

3.4.3 Mexiletine

Mexiletine, used for the treatment of ventricular arrhythmias, blocks the voltage-dependent fast sodium channel [100]. It is assigned to BCS Class 1. Mexiletine has high F_{oral} (80–90 %) and undergoes extensive hepatic metabolism after absorption to a number of inactive metabolites. Less than 10 % of the dose is eliminated in urine as unchanged drug. Its $t_{½}$ is about 10 h [101].

Vozeh and colleagues studied oral mexiletine pharmacokinetics in 27 patients with heart failure, eight patients with liver disease, and 23 cardiac patients without heart failure. Using a population pharmacokinetic analysis with NONMEM, they reported that the population mean CL_{po} was 0.38 L/h/kg, and neither heart failure nor sex were significant covariates of CL_{po} [102]. Kobayashi and colleagues investigated the effects of heart failure on CL_{po} of mexiletine in a large cohort of Japanese patients [103]. A total of 584 patients were included: 116 with NYHA class I or II heart failure, 94 with NYHA class III or IV, and 374 patients without heart failure (controls). Mexiletine (dose not specified) was given three or four times daily. Mean (SD) mexiletine CL_{po} [oral apparent total clearance (CL/F_{oral})] was 0.393 (0.082) for controls, 0.280 (0.10) for patients with NYHA class I or II ($p < 0.05$ vs. controls), and 0.205 (0.075) for NYHA class III or IV heart failure ($p < 0.05$ vs. both controls and NYHA class I or III patients). The authors also noted a significant effect of age on CL_{po} of mexiletine among controls, with a reduction in CL_{po} seen with an increase in age ($p < 0.01$); the effect of age among heart failure patients was not significant.

3.4.4 Pilsicainide

Pilsicainide is a pure sodium channel antagonist with slow recovery properties (Vaughan-Williams class Ic) that is used for the treatment of supraventricular and ventricular tachycardias [104]. It has been approved for the treatment

and prevention of atrial fibrillation in Japan and Korea. Pilsicainide is assigned to BCS Class 1 and is almost completely absorbed after oral administration (approximately 90 %). It is eliminated mainly into the urine as unchanged drug [cumulative amount of unchanged drug excreted into the urine (A_e) >90 %] [105]. Pilsicainide has a $t_{½}$ between 4 and 5 h, which is prolonged in the presence of renal impairment. Since pilsicainide is assigned to BCS Class 1, the intestinal absorption of the drug would unlikely be altered by intestinal tissue edema in patients with heart failure. Its CL_R is dominated by the active secretion, because the value far exceeds the GFR (230–380 mL/min/70 kg) [105]. According to its CL_R, the renal elimination of the drug is capacity limited. Indeed, Takabatake and colleagues demonstrated that the clearance of pilsicainide is negatively correlated with the creatinine clearance [106].

Yokota and colleagues [107] studied the pharmacokinetics and antiarrhythmic effects after oral administrations of pilsicainide at 50 and 100 mg in 17 patients. The authors analyzed the pharmacokinetic data in patients with NYHA class II or III heart failure ($n = 3$) compared with those without ($n = 14$) and found that the mean C_{max} obtained from the patients with heart failure after an oral dose of 50 mg was largely similar to that from those without heart failure [0.39 (0.04) vs. 0.36 (0.04)]. However, the mean AUC_{po} from time zero to infinity ($AUC_{po,\infty}$) and $t_{½}$ obtained from patients with heart failure appeared to be greater than from those without heart failure: 7.03 (0.94) vs. 3.48 (0.50) mg·h/mL for $AUC_{po,\infty}$ and 10.6 (1.4) vs. 4.8 (0.8) h for $t_{½}$, respectively. The data obtained after an oral administration of 100 mg showed a similar trend to that observed after an oral dose of 50 mg. No categorical statements can be drawn based upon these findings because the number of patients with heart failure was small, and no information was available on the renal function in these patients.

