Dependence of Renal Clearance on Urine Flow: A Mathematical Model and its Application

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Abstract □ A mathematical model is developed to explain the dependence of renal clearance on urine flow rate. The model is tested using human data from the literature on compounds that are neither secreted nor reabsorbed by active or pH-sensitive mechanisms. The physiologically derived model explains and predicts the relationship between renal clearance and urine flow for a broad spectrum of compounds (*i.e.*, butabarbital, chloramphenicol, creatinine, ethanol, theophylline, and urea) for which appropriate data are available.

Keyphrases □ Excretion, renal—dependence of renal clearance on urine flow, mathematical model, application, reabsorption (□) Urine flow—dependence of renal clearance, mathematical model, application, reabsorption □ Reabsorption—dependence of renal clearance on urine flow, mathematical model, application

Passive reabsorption is a major process controlling the renal excretion of many organic substances (1, 2). The magnitude of passive reabsorption depends on the nature of the substance, *i.e.*, its lipophilicity and its extent of ionization. It also depends on the urine flow rate and the pH of the luminal fluid in the renal tubule. For a compound readily undergoing reabsorption, its rate of urinary excretion can be elevated by increasing the urine flow (2–4). This dependence on urine flow leads to problems in clinically or pharmacokinetically assessing urine data, because of a large variability in renal clearance or excretion rate–plasma concentration. However, the dependence can be used beneficially. For example, forced diuresis hastens the elimination of drugs and shortens the time required to detoxify patients overdosed on certain drugs (5–7). Experiments have demonstrated this flow dependence of renal excretion (8–11).

In this work a model based upon physiological considerations was derived. Literature data on the renal clearance–urine flow relationship for representative compounds were fitted to the model. Factors determining the urine flow dependence are discussed and exemplified by computer simulation.

BACKGROUND

The functional unit of the kidney, the nephron, is composed of the glomerulus, the proximal tubule, the loop of Henle, the distal tubule, and the collecting duct, each of varying dimensions [Table I, (12)]. The glomerulus receives the arterial blood and a portion of the plasma water is filtered. About two thirds of the glomerular filtrate is reabsorbed isoosmotically in the proximal tubule (13). The wall of the ascending loop of Henle is thought to be relatively impermeable to water. Further reabsorption of water occurs in the distal tubule and collecting ducts. The volume of plasma water filtered per unit of time at the glomerulus, the glomerular filtration rate, is ~120 ml/min in an average 20-year-old male. Because of the extensive reabsorption of water, the urine flow rate averages ~1–2 ml/min. The renal plasma flow, ~650 ml/min, and the glomerular filtration rate are reasonably constant, but because of the variable reabsorption of water in the distal tubule and collecting duct, the urine flow rate is quite variable.

Table I—Dimensions of Renal Tubule in Humans

Segment of Renal Tubule	Length, mm[a]	Outside Diameter, μm[a]	Outer Surface Area,[b] M^2
Proximal	12–24	50–65	6.6
Loop of Henle, thin	0–14	14–22	1.0
thick	6–18	—	
Distal	2–9	20–50	1.2
Collecting duct	22	up to 200	20.7

[a] Obtained from R. F. Pitts (12). [b] π(average outer diameter)(average length) × 2(number of nephrons per kidney) (Ref. 25).

The renal excretion rate of a drug is the net result of filtration, secretion, and reabsorption:

$$\text{rate of excretion} = \text{rate of filtration} + \text{rate of secretion} - \text{rate of reabsorption} \quad \text{(Eq. 1)}$$

Because only drug in plasma water (the unbound drug) is filtered at the glomerulus:

$$\text{rate of filtration} = F\alpha C_p \quad \text{(Eq. 2)}$$

For definition of symbols, see the Appendix.

Substituting Eq. 2 into Eq. 1 and dividing by plasma drug concentration, the renal clearance, a proportionality constant relating the rate of excretion to the plasma drug concentration, is obtained:

$$CL_r = \alpha F + \frac{\text{rate of secretion} - \text{rate of reabsorption}}{C_p} \quad \text{(Eq. 3)}$$

A renal clearance of less than αF, therefore, indicates that reabsorption occurs. If a drug is secreted, reabsorption must then be greater than secretion.

