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Originals

Physiological modelling of renal drug clearance

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Summary. A physiological model of renal drug clearance is presented with the aim of establishing a basis for adjusting drug dosing regimens in renal insufficiency. In agreement with the morphology of blood supply to the nephron, the model assumes serial arrangement of the processes involved in drug excretion. Fractional extraction by filtration in the glomeruli is defined in terms of the product of the unbound fraction of the drug, the filtration fraction being responsible for the limited extraction efficiency of this process. For a description of the limitations of the tubular secretory process by plasma flow through peritubular capillaries, the parallel tube model is utilized. The assumption of direct proportionality between the transport maximum of the secretory process and filtrate flow in the tubules permits a quantitative comparison of the intrinsic tubular secretion clearance and the effectiveness of the filtration process. Provided that the secretory mechanism is highly effective, renal clearance becomes dependent only on kidney plasma flow and the fraction of drug not reabsorbed in the tubules. Tubular reabsorption results only in a proportional decrease in renal clearance.

The model predicts proportionality of renal drug clearance to GFR, which as a rule is used for dosage adjustment of drugs in renal insufficiency, only for compounds exclusively excreted by filtration. Compounds also excreted by tubular secretion in general exhibit a curvilinear relationship. The curvature is less pronounced as an increasing fraction of the drug is protein bound in blood. Therefore, for dosage adjustment of drugs secreted in the tubules and highly bound in blood, proportionality between renal clearance and GFR can serve as a reasonable approximation. According to the model, distinct deviations from simple proportionality, which will require dosage adjustment methods involving assessment both of glomerular and tubular functions of the kidney, can be expected mainly for drugs for which an efficient flow-dependent secretion process is not counteracted by extensive binding of the drug to blood constituents.

Key words: Renal drug clearance, Physiological modelling; drug dosing regimen adjustment, renal insufficiency

Drug regimen adjustments in renal impairment are generally based on the assumption that, in patients with impaired kidney function, the decrease in renal clearance of the drug is proportional to the decline in glomerular filtration rate (GFR), even when tubular secretion is the main process for excretion of the particular agent [1–5]. This approach to adjustment of the dosing regimen in renal insufficiency may be regarded as a reflection of Bricker's Intact Nephron Hypothesis [6], which, in its present version [7], can be interpreted as follows: "If one portion of a nephron is damaged so that either part of its functionality is destroyed, the function of all other segments is decreased by the same degree". Experimental [8] and clinical [4, 9] data demonstrate that the renal clearance of a drug will approach zero in kidney failure, even if the drug is excreted by filtration and also by tubular secretion, which lends support to this hypothesis. On the other hand, there is some evidence that dosing adjustments based on simple proportionality of renal drug clearance to GFR may not be entirely adequate for certain drugs secreted in the tubules due to nonparallel behaviour of GFR and tubular secretion [10, 11].

Resolution of this partial discrepancy requires better understanding of the interrelationships between the individual processes involved in drug excretion by the kidney. Physiological modelling of renal drug clearance in terms of drug delivery to the organ, as controlled by blood flow, of reversible binding of drug to blood constituents, and of the inherent ability of the excretion mechanism to eliminate the drug may represent a powerful tool for this purpose by virtue of its conformity with anatomical and physiological realities.

The classical view considers renal clearance as the sum of positive contributions of glomerular filtration and tubular secretion on the one hand and tubular reabsorption on the other. An implicit assumption of this simple additive concept is the parallel and, therefore, independent functioning of all three mechanisms involved in renal excretion. Even if, tubular reabsorption was subsequently recognised [12] as determined by the rates of glomerular filtration and tubular secretion, the present models [13]

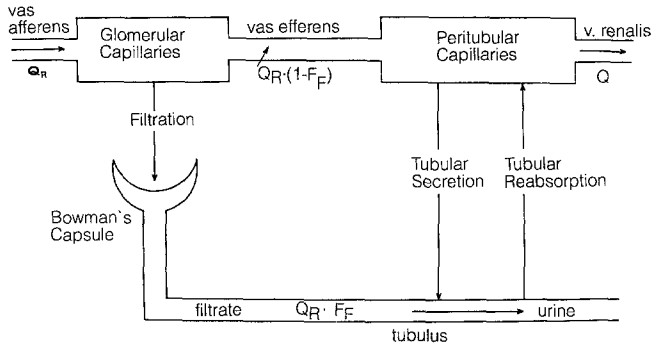

Fig. 1. Block scheme of the physiological model of renal drug clearance

still predict that tubular secretion can be maintained in an unlimited manner in spite of reduced or even suppressed filtration in the glomeruli. This prediction is not consistent with the present interpretation of Bricker's Intact Nephron Hypothesis, but, what is more important, it also does not conform to the morphological arrangement of the blood supply to the nephron.

