DRUG DISTRIBUTION IN RENAL DISEASE

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Irrespective of the route of administration, all drugs eventually reach the general circulation and undergo distribution to various tissues, organs and organelles. The extent of distribution can be quantitated (Riggs, 1963) by estimating the apparent distribution volume \( V_d \):

\[
V_d = \frac{\text{amount of drug in body}}{\text{plasma concentration}}
\]  

(1)

Although this volume is an invaluable pharmacokinetic parameter, certain misconceptions surround its importance:

1 Because many drugs are sequestered in tissues (by solution in body fat, and binding to tissue macromolecules) the volume is an apparent one and only rarely reflects a true morphological space.

2 Many drugs are bound to plasma proteins, and because the majority of analytical techniques measure both protein bound and unbound drug, the apparent volume of distribution may be much greater than conventional methods suggest.

3 The distribution volume of a drug \( V_d \), and its clearance \( \dot{V}_p \) are related (Riggs, 1963) thus:

\[
\dot{V}_p = V_d \times k_{el} = V_d \times \frac{0.693}{T_{1/2}}
\]  

(2)

where \( k_{el} \) and \( T_{1/2} \) are the elimination rate constant and half-life respectively.
\( k_{el} = \frac{\ln 2}{T_{1/2}} \). A drug’s clearance most accurately describes its rate of elimination (either by metabolism or excretion), and since this is independent of distribution volume, \( k_{el} \) (or \( T_{1/2} \)) will vary with \( V_d \).

4. During chronic drug therapy, the ‘steady-state’ concentration of a drug \( (C_{ss}) \) is determined by (Wagner et al, 1965):

\[
C_{ss} = \frac{F \times \text{Dose}}{\dot{V}_p \times T}
\]

where \( F \) and \( T \) are the bioavailability and dosage interval respectively. Therefore, although \( V_d \) will affect drug concentrations after single doses (see Figure 4)

![Figure 4](image-url)

Figure 4. The effects of an increased distribution volume (curve 2) on plasma levels after a single drug dose. Note the reduced peak concentration and longer half-life (despite unaltered clearance)

it will have no influence on ‘steady-state’ levels during multiple dosing.

The extent of drug distribution is influenced by four factors:

(i) The physicochemical properties of the drug.

(ii) Active transport across cell membranes.

(iii) Regional blood flow.

(iv) Binding to tissue and plasma proteins.

(i) **Physicochemical Properties**

The extent to which a drug will diffuse across cell membranes is governed primarily by its molecular weight and its lipid solubility. The latter appears to be especi-
ally important, and the apparent distribution volumes of a series of β-adrenoceptor blocking agents are related to their octanol:water partition coefficients (see Figure 5).

The lipid solubility of a weak electrolyte is governed (Milne et al, 1958) by its degree of ionisation (since only the non-ionised fraction is lipid soluble). Ionisation is a function of the pH of the solution, and it is theoretically possible that the changes in acid-base balance which accompany uraemia might therefore influence the distribution of weak electrolytic drugs. This possibility requires further examination.

(ii) Active Transport

A few drugs require active transport across cell membranes for their effects to be produced. Such drugs bear stereochmical and functional resemblances to endogenous compounds, and include levodopa, adrenergic neurone blocking drugs, some indirect sympathomimetic amines (e.g. tyramine) and possibly methyldopa.

Whether these transport mechanisms are disturbed in patients with renal disease is uncertain. However, neuronal transport may be inhibited by other drugs (particularly by tricyclic antidepressants) and their effects attenuated (Mitchell et al, 1970).
Regional blood flow is a major determinant of the intensity and duration of effect of drugs given on a ‘once-off’ basis (e.g. anaesthetic induction agents, analgesics, and hypnotics). Alterations in regional blood flow must occur in advanced renal disease — partly in association with fluid retention and heart failure, and partly as an accompaniment of the ‘inevitable’ anaemia.

One example of the possible influence of altered regional blood flow on a drug’s distribution appears to be pancuronium: in Newcastle we have shown (McLeod et al, 1976) that in end-stage renal disease the clearance of pancuronium is reduced from $74 \pm 8 \text{ ml/min}$ to $20 \pm 2 \text{ ml/min}$ which is entirely compatible with the known renal excretion of this drug; in addition, however, we have shown that the volume of the ‘central’ compartment is increased from $0.079 \pm 0.009 \text{ l/kg}$ to $0.135 \pm 0.005 \text{ l/kg}$. These facts may explain not only why neuromuscular ‘blockade’ with pancuronium persists for such long periods in patients with impaired renal function, but also why they require larger doses than normal to achieve adequate ‘blockade’.