The renal clearance of a nonpolar compound that is nonionized at physiological conditions shows flow dependence. The extent of the dependence is determined by its lipophilicity and the membrane permeability. For drugs that are not secreted, the renal clearance is expressed by:

$$CL_r = \alpha F - \frac{\text{rate of reabsorption}}{C_p} \quad \text{(Eq. 4)}$$

The following model applies to a drug that is neither secreted nor ionized at physiological pH.

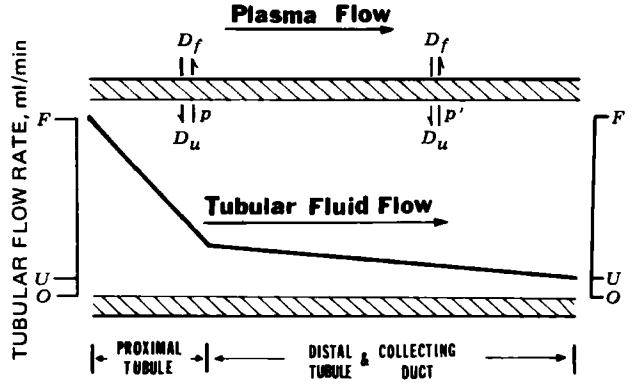

Figure 1—*Schematic diagram of drug and water reabsorption in an average functional nephron. The exchange of drug in luminal fluid (D_u) and free drug in plasma (D_f) is characterized by the permeability constant, P or P′, of each region of the nephron. The decline of the luminal fluid flow rate is assumed to be linear within the proximal and post proximal parts of the tubule. The glomerular filtration rate (F), the urine flow (U), and the origin (O) are also shown on the y-axes.*

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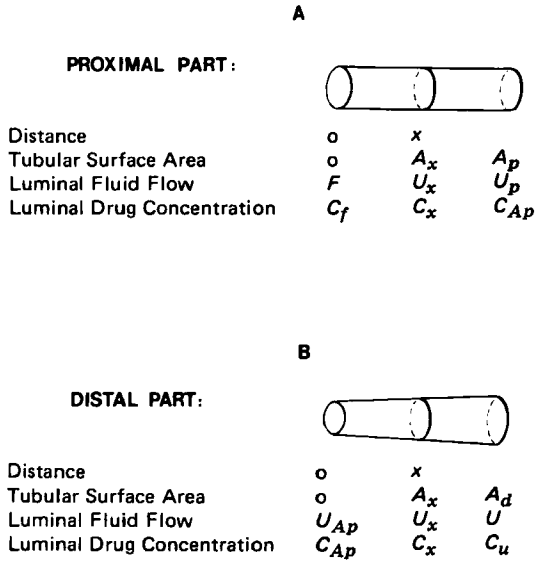

Figure 2—*Scheme for symbols used in model derivation. Proximal part of the renal tubule (A); and distal part of the renal tubule (B).*

THEORETICAL

To develop a model for the urine flow rate dependence of renal clearance for a nonsecreted, poorly ionized drug, the following assumptions are made:

1. Each nephron behaves, on average, as a single functional unit as depicted in Fig. 1.
2. There is a constant reabsorption flux of water within the proximal and distal regions of the tubule. The net rate of the change of luminal fluid volume per unit of surface area of membrane is P_w in the proximal and P'_w in the rest of the nephron. Urine flow alterations reflect a physiological change in P'_w.
3. The rate of reabsorption of a compound at any point in the tubule is proportional to the difference between the concentrations in luminal fluids and in plasma and depends on the permeability of the drug in the tubular membrane. The permeability of the membrane per unit of surface area for a given compound is assumed to be constant within each of the regions of the tubule.

Reabsorption in the Proximal Tubule—At point x, the rate of change of luminal fluid flow is:

$$\frac{dU_x}{dA_x} = -P_w \qquad \text{(Eq. 5)}$$

and the proximal luminal fluid flow, U_x, in the model (Fig. 2A), is described by:

$$U_x = F - P_w A_x \qquad \text{(Eq. 6)}$$

Thus, the luminal fluid flow rate declines from F to $F - P_w A_p$, or U_{Ap}. The rate of reabsorption of drug depends on the permeability constant, P, and the concentration gradient of the exchangeable drug (unbound) across the membrane at point x. Therefore:

$$\text{rate of reabsorption} = P(C_x - \alpha C_p)dA_x \qquad \text{(Eq. 7)}$$

The rate of loss of the drug from the tubule is:

$$-d(U_x C_x) = -U_x dC_x - C_x dU_x \qquad \text{(Eq. 8)}$$

Because these two rates must be the same, it follows that:

$$U_x \frac{dC_x}{dA_x} + C_x \frac{dU_x}{dA_x} = -P(C_x - \alpha C_p) \qquad \text{(Eq. 9)}$$