3.5 Calcium Channel Antagonists

Calcium, both intracellular and extracelluar, has an important function in the contraction of cardiac and vascular smooth muscle [95]. By reduction of the influx of calcium through voltage-sensitive channels within the muscle cells, the calcium channel antagonists cause relaxation of the vascular smooth muscle and vasodilation, with negative inotropic effects in cardiac muscle. However, the pharmacologic effects of the calcium channel antagonists differ between the individual agents, as do their pharmacokinetic properties. Felodipine and nifedipine are described as dihydropyridine calcium channel antagonists. Both of these agents undergo hepatic metabolism to inactive metabolites, followed by renal excretion. The $t_{½}$ of felodipine ranges from 11 to 16 h vs. about 2 h for nifedipine [43].

3.5.1 *Felodipine*

Felodipine is assigned to BCS Class 3. A mass balance study using ^{14}C-felodipine showed that the drug is rapidly and almost completely absorbed after oral administration [108]. Because the clearance of the drug is high (823 mL/min) and only negligible amounts are recovered in urine as unchanged form, it would undergo extensive hepatic metabolism with a flow-dependent clearance [108, 109]. The F_{oral} of the drug is low (range 10–23 %) due to extensive hepatic and, to some extent, gut wall metabolism.

Dunselman and colleagues conducted a study including 23 patients with NYHA class III heart failure (LVEF <40%) who were given a single dose of intravenous felodipine (1 mg) followed by oral felodipine 10 mg twice daily or placebo [110]. After 8 weeks of oral therapy, felodipine was reported to have a mean (range) $t_{½}$ of 22.7 (8.7–35.4) h, with a t_{max} of 1.0 (0.5–4.0) h and a C_{max} of 37 (14–68) nmol/L. F_{oral} was 25 % (12–74 %). The authors also correlated the pharmacokinetic parameters of felodipine and cardiac output. No significant correlation was seen between the AUC_{iv} of intravenous felodipine and cardiac output. However, oral C_{max}, AUC_{po}, and F_{oral} were found to be significantly correlated with cardiac output (r values of 0.83, 0.81, and 0.83, respectively, with $p < 0.01$ for all). Significant correlations were also seen for F_{oral} and AUC_{po} with baseline cardiac output (r values of 0.85 and 0.83, respectively, with $p < 0.01$ for both). Compared with previously published data from middle-aged patients with hypertension and young healthy individuals, patients in this study with heart failure had higher C_{max}, F_{oral}, and AUC_{po} values and lower CL_{po} for oral felodipine. However, these values were similar to those reported for elderly patients with hypertension. No statistical analyses were done between these data.

3.5.2 *Nifedipine*

Nifedipine is assigned to BCS Class 1. It is rapidly and completely absorbed after oral administration when given as an immediate-release formulation [111]. Nifedipine is eliminated mainly by extensive hepatic metabolism and to some extent in the gut wall by CYP3A4; less than 0.1 % of the dose is excreted into the urine unchanged [111].

In one study, Chen and colleagues evaluated the effects of nifedipine 20 mg on the hemodynamic profiles of 27 patients with NYHA class II or IV heart failure; the pharmacokinetic properties of the drug were also investigated and compared with healthy volunteers [112]. For patients with heart failure, mean (SD) AUC was 353 (217)

ng·h/mL, $t_{½}$ was 3.5 (2.6) h, t_{max} was 3.2 (0.8) h, and C_{max} was 31 (6) ng/mL. Similar values were reported for healthy volunteers [378 (185) ng·h/mL, 3.9 (1.6) h, 4.4 (1.2) h, and 32 (6) ng/mL, respectively] with no significant differences seen.

3.6 Digitalis

3.6.1 Digoxin

Digoxin is assigned to BCS Class 3; the F_{oral} of the currently available digoxin tablets is 60–80 % [113]. Digoxin is eliminated mainly by the kidney via glomerular filtration and to some extent via the active tubular secretion [113]. The CL_R of digoxin is capacity limited, because it is largely comparable to the GFR. While the drug has been used for more than 100 years, few studies have reported on the pharmacokinetic changes of the drug in patients with heart failure.

