MECHANISMS OF RENAL EXCRETION OF DRUGS
(WITH SPECIAL REFERENCE TO DRUGS USED BY ANAESTHETISTS)

L. F. PRESCOTT

GENERAL CONSIDERATIONS

Contrary to popular belief, the elimination of active drug by renal excretion is a relatively unimportant mechanism for the termination of drug action. Most drugs are weak electrolytes which are lipid-soluble in the un-ionized state, and as such they cannot be excreted by the kidney because they are extensively reabsorbed. These lipid-soluble drugs are invariably metabolized to more water-soluble derivatives which usually have little or no pharmacological activity and can readily be excreted in the urine. The duration of action is therefore determined largely by redistribution, metabolism, and in the case of the anaesthetic gases, by elimination through the lungs.

On the other hand, some drugs have limited lipid solubility or are highly ionized in the physiological range of pH. They tend to be eliminated largely unchanged by renal excretion and their duration of action may be prolonged in the presence of impaired renal function. Familiar drugs which fall into this category include quaternary ammonium bases, ganglion blocking drugs, non-depolarizing muscle relaxants, many antibiotics, thiazide diuretics, methotrexate, digoxin and barbitone (Table I). From a practical point of view it is obviously important to know whether the major route of elimination of a drug is through metabolism or renal excretion.

TABLE I. Some drugs for which renal excretion is normally an important route of elimination.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Diazoxide</th>
<th>Neomycin</th>
<th>Vancomycin</th>
<th>Penicillin G</th>
<th>Carbenicillin</th>
<th>Ampicillin</th>
<th>Cephalexin</th>
<th>Lincosycin</th>
<th>Tetracycline</th>
<th>Sulphonamides</th>
<th>Cycloserine</th>
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<tbody>
<tr>
<td>Digoxin</td>
<td>Acetazolamide</td>
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<tr>
<td>Barbitone</td>
<td>Chlorothiazide</td>
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<td>Amphetamine</td>
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<tr>
<td>Procainamide</td>
<td>Chloropropamide</td>
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<tr>
<td>Tubocurarine</td>
<td>Phenformin</td>
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<tr>
<td>Gallamine</td>
<td>Colcin</td>
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<tr>
<td>Hexamethonium</td>
<td>Polymixin B</td>
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<tr>
<td>Tetraethylammonium</td>
<td>Kanamycin</td>
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<tr>
<td>Mecamylamine</td>
<td>Streptomycin</td>
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<tr>
<td>Neostigmine</td>
<td>Gentamicin</td>
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<td></td>
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<tr>
<td>Atropine</td>
<td>p-Aminosalicylic acid</td>
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<tr>
<td>Methotrexate</td>
<td>Ethambutol</td>
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<td></td>
<td>α-Methyldopa</td>
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Unfortunately, such information is not always readily available, but since the ability of drugs to enter the brain correlates well with lipid solubility, it can be predicted that drugs with prominent central nervous system activity will be metabolized extensively by the liver and that only small and insignificant amounts will be excreted unchanged in the urine. Thus the actions of all the commonly used narcotic analgesics, local anaesthetics, barbiturates (except barbitone), phenothiazines, butyrophenone derivatives, benzodiazepines and ketamine are terminated by redistribution or hepatic metabolism. The extent of urinary excretion of some narcotic analgesics is shown in Table II.

TABLE II. Renal elimination of narcotic analgesics in man.

<table>
<thead>
<tr>
<th>Analgesic</th>
<th>Percentage of dose appearing unchanged in urine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heroin</td>
<td>0</td>
</tr>
<tr>
<td>Morphine</td>
<td>1-14</td>
</tr>
<tr>
<td>Codeine</td>
<td>3-16</td>
</tr>
<tr>
<td>Pethidine</td>
<td>2-10</td>
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<tr>
<td>Methadone</td>
<td>4</td>
</tr>
<tr>
<td>Propoxyphene</td>
<td>3-10</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>1-12</td>
</tr>
</tbody>
</table>

From Reidenberg, 1971.

For the anaesthetist, the most important drugs which depend on renal function for their elimination are the non-depolarizing muscle relaxants, decamethonium, ganglion blocking drugs, aminoglycoside and other antibiotics, digoxin and possibly procainamide.