In this paper an attempt is made to reconcile the model of renal drug clearance with the structural and functional organisation of the nephron, with the aim of obtaining a more sophisticated basis for the adjustment of drug dosing regimens in renal functional impairment.

Theory

Serial model of renal drug clearance

Renal function, including removal of endogenous and of exogenous compounds, depends at least in part on renal blood flow, or more precisely on plasma flow [14]. A physiological model of renal drug clearance should, therefore, primarily reflect the anatomical arrangement of the blood supply to the nephron as the basic functional unit of the kidney. The basic features of the serial model of renal drug clearance, which is based on the morphological arrangement of blood supply to the nephron, are depicted in Fig. 1. The blood is supplied to each nephron by a short afferent arteriole ("vas afferens"), which divides inside the glomerular capsule into a tuft of small capillary vessels through which plasma is filtered. At the outlet of the glomerular capsule, the glomerular capillaries reunite to form a single "vas efferens", dividing thereafter into the peritubular capillaries. The second set of capillaries supplies the convoluted tubules, where the secretion and reabsorption of the solutes can take place. The peritubular capillaries receive blood from vas efferens that has already been depleted by the fraction of the amount of drug filtered in the glomeruli (E_{GF}). Tubular secretion is therefore arranged in series with glomerular filtration, and drug extraction by secretion in the tubules (E_{TS}) can cover only that fraction of the amount of drug transported by total plasma flow (Q_R) which escaped filtration ($1-E_{GF}$). Simultaneously, it is assumed that a fraction F_R of the total amount secreted and filtered is reabsorbed distal to the site of tubular secretion. The serial arrangement of all the processes involved in renal drug excretion can then be expressed by the general formula for overall renal clearance:

$$CL_R = Q_R \cdot (E_{GF} + (1 - E_{GF}) \cdot E_{TS}) \cdot (1 - F_R) \quad (1)$$

Clearance and extraction of drugs by glomerular filtration

Renal clearance of drugs by glomerular filtration (CL_{GF}) is usually presented as the product of the unbound fraction of drug (f_u) and the glomerular filtration rate (GFR) [3, 15]:

$$CL_{GF} = f_u \cdot GFR \quad (2)$$

Introducing the filtration fraction F_F defined as:

$$F_F = \frac{GFR}{Q_R} \quad (3)$$

the glomerular filtration clearance can be represented by the alternative formula:

$$CL_{GF} = Q_R \cdot F_F \cdot f_u \quad (4)$$

indicating that this parameter is determined not only by the fraction of drug unbound, but also by renal plasma flow as well as by the value of the filtration fraction. The glomerular extraction ratio is then given by:

$$E_{GF} = F_F \cdot f_u \quad (5)$$

Under normal conditions, when GFR = 120 ml/min and renal plasma flow Q_R = 600 ml/min, the filtration fraction amounts to 0.2, thus representing the upper limit of drug extraction in the glomeruli, although that can be attained only by completely unbound drugs. The effectiveness of renal drug extraction by filtration in the glomeruli is relatively low.

Extraction of drugs by tubular secretion

The extraction ratio by tubular secretion (E_{TS}), in agreement with the model scheme depicted in Fig. 1, can be defined as:

$$E_{TS} = \frac{C_{TSi} - C_{TSo}}{C_{TSi}} \quad (6)$$

where C_{TSi} and C_{TSo} represent the drug concentrations flowing into and leaving the secretory segment of the peritubular capillary system, respectively. The following mass-balance equation can be written:

$$Q_{PTS} \cdot C_{TSi} = CLu_{S,\,int} \cdot C_I + Q_{PTS} \cdot C_{TSo} \quad (7)$$