Since Doherty and colleagues [114] reported an impaired absorption of digoxin in one of ten patients with heart failure, there has been concern as to whether the F_{oral} of digoxin would be altered in patients with heart failure. At present, no studies investigating the F_{oral} of digoxin in patients with heart failure as compared with healthy subjects are available. However, Ohnhaus and colleagues [115] studied the absorption of digoxin after a single oral administration in eight patients with severe RHF at the decompensated period and during recovery. Using ^{3}H-digoxin 0.1 mg solution and unlabeled digoxin 0.25 mg tablets they found no significant differences in plasma digoxin concentrations or in any of the calculated pharmacokinetic parameters between the two periods. Applefeld and colleagues [116] studied the steady-state pharmacokinetics of orally administered digoxin at 0.125 or 0.25 mg as tablets in eight patients with RHF during the decompensated and compensated periods. They observed that the mean $AUC_{po,24}$ obtained from patients during the decompensation period was 15 % greater than that obtained during the compensated period. Because there were no statistically significant differences in the $t_{½}$ between the two periods, it was considered that an increase in the F_{oral} would have occurred at the decompensated period. Nevertheless, the magnitude of the change was considered clinically insignificant.

Yukawa and colleagues [117] undertook a population pharmacokinetic analysis of digoxin on 140 samples obtained from 94 elderly (>65 years) patients receiving multiple dosing of oral digoxin. They found that heart failure was a significant negative covariate that was independent from the renal function as assessed by serum creatinine concentrations, but the magnitude of influence on the inter-individual variability of digoxin CL_{po} was clinically insignificant (about 6 %). Using a population pharmacokinetic analysis, Carlton and colleagues [118] also reported that the administration of a systemic vasodilator, epoprostenol, to patients with NYHA class III or IV heart failure decreased the CL_{po} of digoxin by 15 %. Because CL_{CR} values measured before and during the administration of epoprostenol were unchanged, they suggested that epoprostenol-induced gastrointestinal blood flow might have resulted in an increase in the absorption of digoxin. However, the magnitude of this change would be clinically insignificant.

3.7 Diuretics

3.7.1 Loop Diuretics

Loop diuretics (bumetanide, furosemide, and torsemide) are frequently used in the treatment of heart failure [119]. The F_{oral} of furosemide is incomplete (46 %) with considerable intra- and inter-subject variability ranging from 12 to 112 % [120]. In contrast, the F_{oral} of bumetanide and torsemide are near 100 % [121, 122]. Furosemide is assigned to BCS Class 4 and has low solubility and membrane permeability. In contrast, bumetanide and torsemide are assigned to BCS Class 3 and 2, respectively. All have an onset of action within 30–60 min after administration, with $t_{½}$ values of 60–90 min, 2 h, and 3.5 h for bumetanide, furosemide, and torsemide, respectively. Excretion of furosemide is primarily renal, while both bumetanide and torsemide undergo some degree of hepatic metabolism [119]. The alterations in the F_{oral} of loop diuretics in patients with heart failure were reviewed by Sica [123].

3.7.1.1 Bumetanide The F_{oral} of bumetanide is near complete; the drug is in BCS Class 3. Approximately 60 % of a dose of bumetanide absorbed is eliminated by the kidney; the mean CL_R and CL_{po} values of the drug were 108 and 176 mL/min/70 kg in healthy subjects, respectively. CL_R is capacity limited mainly by tubular secretion, because plasma protein binding of the drug is approximately 99 % [124].

Brater and colleagues [14] studied the pharmacokinetics of bumetanide in 20 patients with stable, compensated heart failure after either a 1 or 2 mg dose given orally. They found that patients with heart failure had a delayed appearance of the drug in the urine and a two- to threefold reduction in peak urinary excretion rate compared with normal subjects. The authors attributed these findings to a delayed or diminished rate of absorption of the drug, because the total amounts of drug recovered in urine were comparable between heart failure patients and healthy subjects. They also reported that the $t_{½}$ of the drug obtained

