Clinical Pharmacology in Dentistry

R. A. Cawson

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FOURTH EDITION

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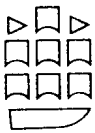

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Preface

The teaching of pharmacology and therapeutics to dental students is a subject which arouses strong feelings among those who have anything to do with it – and even more among those who do not.

It is true that the subject arouses among many – often those who should be most concerned – a violent upsurge of apathy. But it would be fair to suggest of the remainder that there are those at one extreme who regard pharmacology as hardly more relevant to dentistry than, and at least as pretentious as (say), Middle Period Etruscan Studies. At the other extreme there seems to be the belief that the dental student should have a detailed knowledge of the intricacies of actions and interactions of a remarkable number of drugs. It is even possible that there are extremists who believe that the level of knowledge of pharmacology might be at least comparable to that of dental materials. This comparison is perhaps not so bizarre when it is remembered that 'Materials Science' also deals with substances which are used on patients but, unlike drugs, these materials have little effect on his health or life.

Some mischief makers have even suggested that pharmacology and therapeutics are unpopular with students (and some teachers) because, unlike most of the rest of the clinical dental curriculum, they are mildly intellectually demanding. This is a frightening thought. Nevertheless, the dental student has had a broadly based scientific education at least until the start of his clinical years. It seems a pity if this has to go entirely to waste in the only too successful conversion of the dental student into a high-grade technician.

It would be rash indeed to suggest that this book could by any stretch of the imagination provide a compromise acceptable to such deeply entrenched and widely separated forces. If, however, there is any academic dentist (or dental academic) who believes that pharmacology is a subject from which his students should be protected, he forgets that he himself practises the niceties of his craft in an

unusually sheltered environment. He shuts his mind to the fact that when anything goes wrong – if, for instance, the patient is tactless enough to have a heart attack – the experts are called in and the matter is dealt with. The student who happens to see such events does not perhaps appreciate that, once qualified and in practice, he is quite on his own and in a very much more vulnerable position.

The general dental practitioner is giving – not prescribing, but giving – drugs, particularly local or general anaesthetics, on a far greater scale than his medical colleague. As it happens, the pharmacology of these particular groups of agents is far from simple, and if they are to be used safely and intelligently some understanding of basic pharmacology has somehow to be picked up.

The dental surgeon can also prescribe (even within the confines of the National Health Service) nearly a dozen different groups of drugs in well over a hundred different preparations. To add to all this, a quite remarkably high proportion of his patients are already taking drugs for medical purposes. Either these drugs or the disease for which they are given can, now and then, make some dental procedures distinctly hazardous.

As a consequence dental practitioners have – if the demand for postgraduate courses is any guide – a lively interest in this subject. It is hoped, therefore, that this book may also be of help to those already in practice.

Some attempt therefore has to be made to reconcile the predominantly technical nature of the dentist's training with these medical problems he has to assess and manage.

As far as is possible a clinical approach to the subject has been adopted as being more relevant to dental practice and to relate the subject matter to the medicine and surgery courses.

The writing of this book has had, inevitably, to be based on several assumptions.

First, some basic knowledge of pharmacology is necessary to use the drugs relevant to dentistry to best advantage and to protect the patient.

Second, a somewhat wider (but not detailed) knowledge of drugs is needed to understand both how these drugs act and how some of the reactions or interactions can develop.

Third, a rather more detailed knowledge of a few drugs is needed to deal with the various emergencies – uncommon though they may be – that can happen in the dental surgery.

Fourth, it is, to say the least, useful to have some understanding of the nature of the threats which hover over the dental patient under medical treatment.

Finally, it would be pleasant to think that a few dental students might even become interested in pharmacology and its clinical applications. It is, unlike dentistry, one of the areas of advance which in the past 50 years has made most impact on the physical and, perhaps, the mental welfare of the world. If nothing else is certain, there is little doubt that the dentist and the doctor too – unless quite exceptionally lucky – will sooner or later be a recipient of some of these over-numerous drugs.

Somehow, therefore, arbitrary decisions have to be made as to how much of this admittedly vast and sometimes difficult subject can be covered adequately but without suffocating detail. Drugs used in dental practice should presumably be considered more extensively than those which affect dentistry more peripherally, and some sort of balance has to be struck between these different requirements.

Since a brave attempt has been made to keep the text as short as possible, some suggestions have been made as to further reading. This is so rapidly advancing a subject that the choice has been restricted mainly to recent review articles and a few others which seem to be of particular relevance.