where $CLu_{S,\,int}$ represents the intrinsic tubular secretion clearance referred to unbound drug in plasma, C_I the drug concentration in the vicinity of transporting carrier molecules, and Q_{PTS} is the plasma flow entering the peritubular capillary system. As compared to the total renal plasma flow, the latter is diminished by filtration in the glomeruli, thus being equal to:

$$Q_{PTS} = Q_R - GFR = Q_R \cdot (1 - F_F) \quad (8)$$

Now, if for description of the limitations of the tubular secretion process by plasma flow through peritubular capillaries, the "parallel tube model" [16] is accepted, then the

drug concentration C_I should be assumed to be equal to the free fraction of the logarithmic mean concentration in the segment of the peritubular capillary system perfusing the secretory zones of the tubuli, which is given by:

$$C_I = f_u \cdot \frac{C_{TSi} - C_{TSo}}{\ln C_{TSi} - \ln C_{TSo}} \quad (9)$$

Then, by combining Eqs. 7, 8 and 9, the extraction ratio of the drug by tubular secretion is given by the formula:

$$E_{TS} = 1 - \exp\left(-f_u \cdot \frac{CLu_{S,int}}{Q_R \cdot (1 - F_F)}\right) \quad (10)$$

The definition of intrinsic tubular secretion clearance and its relation to filtrate flow in the tubuli

The intrinsic tubular secretion clearance of unbound drug $CLu_{S,int}$, representing the effectiveness of the process not limited by plasma flow, is usually interpreted with respect to the potential saturability of the process [3] as:

$$CLu_{S,int} = \frac{T_{max}}{K'_M + C_I} \quad (11)$$

where T_{max} is the transport maximum (mass. time^{-1}), C_I is the concentration of unbound drug in the vicinity of tubular secretion sites, and K'_M is the Michaelis constant (mass. volume^{-1}) corresponding to the concentration of unbound drug at those sites when the transport rate is equal to $T_{max}/2$.

Such a definition of the intrinsic tubular secretion clearance is fully in agreement with the classical concept of renal tubular secretion [17], which implies that each proximal tubular cell possesses a limited number of transport carriers. However, it is reasonable to assume that the maximal effectiveness with which tubular secretion can operate is also dependent on the rate of drug removal, i.e. on the rate of flow of the filtrate. This view is consistent with the findings of several investigators [18–21], who have observed a dependence of PAH clearance or secretion rate on GFR, i.e. on intraluminal flow. A critical PAH concentration within the tubular lumen, leading to cessation of the transport process, was detected in some of these experiments [19, 20, 22]. Therefore, it is more convenient to define the secretion maximum S_{max} as the maximal amount of drug which can be secreted per unit of time into a unit of filtrate volume, i.e. in terms of the product of maximal drug concentration C_{max} that can appear in the filtrate per unit of time and filtrate flow:

$$S_{max} = C_{max} \cdot GFR = C_{max} \cdot Q_R \cdot F_F \quad (12)$$

The intrinsic tubular secretion clearance is, therefore, represented by the formula:

$$CLu_{S,int} = \frac{C_{max}}{K'_M + C_I} \cdot GFR = \frac{C_{max}}{K'_M + C_I} \cdot Q_R \cdot F_F \quad (13)$$

If the secretion process is far from saturation, e.g. when $K'_M >> C_I$, then this formula simplifies to:

$$CLu_{S,int} = \frac{C_{max}}{K'_M} \cdot GFR = K_{TS} \cdot GFR \quad (14)$$

Table 1. The dependence of model predicted values of unbound drug exctraction by tubular secretion (E_{TS}) and renal clearance (CL_R) of unbound and unreabsorbed drugs on the filtration fraction (F_F) and efficiency of the tubular secretion process (K_{TS}) as compared to glomerular filtration rate

Tubular secretion efficacy	Filtration fraction							
	$F_F = 0.2$		$F_F = 0.1$		$F_F = 0.05$		$F_F = 0.01$	
K_{TS}	E_{TS}	CL^a_R	E_{TS}	CL_R	E_{TS}	CL_R	E_{TS}	CL_R
0	0.00	120.0	0.00	60.0	0.00	30.0	0.00	6.0
1	0.22	225.6	0.11	119.4	0.05	58.8	0.01	11.9
2	0.39	307.2	0.20	168.0	0.10	87.0	0.02	17.9
3	0.53	373.3	0.28	212.9	0.15	115.5	0.03	23.7
5	0.71	460.8	0.43	292.2	0.23	161.1	0.05	35.3
10	0.92	561.6	0.67	421.8	0.41	263.7	0.10	63.1
20	0.99	595.2	0.89	540.6	0.65	400.5	0.18	114.7
30	1.00	599.7	0.96	588.7	0.80	486.0	0.26	161.3

