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MEASUREMENT OF THE RENAL CLEARANCE OF DRUGS

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The concept of renal clearance

The renal clearance of a drug (CL_R) is a measure of the functional ability of the kidney to remove it from the body independent of other pharmacokinetic processes. It is often defined as the volume of plasma from which drug is, in effect, completely removed per unit time by the kidney. Obviously this is a virtual volume, not a real volume. No single millilitre of plasma necessarily has all of its drug removed in one transit through the kidney; rather a fraction is removed from each of the many millilitres of plasma perfusing the organ. This amount is summed and expressed as though it were derived by completely clearing a smaller volume of plasma of all its contained drug.

More simply, renal clearance may be defined in terms of the loss of drug across the kidney, as the product of renal plasma flow (Q_R) and the renal extraction ratio (E_R):

$$CL_R = Q_R . E_R \quad (1)$$

where E_R = (concentration of drug in renal arterial plasma − concentration of drug in renal venous plasma)/concentration of drug in renal arterial plasma. Thus, clearance is plainly seen to have units of flow.

A third definition conceives renal clearance as a proportionality constant relating the rate of drug excretion at time t, (dAe/dt), to its concentration in plasma at time t, (C),:

$$CL_R = \frac{dAe/dt}{C} \quad (2)$$

Although the term 'clearance' usually refers to irreversible removal, in the context of the renal route it often represents the net excretion process as some drug may be transferred back from the kidney to the plasma.

Significance of renal clearance

The measurement of renal clearance is of primary value in probing the mechanisms of drug excretion since it can be used to characterise any process of drug removal in the kidney, whether it be constant or changing, capacity-limited or otherwise. Apart from this there are many other areas where a knowledge of this parameter may be vital.

If renal excretion contributes significantly to the overall elimination of a drug, that is, renal clearance is about 50% or more of total clearance, changes in renal clearance may have profound implications for the duration of pharmacological or toxic effects. It is especially important to know about the renal clearance of drugs that are predominantly excreted in an unchanged form in the urine when dosing patients with lowered kidney function, namely the very young, the elderly and those with renal disease. A knowledge of whether the renal clearance of a drug can be made to become the major component of total clearance may help in the management of overdosage. Measurement of renal clearance may also contribute to an understanding of the mechanisms of specific drug interactions. In drug development it might be preferable to select those compounds with relatively high renal contributions to total clearance since inter-individual variability in metabolic clearance is greater and less predictable than variability in renal clearance. When performing cross-over bioavailability studies on drugs with relatively high renal clearances corrections for intrasubject variability in renal clearance may improve estimates of drug absorption (Kwan & Till, 1973). Furthermore, if the renal clearance of a drug can be perturbed without affecting its non-renal clearance, its measurement can form the basis of a method of determining the absolute extent of drug absorption without use of an i.v. reference dose (Lalka & Feldman, 1974; Poust *et al.*, 1977).

Calculation of renal clearance

Apart from invasive methods using equation (1), methods for calculating renal clearance are mostly based upon equation (2):

Method (I)

Since the instantaneous rate of urinary drug excretion cannot be measured, equation (2) is employed directly in the form:

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$$CL_R = \frac{\Delta Ae/\Delta t}{C_{mid}} \quad (3)$$

where Δ refers to a finite increment of change and C_{mid} is the plasma drug concentration at the mid-point of the urine collection interval.

Note that the renal physiologist usually writes equation (3) in the form:

$$CL_R = \frac{Q_{ur}.C_{ur}}{C_{mid}} \quad (4)$$

where Q_{ur} is urine flow rate and C_{ur} is the concentration of drug in urine. Clearly, the product of these two terms is a rate of drug excretion.

If renal clearance is independent of drug concentration and time the average of several values of the right hand side of equation (3) may be calculated. Alternatively, a plot of $\Delta Ae/\Delta t$ v C_{mid} should give a straight line with a slope equal to renal clearance.

Deviations from the expected line may be apparent, particularly for data collected immediately after an i.v. bolus injection when plasma drug concentrations are falling rapidly (Figure 1). Ideally, C_{mid} should be measured in the arterial circulation (Brun, Hilden & Raaschou, 1949a). If peripheral venous samples are used their early drug content may be considerably lower than that in the renal arteries, especially when the samples are taken from a limb with minimal cutaneous vasodilatation (Kosaka, Takahashi & Mark, 1969). This would tend to cause a positive deviation from the true line. On the other hand, a negative deviation occurs if the observed rate of excretion lags behind the plasma drug concentration. A factor contributing to this possibility is the delay introduced by flow of urine through the dead space of the kidney pelvis and the ureters (Bojesen, 1949). This dead space time is about 5 min, but varies with diuresis (Brun, Hilden & Raaschou, 1949b). Thus, the first sample of urine collected after an i.v. bolus injection of drug may contain less drug than the amount excreted and later ones will contain more. The net effect will be a negative deviation from the expected rate of excretion v plasma drug concentration plot followed by a positive deviation as the plasma drug concentration declines with time (Figure 1). When excretion of drug through the tubular cells contributes significantly to renal clearance, any disequilibrium between the concentration of drug in plasma and that in the renal interstitial fluid may also contribute to deviations from linearity when rate of excretion is plotted against a rapidly changing plasma drug concentration (Conn *et al.*, 1964).