from heart failure patients was approximately two times longer than that obtained from healthy subjects. In a small crossover trial, Cook and colleagues studied the effects of heart failure on the pharmacokinetics of bumetanide [124]. Six patients with NYHA class III or IV heart failure and four healthy subjects were given bumetanide 3 mg orally and intravenously with a 2-day washout period between each dose. Blood samples were drawn prior to the dose and for up to 24 h after for determination of pharmacokinetic parameters. The mean (SD) CL_{CR} at baseline was 118 (7) mL/min for healthy subjects and 45 (12) mL/min for heart failure patients. For oral bumetanide, CL_R was significantly lower in patients with heart failure: 1.03 (0.46) vs. 1.83 (0.38) mL/min/kg ($p < 0.025$). Both t_{max} and $t_{½}$ [96.4 (48.0) and 98.7 (39.9) min] were higher in patients with heart failure than in healthy subjects [74.4 (23.5) and 59.5 (25.0) min], but no statistical significance was found. Of note, no significant differences were seen in the pharmacokinetic parameters (e.g., clearance, CL_R, V_d) between heart failure patients and healthy subjects for intravenous bumetanide. When the extent of availability was calculated by correcting for differences in clearance between oral and intravenous administration, 81 % of F_{oral} was obtained for both patients and healthy subjects. Collectively, the oral absorption of bumetanide was not altered by heart failure. Its elimination may be preserved unless the renal function of patients is severely compromised.

3.7.1.2 Furosemide and Torsemide Furosemide is assigned to BCS Class 4, indicating that its solubility and membrane permeability are low. Several studies have demonstrated that patients with decompensated heart failure would have a delayed and erratic absorption of furosemide compared with healthy subjects [14, 125]. Vasko and colleagues demonstrated that patients showed a 57 % decrease in the absorption lag time, a 27 % decrease in t_{max}, and a 29 % increase in C_{max} along with the recovery from decompensated to compensated status [125]. Because furosemide is largely eliminated into urine as unchanged form, the observed changes in the C_{max} and t_{max} might have been attributable to delayed gastric emptying, reduced intestinal motility, or edema of the intestinal wall. It remains unknown if the physicochemical properties of the drug (low solubility and permeability) were associated with any of the assumed mechanisms of reduced absorption.

Vargo and colleagues investigated the pharmacokinetics of both furosemide and torsemide in 16 patients with NYHA class II or III heart failure and LVEF ≤40 % [126]. In an open-label trial, furosemide was given as 40 mg orally and 20 mg intravenously and torsemide as 10 mg orally and intravenously. Blood samples were taken before and for up to 36 h after drug administration. For the oral dosage form, F_{oral} was found to be 89.3 % for torsemide and 71.8 % for furosemide, based on a ratio of AUC_{po} to AUC_{iv}. Only pharmacokinetic data for torsemide were compared with similar data obtained from healthy subjects reported by other authors [127]. Overall, the pharmacokinetics of orally administered torsemide in heart failure patients did not differ from healthy subjects, with the exception of a prolonged mean (SD) $t_{½}$ [4.9 (3.8) vs. 3.5 (1.2) h] and higher AUC_{po} [4.8 (2.3) vs. 3.7 (1.7) μg·h/mL] in the patient group.

In two later trials, the effects of decompensated heart failure on the pharmacokinetics of torsemide and furosemide were studied. Gottlieb and colleagues [128] studied the pharmacokinetics of furosemide and torsemide in 44 patients with heart failure [NYHA class III or IV heart failure (LVEF ≤40 %)]. Patients with marked fluid overload (>6.8 kg in body weight) were given either furosemide 20–400 mg or torsemide 10–160 mg, based on physicians' judgment. Pharmacokinetic parameters for both drugs were determined both pre- and post-diuresis and the values compared. For furosemide, diuresis had no significant effect on the pharmacokinetic parameters, although there were insignificant increases in many of the pharmacokinetics parameters (e.g., C_{max}, t_{max}, AUC_{po}, and CL_R) after diuresis. For torsemide, however, there was a significant increase in the mean (SD) C_{max} from baseline value to that after diuresis, from 11.0 (5.0) to 13.9 (6.8) μg/mL ($p = 0.04$). In addition, t_{max} decreased significantly from 1.4 (0.82) to 0.81 (0.36) h ($p = 0.001$). No significant differences were seen in other pharmacokinetic parameters, and the results were numerically similar. Bleske and colleagues [129] studied the pharmacokinetics of torsemide in patients with decompensated heart failure in an open-label design and found essentially similar findings to those reported by Gottlieb and colleagues.