MECHANISMS OF RENAL EXCRETION OF DRUGS

The renal excretion of drugs involves the processes of glomerular filtration, passive (non-ionic) reabsorption, active tubular secretion and active reabsorption.

Glomerular filtration.

Drug present in the plasma is filtered at the glomerulus and enters the nephron in the plasma ultrafiltrate. Only non-protein bound drug is available for filtration and glomerular filtration of drug is inversely proportional to the extent of binding to plasma protein. The renal clearance of drugs can
be markedly influenced by changes in the glomerular filtration rate and in patients with advanced renal disease the clearance of drugs is often reduced roughly in proportion to the creatinine clearance (Reidenberg, 1971). In the absence of protein binding and tubular reabsorption or secretion, the renal clearance of a drug would be the same as the glomerular filtration rate—about 125 ml/min.

**Active tubular secretion.**

Many organic acids and drug metabolites are actively secreted by a special proximal tubular transport system (table III) (Weiner and Mudge, 1964). At low plasma concentrations, this system is so efficient that compounds such as p-aminohippurate can be completely cleared from the blood in one circulation through the kidney. The clearance is then equal to the effective renal plasma flow (about 700 ml/min). Plasma protein binding does not interfere with secretion, presumably because of rapid removal of unbound drug and rapid dissociation of the drug-protein complex. Active secretion can be inferred if the net renal clearance of a drug exceeds the simultaneously measured glomerular filtration rate. The converse does not necessarily apply, however, since a drug can be actively secreted and subsequently reabsorbed. A similar active transport system exists for organic bases (Peters, 1960), and drugs such as tetraethylammonium, procainamide, mecamylamine and tolazoline are excreted by this route (table III).

One drug may compete with another for active secretion and thereby slow down its elimination.

**Active tubular reabsorption.**

This occurs with many inorganic ions and physiological compounds such as amino-acids and glucose. Some ions of pharmacological and toxicological interest such as lithium and fluoride are involved in this process, and uric acid is thought to be reabsorbed by an active transport system which is inhibited by uricosuric drugs.

**Passive (non-ionic) tubular reabsorption.**

After filtration at the glomerulus, drug in the tubular fluid is progressively concentrated as water is reabsorbed during its passage down the nephron. If there is no secretion or reabsorption, the concentration of a non-protein-bound drug will increase by a factor of about 5 (125/25) by the end of the proximal tubule, and if the final urine flow rate is 1 ml/min, the concentration factor in the urine will be 125 (125/1) (fig. 1). A strong concentration gradient is established, and if the drug can pass through the tubular epithelium it will be extensively reabsorbed. This epithelium acts as a lipid barrier and allows rapid diffusion of lipid-soluble un-ionized drug but prevents the passage of ionized water-soluble drug or metabolites. A highly lipid-soluble compound will be completely reabsorbed and its concentration in the final urine will approximate to that in the plasma. The renal clearance will therefore be equal to the urine flow rate, or in the example shown in figure 1, only 1 ml/min.

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**TABLE III. Drugs secreted by active tubular transport.**

<table>
<thead>
<tr>
<th>Acids</th>
<th>Bases</th>
</tr>
</thead>
<tbody>
<tr>
<td>p-Aminohippurate</td>
<td>Choline</td>
</tr>
<tr>
<td>Salicyclic acid</td>
<td>Histamine</td>
</tr>
<tr>
<td>Probenicid</td>
<td>Mecamylamine</td>
</tr>
<tr>
<td>Phenylbutazone</td>
<td>Tetraethylammonium</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>Hexamethonium</td>
</tr>
<tr>
<td>Phenol red</td>
<td>Pempidine</td>
</tr>
<tr>
<td>Diodrast</td>
<td>Tolazoline</td>
</tr>
<tr>
<td>Penicillin</td>
<td>Procaine</td>
</tr>
<tr>
<td>Sulphonamides</td>
<td>Procainamide</td>
</tr>
<tr>
<td>Chlorothiazide</td>
<td>Quinacrine</td>
</tr>
<tr>
<td>Acetzolamide</td>
<td></td>
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<tr>
<td>Chlorpropamide</td>
<td></td>
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<tr>
<td>Methotrexate</td>
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<tr>
<td>Dapsone</td>
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<td>Ghucronides</td>
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<tr>
<td>Etheral sulphates</td>
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<tr>
<td>Oxalic acid</td>
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</tbody>
</table>
The effect of urine pH and flow rate.