By substituting Eqs. 5 and 6 into Eq. 9:

$$(F - P_w A_x)\frac{dC_x}{dA_x} + C_x(P - P_w) = \alpha C_p P \qquad \text{(Eq. 10)}$$

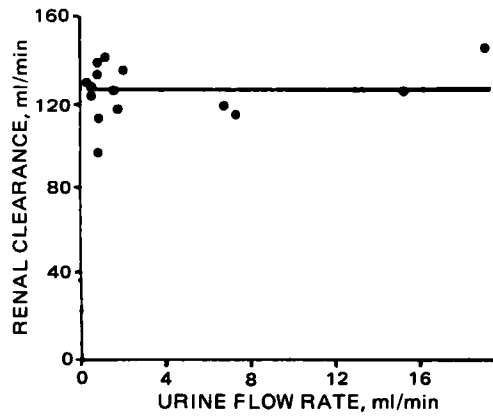

Figure 3—*Relationship between renal clearance of creatinine and urine flow rate. Data from Ref. 14. The solid line is the computer fit using the model.*

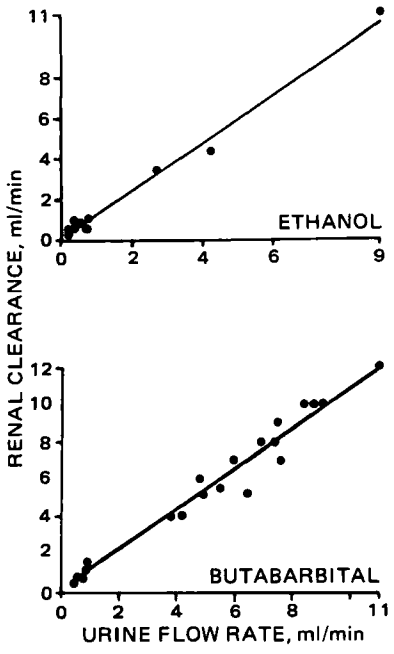

Figure 4—*Urine flow-dependence of renal clearance for ethanol and butabarbital. Data from Refs. 14 and 7, respectively. Solid lines are the computer fits of the model.*

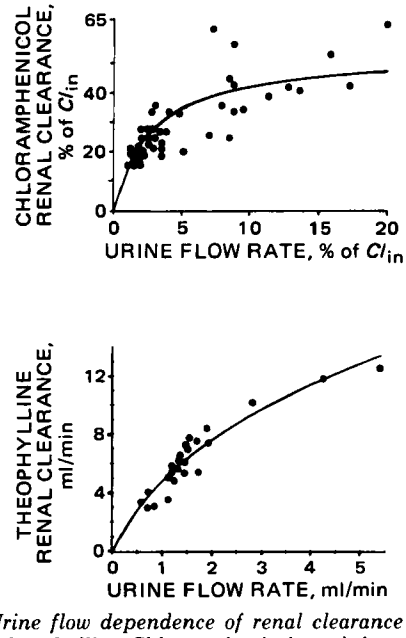

Figure 5—*Urine flow dependence of renal clearance for chloramphenicol and theophylline. Chloramphenicol renal clearance and urine flow were normalized by inulin clearance (CL_{in}). Data for chloramphenicol are from Ref. 15. The theophylline data are unpublished (17). Solid lines are the computer fits of the model.*

Table II—Parameter Values of Model[a]

Parameter	Urea[b] A	Urea[b] B	Urea[b] C	Creatinine	Ethanol	Butabarbital	Chloramphenicol	Theophylline
ϵ, ml/min	6.7	8.0	9.1	0	665	120	13.9	27.5
δ	0.013	0.016	0.018	0	5	1.01	0.028	0.25
α	1	1	1	1	1	0.72[c]	0.47[d]	0.47[e]
F, ml/min	125	85	145	125	140	120	133	118

[a] ϵ, δ, and F values from fit of Eq. 28 to data (7, 14–18). [b] From three subjects. [c] Ref. 19. [d] Ref. 20. [e] Ref. 17.

