Br. J. Pharmac. Chemother. (1967), **30**, 30–34.

THEORETICAL CONSIDERATIONS RELATING TO THE AMOUNT OF DRUG REABSORBED BY THE RENAL TUBULES

BY

B. K. MARTIN

From the Nicholas Research Institute, Slough, Bucks
(*Received September* 14, 1966)

The oral administration of certain drugs can give rise to local damage of the stomach and a similar effect is then frequently observed in the kidney; thus aspirin causes exfoliation of mucosal cells in the stomach (Croft, 1963) and of tubular cells in the kidney (Scott, Denman & Dorling, 1963; Prescott, 1965). Certain common features exist between these two sites, for the kidney " recapitulates in miniature " (Martin, 1966) the same process of drug absorption as the stomach, in so far as reabsorption of drug can occur in the renal tubules and this also takes place from an acidic environment. The pH gradient in the kidney is considerably less than that in the stomach and the amount of drug which is reabsorbed in the tubules may also be much less, but the latter aspect has received little attention. The extent of drug or metabolite reabsorption in the tubules is also of importance in other considerations of nephrotoxicity. In the absence of tubular reabsorption the concentration of drug or metabolite in the urine will be about a hundred times greater than the concentration of free (unbound) compound in the plasma, and the simultaneous change in pH may be such that the compound is present in excess of its solubility and is deposited from solution. This is exemplified by the acetyl derivatives of certain sulphonamides.

The following considerations attempt to assess the amount of drug which is reabsorbed by the renal tubules in the course of drug elimination and to relate this to the amount of drug absorbed from the gut. This treatment involves the formulation of specific rate constants for the glomerular filtration, tubular absorption and tubular secretion of drug.

The glomerular filtration of blood gives rise to an ultrafiltrate which has a concentration of drug equal to that of the free (unbound) drug in plasma. Drug which is excreted in the glomerular filtrate can be partly reabsorbed as the filtrate passes along the renal tubules, this gives rise to recycling of drug, and loss by urinary excretion then tends to be minimal. Drug can also be added to the filtrate by a process of tubular secretion and, when this process predominates, urinary excretion of drug tends to be maximal. Simultaneously, drug is also eliminated by routes other than urinary excretion and the loss of drug from the body by each route can often be described by first order kinetics. The total amount of drug reabsorbed by the tubules in the course of drug elimination will therefore depend not only on the rate of tubular reabsorption, but also on the magnitude of the rate constants which govern the elimination of drug by all routes.

The glomerular filtration rate is relatively constant, but the concentration of drug contained in the filtrate will decline exponentially as drug elimination proceeds and the excretion of drug by glomerular filtration can be expressed by a first order rate constant, k_g, so that,

$$\frac{dD_G}{dt} = k_g D \quad \ldots\ldots (1)$$

where D_G is the amount of drug filtered by the glomeruli and D is the amount of drug in the body at time t.

The rate of excretion of drug in urine represents the combined effect of glomerular filtration, tubular absorption and tubular secretion of drug, and this may be expressed in the form:

$$\frac{dD_U}{dt} = \frac{dD_G}{dt} - \frac{dD_A}{dt} + \frac{dD_S}{dt} \quad \ldots\ldots (2)$$

where D_U, D_A and D_s are respectively the amounts of drug excreted in the urine, absorbed by the tubules and secreted by the tubules.

$$\text{If } \frac{dD_U}{dt} = k_d D \quad \ldots\ldots (3)$$

$$\text{and } \frac{dD_A}{dt} = k_a D \quad \ldots\ldots (4)$$

$$\text{and } \frac{dD_S}{dt} = k_s D \quad \ldots\ldots (5)$$

$$\text{then, from equations (1) and (2), } k_d = k_g - k_a + k_s \quad \ldots\ldots (6)$$

where k_d, k_a and k_s are first order rate constants which respectively describe the urinary excretion, tubular absorption and tubular secretion of drug.

Equation (6) shows that when $k_a > k_s$ (net tubular absorption of drug) then $k_d < k_g$ and the urinary excretion of drug is less than its rate of glomerular filtration. When $k_s > k_a$ (net tubular secretion of drug) then $k_d > k_g$ and the excretion of drug exceeds its rate of glomerular filtration.