[a] $ml \cdot min^{-1}$

Under such conditions direct proportionality between GFR and the intrinsic tubular secretion clearance should be expected. The proportionality constant K_{TS} given by the ratio C_{max}/K'_M then defines the effectiveness of tubular secretion process as compared to the glomerular filtration rate in the absence of any supply limitations.

Using this approximation the following expression for the extraction ratio by tubular secretion is obtained:

$$E_{TS} = 1 - \exp\left(-\frac{f_u \cdot K_{TS} \cdot F_F}{1 - F_F}\right) \quad (15)$$

It is evident from this formula that extraction by tubular secretion is independent of plasma flow and can be regarded as constant only if the filtration fraction remains constant.

The data in Table 1 show that under normal conditions, i.e. when the filtration fraction is about 0.2, intrinsic tubular secretion clearance exceeding the glomerular filtration rate would suffice to achieve almost complete extraction of a totally unbound drug. This indicates that, in contrast to filtration in the glomeruli, where the upper limit of extraction is about 20%, the secretory process may be much more efficient. Even if filtration is reduced, then a highly effective mechanism of secretion may still ensure extensive extraction of the drug. However, as Equation (16) predicts, the apparent efficiency of extraction is reduced by drug binding, but in contrast to filtration, in an exponential manner.

Physiological model of renal drug clearance

The definition of the extraction ratios for glomerular filtration and tubular secretion enables us to formulate the physiologically based model of renal drug clearance in the form:

$$CL_R = Q_R \cdot (f_u \cdot F_F + (1 - f_u \cdot F_F) \cdot (1 - \exp(-\frac{f_u \cdot K_{TS} \cdot F_F}{1 - F_F}))) \cdot (1 - F_R) \quad (16)$$

According to this model renal clearance of the drug should generally be determined by renal plasma flow, the

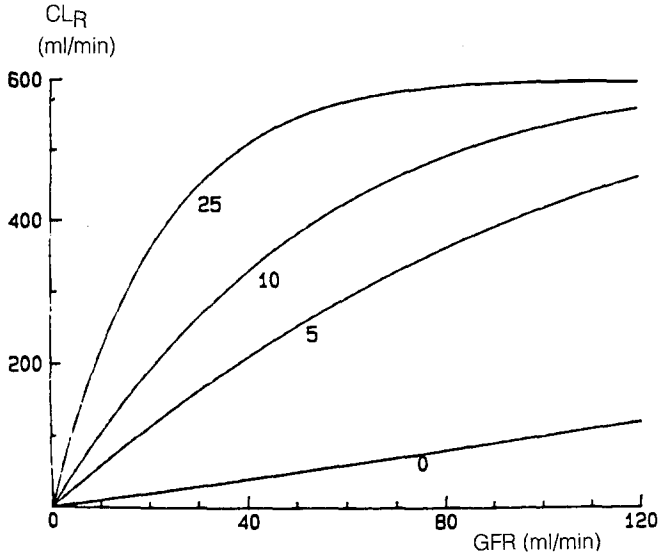

Fig. 2. Effect of varying tubular secretory efficiency (K_{TS} = 0, 5, 10 and 25) on the relationship between glomerular filtration rate and the renal clearance of hypothetical drugs which are not bound to plasma proteins (f_u = 1) and are not reabsorbed (F_R = 0) in the tubules. Renal plasma flow Q_R = 600 ml/min