Most drugs are weak acids or bases and, as we have seen, only the un-ionized form is lipid-soluble and able to be reabsorbed by passive diffusion. The degree of ionization depends on the pKa (the negative logarithm of the dissociation constant) and the pH. The stronger the acid the lower the pKa value, and the stronger the base the higher the pKa. Weakly basic drugs are ionized in acid solutions and un-ionized in alkaline solutions, and the converse applies for weak acids. It follows that the renal clearance of weak acids is increased if the urine is made alkaline because more of the drug will be present in the ionized state and will be excreted since it cannot be reabsorbed. Similarly, the clearance of weakly basic drugs is low in alkaline urine, but can be increased if the urine is acidified (Milne, Schribner and Crawford, 1958). Strong acids and bases will be virtually completely ionized over the whole physiological range of urine pH and their excretion will be unaffected by changes in urine pH. The critical range of pKa values for pH-dependent excretion is about 3.0–7.5 for acids and 7.5–10.5 for bases (Milne, 1965).

pH-dependent renal excretion has been demonstrated for many drugs including amphetamine, pseudo-ephedrine, fenfluramine, pethidine, lignocaine, prilocaine, quinine, quinidine, tricyclic antidepressants, chloroquin, mepacrine, mecarnylamine, sulphonamides, acetazolamide, phenobarbitone, phenylbutazone, and salicylic acid. In some cases, the change in renal clearance is sufficient to cause a significant change in the biological half-life of a drug. For example, the mean plasma half-life of pseudo-ephedrine in three volunteers fell from 13.4 to 4.7 hours when the urine pH was reduced from 8 to 5 (Kuntzman et al., 1971). More often, this effect is of little practical significance because hepatic metabolism is the dominant mechanism of drug inactivation and elimination.

Diuresis may increase the renal clearance of drugs which are reabsorbed since the concentration gradient is reduced and urine volume increased. On theoretical grounds, however, there should be no change with drugs which are not reabsorbed. These principles form the basis of the use of forced alkaline diuresis for the treatment of salicylate and phenobarbitone intoxication. Similarly, forced acid diuresis can be employed to accelerate the removal of amphetamine or fenfluramine taken in overdosage. These measures are, of course, only applicable to a few drugs that are normally excreted unchanged in the urine to a significant extent and have suitable pKa values. Forced alkaline diuresis is quite useless in the treatment of intoxication with short and medium acting barbiturates because these drugs are virtually completely reabsorbed and metabolized by the liver.

Kinetic aspects.

When equilibrium has been reached between drug in plasma and the tissues, the rate of elimination is usually proportional to the plasma concentration of the drug. This rate is determined by the volume of distribution and the plasma clearance of drug. The volume of distribution is that volume in which the administered dose would have to be diluted to give the observed concentration of drug in the plasma, assuming complete absorption and distribution with no loss through elimination. When the volume of
distribution is large, the plasma concentration of drug is low, reflecting extensive uptake of drug by the tissues. The time taken for elimination of 50 per cent of the drug (half-life, \( t_\frac{1}{2} \)), is given by the following relationship:

\[
t_\frac{1}{2} = \frac{\log_2 2 \times \text{volume of distribution}}{\text{clearance}}
\]

Butler (1958) calculated the half-life of a number of hypothetical drugs eliminated entirely by renal excretion for an adult with an extracellular fluid volume of 15 l, total body water volume 50 l, glomerular filtration rate 125 ml/min, renal plasma flow 700 ml/min and urine flow 1 ml/min (table IV). Drug A, distributed in the extracellular water and actively secreted by the tubules has a half-life of only 15 min, while at the other end of the scale drug E is highly bound to tissues, completely reabsorbed, and has a half-life of 93 years! Hexamethonium and penicillin G fall somewhere between drugs A and B, and compounds such as mepacrine and thiopentone would have a half-life approaching 90 years if they were not metabolized by the liver.