Wargo and Banta [119] performed a comprehensive review of the loop diuretics. They reached the conclusion that torsemide and bumetanide have higher oral absorption than furosemide and their pharmacokinetics would be less susceptible to heart failure-induced physiological changes in the intestinal tract and the kidney. Based on these data, torsemide or bumetanide rather than furosemide should be considered as first-line treatment for fluid overload in patients with heart failure.

3.7.2 Mineralcorticoid Receptor Antagonist

3.7.2.1 Eplerenone Eplerenone is a selective mineralcorticoid receptor antagonist that has been shown to improve the long-term mortality and morbidity of patients with systolic heart failure (NYHA class II) [130]. Eplerenone is assigned to BCS Class 2. The F_{oral} of the drug is

unknown, but a mass balance study conducted in eight healthy subjects using ^{14}C-labelled eplerenone showed that 67 and 32 % of an orally administered dose was recovered in the urine and feces, respectively, suggesting good oral absorption [131]. Eplerenone is extensively metabolized and less than 5 % of a dose is recovered in the urine as unchanged drug. No active metabolites have been identified at present. The mean CL_{po} is 10 L/h (167 mL/min, capacity limited), and the mean CL_R is 0.07–0.15 L/h (1–2.5 mL/min, capacity limited) [132].

The pharmacokinetics of eplerenone were studied after repeated oral administration of 50 mg in eight patients with heart failure (NYHA class II to IV) and eight matched (sex, age, weight) healthy controls. The results showed that the steady-state AUC_{po} and C_{max} values obtained from heart failure patients were 38 and 30 % higher, respectively, than those obtained from the control subjects [133].

3.7.3 Vasopressin Receptor Antagonist

3.7.3.1 Tolvaptan Tolvaptan is a selective vasopressin V_2-receptor antagonist that is approved for the treatment of hypervolemic and euvolemic hyponatremia for patients with heart failure and SIADH (syndrome of inappropriate antidiuretic hormone) in most countries. It is assigned to BCS Class 2 because of its low solubility. The mean (SD) F_{oral} is 56 (10) % in healthy subjects [134]. Tolvaptan is eliminated almost exclusively by hepatic metabolism, and its clearance is 2.3 (0.8) mL/min/kg (161 mL/min/70 kg). Thus, it would not be subject to an extensive hepatic first-pass metabolism, and its CL_H is capacity limited.

Van Wart and colleagues studied the population pharmacokinetics of tolvaptan using data obtained from 93 healthy subjects, 628 patients with heart failure (NYHA classes I to IV), and 24 patients with hepatic cirrhosis. They reported that the population mean CL_{po} of tolvaptan was 16.0 L/h; body weight, presence of heart failure, and hepatic cirrhosis were independent covariates of CL_{po}. As for heart failure, the results showed that the CL_{po} of the drug obtained from patients with NYHA classes I or II and II or IV was reduced by 58.2 and 45.5 %, respectively, as compared with that of healthy subjects [135]. Yi and colleagues studied the pharmacokinetics of tolvaptan in healthy Korean men after single oral doses of 30 and 60 mg and reported that the mean (SD) CL_{po} of the drug was 25.9 (8) and 35.6 (15.8) L/h, respectively [136]. These data indicate that systemic exposure of tolvaptan may be increased by approximately double in patients with heart failure compared with healthy subjects. It remains unclear whether the changes in AUC_{po} of tolvaptan in patients with heart failure may be attributed to either improved F_{oral} or impaired hepatic metabolism.

3.8 Oral Anticoagulants

3.8.1 Rivaroxaban

Rivaroxaban is a factor Xa inhibitor used for the prevention and treatment of thromboembolic events [137]. Following oral administration, rivaroxaban is well-absorbed, with bioavailability of 66 % or more, depending on the dose given. The clearance of rivaroxaban was shown to be 10 L/h (170 mL/min), of which 75 % was attributed to hepatic elimination based on studies in healthy subjects [138, 139]. The CL_H and CL_R of rivaroxaban are both capacity limited. Most of a dose of rivaroxaban undergoes hepatic metabolism via CYP (3A4, 3A5, and 2J2) and non-CYP mechanisms with the metabolites and unchanged drug excreted via the renal and fecal routes [140]. Both renal and hepatic dysfunction may affect the pharmacokinetics of rivaroxaban, with increases in AUC_{po} seen in both populations.