On rearrangement:

$$\frac{dC_x}{dA_x} + \left(\frac{P - P_w}{F - P_w A_x}\right) C_x = \frac{\alpha C_p P}{F - P_w A_x} \qquad \text{(Eq. 11)}$$

Integration of this first-order linear differential equation gives:

$$C_x = \frac{\alpha C_p \delta}{\delta - 1} + \beta (F - P_w A_x)^{-W} \qquad \text{(Eq. 12)}$$

where $W = 1 - \delta$, δ is P/P_w, and β is the constant of integration. Because only the unbound drug is filtered at the glomerulus, the drug concentration in the initial filtrate, where A_x is zero, is αC_p. Accordingly, the integration constant is:

$$\beta = -\alpha C_p \left(\frac{1}{\delta - 1}\right) F^W \qquad \text{(Eq. 13)}$$

and the luminal drug concentration at any point x within the proximal tubule is:

$$C_x = \frac{\alpha C_p}{\delta - 1}\left[\delta - \left(\frac{F}{F - P_w A_x}\right)^W\right] \qquad \text{(Eq. 14)}$$

At the end of the proximal tubule, the luminal concentration becomes:

$$C_{Ap} = \frac{\alpha C_p}{\delta - 1}\left[\delta - \left(\frac{F}{F - P_w A_p}\right)^W\right] \qquad \text{(Eq. 15)}$$

Because ~70% of the glomerular filtrate is reabsorbed in the proximal tubule (13), $P_w A_p$ can be approximated by $0.7F$. Therefore:

$$C_{Ap} = \frac{\alpha C_p}{\delta - 1}(\delta - 0.3^{-W}) \qquad \text{(Eq. 16)}$$

Reabsorption in the Distal Tubule and the Collecting Duct—The luminal flow through an annulus at point x in the distal part of the nephron (Fig. 2B) is:

$$U_x = 0.3F - P'_w A_x \qquad \text{(Eq. 17)}$$

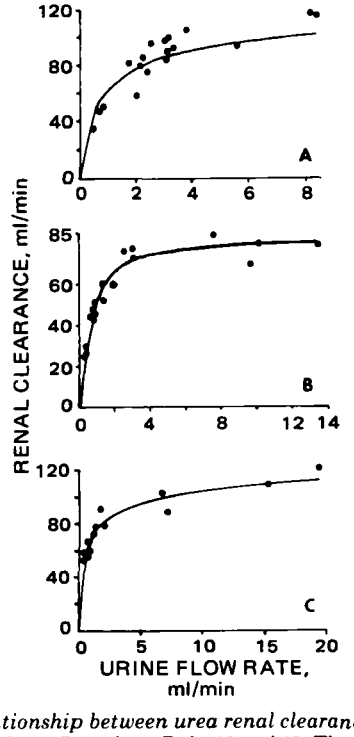

Figure 6—*Relationship between urea renal clearance and urine flow rate in three subjects. Data from Refs. 16 and 18. The solid lines are the computer fits of the model.*

The rate of reabsorption of luminal fluid at any annulus is obtained from the derivative of Eq. 17, *i.e.*:

$$\frac{dU_x}{dA_x} = -P'_w \qquad \text{(Eq. 18)}$$

The rate of reabsorption of the drug within the annulus at point x is:

$$\text{rate of reabsorption} = P'(C_x - \alpha C_p) dA_x \qquad \text{(Eq. 19)}$$

By equating Eqs. 8 and 19, with substitution of Eqs. 17 and 18, and rearranging, we obtain:

$$\frac{dC_x}{dA_x} + \left(\frac{P' - P'_w}{0.3F - P'_w A_x}\right) C_x = \frac{\alpha C_p P'}{0.3F - P'_w A_x} \qquad \text{(Eq. 20)}$$

On integrating:

$$C_x = \frac{\alpha C_p P'}{P' - P'_w} + \gamma (0.3F - P'_w A_x)^{-Z} \qquad \text{(Eq. 21)}$$

where $Z = 1 - P'/P'_w$, and γ is the constant of integration. The drug concentration at the entry of distal tubule ($A_x = 0$) is that at the end of the proximal tubule (Eq. 16). Therefore, solving for the integration constant using Eqs. 16 and 21 (when $A_x = 0$), the luminal drug concentration at any point x within the distal part of the nephron is:

$$C_x = \alpha C_p \left[\frac{P'}{P' - P_w'} + \left(\frac{\delta}{\delta - 1} - \frac{0.3^{-W}}{\delta - 1} - \frac{P'}{P' - P'_w}\right)(0.3F)^Z (0.3F - P'_w A_x)^{-Z}\right] \qquad \text{(Eq. 22)}$$