**Table IV. Half-life of some hypothetical drugs eliminated entirely by renal excretion.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Volume of distribution (l.)</th>
<th>Renal clearance (ml/min)</th>
<th>Half-life</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>15</td>
<td>700</td>
<td>15 min</td>
</tr>
<tr>
<td>B</td>
<td>50</td>
<td>700</td>
<td>50 min</td>
</tr>
<tr>
<td>C</td>
<td>50</td>
<td>125</td>
<td>4.7 hr</td>
</tr>
<tr>
<td>D</td>
<td>50</td>
<td>1</td>
<td>24 days</td>
</tr>
<tr>
<td>E</td>
<td>70,000</td>
<td>1</td>
<td>93 years</td>
</tr>
</tbody>
</table>

From Butler, 1958.

**DISCUSSION**

Although renal excretion of unchanged drug is an important route of elimination for relatively few drugs, the anaesthetist is directly involved in the case of decamethonium and the non-depolarizing muscle relaxants. These quaternary bases are highly ionized and are largely removed by renal excretion. There have been numerous reports of prolonged paralysis following the use of these drugs in patients with renal failure, and gallamine has usually been involved (Fairley, 1950; McQuillen, Cantor and O'Rourke, 1968; Pittinger, Eryasa and Adamson, 1970; Riordan and Gilbertson, 1971). One patient, a 37-year-old woman with a perforated gastric ulcer and renal failure, was given 120 mg of gallamine and required assisted ventilation for 5 days. Muscle power returned when haemodialysis was carried out (Feldman and Levi, 1963). Another patient with renal impairment remained flaccid for 2 days following administration of 120 mg of gallamine, and the response to peripheral nerve stimulation was eventually restored following peritoneal dialysis (Lowenstein, Goldfine and Flacke, 1970). Singer, Dutton and Way (1971) also found it necessary to resort to haemodialysis in two anephric patients with prolonged refractory paralysis following injection of large doses of gallamine. Although gallamine is thought to be excreted entirely unchanged in the urine, its effects are not necessarily greatly prolonged in patients with severe renal disease (Churchill-Davidson, Way and de Jong, 1967).

Tubocurarine and dimethylcurarine are eliminated partly by metabolism and partly by renal excretion. The complete fate of diallylnortoxiferine, hexafluorenium, dacuronium and pancuronium is uncertain, but with all, a significant proportion of the dose is likely to be excreted unchanged in the urine (Mahfouz, 1949; Meijer and Weitering, 1970; Foldes, 1970). Termination of neuromuscular block after a single dose of these muscle relaxants probably depends more on redistribution to inactive tissues than on elimination, and the progressive prolongation of action observed with successive doses is conveniently explained by limited availability or saturation of tissue binding sites. Tubocurarine is often given to patients with impaired renal function without incident, and Churchill-Davidson, Way and de Jong (1967) were able to reverse its effects without difficulty in each of six patients with no renal function. However, prolonged apnoea ultimately requiring dialysis was recently described in a patient with renal failure given large doses of tubocurarine (Riordan and Gilbertson, 1971), and prolonged effects have been observed in similar circumstances with repeated doses of pancuronium (Stojanov, 1969).

The anaesthetist must concern himself not only with drugs which he himself administers, but also with drugs given by others. The antibiotics are of particular importance since most accumulate rapidly in the presence of renal failure, and streptomycin, neomycin, polymixin B, kanamycin and colistin potentiate non-depolarizing muscle relaxants and can themselves cause block (Emery, 1963; McQuillen, Cantor and O'Rourke, 1958; Pittinger, Eryasa and Adamson, 1970). It is significant that prolonged muscle paralysis induced by gallamine and tubocurarine in patients with renal disease has been
associated with the simultaneous administration of streptomycin and kanamycin (Feldman and Levi, 1963; McQuillen, Cantor and O'Rourke, 1968; Lowenstein, Goldfine and Flacke, 1970).

Surprisingly little information is available concerning the precise mechanisms of renal excretion of the muscle relaxants. Like other quaternary ammonium bases, they are probably actively secreted by the transport system for bases, and this raises the possibility of competition from other basic drugs. Singer, Dutton and Way (1971), referring to prolonged paralysis induced by gallamine in anephric patients commented as follows: "... experiences with such patients increase the potential for understanding the metabolism and excretion of certain drugs where such opportunities did not previously exist". This statement is surprising since it has been known for over 20 years that gallamine is excreted entirely unchanged in the urine. It is not enough simply to know that a drug usually has a certain duration of action. It is essential to know how its action is terminated and the mechanisms of inactivation and elimination.