One study was conducted that evaluated the effects of acute as well as chronic heart failure on the pharmacokinetics of rivaroxaban [141]. Six patients with acute decompensated heart failure were randomized in a 2:1 ratio to either rivaroxaban 10 mg or enoxaparin 40 mg each given once daily for 6 days (Cohort 1). A second group of patients with stable NYHA class III or IV heart failure received either rivaroxaban 10 mg or placebo in a blinded, randomized fashion for 6 days (Cohort 2). Exposure to rivaroxaban was higher in Cohort 1 than in Cohort 2 on days 1 and 6 of treatment, based on C_{max} and AUC_{po}. These differences were greater on day 1 than on day 6 (approximately 22 % higher vs. 10–16 % higher on day 6). For Cohort 1, mean (SD) C_{max} values on days 1 and 6 were 238 (88.5) and 251 (55.6) ng/mL; for Cohort 2, these values were 197 (73.9) and 216 (82.8) ng/mL, respectively. $AUC_{po,24}$ values for Cohort 1 on days 1 and 6 were 2,184 (779) and 2,609 (668) ng·h/mL. For Cohort 2, these values were 1,770 (372) and 2,369 (741) ng·h/mL, respectively. However, no statistical analyses were provided for these data. The $t_{½}$ on day 6 for Cohort 1 was 7.04 (2.56) h and 7.95 (1.88) h for Cohort 2, similar to values reported for the adult population (5–9 h) and shorter than that seen with renal impairment (8.7–9.5 h) [137, 139]. The pharmacodynamic properties of the drug were similar between the two cohorts [141].

3.9 Miscellaneous

3.9.1 Antipyrine

Antipyrine is assigned to BCS Class 1. The drug has frequently been used for assessing the activity of hepatic enzymes for drug metabolism, because it is almost completely absorbed after oral administration, extensively

metabolized by the liver (mainly by CYP1A2 and CYP3A4), and has low plasma protein binding [142]. Rissam and colleagues studied the pharmacokinetics of antipyrine after oral dosing in ten female patients with heart failure as compared with ten age-matched healthy female subjects [143]. The study showed that the AUC_{po} and $t_{½}$ of the drug obtained from patients were 40 and 32 % higher than the corresponding values obtained from the controls. The authors concluded that patients with heart failure may have impaired drug-metabolizing enzyme activity.

3.9.2 Fluvoxamine

Fluvoxamine is a selective serotonin reuptake inhibitor that is widely used for the treatment of depression, obsessive-compulsive disorder, and other related conditions. The drug is assigned to BCS Class 1. Following oral administration of ^{14}C-fluvoxamine, 94 % of the radioactivity was recovered in the urine within 71 h, indicating almost complete gastrointestinal absorption [144]. The F_{oral} of the drug is 53 %, a result of significant presystemic first-pass metabolism [145].

Orlando and colleagues studied the effects of age and chronic heart failure on the pharmacokinetics of fluvoxamine after a single oral administration of 50 mg in ten healthy young adults, ten healthy elderly subjects, and ten elderly patients with heart failure (NYHA class III or IV) [146]. It was found that increases in age in healthy subjects altered the oral disposition kinetics; the mean (SD) CL_{po} obtained from healthy elderly subjects [1.12 (0.07) L/h/kg] was reduced by 50 % ($p < 0.05$) compared with that obtained from healthy young subjects [2.25 (0.66) L/h/kg]. However, the presence of heart failure had no significant effects on any of the pharmacokinetic parameters between the age-matched healthy elderly subjects and elderly patients with heart failure.