No doubt this book will turn out to be both too long *and* too short (according to whoever reads it), so that the treatment of the different types of subject matter is hopelessly unbalanced and that the proposals for additional reading are wildly capricious.

No doubt, too, the title is ill-chosen and some of the facts are wrong. But sad though it may be, this is the best that we can do.

Alas, things do not get easier for the reader, as pharmacology and therapeutics (unlike so much of dentistry) have an unfortunate tendency to advance. New editions of the British National Formulary now appear every 6 months and the latest edition at the time of writing had 43 new preparations added. Only a few of these, of course, are major new drugs and as a result of clinical experience many other drugs are discarded.

Change is nevertheless, forced upon one and there have been sufficient changes in this field to make another edition necessary.

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R. A. C.
R. G. S.

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Drugs: administration, absorption and fate

A drug is any substance used for the treatment or diagnosis of disease or to modify a physiological process. Obviously penicillin, which is used to treat infections, is a drug. But it can sometimes be difficult to decide whether a substance is a drug or not. A knowledge of what it is being used for will usually clarify the situation. If soap is being used for cosmetic reasons it is not a drug, but if used to treat a skin disease (such as acne vulgaris) it is a drug.

Originally all drugs were used in a crude form from animal, plant or mineral sources but an increasing number of new drugs are completely synthetic and built up from simple chemical precursors. Some drugs, such as aspirin and ephedrine, which were discovered as plant products are now synthesised *de novo*. Nevertheless there are still drugs which are extracted from plants, micro-organisms or tissues: examples are digitalis, antibiotics and hormones.

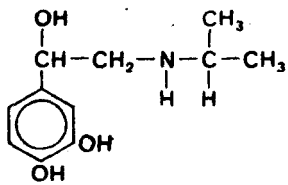
Receptor sites

One of the most striking features of many drugs is the remarkably low concentration at which they act. There are several examples where it has been estimated that the drug may be so highly diluted in the body fluids that only a few molecules are available to act on each cell. Even so the effects of these agents may be profound and widespread. These considerations suggest that it is not the entire cell which is the target of drug action but there are a small number of highly sensitive sites in each cell on which the substance acts. These sensitive sites are called ***drug receptors*** and are specific for different drugs. This implies that cells which do not normally respond to a particular drug do not contain receptors for that drug. Once a drug binds to its specific receptor, it changes the receptor in a way which leads to the observable response of the cell as a whole.

Even minor alterations in the structure of a drug can produce large changes in its effects. Its actions may be enhanced, or abolished or its selectivity changed with the result that its action is enhanced on one organ but diminished on another. An example is the modification of isoprenaline to produce salbutamol.

Isoprenaline relaxes bronchial smooth muscle and also stimulates the rate of beating of the heart. Salbutamol by contrast relaxes bronchial muscle but has little effect on heart rate. Because of this it is suggested that isoprenaline receptors in the bronchi are different from those in the heart — the bronchial receptors can also be stimulated by salbutamol, whilst those in the heart pacemaker cannot.

The following formulae illustrate the fact that an apparently trivial structural change results in a major difference in effect.



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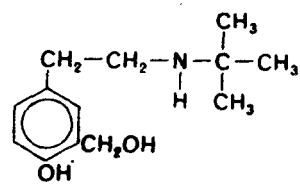


SALBUTAMOL

Competitive inhibition

Another important consequence of chemical modification of drugs which stimulate specific receptors is that the new compound may bind to the receptor but fail to stimulate it. In other words if the original drug and its modified form are administered simultaneously the two compete for the same receptor. The higher the concentration of competitor the more completely will it bind to the receptor and prevent its stimulation by the original drug. This is known as *competitive inhibition*.

Histamine is a substance which stimulates two types of receptor namely H_1 and H_2. Stimulation of H_1 receptors causes increased capillary permeability and relaxation of smooth muscle in some organs. The H_1 antihistamine drugs, such as chlorpheniramine, prevent these actions of histamine by binding to histamine receptors in capillary endothelium and smooth muscle cells and so blocking access of histamine to these sites. In this way chlorpheniramine acts as a competitive antagonist to histamine. In a similar way the H_2

receptor antagonist, cimetidine, blocks the secretion of acid by the stomach, which is normally mediated by the H_2 actions of histamine.