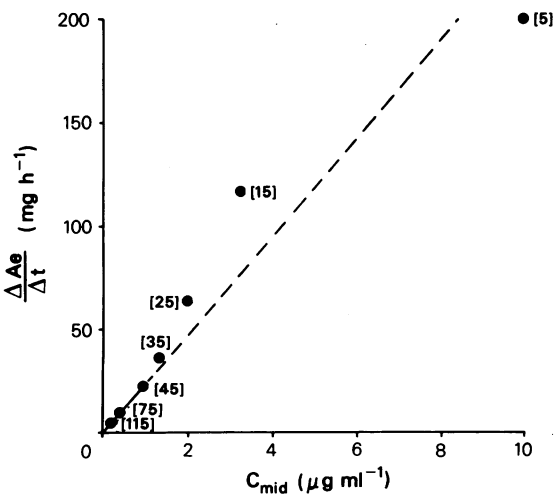

Figure 1 Relation between urinary excretion rate ($\Delta Ae/\Delta t$) and mid-point serum concentration (C_{mid}) of penicillin G at different times after i.v. injection of 100 mg of the drug in man. The subject was able to empty his bladder at will so that urine samples could be collected at intervals down to 5 min. Note the negative deviation followed by a positive deviation from the line representing constant renal clearance as serum drug concentration declines. Numbers by each point indicate time in minutes after injection. (Data from Heatley, 1956.)

The accuracy of estimates of renal clearance obtained using equation (3) will depend upon the urine collection interval. However, Martin (1967) has calculated that when the decline of dAe/dt is exponential, the error arising from the use of $\Delta Ae/\Delta t$ does not exceed 2% even when Δt is as large as one half-life of the drug. The error will differ from this when the decline of dAe/dt is not first-order but should be less than normal experimental error if Δt is reasonably small. Again, the greatest errors are likely to be seen using data collected during the distribution phase after i.v. bolus injection of drug. If necessary, the logarithmic mean of the plasma drug concentration during the urine collection interval may be used to calculate renal clearance.

Mathematical problems with the choice of Δt are, of course, avoided completely if renal clearance can be measured under steady-state conditions (ss) during constant rate i.v. infusion of drug. In this case:

$$CL_R = \frac{(\Delta Ae/\Delta t)_{ss}}{C_{mid,\,ss}} \quad (5)$$

A practical lower limit for Δt is about 0.5 h. After micturition the volume of urine remaining inside the bladder in a normal subject is about 1–2 ml (Griffiths, 1980). Therefore, assuming a normal urine flow of 1–2 ml min^{-1}, the volume error in urine collection every 0.5 h would be up to 7%. Accurate urine collections would necessitate bladder catheterization and wash-out with a measured volume of sterile water or saline. A diuresis induced by the oral administration of 200–400 ml of water every 20 min according to urine flow may also be helpful in reducing errors in drug recovery resulting from incomplete bladder emptying.

If there is appreciable reabsorption of drug from the bladder this may impose an upper limit on Δt. Thus, Colburn (1978) observed that saccharin was cleared from rat plasma more quickly when the urine was removed from the bladder at 5 min intervals than when it was left for 60 min. In general, the reabsorption of drugs from the urinary bladder has not been widely studied (Borzelleca, 1965).

Method (II)

Expressing the right hand side of equation (2) as dAe/C.dt and integrating the top and bottom with respect to time yields:

$$CL_R = \frac{Ae}{AUC} \quad (6)$$

where Ae is the cumulative amount of drug excreted unchanged in the urine up to time t and AUC is the area under the plasma drug concentration versus time curve up to time t. In the limit, the right hand side of equation (6) goes to infinity, therefore, renal clearance is also given by:

$$CL_R = \frac{Ae\,(\infty)}{AUC\,(\infty)} \quad (7)$$

where Ae (∞) is the total amount of drug recovered unchanged in the urine and AUC (∞) is the area under the plasma drug concentration versus time curve extrapolated to infinity. If the drug is known to be eliminated entirely in the urine, Ae (∞) may be replaced by the dose in equation (7) and renal clearance can be determined without measurement of drug in urine.

Like method (I) the approach based upon equations (6) and (7) gives a time-average value of renal clearance, but over a longer time interval. Since it requires more prolonged urine collections it is invalidated if samples are incomplete. However, unlike that of method (I), the accuracy of method (II) is not affected by any unacknowledged error in the time of collection of sequential samples or by incomplete bladder emptying. Of necessity, method (II) will be less sensitive to changes in renal clearance with time than method (I).

Although the use of equations (6) and (7) demands a continuous urine collection, the method could also be used to estimate renal clearance over any period of time, t_1 to t_2, after drug administration.

Thus:

$$CL_R = \frac{Ae\,(t_1, t_2)}{AUC\,(t_1, t_2)} \quad (8)$$

The simplest methods of accurately estimating AUC values include the use of a planimeter or the application of the trapezoidal rule. For data obtained after extravascular drug input Chiou (1978) advocates the linear trapezoidal method be used for pre-peak and plateau data and the logarithmic trapezoidal method for post-peak data.

In addition to methods (I) and (II), less direct methods which depend upon the specification of a compartmental model may also be used to calculate renal clearance (Garrett, 1978). These, however, are superfluous.

Chemical aspects

The accuracy of any estimate of renal clearance will obviously depend upon the use of a specific assay method for the drug in question. It is also important to check the stability of the compound in plasma and urine samples.

A more subtle complication arises if metabolites of drug excreted in the urine are unstable and revert back to the parent compound on standing, thereby resulting in an overestimate of its renal clearance. Perhaps the best example of this relates to the lability of ester glucuronides of drugs such as ketoprofen, naproxen and probenecid. Initial reports suggested that appreciable quantities of these compounds are excreted unchanged in the urine. However, if precautions are taken to assay urine samples immediately after short collections, virtually all of these drugs are found in the form of their ester glucuronides (Upton *et al.*, 1980). Even the minute amount of unchanged drug detected under these circumstances may be an artefact derived from hydrolysis of the conjugate while still inside the bladder.