3.9.3 Hydralazine

Hydralazine is a vasodilator and is approved for the treatment of hypertension and heart failure when given orally. Hydralazine is assigned to BCS Class 1. It undergoes a significant first-pass effect and, therefore, the F_{oral} is low. The F_{oral} is dependent on the phenotype of *N*-acetyltransferase activity; it is 9.5 % for subjects with the fast acetylator phenotype and 31.3 % for those with the slow acetylator phenotype [147]. Crawford and colleagues [148] studied the pharmacokinetics of hydralazine in ten patients with heart failure (NYHA class III) and demonstrated that the mean (SD) value for F_{oral} of the drug in heart failure patients [16.4 (12.1) %] was largely similar to that of patients with normal cardiac function [147]. However, Hanson and colleagues studied the pharmacokinetics of hydralazine after oral administration in severe heart failure patients (two, two, and three patients for NYHA class III, III/IV, and IV, respectively) as compared with eight patients with hypertension [149]. They demonstrated that the mean (SD) C_{max} and AUC_{po} from time zero to 4 h ($AUC_{po,4}$) for hydralazine obtained from patients with heart failure were approximately twofold higher, but statistically insignificant, than those obtained from hypertensive patients with preserved cardiac function: 1.5 (0.9) vs. 0.8 (0.3) nmol/mL for C_{max} and 208 (143) vs. 94 (44) nmol·h/mL for $AUC_{po,4}$, respectively. Based on these findings, it may be concluded that heart failure may have modestly increased the systemic exposure of hydralazine after oral administration.

3.9.4 Midazolam

Midazolam is assigned to BCS Class 1. A mass balance study using ^{14}C-midazolam showed that it is almost completely absorbed, and only 5 % of the dose was recovered in urine as unchanged drug [150]. Midazolam is mainly eliminated by hepatic metabolism with an intermediate hepatic extraction ratio based on its clearance (290–630 mL/min) [151]; CYP3A4 is mainly involved in its hepatic metabolism [152]. The F_{oral} of the drug is approximately 40 % due to its extensive hepatic first-pass metabolism by CYP3A4 [153]. Midazolam has been used widely as a model compound for assessing hepatic CYP3A activity [154].

Patel and colleagues studied the pharmacokinetics of midazolam after intravenous and oral administration in six patients with heart failure (NYHA class II or III) and six age- and sex-matched healthy subjects. The authors reported that the mean (SD) clearance of the drug was significantly ($p < 0.05$) reduced in heart failure patients as compared with the controls: 376 (92) vs. 551 (155) mL/min, respectively. While the mean (SD) AUC_{po} obtained from heart failure patients was 47 % greater than that obtained from healthy subjects [151 (48) vs. 103 (50) ng·h/mL, respectively], the difference was not statistically significant because of larger inter-individual variability in the oral pharmacokinetic parameters than with intravenous data [155].

3.9.5 Theophylline

Theophylline is a bronchodilator used for the treatment of bronchial asthma. The drug is almost completely absorbed after oral administration, except for the extended-release formulation [156]. Theophylline is assigned to BCS Class 1. The drug is extensively metabolized in the liver with a low extraction ratio (capacity limited) in adults, and only

10–13% of an oral dose is eliminated into urine as unchanged drug in adults [157]. The drug has been used as a probing drug for the activity of the hepatic CYP1A2 enzymes [158].

Cuzzolin and colleagues studied the effect of sex and heart failure on the pharmacokinetics of a slow-release theophylline formulation in elderly patients [159]. A dose of 700 mg/day was given orally for 3 days to 26 male and female geriatric subjects; 15 were healthy adults (mean age 75 years) with no concomitant drug use and 11 were patients (mean age 77 years) with NYHA class II or III heart failure. Mean (SD) t_{max} values obtained from male and female patients with heart failure were significantly ($p < 0.05$) prolonged as compared with the respective values for control subjects [7.2 (1.8) vs. 4.3 (0.7) h and 7.3 (1.6) vs. 3.7 (0.8) h]. In addition, male patients with heart failure had a significant reduction in the mean (SD) CL_{po} as compared with the male healthy subjects: 0.04 (0.03) vs. 0.13 (0.08) L/h/kg, respectively. Ueno and colleagues also studied theophylline disposition during the steady-state condition in 16 Japanese patients with heart failure (NYHA class II or above) and 16 patients without heart failure. The authors reported that the mean (SD) CL_{po} of the drug in patients with heart failure was reduced by 43 % as compared with that in patients without heart failure ($p < 0.01$) [160].