Species specificity

A final example of some of the many remarkable properties of drugs is that of species specificity. Bacterial chemotherapy is an application of this phenomenon. The essential feature of this form of chemotherapy is that some drugs can destroy the cells of bacteria within a patient without harming the patient himself. One mechanism by which this is attained is that the drug can inhibit or destroy a component in the bacterial cell, which is not present in the host's cells. Penicillin and the cephalosporins for example prevent the synthesis of an adequate bacterial cell wall. Animal cells possess no cell wall and are therefore completely unharmed.

Drug administration

The most rapid and sure method of introducing drugs into the body is by injection but oral administration is simpler, safer, cheaper and less unpleasant. Drugs can be injected subcutaneously, intramuscularly, intravenously or intra-arterially. Intravenous and intra-arterial injections give the highest and most rapid rises in drug concentration in the circulation. Subcutaneous injections produce more prolonged circulatory levels of the drug but the rate of rise is slower and the peak concentration is lower. Intramuscular injections have intermediate effects between intravascular and subcutaneous administration.

Absorption of drugs

The most important mechanism for drug absorption at cellular level is passive diffusion. This is not dependent on metabolic energy but is determined merely by a concentration gradient and by the ability of the drug to pass through the cell membrane. Cell membranes contain a large amount of lipid, and it is generally the lipid-soluble, uncharged forms of the drug which can pass through. Many drugs contain acidic or basic parts in their molecules and these may exist in ionised (charged) or unionised (uncharged) forms. It is the unionised forms which are more fat-soluble and these more readily pass through cell membranes. Thus, basic drugs are best absorbed

in an alkaline environment and acidic drugs in an acid environment. Non-polar and lipid substances are usually well absorbed.

Absorption from the alimentary tract

Some drugs such as the bronchodilator isoprenaline and the anti-anginal agent glyceryl trinitrate, are absorbed directly through the oral (sublingual) mucosa into the circulation. Not only does the effect of the drugs absorbed in this way come on rapidly, but they do not have to pass first through the liver via the portal circulation. When these drugs are swallowed, less reaches the systemic circulation because of partial metabolism by the liver.

A few drugs (such as aspirin and alcohol) are partly absorbed through the stomach wall but most drugs which are effective when given orally are absorbed in the upper part of the small intestine.

Pulmonary absorption

Anaesthetic gases and vapours, liquid aerosols and solid particles are given and absorbed via the lungs. Absorption into the circulation is mainly from the alveoli and alveolar ducts. In the adult human lung the area of these respiratory surfaces is 60 square metres, i.e. the area of the deck of a large motor cruiser.

An important advantage of administering bronchodilator aerosols directly into the respiratory tract (such as isoprenaline and salbutamol) by this route is that they are sprayed into the lungs and produce a high local concentration. The blood levels are relatively low and this reduces the danger of systemic toxic effects.

The absorption of anaesthetic gases is governed by their solubility, their rate of entry into the tissues and the rates of pulmonary blood flow and respiration. The longer the time a patient is exposed to an inhaled anaesthetic, the greater the amount of anaesthetic agent that enters the tissues from the plasma. The plasma/tissue difference in concentration therefore falls during exposure to the anaesthetic.

Having entered the body, the main route of excretion of volatile anaesthetics is from the lungs. Some of the drug remains for several hours in adipose tissue and other cells, but this is usually a relatively small proportion.

Liquid aerosols and solid particles can be inhaled as far as the bronchioles if the droplet or particle size is less than 2μ. Particles of 10μ reach the small bronchi. Thus the smaller the particle size, the greater the surface area reached for absorption.

Drug absorption through the skin

Drugs are often applied directly to the skin to treat skin diseases. Apart from the local physical properties of the application — which may in themselves be beneficial — local application gives a high tissue concentration to the affected part, with a much lower concentration elsewhere (assuming there is some diffusion and absorption into the circulation). Even for local effectiveness some of the drug must be absorbed and this takes place through the stratum corneum. Absorption is most rapid where the stratum corneum is thinnest and is further enhanced by warming the skin and increasing its hydration. Plastic occlusive dressings over steroid creams (for instance) greatly enhance and prolong their action, and also increase systemic absorption.

Glyceryl trinitrate, used in the treatment of angina pectoris, can be absorbed following application to the skin in the form of a cream.

Protein binding

Once a drug has been absorbed it travels throughout the body in the plasma. Although some of the drug is simply dissolved in the plasma, some is bound to plasma protein. The protein bound form is generally inactive, and it is the free form which is pharmacologically active. Many drugs are bound to the albumin component of the plasma proteins. These include the coumarin anticoagulants, indomethacin, aspirin, barbiturates, digitalis and tetracyclines.