Physiological and physicochemical determinants of renal clearance

The major processes involved in the renal clearance of drugs are glomerular filtration, active secretion and passive reabsorption (Weiner, 1975). The first two give a positive contribution while the last gives a negative contribution:

$$CL_R = \frac{\text{Rate of filtration} + \text{Rate of secretion} - \text{Rate of reabsorption}}{C} \quad (9)$$

Active reabsorption is also a possibility but, with the exception of many endogenous compounds that may be given exogenously (e.g. sugars, amino acids and vitamins) and of oxypurinol, a metabolite of allopurinol, there are few examples of drugs which have been proved to undergo this process (Torretti & Weiner, 1976). Salicylate, probenecid and other drugs that block the reabsorption of urate may do so by acting as competitive substrates. However, since they are also extensively reabsorbed by passive diffusion it is difficult to recognise any participation in an active reabsorption process (Weiner & Fanelli,

1974). Passive secretion of drugs is considered to be an unlikely possibility on the basis of unfavourable concentration gradients and blood flow considerations (Torretti & Weiner, 1976). The processes of intra-renal drug distribution and metabolism complicate the measurement of renal clearance and are discussed separately.

Glomerular filtration

Since the mechanism of this process is one of ultrafiltration the concentration of filtered drug is essentially equal to the concentration of unbound drug in plasma (Cu). Hence:

$$\text{Rate of filtration} = \text{GFR.Cu} = \text{GFR.fu.C} \quad (10)$$

(where GFR = glomerular filtration rate and fu = unbound fraction of drug in plasma. Note that, ideally, the value of Cu should be corrected for the fact that 7–8% of plasma volume is occupied by macromolecules (Weiner, 1975)).

If glomerular filtration is the only mechanism of renal elimination of a compound (i.e. rate of filtration = rate of excretion), then:

$$CL_R = \text{fu.GFR} \quad (11)$$

Active secretion

There appear to be several active transport mechanisms in the proximal tubule capable of causing the secretion of drugs, the most important being the separate organic anion and organic cation systems (Weiner, 1975; Torretti & Weiner, 1976).

Using an approach originally applied to describe the hepatic clearance of drugs, the following equation was suggested to express the rate of renal tubular secretion (Levy, 1980):

$$\text{Rate of secretion} = \frac{Q_{R'}.\text{fu}.CLu_{S,\,int}.C}{Q_{R'} + \text{fu}.CLu_{S,\,int}} \quad (12)$$

where $Q_{R'}$ is the flow rate of plasma perfusing the renal tubular secretion sites and $CLu_{S,\,int}$ is the intrinsic renal tubular clearance referred to unbound drug in plasma. The latter represents the clearance by secretion of free drug in the absence of any flow considerations. Two limiting cases of this equation are of interest. When $Q_{R'} \gg \text{fu}.CLu_{S,\,int}$ the rate of secretion approaches $\text{fu}.CLu_{S,\,int}.C$ and is seen to be a function of the concentration of *unbound* drug in the plasma. The secretion of frusemide in the isolated perfused rat kidney is consistent with this expectation (Bowman, 1976). Conversely, when $Q_{R'} \ll \text{fu}.CLu_{S,\,int}$ the rate of secretion tends to $Q_{R'}.C$. On approaching this limit the rate of renal tubular secretion will be a function of *total* drug in plasma since an avid removal mechanism operating on unbound drug causes dissociation of bound drug which then also becomes available for secretion during transit through the kidney.

Since there appear to be limited quantities of the specific membrane carriers that effect active secretion processes, the mechanism is saturable. Accordingly, within the limits of experimental determination, the kinetics of the systems can be described by the Michaelis-Menten treatment (Weiner, 1975; Torretti & Weiner, 1976) such that intrinsic renal tubular clearance may be written in the form:

$$CLu_{S,\,int} = \frac{\text{Tmax}}{K_m' + \text{Cu}} \quad (13)$$

or, when referenced to total drug in plasma:

$$CL_{S,\,int} = \frac{\text{Tmax}}{K_m + C} \quad (14)$$

where Tmax is the transport maximum (mass.time^{-1}) and K_m' and K_m refer to the Michaelis constants (mass. volume^{-1}) for unbound and total drug, respectively.

If glomerular filtration and active secretion are the only mechanisms of renal elimination, renal clearance is given by:

$$CL_R = \text{fu.GFR} + \frac{Q_{R'}.\text{fu}.CLu_{S,\,int}}{Q_{R'} + \text{fu}.CLu_{S,\,int}} \quad (15)$$

In the limit, when active secretion is rapid compared to plasma flow, this equation reduces to:

$$CL_R = \text{fu.GFR} + Q_{R'} \quad (16)$$

Since the maximum value of $Q_{R'}$ will be the difference between total renal plasma flow (Q_R) and GFR, then the maximum possible value of renal clearance is given by:

$$CL_R = \text{fu.GFR} + (Q_R - \text{GFR}) \quad (17)$$

Under these circumstances and if drug is not bound to plasma protein its renal clearance should be identical to renal plasma flow. Division of CL_R by fu gives renal clearance referenced to unbound drug. Doing the same to the right hand side of equation (17) indicates, therefore, that this value may exceed total renal plasma flow.

Apart from that bound to plasma proteins any drug carried by the erythrocytes may also be available for active secretion. In this case, provided that equilibration of drug between erythrocytes and plasma is rapid, the value of C in equation (15) may be replaced by the concentration of drug in whole blood, and the other terms redefined with reference to this concentration. The validity of this modification is difficult to establish, however, since a proportion of the erythrocytes may be separated off by 'plasma skimming' and shunted into the renal veins without contacting the renal tubules (Milne, Scribner & Crawford, 1958; Levy, 1980).

Passive reabsorption

Passive reabsorption may occur throughout the nephron. The driving force is largely supplied by reabsorption of water which concentrates the urine with respect to plasma. Since normal urine flow is about 1–2 ml min^{-1} drug may be concentrated in the urine at least 100 fold compared to the concentration of unbound drug in plasma (i.e. $GFR/Q_{ur} \sim 100$).