At the end of the collecting duct ($A_x = A_d$) the luminal concentration is the observed urine concentration (C_u), therefore:

$$C_u = \alpha C_p \left[\frac{P'}{P' - P'_w} + \left(\frac{\delta}{\delta - 1} - \frac{0.3^{-W}}{\delta - 1} - \frac{P'}{P' - P'_w}\right)\left(\frac{0.3F}{U}\right)^Z\right] \qquad \text{(Eq. 23)}$$

The ratio of urine and plasma concentrations becomes:

$$\frac{C_u}{C_p} = \alpha \left[\frac{P'}{P' - P'_w} + \left(\frac{\delta}{\delta - 1} - \frac{0.3^{-W}}{\delta - 1} - \frac{P'}{P' - P'_w}\right)\left(\frac{0.3E}{U}\right)^Z\right] \qquad \text{(Eq. 24)}$$

The value of P'_w is related to the luminal flow rates at two boundaries, $0.3F$ and U, *i.e.*, at the end of the distal region, P'_w is $(0.3F - U)/Ad$ (from Eq. 17). To minimize the number of parameters and to simplify the final form of the model, let:

$$\epsilon = P'Ad \qquad \text{(Eq. 25)}$$

and therefore:

$$\frac{P'}{P'_w} = \frac{\epsilon}{0.3F - U} \qquad \text{(Eq. 26)}$$

Renal clearance relates the urinary excretion rate to the plasma drug concentration. Experimentally, the excretion rate is calculated from urine flow and drug concentration in urine:

$$Cl_r = U\frac{C_u}{C_p} \qquad \text{(Eq. 27)}$$

and from Eqs. 24 and 26, the dependence of renal clearance on urine flow, α, δ, ϵ, and F is obtained:

$$Cl_r = \alpha U \left[\frac{\epsilon}{\epsilon - 0.3F + U} + \left(\frac{0.3^{-W} - \delta}{W} - \frac{\epsilon}{\epsilon - 0.3F + U}\right)\left(\frac{0.3F}{U}\right)^Z\right] \qquad \text{(Eq. 28)}$$

where $W = 1 - \delta$, and $Z = 1 - \epsilon/0.3F - U$.

Renal clearance and urine flow data for compounds demonstrating various degrees of urine flow dependence, namely, alcohol (14), chlor-

amphenicol (15), creatinine (16), butabarbital (7), theophylline (17), and urea (16, 18) were used to test the validity of the model. When tables of data were not available (*i.e.*, chloramphenicol and butabarbital), renal clearance and urine flow values were estimated from figures in the respective references using a ruler with a millimeter scale. Intraindividual values were used except for chloramphenicol, for which renal clearance and urine flow were normalized to inulin clearance (CL_{in}), *i.e.*, CL_r/CL_{in} and U/CL_{in}. Data analysis and graphical examination of the urine flow dependencies were performed by nonlinear regression of Eq. 28 using the PROPHET computer system. The best-fits of the parameters were determined by the minimized residual sum of squares.

RESULTS AND DISCUSSION

The passive diffusion of a drug across the tubular membrane proceeds toward an equilibrium state in which the diffusible species attains the same concentration in both luminal and plasma fluids. The reabsorption of water along the renal tubule produces disequilibrium with an increased concentration of drug in the luminal fluid. The greater the reabsorption of water, the more the drug is concentrated and, perhaps, the longer it stays in the tubule. Drugs can be classified into three categories: one in which no drug is reabsorbed, one in which drug is reabsorbed to equilibrium, and one in which drug is reabsorbed but equilibrium is not achieved.

