Today's Treatment

Clinical pharmacology

Elimination of drugs

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This article outlines the principles of drug elimination, principally by the liver and kidneys. Most elimination processes of drugs follow first-order elimination kinetics. In such processes a defined and constant fraction of a drug—for example, half—is irreversibly eliminated in a constant time. The half-life time ($t_{1/2}$) in such first-order processes is the time taken for the concentration of the drug to fall to half its previous value, regardless of the initial concentration of the drug. Some drugs—for example, ethyl alcohol—follow zero-order elimination kinetics. In these processes elimination of the drug occurs at a constant rate, because the enzymes responsible for metabolism of drugs, and the active excretion processes particularly in the kidney, become saturated.

Drug clearance

Total drug clearance is the sum of the drug elimination processes. These include renal, hepatobiliary, faecal, pulmonary, and dermal. Secretions also contribute to the elimination of drugs—for example, in saliva and milk. Clearance is defined as the volume of the body compartment from which drug is removed in unit time. Drug clearance is usually a more useful indicator of the efficiency of the elimination process of a drug than the $t_{1/2}$, because the latter may be a poor index for some drugs and may even be misleading because it depends on the volume of distribution of the drug. An illustrative analogy is two buckets of unequal sizes, each filled with water, with equal outlet holes at their bases. The water escapes under the influence of gravity with equal amounts of water being lost from each bucket. If the experiment is repeated, but equal amounts of drug are dissolved in both the large and small bucket, the clearance of the drug will be the same from both the large and small bucket. The $t_{1/2}$ will not be the same, however, being longer for the larger bucket because the $t_{1/2}$ relates to the capacity of the bucket (analogous to the volume of distribution of the drug) and inversely to the clearance.

The apparent volume of distribution (V_d) is the theoretical volume of the body compartments required to contain the amount of drug if it were uniformly distributed throughout the body in the same concentration as it is present in the blood. It should be understood that such compartments do not usually relate to recognised anatomical body spaces. Reversible distribution of drugs, as discussed in earlier articles in this series, is

influenced by the lipid solubility of the drug. The more lipid soluble the drug is, the more distribution into lipid compartments takes place and hence the larger is the V_d of the drug, thus affecting its elimination.

Drug clearance is also influenced by the rate of delivery of the drug to the organs of elimination, principally the liver and kidney, and by the capacity of the organs to eliminate the drug. In clinical practice most drugs are swallowed and with some, for example, propranolol, the bioavailability is low because only a fraction of the oral dose administered reaches the systemic circulation due to extensive presystemic or first-pass elimination during absorption from the gut and passage through the liver. A drug such as propranolol is said to be subject to high hepatic intrinsic clearance and, therefore, has a high extraction ratio. If the intrinsic clearance is high the rate-limiting step in the elimination of the drug is hepatic blood flow. Such elimination is described as blood-flow limited or non-restrictive. Examples of other drugs concerned in such elimination include lignocaine, labetalol, metoprolol, chlormethiazole, morphine, pentazocine, and pethidine. An example of a drug subject to high renal clearance is para-amino hippuric acid, which has long been used to measure renal plasma flow. For drugs with high clearance values, whether given by mouth or intravenously, drug binding to plasma or tissue proteins does not greatly influence elimination of the drug because rapid dissociation of bound drug occurs, allowing elimination of both unbound and bound drug.

If the capacity of the organ of elimination to remove drugs is low, the removal process is the rate-limiting step and such elimination is capacity-limited or restrictive. For such drugs hepatic clearance depends on the concentration of free drug available to the elimination process, which depends on the extent of drug-protein binding but not on blood flow. Many drugs concerned in capacity-limited processes are bound to plasma albumin—for example, warfarin, phenytoin, diazepam, and tolbutamide. Reduction in the degree of protein-binding of such drugs does not result in a change in steady-state concentration of free drug because any transient increase in free unbound drug, as a result of displacement from protein-binding sites, increases its availability for elimination. A reduction in drug-protein binding, however, leads to reduced steady-state total drug concentration and this could mislead the clinician, as has been shown in the example of the anticonvulsant drug phenytoin, which was administered to hypoalbuminaemic and control patients. The concentration of free drug was similar in the two groups, but the total concentration in the hypoalbuminaemic group was half that of the control group. Since it is the concentration of free drug that relates to pharmacological effect, and not of total drug (the concentration usually measured by routine hospital laboratories), unnecessary alterations in dosage based on the total concentration of drug in the blood, with predictable resultant toxicity, should be avoided. In general a clinically relevant drug-drug or drug-host interaction is unlikely to occur

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as a result of alterations in drug protein-binding unless free drug clearance is reduced because of reduced capacity for clearance by the organs of elimination together with increased free drug concentrations occurring because of reduced binding to proteins.

Renal excretion is the net effect of glomerular filtration, renal tubular reabsorption, and secretion.