One consequence of drugs being protein bound is prolongation of their effect in the body. Drugs which are mainly bound to plasma proteins have a prolonged action because it is only the free, unbound form of the drug which is attacked by drug metabolising enzymes and later excreted in the urine.

For any particular concentration of a drug in the blood, only a proportion (corresponding to the unbound form) is pharmacologically active. One type of harmful drug interaction can result from this situation. Warfarin, for instance, is a drug used in the prevention of thrombosis because of its anticoagulant action. It is partly protein bound in the plasma. If another drug (such as chloral) is given and displaces warfarin from its binding sites on the albumin molecule, a higher proportion of warfarin is then free to act. The pharmacological effect of the warfarin is therefore increased and this can result in haemorrhage.

Metabolism and fate of drugs in the body

The effect produced by a drug does not persist indefinitely, but sooner or later ceases. The fall in plasma concentration of the drug often parallels the fall-off in the effect of the drug. The graph of plasma concentration against time generally follows a logarithmic pattern and therefore the rate of descent of the curve can be expressed as a half-life ($t_{\frac{1}{2}}$) in the same way as other processes (such as radioactive decay) which diminish in a logarithmic pattern. This is due partly to metabolic destruction of the drug and partly due to excretion. The relative importance of these two mechanisms varies from drug to drug.

The liver is the principal organ involved in drug metabolism but others, such as kidney and intestine, are also involved to a lesser extent. Within the cell, the most important organelle carrying out metabolic transformations of drugs is the smooth endoplasmic reticulum. This constitutes the so-called microsomal fraction of the cell.

Drugs may be metabolised by two types of mechanism:

1. Conversion.
2. Synthesis.

1. Metabolic conversion. The structure of drugs may be modified in the body by simple chemical reactions. Important examples are oxidation and hydrolysis.

Many drugs are inactivated by oxidation by the microsomal (drug-metabolising) enzymes in the liver. Morphine and most of the barbiturates have their actions terminated in this way. In severe liver disease (such as advanced cirrhosis) or in patients who have been given monoamine oxidase inhibitor drugs (for depression) these oxidising systems do not function adequately. Thus if morphine or a barbiturate is given to such patients, it will cause profound and prolonged sedation with deep depression of respiration.

Suxamethonium is a muscle relaxant drug which acts on the motor end-plate. It has a very short action (usually less than 5 minutes) because it is rapidly hydrolysed by plasma pseudocholinesterase. This drug is therefore used when very short-lived muscular relaxation is wanted. Some patients (about one in 4000 of the population) lack pseudocholinesterase in their plasma. These people appear perfectly normal until they are given suxamethonium. This produces muscular (including respiratory) paralysis for many hours. During this time, life has to be maintained by applying positive

pressure artificial respiration until the effects of the suxamethonium have ceased.

2. *Metabolic synthesis.* Synthesis in the present context means conjugation of the drug with another chemical grouping or molecule. This may produce an increase in polarity and water solubility, decrease in pharmacological activity and greater ease of excretion.

One form of conjugation of drugs is with glucuronic acid. Glucuronic acid is derived from glucose, and is combined with some drugs in the liver. Such glucuronidation is carried out by the smooth endoplasmic reticulum of the hepatic parenchymal cells. Aspirin and chloramphenicol are examples of two drugs handled in this way. In new-born infants — particularly those born before full term — the drug conjugating mechanisms may be incompletely developed and fail to function for several days after delivery. If such a child is given chloramphenicol during the early days of life very little of the drug is converted to chloramphenical glucuronide (inactive) and most remains in the nonconjugated active form. Thus unusually high blood levels of the free antibiotic are present and cause toxic effects, in particular circulatory collapse.

Factors which modify drug metabolism

These may be split up into:

1. Genetic.
2. Physiological.
3. Environmental influences.

1. *Genetic constitution* is a not uncommon cause of variation in drug metabolism. Mention has been made of deficiency of plasma pseudocholinesterase, which greatly prolongs the action of suxamethonium. This is inherited as a non sex-linked (i.e. autosomal) recessive trait.

About a third of Europeans have inherited the ability to inactivate rapidly some drugs by acetylation. Thus they rapidly inactivate such drugs as the anti-tuberculous agent isoniazid, the antihypertensive hydralazine and the antidepressant nialamid.

Genetic factors may also alter responsiveness to drugs and the ability to develop toxic effects. Thus some patients are resistant to anticoagulants of the coumarin type such as warfarin. Large populations of rats and mice as a result of selection have also developed resistance to warfarin which is a widely used rat-poison.