In the special case when reabsorption goes to equilibrium, $C_{ur} = Cu$ and substitution into equation (4) gives:

$$CL_R = \frac{Q_{ur}.Cu}{C} = Q_{ur}.fu \qquad (18)$$

Accordingly, the renal clearance of drugs that are largely reabsorbed should be sensitive to changes in urine flow, a condition which requires that the drug must be sufficiently non-polar. Examples of such drugs, whose urine concentration approaches their unbound concentration in plasma, include ethanol, phenytoin and theophylline (Rowland & Tozer, 1980). Equation (18) also predicts that if the plasma binding of drug is extensive, its renal clearance will be extremely low. Changes in urine flow will not influence the clearance of polar drugs that are not reabsorbed (e.g. gentamicin, penicillin); only their concentrations in urine will be affected.

If a drug is a weak acid or a weak base the extent of its reabsorption may vary with urine pH as well as urine flow. Adjustment of pH mostly occurs at the end of the distal tubule and in the collecting duct.

Assuming that reabsorption is specific for the un-ionized drug species and that this species is sufficiently lipid-soluble that its reabsorption goes to equilibrium, then equation (18) is modified as follows (Milne *et al.*, 1958; Rowland & Tozer, 1980): For weak acids:

$$CL_R = fu.Q_{ur}\left[\frac{1 + 10^{(pH_{ur} - pKa)}}{1 + 10^{(pH_{plasma} - pKa)}}\right] \qquad (19)$$

The same equation is applicable to weak bases after inversion of the signs within both inner brackets; thus (pH − pKa) becomes (pKa − pH).

In practice, however, equation (19) and the analogous one for weak bases are rarely accurate in predicting observed clearances. Reasons for this have been discussed at length (Milne *et al.*, 1958; Weiner, 1975; Mudge, Silva & Stibitz, 1975) and include partial permeability of the ionized drug, false reference to arterial rather than renal capillary plasma and failure to obtain equilibrium owing to diffusion limitations. The latter possibility implies that the rate of reabsorption will depend not only upon equilibrium considerations but also on kinetic factors. These will largely be a function of the diffusion coefficient of the un-ionized drug and the fraction of un-ionized drug in the lumen of the tubule. Provided that the permeability of the un-ionized form is sufficiently high, both equilibrium and kinetic considerations indicate that the renal clearance of weak acids with pKas of 3–7.5 and of weak bases with pKas of 7.5–12 will be sensitive to changes in urine pH (Weiner & Mudge, 1964; Rowland & Tozer, 1980).

Because of the uncertainties surrounding the control of rate of reabsorption, it is best to define it operationally, in terms of the fraction of the amount of drug filtered and secreted that is reabsorbed. This fraction, F_{reabs}, will be a constant if urine pH and flow are fixed. Therefore, renal clearance becomes (Levy, 1980):

$$CL_R = fu.GFR + \frac{Q_{R'}.fu.CLu_{S,int}}{Q_{R'} + fu.CLu_{S,int}} - F_{reabs}\left[fu.GFR + \frac{Q_{R'}.fu.CLu_{S,int}}{Q_{R'} + fu.CLu_{S,int}}\right] \qquad (20)$$

Note that equation (20) indicates that F_{reabs} is the same for filtration and secretion, a reasonable assumption since most reabsorption occurs distal to secretion.

Renal haemodynamics

Alterations in renal perfusion can modify the renal clearance of a drug through effects on GFR, tubular secretion and tubular reabsorption (Duchin & Schrier, 1978).

Normally, modest increases or decreases (10 to 20%) in renal blood flow within the autoregulation range do not result in proportional changes in GFR. Severe renal ischaemic episodes, however, do lead to a significant lowering of both renal blood flow and GFR. The effect of renal blood flow on tubular secretion has already been considered (equation (12)). Volume depletion and a lowered sodium intake may reduce both renal blood flow and GFR while saline infusion and osmotic diuretic administration may increase renal blood flow and water excretion. These changes would also tend to enhance and impair, respectively, the passive reabsorption of drugs.

Interpretation of renal clearances of drugs measured in patients must take the above factors into account and also the possibility that common diseases, such as heart, liver and renal failure, may be associated with abnormal renal perfusion (Duchin & Schrier, 1978).

Vigorous exercise can decrease renal blood flow by as much as 35% and this had been shown to lower the renal clearance of atenolol by about 8% (Mason *et al.*, 1980).

Many drugs can alter renal haemodynamics and, therefore, have the potential for modifying their own clearance and that of other compounds. Agents

causing renal vasoconstriction include noradrenaline, adrenaline and organomercurial and thiazide diuretics, while prostaglandins, dopamine, glucagon, frusemide and ethacrynic acid can increase renal blood flow. Potent vasodilators such as minoxidil, sodium nitroprusside and diazoxide may diminish renal perfusion when autoregulation is impaired (Duchin & Schrier, 1978).

Auto-inhibition of renal clearance mediated by an effect on renal blood flow is a possible explanation for the marked time-dependent decrease in the renal clearance of bethanidine (Shen *et al.*, 1975; Chremos *et al.*, 1976), debrisoquine (Silas *et al.*, 1978) and guanethidine (Hengstmann, 1980) after single doses. In each case changes in clearance occurred in the absence of any noticeable hypotensive response and may have been the result of intra-renal release of noradrenaline leading to renal vasoconstriction.

Effects of renal disease

As a general rule the renal clearance of drugs parallels the decline of GFR in renal impairment, even when tubular secretion is the main route of excretion. The decrease in renal blood flow is generally proportional to the lowering of GFR limiting any compensation by tubular secretion of a deficient glomerular excretion (Fabre & Balant, 1976). Complicating the issue, however, are potential decreases in plasma drug binding (Reidenberg, 1976) and inhibition of the secretion of acidic drugs by the accumulation of endogenous organic acids when the GFR is very low (< 25 ml min^{-1}) (Duchin & Schrier, 1978; Rose, Pruitt & McNay, 1976; Rose, O'Malley & Pruitt, 1977).