The glomerulus produces an ultrafiltrate, and only free drug is filtered. The glomerular filtration rate is roughly 10% of renal blood flow and when reduced by renal malfunction may lead to delayed excretion of drugs and their metabolites. This subject has been reviewed recently.¹

When reabsorption is by passive diffusion, the pH of the dilute tubular urine is important, for this determines the relative proportions of ionised and unionised drug present, the latter being reabsorbed by diffusion. This principle has been made use of in forced diuresis: if the increased urinary flow rate achieved is combined with a judicious manipulation of pH of the tubular urine, increased drug elimination may be achieved. Thus forced alkaline diuresis which allows for an acidic drug to be in its ionised form promotes the excretion of drugs such as phenobarbitone and salicylate, whereas amphetamine excretion is enhanced in an acidic environment. Such forced diuretic procedures are inefficient and of little value when the amount of drug eliminated per unit time is a small fraction of the total in the body—for example, with digoxin; they are also not of benefit where drugs are more efficiently eliminated by metabolism—for example, most barbiturates, tricyclic antidepressants, and the benzodiazepines.

If reabsorption is by carrier transport then competition for the transport site will allow more drug to be eliminated. This is seen in the action of uricosuric agents on urate reabsorption and also the action of diuretics in promoting the excretion of sodium and chloride.

The main site of tubular secretion of drugs is the proximal convoluted tubule. Secretion is via an acidic or basic pump mechanism having the characteristics of active transport. Thus organic acids such as urate and penicillin and the end products of metabolism—the glucuronides and sulphates—participate in the acid pump while bases like choline and histamine are transported by the other route. Competition for the transport sites

may not occur between the acid and base carriers but competition within the sites can take place. The often quoted example of the reduced elimination of penicillin in the presence of probenecid is an example of this. The active transports are very efficient, and for highly cleared drugs may eliminate the bound form of the drug, as discussed earlier. This is seen in the case of penicillin-G where roughly 90% of the antibiotic eliminated is by secretion, which proves a more efficient process than glomerular filtration.

Conclusion

We have outlined some of the drug factors and principles underlying the elimination of drugs. Patient factors have not been discussed, but they also greatly influence drug clearance. Modification of dosages has been suggested for many drugs in patients with renal insufficiency¹ and at the extremes of age.^{2,3} Although studies with model drugs, such as propranolol, have been reported in patients with hepatic cirrhosis^{4,5} and thyrotoxicosis,⁶ the influence on the clearance of many commonly used drugs and of other diseases and patient factors, such as the effect of additional concurrent medication, remains to be clearly established.

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MATERIA NON MEDICA

Welshmen

There are two types of Welshman; the mountain Welshman—thin and wiry—and the valley Welshman—rolling and wallowing. The two meet in shoals on a Saturday night in the Neuadd Arms, the social centre of Llanwrtyd Wells. Llanwrtyd Wells is a gem of a town, a Llaregub of mid-Wales nestling under the desolate Cambrian mountains, a town of one butcher, two shops, and six pubs. A town of welcoming friendly people. People like Dai Arthur, a mountain Welshman, a septuagenarian who has cycled the four miles to the pub and back to his hillside farm each night for nobody knows how long. People like Cos, a valley Welshman, still affronted at "Trout," who he insists employed dubious tactics to win a close-fought long-remembered battle of bar quoits, the upturned mug forming a third lens to his pebble bespectacled face. And people like Monique. Monique taught us how to ride.

The inactivity of the Michaelmas madness in the Service led us to the Mid-Wales Riding Centre to school. And school it was. First lesson "tacking up," not through the wind, though it may well have been, but strapping exotic leather-wear to the huge beast Whisky's head. Monique embridles him in a trice. "Now you," in her Francais-accented Welsh.

The insertion of the bit is terrifying. You have to put your thumb in

the horse's mouth, in their warm and slobbery mouths. It is not an everyday duty, putting your thumb in a horse's mouth. You have to prise apart their lips, head in wrestling lock (horse's head that is), and press down on their gum. Whisky, now savage—massive teeth growing carnivorous, mad rolling eyes rolling madder, bubbling saliva frothing frothier, tosses his great head in rebellion but suddenly that tangle of old leather straps is emplaced and the beast is docile. Next to clean his great clumsy feet, bending over, hoof heaving, blood rushes to head, go dizzy, no whisky for me tonight.

Next day, coxa vara, buttocks awarer, it is into the mountains. Delight as the beast behaves. An exhilarating canter on forest paths high above the sleepy mid-winter town; higher still a buzzard circles patiently. In the misty valley the Ifon runs fast at this time of year and almost drowns out the clipping hooves.

In three days Monique manages to make us almost adequate horsemen. We have learnt why horses may go lame, and how and what to feed them on. We know of a farrier's work, his skill with hammer and anvil. But we also know from the ageless Dai of Llanwrtyd in its heyday, from David, geologist turned farmhand, of the glaciers which swept and furrowed the Cambrians, from the Builth Male Voice Choir the soaring beauty of Welsh singing. But we also know of the bubbling welcome and easy peace in the hillside.—W G THOMAS (surgical registrar, London).