Changes in regional blood flow will not alter plasma drug levels during chronic administration once ‘steady-state’ has been reached. There is, however, one important exception to this rule — changes in blood flow in the eliminating organ. Some drugs (e.g. propranolol, lignocaine) are metabolised so avidly by the liver that their clearances are dependent on liver blood flow and not on metabolic activity (Nies et al, 1976). Changes in liver blood flow will have profound effects on drug clearance and (see equation 3) result in appropriate changes in blood level. The effects of advanced renal disease on liver blood flow appear to have received little attention.

(iv) Tissue and Plasma Protein Binding

Many drugs are bound to plasma proteins (usually albumin). Bound drug is unavailable for distribution to tissues, elimination by glomerular filtration or hepatic metabolism. (However, drugs which are actively secreted by the proximal renal tubules, and drugs with high hepatic clearances, have organ extraction ratios which include protein-bound drug as well as free drug.) Reduced protein binding will therefore tend to produce higher free concentrations of drug which is available for distribution both to target organs (causing enhanced drug effects), and to eliminating organs (causing increased drug excretion or metabolism). The net consequences will be different after single doses, and during multiple dosing at ‘steady state’.

a) Single doses After single drug doses, reduced binding will lead to higher blood levels of ‘free’ drug, and to enhanced biological effects: elimination will be more rapid, so the effects will be of shorter duration. The area under the plasma water concentration time curve will be unaltered.
b) Multiple dosing  During multiple dosing at ‘steady state’, reduced binding will produce a transient rise (see Figure 6) in free concentration. However, the combination of extravascular distribution and enhanced elimination will both operate towards restoring equilibrium. When equilibrium has been re-established, the free

![Graph showing total and free concentrations over time with a peak effect](image)

Figure 6. The effects of reduced plasma protein binding on (from above down) the total and free drug levels, and the intensity of the pharmacological effect

concentration will be identical with that observed before binding was diminished, but the total concentration will be less. The pharmacological effects (see Figure 6) of a reduction in plasma protein binding will therefore consist initially of an increase, followed (over a variable length of time depending on the rate of distribution and elimination) by a restoration to ‘normal’.

Reduced plasma protein binding has been described for many drugs in patients with advanced renal disease (Koch-Weser & Sellars, 1976): these include digitoxin, phenytoin, sulphonamides, clofibrate, diazoxide, frusemide, barbiturates, phenylbutazone, quinidine and triamterene. This reduction is partly due to hypoproteinemia, but is also due to conformational changes in the plasma proteins themselves (Reidenberg et al, 1971; Shoeman & Azarnow, 1972). Two important consequences follow:

a. Single doses of highly protein-bound drugs will tend to cause greater effects in uraemic patients than in ‘normal’ persons: the enhanced hypotensive action of intravenous diazoxide appears to be an important example of this (Pearson & Breckenridge, 1976).

b. Patients with advanced renal disease will display therapeutic and toxic effects of drugs at total plasma levels considerably less than those observed in ‘normal’ persons. Dosage adjustment of phenytoin therapy,
for example, in the light of plasma level data will require control (Reidenberg et al, 1971) at a plasma level of approximately 4–8 µg/ml: a better alternative, however, is to measure free drug levels (or salivary concentrations) and maintain these at 1–2 µg/ml.

Drugs also bind to tissue macromolecules. For technical reasons this has been the subject of little systematic study. However, binding to red blood cells (Beer- mann et al, 1975) has been described for a number of drugs. In particular, chlor-thalidone (Dieterle et al, 1976) has been shown to bind avidly to red cell carbonic anhydrase, and as a consequence the red cell:plasma concentration ratio ranges from 50:1 to 100:1 (Collste et al, 1976). The importance of this is uncertain, but clearly could be crucial in anaemic states — especially if the phenomenon applies to other diuretics.

CONCLUSIONS

Alterations in drug distribution which may accompany advanced renal disease have important practical implications:

1 The dependence of half-life on distribution volume makes the former a less useful measure of drug elimination rate.

2 After single doses, drug effects may differ in both intensity and duration as compared to normal. The direction of the change will depend on the direction of the alteration in distribution.

3 During multiple dosing, drug effects will not be altered unless there is an associated change in clearance. However, therapeutic ‘control’ will occur at lower total plasma levels but at ‘normal’ free drug concentrations.

References

Collste, P, Garle, M, Rawlins, MD and Sjoqvist, F (1976) European Journal of Clinical Pharmacology, 9, 319
Milne, MD, Scribner, BH and Crawford, MA (1958) American Journal of Medicine, 24, 709
Nies, AS, Shand, DG and Wilkinson, GR (1976) Clinical Pharmacokinetics, 1, 135

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