4 Interpretation of the Pharmacokinetic Changes Observed in Patients with Heart Failure

There has long been concern regarding the attenuation of drug absorption in patients with heart failure due to gastrointestinal pathophysiology (e.g., hypoperfusion, congestion, edema). We examined the influence of heart failure on the extent of drugs' gastrointestinal absorption by AUC_{po} and the absorption rate by C_{max} and t_{max}. We also assessed the effects of heart failure on the gastrointestinal absorption in the light of BCS classification of drugs. We hypothesized that the gastrointestinal absorption of drugs with either a low solubility in aqueous media, a low permeability into the intestinal epithelial cells, or a combination of both (i.e., BCS Classes 2, 3, and 4) may be more susceptible to heart failure-induced changes in the gastrointestinal tissues. Based on the available literature, it was found that none of the drugs examined, except for lisinopril (BCS Class 3), showed an apparent reduction in AUC_{po} in patients with heart failure as compared with healthy subjects. While the C_{max} and t_{max} of furosemide (BCS Class 4) in patients with heart failure appeared reduced and prolonged compared with healthy subjects, the AUC_{po} was not reduced between the groups. However, the possibility that reduced drug absorption might have been compensated by reduced systemic elimination, thereby showing an unaltered AUC_{po}, cannot totally be disregarded. We also identified two drugs in BCS Class 4 (furosemide and candesartan cilexetil). No apparent changes were observed for the oral pharmacokinetic parameters of candesartan in heart failure patients. We consider that information on BCS classification may not be useful for predicting alterations in gastrointestinal absorption in patients with heart failure.

As for drugs assigned to BCS Class 1, the changes observed in AUC_{po} in patients with heart failure may be attributed to changes in the systemic elimination. For drugs mainly eliminated by hepatic metabolism, changes observed in AUC_{po} could be attributed to changes in f_u or in CL_{int}. Assuming that heart failure per se is not associated with drastic changes in plasma protein binding, the changes observed may result from changes in drug-metabolizing activity. In this context, the findings that the AUC_{po} values of midazolam, antipyrine, and theophylline were reduced in patients with heart failure as compared with healthy subjects are interesting, since these drugs are used extensively as model drugs for assessing hepatic enzyme activity. Nevertheless, the magnitude of changes in AUC_{po} for these drugs was at most 50 %, suggesting the clinical implications would be limited.

As for drugs with flow-dependent CL_R (i.e., those mainly eliminated by the kidneys), the effects of heart failure on drug elimination are still widely unknown. As far as we can determine, the oral pharmacokinetics of those drugs have not been studied, and it remains to be seen if such drugs would have an altered AUC_{po} in patients with heart failure.

5 Therapeutic Implication and Conclusion

Theoretically, heart failure may affect the absorption and disposition of orally administered drugs via substantial reductions in the systemic blood flow through drug elimination organs (i.e., liver and kidney) and mesenteric tissues where drug absorption takes place. While our knowledge of the effects of heart failure on the pharmacokinetics of orally administered drugs is limited mainly to data obtained from patients with NYHA class II and III heart failure, the accumulated data suggest that heart failure per se would elicit clinically relevant alterations in the pharmacokinetics of orally administered drugs. However, this effect may be expected in only a few drugs, unless hepatic or renal functions are substantially compromised secondarily. One issue regarding available data is that controlled clinical studies can generally be conducted only with patients with mild to moderate heart failure. In addition, few clinical studies were conducted for investigating the effects of

long-standing heart failure on the pharmacokinetics of orally administered drugs. Furthermore, the effects of heart failure on the pharmacodynamics of drugs have been studied less extensively than the effects on pharmacokinetic parameters.

For investigational new drugs, their pharmacokinetics are only required to be studied in special populations, including those with hepatic or renal dysfunction, elderly patients and, sometimes, the pediatric population. Updating the review of pharmacokinetics of orally administered drugs in patients with heart failure, the authors noticed that certain drugs showed substantial changes in AUC with a large inter-individual variability compared with healthy subjects. In this context, we consider that patients with heart failure may be considered as another special population for investigational new drugs, with regards to use of these drugs for the treatment of heart failure.

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