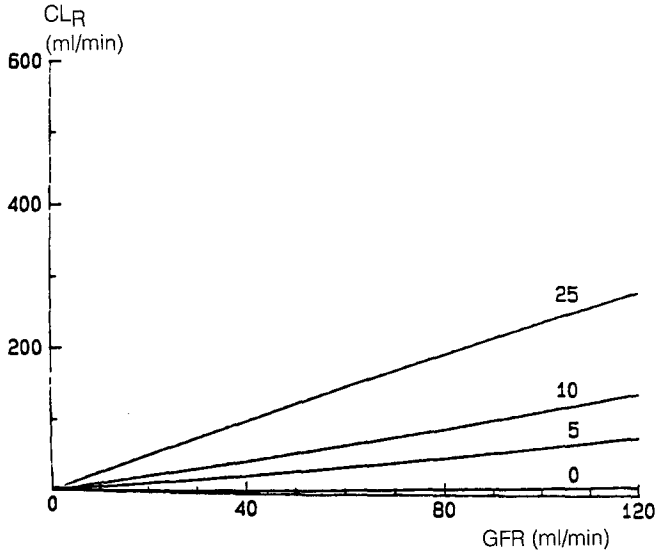

Fig. 3. Effect of varying tubular secretory effectivity (K_{TS} = 0, 5, 10 and 25) on the model-predicted relationship between glomerular filtration rate and renal clearance of hypothetical drugs which are highly bound to plasma proteins (f_u = 0.1) and are not reabsorbed (F_R = 0) in the tubules. Renal plasma flow Q_R = 600 ml/min

filtration fraction, the effectiveness of tubular secretion as compared to glomerular filtration rate, the fraction of drug unbound in plasma, and the fraction of drug reabsorbed in the tubules. The formula shows that due to the serial arrangement of tubular secretion with glomerular filtration, extraction by secretion is supply-limited, which means that reduced filtration leads to an increase in the peritubular load and vice versa. However, provided the secretory mechanism is highly effective, the exponential term tends to zero and Equation (16) reduces to:

$$CL_R = Q_R \cdot (1 - F_R) \tag{17}$$

It is evident that under such conditions renal clearance becomes dependent only on renal plasma flow and the fraction of drug not reabsorbed in the tubules. The data in Table 1 demonstrate that the renal clearance of drugs not reabsorbed approaches renal plasma flow when the tubular secretion efficiency ranges between 20–30% and the filtration fraction is normal. However, the data also show that an efficient secretion mechanism can maintain a satisfactory clearance of unbound drugs from the body even if the filtration fraction is considerably reduced. On the other hand, a defect in the tubular secretion mechanism leading to a reduction of tubular secretion efficiency would depress renal clearance, even if the filtration fraction were to remain normal.

Table 2. Dosage adjustment factors (%) based on renal clearance ratio as function of tubular secretory efficiency (K_{TS}) and glomerular filtration rate (GFR)

	K_{TS}							
	0	1	2	3	5	10	20	30
GFR (ml/min)								
60	50.0	51.6	54.3	57.1	62.7	75.3	90.7	96.8
30	25.0	26.2	28.1	30.3	35.0	46.9	62.2	80.5
10	8.3	8.8	9.6	10.5	12.5	18.5	30.1	40.9

Application

The dependence of renal drug clearance on glomerular filtration rate

The physiological model derived in the theoretical section can be transformed by use of Eq. 3 into a relationship of the form:

$$CL_R = (f_u \cdot GFR + (Q_R - f_u \cdot GFR) \cdot (1 - \exp(-\frac{f_u \cdot K_{TS} \cdot GFR}{Q_R - GFR}))) \cdot (1 - F_R) \tag{18}$$

It is evident that simple proportionality of renal clearance to GFR can be expected only in the case when drug excretion by the kidney is limited to its filtration in the glomeruli (K_{TS} = 0), because then Eq. (18) reduces to:

$$CL_R = f_u \cdot GFR \tag{19}$$

When tubular secretion is also involved ($K_{TS} > 0$), and reabsorption is not operative, there is a curved relationship with increasing effectiveness of tubular secretion (Fig. 2) and renal clearance will exceed the GFR with an upper limit at the rate of plasma flow through the kidney. Changes in the fraction of drug reabsorbed distal to the secretory segment of the nephron should result only in a proportional decrease in renal clearance, not affecting the character of the relationship.

Protein binding reduces the effectiveness both of tubular secretion and filtration. As a result of this fact, the curvature of the relationship is suppressed in relation to the

increasing fraction of the drug which is bound. Thus, even for relatively highly effective tubular secretion, the relationship may approximate a straight line if the fraction of the drug unbound is low (Fig. 3).