Substituting equations (1), (3) and (5) in equation (2):

$$\frac{dD_A}{dt} = (k_g + k_s - k_d) D \quad \ldots\ldots (7)$$

When drug elimination is first order, $D = D_o e^{-Kt}$ where K is the first order rate constant governing elimination of drug by all routes and D_o is the amount of drug in the body at $t = 0$, then:

$$\frac{dD_A}{dt} = (k_g + k_s - k_d) D_o e^{-K} \quad \ldots\ldots (8)$$

$$D_A = (k_g + k_s - k_d)\, D_o \int_o^t e^{-Kt}\, dt = \frac{(k_g + k_s - k_d)}{K} D_o (1 - e^{-Kt}) \quad \ldots\ldots (9)$$

If $D_{A\infty}$ denotes the value of D_A when drug elimination is complete ($t = \infty$), then,

$$D_{A\infty} = \frac{(k_g + k_s - k_d)}{K} D_o \quad \ldots\ldots (10)$$

$$\text{and } \frac{D_{A\infty}}{D_o} = \frac{k_g + k_s - k_d}{K} \quad \ldots\ldots (11)$$

This ratio is independent of the value of D_o—that is, of the amount of drug initially present in the body—and D_o can, therefore, for the present purpose, be equated to the dose of drug administered. Equation (11) therefore provides an expression which relates the total amount of drug absorbed in the tubules to the amount absorbed from the gut.

It will be shown that k_g can be determined experimentally, k_d and K are available by the standard methods employed in the kinetic study of drug elimination, but the value of k_s cannot be readily assessed. In seeking a simple solution when there is net tubular absorption of drug, k_a in the above derivation can be replaced by k'_a equal to $(k_a - k_s)$ and representing in effect a *net* absorption rate constant, so that $D_{A\infty}$ will then represent only the net amount of drug reabsorbed by the tubules, $D_{A\infty}$ (net). On this basis, equation (11) becomes:

$$\frac{D_{A\infty}\ (\text{net})}{D_o} = \frac{k_g - k_d}{K} \quad \ldots\ldots (12)$$

If tubular secretion also takes place, then the actual amount of drug which is reabsorbed will be larger than the calculated net value of $D_{A\infty}$.

For the evaluation of k_g, equation (1) can be expressed in the form:

$$k_g = \frac{dD_G}{dt} \Big/ D = \frac{C_g V_g}{D} = \frac{C_f V_g}{D} \quad \ldots\ldots (13)$$

where V_g = Glomerular filtration rate (l/hr),

C_g = Concentration of drug in glomerular filtrate at time t,

C_f = Concentration of free (unbound) drug in plasma at time t,

and C_f, V_g and D can be determined experimentally.

In the following considerations relating to a model drug, a value of 5.7 l/hr is assigned to V_g, and C_f is calculated on the basis that the free drug is uniformly distributed in a volume of 42.0 l. For the model drug which exhibits no binding in plasma or tissues, k_g has a value of 0.14 hr^{-1} (Equation (13)). If $K = 0.13$ hr^{-1} and $k_d = 0.01$ hr^{-1}, then $D_{A\infty}$ (net)/D_o = 1 (Equation (12)). It is conceivable, therefore, that for certain drugs the net amount of drug absorbed by the tubules can well equal, and in some instances may even exceed, the amount of drug absorbed by the gut. The ratio will tend to be large when the drug is slowly eliminated and when it is eliminated predominantly in the form of metabolites. The tubular cells can therefore be involved in drug reabsorption to a considerable extent when very little unchanged drug appears in the urine—a fact which is frequently overlooked.

The glomerular-filtration rate constant of a drug (k_g) is governed by the drug's distribution. The binding of drug to tissue proteins or the partition of drug in body fat has the effect of decreasing k_g. The effect of plasma protein binding, in the absence of any appreciable binding in other tissues, is calculated for a number of model drugs in Table 1.

TABLE 1

CALCULATED VALUES OF THE DRUG GLOMERULAR FILTRATION RATE CONSTANT (k_g) FOR A NUMBER OF MODEL DRUGS

Drug in body (D) = 1,000 mg. The concentration of free drug (C_f) and bound drug in plasma are calculated for a plasma volume of 3·0 l., the free drug is uniformly distributed in a volume of 42·0 l. and the glomerular filtration rate (V_g) is 5·70 l./hr. (a) and (b) represent the distribution when 25% and 50% respectively of the total drug in the body is bound to the plasma proteins