If a drug is not reabsorbed at all (*e.g.*, creatinine, inulin, gentamicin, and kanamycin), the δ and ϵ values approach zero and the urinary excretion rate is the filtration rate. Under these conditions, the renal clearance is αF (Eq. 4) and is independent of urine flow. This relationship is demonstrated by creatinine (Fig. 3). If a drug is reabsorbed to equilibrium, its ability to diffuse must be equal to or greater than that of water. This category is exemplified by alcohol and butabarbital (Fig. 4), compounds with high δ and ϵ values (Table II). Because of the rapid exchange of the drugs, their plasma unbound and urine concentrations are identical at all urine flow conditions. As the values of δ and ϵ approach infinity (Eq. 28), the renal clearance becomes:

$$CL_r = \alpha U \qquad \text{(Eq. 29)}$$

Within the range of plasma concentrations in which there is a constant fraction unbound, a linear relationship between CL_r and U is observed (Fig. 4).

For many drugs with medium δ and ϵ values, equilibrium is not achieved, because the diffusional rate of the drug (*e.g.*, theophylline, chloramphenicol, and urea) is less than that of water. Various degrees of water reabsorption in the distal portion of the tubule result in various urine flow rates and different disequilibrium states. For theophylline and similar drugs, a convex-ascending relationship can be observed for flow-dependent renal clearance (Fig. 5). Among compounds in this group, urea has received the most attention. Urea clearance increases markedly with urine flow, up to ~3 ml/min, and thereafter increases only slightly if at all (Fig. 6). The model visually fits the urea data well and predicts an asymptotic value of αF; *i.e.*, at higher urine flow rates virtually all the filtered urea is excreted into the urine. This is a classic example of urine flow dependence of renal clearance.

Changes in renal clearance with urine flow predicted by the model for compounds of varied permeability are shown in Fig. 7. The larger the permeability as reflected by δ and ϵ, the greater the dependence on urine flow, and the smaller the value of renal clearance.

It is the unbound drug in plasma that is filtered at the glomerulus. Consequently, the greater the value of α, the larger the filtered load (Eq. 2) for a given plasma concentration. For two compounds of the same permeability, the one with the higher value of α is expected to have the higher renal clearance. This conclusion applies to drugs in all three categories.

There are three more factors to be considered to complete a general model for flow-dependent renal clearance of all drugs. They are: secretion, active reabsorption, and the change of pH in the tubular fluid along the nephron. The present model does not incorporate these factors. The compounds discussed here were chosen because they are neither secreted nor extensively ionized at physiological pH.

Secretion is an active process. If a drug is highly secreted into the lumen, its plasma concentration along the tubule may decline dramatically even if highly bound to plasma proteins. This leads to a perfusion limitation in the excretion of the drug and difficulty in estimating the concentration gradient along the tubule. Furthermore, only a portion of the renal blood flow reaches the distal part of the nephron. These considerations make prediction of urine flow dependence difficult.

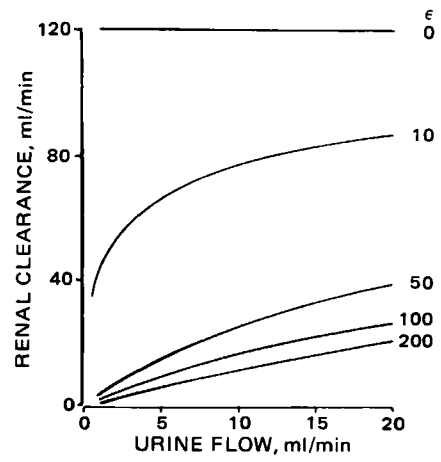

Figure 7—*Simulation of the effect of permeability on the urine flow-dependence of drug renal clearance. Values of parameters used in simulation were: drug unbound fraction in plasma, 1.0; glomerular filtration rate, 120 ml/min; $\epsilon/\delta = 100$.*

Active reabsorption usually occurs for endogenous compounds, *e.g.*, vitamins, electrolytes, glucose, and amino acids. However, the reabsorption process for drugs, mostly exogenous compounds, is mainly passive diffusion. Therefore, the model was restricted to the passive processes.