Implications for drug dosage adjustment

Correct dose adjustment in renal insufficiency intended to reduce the toxicity of drugs excreted predominantly by the kidney requires quantification of kidney function as the first step [23, 24]. Glomerular filtration rate, usually measured as creatinine clearance, as a rule is regarded as an index of renal impairment [1–5]. However, for drugs for which tubular secretion is also involved in their excretion, the ratio of drug clearance by the impaired ($CL_R(I)$) and normally functioning ($CL_R(N)$) kidney would represent a more appropriate criterion. A general formula for the dosage adjustment factor R, which is based on this concept and indicates the fraction of the normal dose suitable for use in renal insufficiency, was formulated in [25] as:

$$R = 1 - f_e \cdot \left(1 - \frac{CL_R(I)}{CL_R(N)}\right) \qquad (20)$$

where f_e is the fraction of drug excreted unchanged in urine with normal kidney function.

Dose adjustment factors calculated in this way for different values of tubular secretory efficiency (K_{TS}) and glomerular filtration rate (GFR) are summarised in Table 2. It is assumed that the drug is completely excreted in urine in the unchanged form. The data show that, especially for drugs whose renal clearance is limited by kidney plasma flow (K_{TS} = 20–30), dose adjustment cannot follow changes in GFR if the defect is located solely in the glomerulus. This means that in patients with glomerulonephritis, at a stage when no change in tubular function can be observed, dosage adjustment according to GFR would lead to a serious underestimation of the capacity of the kidney to excrete the drug, and in consequence to underdosing of the patient. However, in renal failure, when the reduction of drug clearance is due also to decreased tubular secretion of the drug, as manifested by a reduction in K_{TS}, this underestimate would naturally be less pronounced.

Therefore, for dosage adjustment of drugs whose excretion is limited by renal plasma flow, and which are only moderately bound to plasma proteins, GFR cannot be considered a measure of total kidney function. Dosage adjustment procedures involving assessment of filtration as well as the secretory functions of the kidney are recommended.

Discussion

With respect to the classical definition of renal clearance, the present model represents further development towards a more physiological interpretation of renal clearance.

The definition of the extraction ratio for glomerular filtration has permitted the introduction of the filtration fraction as an important parameter affecting renal clearance. In this way drug extraction by filtration in the glomeruli becomes dependent not only on the fraction of drug which is unbound in plasma, but also on physiological determinants, e. g. on changes in blood pressure in glomerular capillaries, osmotic pressure of blood proteins and back pressure in the glomerular capsule all of which participate in regulation of the filtration fraction [26]. The fact that extraction in the glomeruli is dependent on the filtration fraction also makes it responsible for the relatively low extraction efficiency of the filtration process.

As far as tubular secretion is concerned, here, instead of the venous equilibration model previously proposed as a description of the process [13], the parallel tube model has been taken into consideration. The reason for this choice lies in the fact that this model can be regarded as a generalisation to saturation kinetics of the single capillary model of first order uptake or elimination in capillary physiology [16, 27]. The diversity so created was in model description is only apparent because the venous equilibration model appears only to be an approximation of the parallel tube model for low values of the exponent.

Another important feature of the model is that, in contrast to all previous models, tubular secretion is arranged in series with glomerular filtration. In consequence, a reduced glomerular filtration rate will lead to an increase in the peritubular load and vice versa. Another way in which alterations in glomerular filtration rate may influence tubular secretion is via the relationship between the secretion maximum and the intraluminal flow, i. e. the GFR. In this way drug extraction by secretion is made independent of plasma flow, its dependence on the filtration fraction being consistent with the finding of a highly significant correlation between the filtration fraction and the extraction of PAH by the rat kidney [21].