Drug in plasma			
Concentration of free drug (mg/l.)	Concentration of bound drug (mg/l.)	% bound	k_g (hr^{-1})
23·8	0	0	0·136
22·2	22·2	50	0·127
21·5	32·3	60	0·123
20·4	47·6	70	0·116
18·5	74·1	80	0·106
17·9	83·3	82·3 (a)	0·102
14·5	130·4	90	0·083
11·9	166·7	93·3 (b)	0·067
10·1	191·9	95	0·058
5·3	259·3	98	0·030

The value of k_g is related to the fraction of the total drug in the body which is bound and considerations based on the fraction of the drug in plasma which is bound are misleading. Thus, when 60% of the drug in plasma is bound, k_g is decreased by only 10%; when however 25% of the drug in the body is bound there is a 25% decrease in k_g, but this corresponds to a plasma binding of 82% (Table 1). Similar considerations to this effect have been expressed previously (Martin, 1965).

The extension of the calculations exemplified in Table 1 would imply, probably falsely, that the effect on k_g is the same when drug is bound to the plasma proteins as when the same amount of drug is bound in any other tissue. The model system is, however, based on the assumption that equilibrium distribution of drug is maintained throughout, this may well be closely approached when the bound drug circulates in plasma. It is unlikely to be so when the drug is bound in certain tissues possessing a relatively small blood flow, and equilibrium distribution may then be replaced by a steady-state distribution of drug.

Equations (11) and (12) are applicable only when drug elimination is first order. The elimination rate constant of salicylic acid decreases considerably with increase of dose (Cummings & Martin, 1964; Bedford, Cummings & Martin, 1965; Levy, 1965). When the amount of salicylic acid in the body is small (300 mg), $k_d = 0.01\ hr^{-1}$, $K = 0.2\ hr^{-1}$, and if $k_g = 0.116\ hr^{-1}$ (Table 1, 70% plasma protein binding) then $D_{A\infty}$ (net)/$D_o = 0.5$. Calculations indicate that this ratio may become greater than 1 during continuous salicylate therapy when $K = 0.05\ hr^{-1}$ or less. The recycling of salicylic acid by the kidney is therefore much greater after larger doses of aspirin.

Any attempt to relate mucosal damage in the stomach to tubular damage in the kidney in terms of the amount of drug absorbed at these sites must also involve consideration of

the amount of drug transported per unit area of absorbing surface in unit time (Martin, 1964). Absorption of drug in the gut can be complete in 1–2 hr whereas the rate of drug reabsorption in the tubules declines over a much longer period and is governed by the elimination rate constant of the drug.

SUMMARY

1. Specific rate constants have been formulated which relate the rate of glomerular filtration of drug, the rate of tubular absorption and the rate of tubular secretion of drug to the amount of drug in the body.

2. An expression has been derived which relates the amount of drug absorbed by the renal tubules to the amount of drug absorbed from the gut.

3. The net amount of drug absorbed by the tubules can be calculated and in certain instances this may well exceed the amount of drug which is administered.

REFERENCES

BEDFORD, C., CUMMINGS, A. J. & MARTIN, B. K. (1965). A kinetic study of the elimination of salicylate in man. *Br. J. Pharmac. Chemother.*, **24**, 418–431.

CROFT, D. N. (1963). Aspirin and the exfoliation of gastric epithelial cells. *Br. med. J.*, *ii*, 897–901.

CUMMINGS, A. J. & MARTIN, B. K. (1964). Factors influencing the plasma salicylate concentration and urinary salicylate excretion after oral dosage with aspirin. *Biochem. Pharmac.*, **13**, 767–776.

LEVY, G. (1965). Pharmacokinetics of salicylate elimination in man. *J. Pharm. Sci.*, **54**, 959–967.

MARTIN, B. K. (1964). In *Absorption and Distribution of Drugs*, ed. BINNS, T. B., pp. 165–172. Livingstone, London.

MARTIN, B. K. (1965). Potential effect of the plasma proteins on drug distribution. *Nature, Lond.*, **207**, 274–276.

MARTIN, B. K. (1966). In discussion of paper by D. N. Croft. The action of analgesic substances on the gastric mucosa. *J. Pharm. Pharmac.*, **18**, 363.

PRESCOTT, L. F. (1965). Effects of acetylsalicylic acid, phenacetin, paracetamol, and caffeine on renal tubular epithelium. *Lancet*, *ii*, 91–95.

SCOTT, J. T., DENMAN, A. M. & DORLING, J. (1963). Renal irritation caused by salicylates. *Lancet*, *i*, 344–348.