Effects of age

The renal clearance of drugs per unit of body surface area is generally lower in neonates and infants (Rane & Wilson, 1976; Morselli, 1976; Morselli, Franco-Morselli & Bossi, 1980) and in the elderly (Crooks, O'Malley & Stevenson, 1976) compared to that in normal young adults. However, the exact effect of age on clearance may vary considerably depending upon the particular drug since the different processes involved in renal excretion mature and deteriorate at different rates. Also, in the newborn, the effects of a low GFR and immature secretory systems may be offset to some extent by relatively low plasma drug binding compared to that in adults and by a low reabsorptive capacity owing to a relative inability to concentrate urine and, possibly, to the presence of protein in the glomerular filtrate (Morselli, 1976; Morselli *et al.*, 1980). A relatively low urinary pH in neonates could further help to reduce the reabsorption of basic drugs. Providing that the fraction of water reabsorbed is constant, these considerations suggest that changes in urine flow should have less effect on renal drug clearance in newborn babies compared to adults. Hogg *et al.* (1977) have observed, however, that the rate of urinary excretion of pethidine is exquisitely sensitive to urine flow in the neonate. They rationalised this on the basis that changes in urine flow in these patients are more likely to be mediated by variability in renal plasma flow affecting GFR than by the effects of fluid intake.

Elucidation of renal processes from measurement of renal clearance

Net process

Substitution of rate of filtration by fu.GFR in equation (9) and rearranging gives:

$$\frac{CL_R}{fu.GFR} = 1 + \left[\frac{\text{Rate of secretion} - \text{Rate of reabsorption}}{fu.GFR.C} \right] \quad (21)$$

Therefore, if the free fraction of drug in plasma and the glomerular filtration rate are measured, the ratio of the renal clearance of drug divided by their product provides information on the relative importance of the various processes involved in excretion. A ratio of less than one signifies net reabsorption; a ratio of unity indicates that either the drug only undergoes filtration or that its rates of secretion and reabsorption are equal; and a ratio greater than one indicates net secretion.

Renal clearance as a function of plasma drug binding

Equation (20) predicts that as plasma drug binding decreases renal clearance will increase. Therefore, if renal clearance values are not constant within an experiment in which plasma drug concentration varies this may be explained by progressive saturation of binding at high concentrations.

Levy (1980) has indicated how the relationship between renal clearance and plasma binding may be useful in the interpretation of mechanisms of excretion. For the limiting case where secretion rate is a function of unbound drug concentration in plasma, equation (20) simplifies to:

$$CL_R = fu. \left[GFR + CLu_{S,int} - F_{reabs} (GFR - CLu_{S,int}) \right] \quad (22)$$

Therefore, assuming that secretion mechanisms are far from saturation, a plot of renal clearance versus fu should be linear and should pass through the origin. Data obtained for salicylic acid in rats appear to be

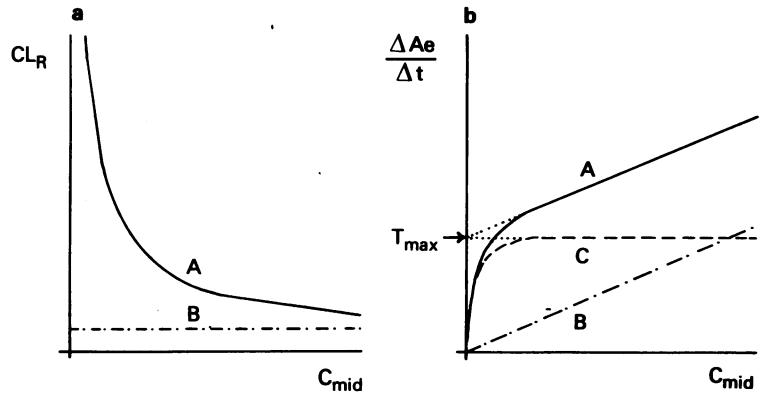

Figure 2 (a) Relationship of renal clearance to plasma drug concentration. Curve (A): drug undergoes filtration plus saturable secretion; Line (B): drug undergoes filtration only.
(b) Relationship between rate of urinary excretion and plasma concentration of a drug undergoing filtration plus saturable secretion. Curve (A): observed data; line (B): represents the contribution of glomerular filtration; curve (C): represents the difference between curve (A) and line (B) and gives the excretion rate by tubular secretion as a function of plasma drug concentration. Tmax = transport maximum of the secretory process.

consistent with this expectation (Levy, 1980). If reabsorption can be minimised, for example by manipulating urine pH in the case of partially-ionized drugs, it should be possible to solve equation (22) for $CLu_{S,int}$ and, in turn, for F_{reabs}.

For the limiting case where secretion is a function of total drug concentration in plasma, equation (20) simplifies to:

$$CL_R = fu.GFR\,(1 - F_{reabs}) + CL_{S,int}\,(1 - F_{reabs}) \quad (23)$$

Thus, assuming again that secretion mechanisms are far from saturation, a plot of renal clearance versus fu yields a straight line with a positive intercept. Since the slope divided by the intercept is $GFR/CL_{S,int}$, a knowledge of GFR allows $CL_{S,int}$ to be determined without experimental manipulations involving alteration of reabsorption or administration of competitors of the secretion mechanism. Knowing $CL_{S,int}$, F_{reabs} may then be calculated by rearranging equation (23). Data obtained for sulphisoxazole in rats are consistent with equation (23) (Yacobi & Levy, 1979).

Renal clearance and saturation of carrier transport

If active secretion becomes capacity-limited total renal clearance will decrease as drug concentration increases (Figure 2a). The parameters describing the secretion process are best examined from a plot of rate of excretion against plasma drug concentration. This will not give a straight line passing through the origin (curve A, Figure 2b). However, assuming a constant plasma binding, the data at higher concentrations will be linear and, if there is no reabsorption, the extrapolated intercept will estimate the transport maximum, Tmax. The line constructed parallel with this linear segment and passing through the origin (line B, Figure 2b) will have a slope equal to fu.GFR. By subtracting line B from curve A, curve C is plotted which represents the rate of secretion as a function of plasma drug concentration. This may then be characterised by the Michaelis-Menten equation to yield values of Tmax and Km for the transport process.