Renal excretion plays an insignificant role in the termination of action of the narcotic analgesics, local anaesthetics, phenothiazines, butyrophenone derivatives and benzodiazepines even when excretion is pH-dependent with optimum conditions of urine pH. For example, with highly acid urine, only about 22 per cent of a dose of pethidine appears unchanged in the urine, while the combined excretion of pethidine and norpethidine is reduced to 4 per cent in alkaline urine (Asatoor et al., 1963). Suxamethonium and propanidid are hydrolyzed by plasma and tissue esterases (Doenicke et al., 1968), and although the activity of plasma cholinesterase may be reduced in uraemia, this seems to be of little practical importance (Reidenberg, 1971). In the presence of renal impairment digoxin and procainamide must be given in reduced dosage to avoid toxicity, and cumulation of atropine and neostigmine is theoretically possible since both drugs are excreted unchanged in the urine to the extent of 20–60 per cent.

The mechanisms of renal excretion of drugs are also of importance in the context of nephrotoxicity. A distal tubular lesion characterized by polyuria, resistance to vasopressin, weight loss, hypernatraemia and azotaemia has been observed in a minority of patients exposed to methoxyflurane, but it is most unlikely that the drug itself is responsible. Methoxyflurane is metabolized by the liver to dichloroacetic and methoxyfluoroacetic acids, carbon dioxide, inorganic fluoride and oxalic acid (Holaday, Rudofsky and Truehaft, 1970), and nephrotoxicity is associated with extensive metabolism and high serum and urine concentrations of fluoride and oxalic acid (Taves et al., 1970; Mazze, Trudell and Cousins, 1971). Both these compounds are recognized nephrotoxins, but most attention has been directed to the role of fluoride. However, oxalic acid is actively secreted by the proximal tubules (table III), and is concentrated in the lower nephron to the extent that crystals may form there. This is precisely the site of the lesion and oxalic acid may contribute directly to the nephrotoxicity associated with methoxyflurane anaesthesia.

CONCLUSION

Drugs are filtered at the glomerulus and some are also secreted in the proximal tubules by active transport systems. Lipid-soluble drugs are extensively reabsorbed as the tubular fluid is concentrated in its passage down the nephron, and with weak acids and bases the extent of reabsorption may be determined by the pKa of the drug and the urine pH. In addition, some compounds undergo active reabsorption. Renal excretion is not an important route of elimination for the majority of drugs used by anaesthetists. Decamethonium and the non-depolarizing muscle relaxants are important exceptions, and paralysis may be prolonged if these drugs are given to patients with renal failure. Furthermore, their effects are potentiated by streptomycin, kanamycin, neomycin, polymyxin B and colistin, and these antibiotics also depend largely on renal excretion for their elimination. It is essential to know how the action of a drug is terminated and the mechanisms involved in its inactivation and elimination.

REFERENCES


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**THE SOCIETY OF ANAESTHETISTS OF HONG KONG**

The Society wishes to remind all colleagues that it is intended to hold the Post World Congress Meeting in Hong Kong on September 24, 1972. The registration fee for the meeting and the social part, which includes Chinese Dinner and show, is £5 per person. Applications, together with remittance, should be sent to Dr M. L. Yeung, Hon. Secretary, The Society of Anaesthetists of Hong Kong, c/o Queen Mary Hospital, Hong Kong, to arrive not later than April 30, 1972.

The Society intends to hold an ADDITIONAL Post World Congress Meeting in Hong Kong for the benefit of those Anaesthetists who will not be able to be here on September 24. This second meeting will take place on either Sunday, October 1 or Monday, October 2, 1972. Registration fee for the Second meeting will be £3 (including buffet) and applications and remittances should also be sent to Dr M. L. Yeung, Hon. Secretary, The Society of Anaesthetists of Hong Kong, c/o Queen Mary Hospital, Hong Kong, to arrive not later than April 30, 1972. The scientific part will include talks and film of topical interest.