An example of vulnerability to a particular toxic effect is the inherited deficiency of the red cell enzyme glucose-6-phosphate de-

hydrogenase. Such patients may develop an acute haemolytic anaemia when given certain antimalarials (such as primaquine and pamaquine) or antibacterials (such as nitrofurantoin and sulphonamides).

2. *Physiological factors.* Age is one such variable. In the new-born excessively high levels of such drugs as chloramphenicol may be produced due to immaturity of the microsomal drug conjugating system. In old age toxic effects to digoxin (a cardiac glycoside) and streptomycin (an antibiotic) are common, partly due to diminished renal function and impaired excretion.

Malnutrition, if severe, may prolong the action of some drugs (in particular the hypnotics and tranquillisers) due to poor hepatic function.

Liver disease — including cirrhosis and obstructive jaundice — may also slow down the removal of drugs which are conjugated and then excreted into the bile.

3. *Environmental influences.* Previous exposure to drugs is an example. The barbiturates are powerful inducers of drug metabolising enzymes. Even a few doses of a barbiturate increase the ability of the liver to metabolise a wide range of drugs. Thus if a patient is taking a barbiturate regularly and at the same time he is given the anticoagulant warfarin the latter has to be given in a higher than usual dose to produce the same anticoagulant effect. This is because the metabolism of warfarin by the liver has been accelerated. A well recognised danger of this situation is that if the patient suddenly stops taking barbiturates, but continues to take the same dose of warfarin he may suffer serious haemorrhage. This is because withdrawal of the barbiturate allows the drug metabolising enzymes in the liver quickly to fall to their previous (non-induced) level of activity. The warfarin is not then broken down so rapidly and attains much higher blood levels. Similarly in women given inducing agents such as the barbiturates, the contraceptive pill may become ineffective unless the dose of the oestrogen component is raised.

On the other hand, monoamine oxidase inhibitor drugs (such as nialamid), which are used in the treatment of depression, inhibit oxidising enzymes in the liver. If morphine, which is normally oxidised in the liver, is given at the same time as nialamid, it will have an enhanced effect.

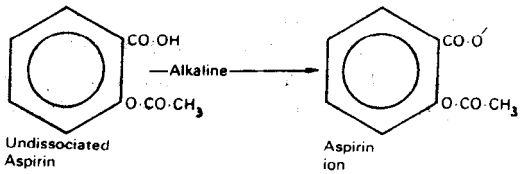
Drug excretion

Drugs may leave the body unchanged or in a metabolically altered form.

The most important organ of excretion is the kidney. Most renal excretion is via the glomerular filtrate. The sequence of events is this: arterial blood flows into the afferent arterioles of the glomeruli of the kidney. Some of the plasma is filtered through the glomerular membrane and enters the lumen of the renal tubules. Some of the solutes in the filtered plasma (which include electrolytes, metabolites and drugs) are to a variable extent reabsorbed via the tubular epithelium back into the plasma; the remainder enters the collecting ducts to be excreted in the urine. An important consequence is that the less the tubular reabsorption of drug, the more rapidly will it appear in the urine. To some extent this can be varied with individual drugs, particularly if they are acids or bases. Acids and bases exist in uncharged (undissociated) and charged (ionised) forms.

In acid solutions, acids are mainly undissociated while bases are mainly ionised. In alkaline conditions the situation is reversed: acids are mainly ionised and bases non-ionised.

It is a general rule that drugs can enter cells if they are uncharged and they cannot pass through even the outer cell membrane if they carry a charge. These phenomena are used in the treatment of some forms of drug overdose. Aspirin is a weak acid. When an overdose has been taken, excretion can be greatly accelerated by making the urine alkaline — usually by an infusion of sodium bicarbonate. The alkalinity of the urine encourages dissociation of the aspirin:



The ion thus formed carries a charge and therefore cannot be reabsorbed by the tubular epithelial cells. The aspirin which has entered the lumen of the renal tubule has then only one way out and this is via the collecting ducts into the urine.

Conversely the base amphetamine can be excreted more rapidly by increasing the acidity of the urine.

Many drugs retain their charge virtually unchanged throughout the entire pH range possible in body fluids. Streptomycin for example remains strongly positively charged at all physiological pH values, and the entire amount of streptomycin is filtered via the glomeruli and is excreted in the urine with almost no renal tubular epithelial reabsorption.

Occasionally renal excretion of a drug exceeds that entering the