In practice, the analysis of secretion processes in this manner may be complicated by concentration-dependent plasma binding which will tend to offset the effects of saturable secretion on the clearance versus drug concentration relationship. Saturable active reabsorption will do the same and, in common with passive reabsorption, will prevent the calculation of true transport maxima (Garrett, 1978; Weiner *et al.*, 1961).

It may be possible to estimate the contribution of active secretion to overall renal clearance of a drug by co-administration of an inhibitor of the transport process. For example, the secretory component of digoxin clearance was determined by comparing renal clearance of the drug before and after blockade with spironolactone (Steiness, 1974). A difficulty with this approach, however, is knowing when inhibition is complete. It may be prudent to assess the effects of several dose levels of the inhibitor.

Renal clearance as a function of urine flow and pH

A contribution of passive reabsorption to the renal clearance of a drug will be apparent if the value of

clearance varies with urine flow, urine pH or both. These, in turn, will be dependent upon fluid intake, diet, posture and day–night cycle. Also, the drug itself may induce changes in urine flow or pH resulting in concentration- and time-dependent renal clearance. Ethanol and nicotine, which influence urine flow by decreasing and increasing ADH secretion, respectively, are examples of such drugs (Haggard, Greenberg & Carroll, 1941; Matsukura *et al.*, 1979).

It may be possible to determine the total extent to which reabsorption contributes to net excretion by suppressing it through manipulation of urine flow or pH. In the case of amphetamine it appears that reabsorption is negligible when urine pH is maintained just below 5 by the administration of ammonium chloride, since increases in urine flow under these conditions cause no further increase in excretion of the drug (Beckett & Rowland, 1965). On the other hand, even when urine is alkalinized to a pH of about 7.6 by administration of sodium bicarbonate, the renal clearance of phenobarbitone can still be enhanced by fluid-loading, indicating that its reabsorption is difficult to suppress completely (Linton, Luke & Briggs, 1967).

Although it is relatively easy to control urine pH at extreme values, intermediate values cannot be maintained consistently. For this reason, quantitative relationships between the extent of tubular reabsorption of drugs, (F_{reabs}), and urine pH are difficult to obtain. However, an approach to this problem was suggested by Beckett, Boyes & Tucker (1968a,b) using amphetamine as an example.

Renal clearance and renal drug metabolism

If a drug is metabolised by the kidney as well as by the liver, its renal clearance, measured in the normal way, will be an underestimate. Renal metabolism should be suspected if the apparent renal clearance of a metabolite when formed from the parent drug exceeds its renal clearance measured after it has been administered *per se*. Renal metabolism of a number of compounds has been demonstrated, mainly involving pathways of acetylation, demethylation and glycine conjugation (Wan & Riegelman, 1972a; Bekersky *et al.*, 1980).

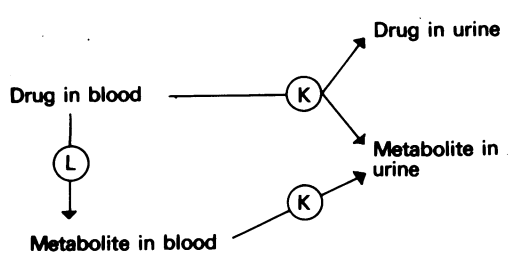

Figure 3 Scheme of drug elimination involving the production of a single end-metabolite in both liver (L) and kidney (K).

Consider the simplest case where a drug forms a single metabolite in both liver and kidney and this metabolite when administered as itself is cleared solely by the kidney (Figure 3). If it can be assumed (1) that metabolite formed in the kidney cannot be reabsorbed back into the blood; (2) that any transport limitations within the tubule cell are the same when metabolite is formed there and when it is presented from the blood; and (3) that the drug does not interfere with the renal clearance of metabolite and *vice-versa*, methods are available which allow calculation of the true renal clearance of drug and of the fraction of total drug metabolism that occurs in the kidney (Wan & Riegelman, 1972a; Garrett, 1978). The latter is given by:

$$\frac{fm_R}{fm} = 1 - \frac{CL_R\,(m)}{CL_R\,(m)_{app}} \qquad (24)$$

where fm is the fraction of the dose metabolised, fm_R is the fraction of the dose metabolised in the kidney, CL_R (m) is the renal clearance of metabolite after giving it *per se* and $CL_R\,(m)_{app}$ is the apparent renal clearance of metabolite after administration of drug.

The above approach has been used to estimate the renal contribution to the overall metabolism of methyldigoxin in man (Hinderling, Garrett & Wester, 1977), benzoic and *p*-aminobenzoic acids in animals (Wan & Riegelman, 1972a; Wan, Von Lehmann & Riegelman, 1972) and salicylic acid in animals and man (Wan & Riegelman, 1972b; Von Lehmann *et al.*, 1973). Riegelman's group used simultaneous i.v. infusions of drug and radiolabelled metabolite in their experiments. Unfortunately, however, although they demonstrated that the presence of drug did not alter the rate of urinary excretion of labelled metabolite, they did not monitor the plasma concentration of this species. It is possible, therefore, that the drug might have influenced the renal clearance of metabolite which would invalidate determinations of fm_R/fm using equation (24) (Kamath & Levy, 1974).

In a clinical context it may be important to know which drugs are extensively metabolised in the kidney as this may have implications for dosage in patients with renal failure if the disease is associated with impaired function of kidney enzyme systems.

Summary

In this review I have considered the definition of renal clearance, reasons for measuring and methods of calculating its value for drugs, physiological and physicochemical determinants of renal clearance and its use in the elucidation of mechanisms of drug elimination by the kidneys.

References

BECKETT, A.H. & ROWLAND, M. (1965). Urinary excretion kinetics of amphetamine in man. *J. Pharm. Pharmac.*, **17**, 628–639.