Moreover, the relationship assumed between the secretion maximum and glomerular filtration rate offers a quantitative comparison of the intrinsic capacity of the secretory mechanism with the effectiveness of the filtration process in terms of the ratio $C_{max}/K_M = K_{TS}$. Numerical calculations then revealed that for cases when C_{max} greatly exceeded K_M, tubular secretion represented an excretion mechanism, which was much more powerful than filtration, its upper limit being the plasma perfusion rate of the kidney. The magnitude of the tubular secretory efficiency (K_{TS}) can serve, therefore, as valuable information whether or not extraction of the drug in question by the kidney is perfusion limited. It is interesting to note in this connection that estimates of tubular secretory efficiency and of the fraction of the drug reabsorbed can be evaluated from clinical data, as demonstrated in a subsequent report [XX]. Preliminary analysis of this type [Janků, unpublished] showed that the tubular secretory efficiency for ampicilin, amoxicilin and of the cephalosporine ceforamid was in the range 20–30, when limitation by perfusion was predominant.

The prediction by the model that protein binding will reduce the effectiveness of the secretion process is in agreement with the finding in the isolated perfused rat kidney [28, 29] and in healthy volunteers [30] that diminution of plasma albumin increases the renal clearance of furosemide, which is extensively bound to plasma proteins

(91–99%) and is subject to tubular secretion [31]. On the other hand, the renal clearance of furosemide is decreased after albumin infusion in patients with nephrotic syndrome [32]. Similarly, pharamcokinetic analysis of the renal handling of sulphamethizole has shown that its tubular secretion is dependent upon its unbound concentration in plasma [33].

It can also be deduced from the model that, even when the filtration fraction is reduced and in the absence of substantial reabsorption in the tubules, a highly efficient and perfusion limited secretory process is able to maintain a fairly high clearance of unbound compounds from the body, unless GFR does not approach a negligible value. This is consistent with the observation [10] that the urinary excretion of chlorpropamide, which is mainly via the tubules, remains almost undisturbed by a reduction in GFR: in glomerulopathies the half-life of chlorpropamide is practically normal. Due to the nonlinear character of the dependence of renal clearance on GFR, the latter parameter cannot generally be considered a measure of total kidney function for the dosage adjustment of drugs of this type in renal impairment. However, as revealed by simulation experiments, the curvilinearity of the relationship between renal drug clearance and GFR can be substantially suppressed by high drug binding, because then only a small fraction of the drug supplied by peritubular capilaries is available for secretion. This means that for highly bound drugs secreted in the tubules direct proportionality of renal clearance to GFR can serve as a reasonable approximation. Within the range of interindividual variability distinct deviation from simple proportionality can be detected mainly for drugs for which an efficient flow-limited secretory process is not counteracted by extensive binding to blood constituents. This deduction is in good agreement with the findings [11] of inappropriate GFR-based dosage adjustment for ampicillin and cephalexin, which, in parallel with their flow-limited secretion, are only moderately bound (15–20%) in blood. For such drugs dosage adjustment procedures involving assessment both of the filtration and secretory function of the kidney would be preferable, as proposed by Hori et al. [34].

It can be concluded that physiological modelling of renal clearance can be effective in explaining the apparent contradictions between the complex renal excretion mechanisms and Bricker's Intact Nephron Hypothesis. This is because, in contrast to previous models, not only the intrinsic capacities of the renal excretory mechanisms, but also the rate of drug supply to the nephron as well as of the rate of drug removal from the secretion sites are recognised as important factors affecting overall drug excretion by the kidney.

Appendix

List of symbols

C_I	Drug concentration in the vicinity of transporting carrier molecules
C_{TSi}	Drug concentration flowing into the secretory segment of the peritubular capillary system
C_{TSo}	Drug concentration flowing out of the secretory segment of the peritubular capillary system
C_{max}	Maximal drug concentration that can appear in the filtrate
CL_{GF}	Clearance by filtration in the glomeruli
CL_R	Renal clearance
$CL_R(I)$	Renal drug clearance at impaired kidney function
$CL_R(N)$	Renal drug clearance at normal kidney function
$CLu_{S,\,int}$	Intrinsic tubular secretion clearance of unbound drug
GFR	Glomerular filtration rate
E_{GF}	Filtration extraction ratio
E_{TS}	Secretion extraction ratio
F_F	Filtration fraction
F_R	Fraction of drug reabsorbed in the tubules
f_e	Fraction of drug excreted unchanged into urine
K'_M	Michaelis constant
K_{TS}	Tubular secretory efficiency compared to GFR
Q_{PTS}	Plasma flow entering the peritubular capillary system
Q_R	Renal plasma flow
S_{max}	Secretion maximum
T_{max}	Transport maximum

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