The luminal fluid starts with a pH of 7.4 at the glomerulus and ends its journey at a pH of 4.5–8.0 (1). Usually, the urine pH is 6.25 ± 0.36 (mean ±*SD*). There is evidence that the greater change of pH occurs in the distal part of the nephron, *i.e.*, mostly in the collecting ducts (21–23). For acidic and basic compounds with pKa values sensitive to physiologic pH changes, their fractions nonionized vary with their location in the tubule. Of the compounds tested, only butabarbital (pK_a = 7.9) and theophylline (pK_a = 8.8) are slightly ionizable at physiologic pHs. The urine pH was not reported with the data of butabarbital. It was assumed that samples were collected under these conditions and the pH sensitivity of butabarital renal clearance is not expected. In one theophylline study, subjects took ammonium chloride orally to maintain acidic urine. The urine pH was successfully maintained below 5.5 under normal urine flow conditions. However, the urine pH increased when urine flow rate was increased (due to the diuretic effect of theophylline). Presumably, at high urine flow rates, the controlling mechanism (located mainly in the collecting ducts) has less effect on the pH of the fluid. Therefore, the pH of the tubular fluid not only varies with the distance the luminal fluid travels in the tubule, but also is a function of urine flow rate.

The model explains and predicts the dependence of renal clearance on permeability and urine flow. The model was tested using literature data for compounds that are apparently not secreted, actively reabsorbed, or pH sensitive, but represent a wide spectrum of lipophilicity. From the fits of the model, it can be concluded that the urine flow dependence of renal clearance can be adequately described and predicted by our physiologically derived model.

APPENDIX

A_d = Surface area of the distal tubule and collecting ducts, centimeter squared
A_p = Surface area of the proximal tubule, centimeter squared
A_x = Surface area of membrane from the integration starting point to point x, centimeter squared
C_{Ap} = Concentration of the drug in luminal fluid at the end of the proximal tubule, micrograms per milliliter
C_f = Free drug concentration in plasma, micrograms per milliliter
CL_r = Renal clearance of the drug, milliliter per minute
C_p = Total drug concentration in plasma, micrograms per milliliter
C_u = Drug concentration in urine, micrograms per milliliter
C_x = Luminal drug concentration in annulus at point x, micrograms per milliliter
F = Glomerular filtration rate, milliliter per minute
P = Permeability constant of the drug in the proximal tubule, centimeters per minute

P' = Permeability constant of the drug in the distal tubule and collecting ducts, centimeter per minute
P_w = Reabsorption flux of water in the proximal tubule, centimeter per minute
P'_w = Reabsorption flux of water in the distal tubule and collecting duct, centimeter per minute
pK_a = The dissociation constant of the drug
U = Urine flow rate, millimeter per minute
U_{Ap} = Luminal fluid flow rate at the end of the proximal tubule, milliliter per minute
U_x = Luminal fluid flow rate in annulus at point x, millimeter per minute
α = Unbound fraction of drug in plasma
δ = Ratio of P/P_w
ϵ = Product of $P'A_d$, ml/min

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Absorption Kinetics and Steady-State Plasma Concentrations of Theophylline Following Therapeutic Doses of Two Sustained-Release Preparations

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Abstract □ Ten healthy volunteers received two sustained-release preparations as a single and multiple dose regimen in an open crossover study. Plasma theophylline concentrations were measured by an enzyme immunoassay. The limited fluctuation of the theophylline levels at steady state, with twice daily administration, clearly demonstrated the marked sustained release properties of both preparations. Results indicate similar properties for the two preparations. Significant correlations between the single dose period and steady state were found for C_{max} and AUC (r = 0.76 and 0.87, respectively) with one formulation, whereas this was not the case for the other (r = 0.27 and 0.49). The daily dose necessary to keep the plasma concentration within the therapeutic range of 55–110 μmole/liter varied from 7.9 to 22.9 mg/kg. Only mild side effects were recorded, but they were not correlated to the plasma theophylline concentration.

Keyphrases □ Absorption—kinetics and steady-state plasma concentrations of theophylline following therapeutic doses of two sustained-release preparations □ Kinetics—absorption and steady-state plasma concentrations of theophylline following therapeutic doses of two sustained-release preparations □ Theophylline—absorption kinetics and steady-state plasma concentrations following therapeutic doses of two sustained-release preparations

Theophylline produces relaxation of bronchial smooth muscles and is widely used in the treatment of reversible obstructive lung disease. The bronchodilator effect of theophylline increases with serum concentrations over a range of 28–110 μmoles/liter (5–20 μg/ml), but at levels of >110 μmoles/liter there is an increased risk of serious toxicity (1). Maximal bronchodilation with minimal toxicity occurs at levels between 55–110 μmoles/liter (10–20 μg/ml), and this is therefore normally considered the therapeutic range (2). It is very difficult to maintain serum

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