BECKETT, A.H., BOYES, R.N. & TUCKER, G.T. (1968a). Use of the analogue computer to examine the quantitative relation between urinary pH and kidney reabsorption of drugs partially ionized at physiological pH. *J. Pharm. Pharmac.*, **20**, 269–276.

BECKETT, A.H., BOYES, R.N. & TUCKER, G.T. (1968b). Use of the analogue computer to predict the distribution and excretion of drugs under conditions of fluctuating urinary pH. *J. Pharm. Pharmac.*, **20**, 277–282.

BEKERSKY, I., COLBURN, W.A., FISHMAN, L. & KAPLAN, S.A. (1980). Metabolism of salicylic acid in the isolated perfused rat kidney. Interconversion of salicyluric and salicylic acids. *Drug. Metab. Dispos.*, **8**, 319–324.

BOJESEN, E. (1949). The function of the urinary tract as 'dead space' in clearance experiments. *Scand. J. clin. lab. Invest.*, **1**, 290–294.

BORZELLECA, J.F. (1965). Drug movement from the isolated urinary bladder of the rabbit. *Arch. int. Pharmacodyn.*, **154**, 40–50.

BOWMAN, R.H. (1975). Renal secretion of ^{35}S furosemide and its depression by albumin binding. *Am. J. Physiol.*, **229**, 93–98.

BRUN, C., HILDEN, T. & RAASCHOU, F. (1949a). The significance of the difference in systemic arterial venous blood concentrations in renal clearance methods. *J. clin. Invest.*, **28**, 144–152.

BRUN, C., HILDEN, T. & RAASCHOU, F. (1949b). Examinations in of the delay-time of the kidney. *Scand. J. clin. lab. Invest.*, **1**, 348.

CHIOU, W.L. (1978). Critical evaluation of the potential error in pharmacokinetic studies using the linear trapezoidal rule method for the calculation of the area under the plasma level–time curve. *J. Pharmacokin. Biopharm.*, **6**, 539–546.

CHREMOS, A.N., SHEN, D., GIBALDI, M., PROCTOR, J.D. & NEWMAN, J.H. (1976). Time-dependent change in renal clearance of bethanidine in humans. *J. pharm. Sci.*, **65**, 140–142.

COLBURN, W.A. (1978). Absorption of saccharin from rat urinary bladder. *J. pharm. Sci.*, **67**, 1493–1494.

CONN, R.B., SABO, A.J., LANDES, D. & HO, J.Y.L. (1964). Inconstancy of renal clearance values with changing plasma concentrations. *Nature (Lond.)*, **203**, 143–146.

CROOKS, J., O'MALLEY, K. & STEVENSON, I.H. (1976). Pharmacokinetics in the elderly. *Clin. Pharmacokin.*, **1**, 280–296.

DUCHIN, K.L. & SCHRIER, R.W. (1978). Interrelationship between renal haemodynamics, drug kinetics and drug action. *Clin. Pharmacokin.*, **3**, 58–71.

FABRE, J. & BALANT, L. (1976). Renal failure, drug pharmacokinetics and drug action. *Clin. Pharmacokin.*, **1**, 99–120.

GARRETT, E.R. (1978). Pharmacokinetics and clearances related to renal processes. *Int. J. clin. Pharmac. Biopharm.*, **16**, 155–172.

GRIFFITHS, D.J. (1980). *Urodynamics.* Medical Physics Handbooks No. 4 pp. 3, Bristol: Hilger.

HAGGARD, H.W., GREENBERG, L.A. & CARROLL, R.P. (1941). Studies on the absorption, distribution and elimination of alcohol. VIII. The diuresis from alcohol and its influence on the elimination of alcohol in the urine. *J. Pharmac. exp. Ther.*, **71**, 349–357.

HEATLEY, N.G. (1956). Comparative serum concentration and excretion experiments with benzyl penicillin (G) and phenoxymethyl penicillin (V) on a single subject. *Ant. Med. Clin. Ther.*, **2**, 33–41.

HENGSTMANN, J.H. (1980). Guanethidine: Pharmacokinetics during acute and chronic treatment and influence upon the peripheral sympathetic nervous system. *Arch. int. Pharmacodyn.*, Symposium on Clinical Pharmacology of Antihypertensive Agents, Supplement, pp. 17–20.

HINDERLING, P.H., GARRETT, E.R. & WESTER, R.C. (1977). Pharmacokinetics of beta-methyldigoxin in healthy humans. I: Intravenous studies. *J. pharm. Sci.*, **66**, 242–253.

HOGG, M.I.J., WIENER, P.C., ROSEN, M. & MAPLESON, W.W. (1977). Urinary excretion and metabolism of pethidine and norpethidine in the newborn. *Br. J. Anaesth.*, **49**, 891–898.

KAMATH, B.L. & LEVY, G. (1974). Renal contribution to drug biotransformation. *J. pharm. Sci.*, **63**, 1342–1343.

KOSAKA, Y., TAKAHASHI, T. & MARK, L.C. (1969). Intravenous thiobarbiturate anaesthesia for Caesarian section. *Anesthesiology*, **31**, 489–506.

KWAN, K. & TILL, A. (1973). Novel method for bioavailability assessment. *J. pharm. Sci.*, **62**, 1494–1497.

LALKA, D. & FELDMAN, H. (1974). Absolute drug bioavailability: Approximation without comparison to parenteral dose for compounds exhibiting perturbable renal clearance. *J. pharm. Sci.*, **63**, 1812.

LEVY, G. (1980). Effect of plasma protein binding on renal clearance of drugs. *J. pharm. Sci.*, **69**, 482–483.

LINTON, A.L., LUKE, R.G. & BRIGGS, J.D. (1967). Methods of forced diuresis and its appliction in barbiturate poisoning. *Lancet*, **ii**, 377–380.

MARTIN, B.K. (1967). Drug urinary excretion data—some aspects concerning the interpretation. *Br. J. Pharmac.*, **29**, 181–193.

MASON, W.D., KOCHAK, G., WINER, N. & COHEN, I. (1980). Effect of exercise on renal clearance of atenolol. *J. pharm. Sci.*, **69**, 344–345.

MATSUKURA, S., SAKAMOTO, N., TAKAHASHI, K., MATSUYAMA, H. & MURANAKA, H. (1979). Effect of pH and urine flow on urinary nicotine excretion after smoking cigarettes. *Clin. Pharmac. Ther.*, **25**, 549–554.

MILNE, M.D., SCRIBNER, B.H. & CRAWFORD, M.A. (1958). Non-ionic diffusion and the excretion of weak acids and bases. *Am. J. Med.*, **24**, 709–729.

MORSELLI, P.L. (1976). Clinical pharmacokinetics in neonates. *Clin. Pharmacokin.*, **1**, 81–98.

MORSELLI, P.L., FRANCO-MORSELLI, R. & BOSSI, L. (1980). Clinical pharmacokinetics in newborns and infants: Age-related differences and therapeutic implications. *Clin. Pharmacokin.*, **5**, 485–527.

MUDGE, G.H., SILVA, P. & STIBITZ, G.R. (1975). Renal excretion by non-ionic diffusion. The nature of the disequilibrium. *Med. Clin. N. Am.*, **59**, 681–698.

POUST, R.I., MALLINGER, A.G., MALLINGER, J., HIM-

MELHOCH, J.M., NEIL, J.F. & HANIN, I. (1977). Absolute availability of lithium. *J. pharm. Sci.*, **66**, 609–610.

RANE, A. & WILSON, J.T. (1976). Clinical pharmacokinetics in infants and children. *Clin. Pharmacokin.*, **1**, 2–24.

REIDENBERG, M.M. (1976). The binding of drugs to plasma proteins from patients with poor renal function. *Clin. Pharmacokin.*, **1**, 121–125.

ROSE, H.J., PRUITT, A.W. & McNAY, J.L. (1976). Effect of experimental azotemia on renal clearance of furosemide in the dog. *J. Pharmac. exp. Ther.*, **196**, 238–247.

ROSE, H.J., O'MALLEY, K. & PRUITT, A.W. (1977). Depression of renal clearance of furosemide in man by azotemia. *Clin. Pharmac. Ther.*, **21**, 141–146.

ROWLAND, M. & TOZER, T. (1980). *Clinical Pharmacokinetics*, pp. 49–64. Philadelphia: Lea & Febiger.

SHEN, D., GIBALDI, M., THORNE, M., BELLWARD, G., CUNNINGHAM, R., ISRAELI, Z., DAYTON, P.L. & McNAY, J. (1975). Pharmacokinetics of bethanidine in hypertensive patients. *Clin. Pharmac. Ther.*, **17**, 363–373.

SILAS, J.H., LENNARD, M.S., TUCKER, G.T., SMITH, A.J., MALCOLM, S.L. & MARTEN, T.R. (1978). The disposition of debrisoquine in hypertensive patients. *Br. J. clin. Pharmac.*, **5**, 27–34.

STEINESS, E. (1974). Renal tubular secretion of digoxin. *Circulation*, **50**, 103–107.

TORRETTI, J. & WEINER, I.M. (1976). The renal excretion of drugs. In *Methods in Pharmacology*, vol. 4A Renal Pharmacology, pp. 357–379. New York: Plenum.

UPTON, R.A., BUSKIN. J.N., WILLIAMS, R.L., HOLFORD, N.H.G. & RIEGELMAN, S. (1980). Negligible excretion of unchanged ketoprofen, naproxen and probenecid in urine. *J. pharm. Sci.*, **69**, 1254–1257.

VON LEHMANN, B., WAN, S.H., RIEGELMAN, S. & BECKER, C. (1973). Renal contribution to overall metabolism of drugs. IV: Biotransformation of salicylic acid to salicyluric acid in man. *J. pharm. Sci.*, **62**, 1483–1486.

WAN, S.H. & RIEGELMAN, S. (1972a). Renal contribution to overall metabolism of drugs. I: Conversion of benzoic acid to hippuric acid. *J. pharm. Sci.*, **61**, 1278–1284.

WAN, S.H. & RIEGELMAN, S. (1972b). Renal contribution to overall metabolism of drugs. II: Biotransformation of salicylic acid to salicyluric acid. *J. pharm. Sci.*, **61**, 1284–1287.

WAN, S.H., VON LEHMANN, B. & RIEGELMAN, S. (1972). Renal contribution to overall metabolism of drugs. III: Metabolism of *p*-aminobenzoic acid. *J. pharm. Sci.*, **61**, 1288–1292.

WEINER, I.M. (1975). Excretion of drugs by the kidney. In *Handbook of Experimental Pharmacology*, Concepts in Biochemical Pharmacology Part 1, ed. Brodie, B.B., Gillette, J.R. & Ackerman, H.S., pp. 328–352. Berlin, Heidelberg & New York: Springer.

WEINER, I.M. & FANELLI, G.M. (1974). Bidirectional transport: Urate and other organic anions. In *Recent Advances in Renal Physiology and Pharmacology*, ed. Wesson, L.G. & Fanelli, G.M., pp. 53–68. Lancaster: MTP.

WEINER, I.M. & MUDGE, G.H. (1964). Renal tubular mechanisms for excretion of organic acids and bases. *Am. J. Med.*, **36**, 743–762.

WEINER, I.M., GARLID, K.D., ROMEO. J.A. & MUDGE, G.H. (1961). Effects of tubular secretion and reabsorption on titration curves of tubular transport. *Am. J. Physiol.*, **200**, 393–399.

YACOBI, A. & LEVY, G. (1979). Effect of serum protein binding on sulfisoxazole distribution, metabolism and excretion in rats. *J. pharm. Sci.*, **68**, 742–746.