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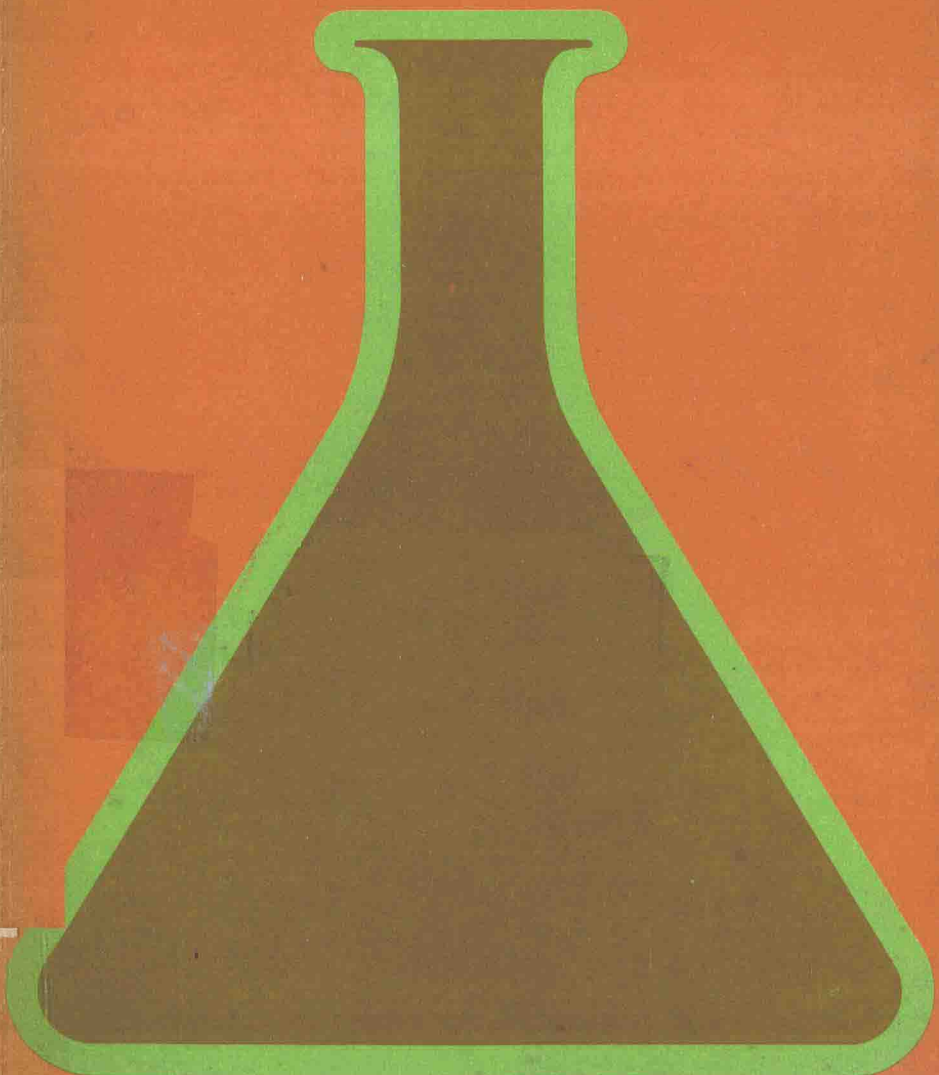
DENTAL PHARMACOLOGY

George W Pennington / T N Calvey / T C A O'Neil

Fourth Edition



Dental Pharmacology

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Dental Pharmacology

Preface to Fourth Edition

In recent years, the importance of pharmacology and therapeutics to the dental student and practitioner has been widely recognised. Clinical dentistry is increasingly concerned with the actions, uses, and possible complications of drug therapy. We believe that the publication of the fourth edition of this book reflects the interest of the practising dentist, as well as the dental student, in one of the more important non-technical aspects of his or her professional work.

In this edition, the general arrangement of the book has been preserved, although many of the Chapters have been extensively revised to take account of recent advances in pharmacology and the introduction of new drugs. Emphasis has again been placed on drugs in current use in medicine or dentistry. The implications of the Misuse of Drugs Act in dental practice has been considered, and a selected list of references for further reading have been restored to the end of each Chapter.

As in previous editions, the book aims to provide the scientific basis for the logical use of drugs by the dental practitioner. The text emphasises the possible adverse effects of drugs, including the various interactions between drugs which may occur in dental practice. We hope that the book will be used by both undergraduates and by the practising dental surgeon.

Our sincere thanks are due to our many colleagues for their help and constructive criticism of various sections of the book.

Preface to First Edition

In preparing this book I have been guided by the needs of both the dental student and the practising dental surgeon.

It has been my intention to supply, in addition to the essential pharmacological knowledge which the dentist needs to know, an account of that 'background to pharmacology' which is so often neglected in the education of the dental student and practitioner.

Many subjects are only briefly mentioned. It is hoped that the discerning reader will be encouraged to delve further into the storehouse of pharmacological knowledge which in recent years has accumulated so rapidly.

Although a complete bibliography has not been attempted, a number of references have been included at the end of each chapter. It is hoped that these will prove of interest to the student who wishes to probe a little deeper into the literature.

My sincere thanks are due to Professor Andrew Wilson, Professor of Pharmacology and General Therapeutics in the University of Liverpool, and to Professor Paul Cannon, Professor of Pharmacology the National University of Ireland, for their many helpful discussions and criticisms during the preparation of this book.

It is a pleasure to acknowledge the help I have received from many postgraduates and undergraduate colleagues, and in particular from Dr Austin Darragh and Dr Nial Hogan.

I must also express my gratitude to my secretary, Mrs Joan Gallen, for her diligent assistance.

Contents

Chapter 1
General Principles of Pharmacology

Drugs can be defined as agents that act on or affect living cells. The science of pharmacology (the study of drugs) thus covers an extremely wide field. Few biomedical scientists are entirely unconcerned with drugs and their actions.

Pharmacology is a hybrid science; it is closely related to more basic disciplines (for instance, physiology and biochemistry) as well as the practical aspects of drug use in man. It has been historically linked with other subjects that are now of little importance, such as materia medica (the sources, description, and preparation of drugs) and pharmacognosy (the identification, recognition, and study of plant drugs).

In recent years, the development of clinical pharmacology has recognised that the use of drugs in man should be based on sound scientific principles. Therapeutics is a closely related subject that is concerned with the use of drugs in the treatment of disease.

The source of drugs in current use

Most drugs in current use (particularly those introduced during the last thirty years) are chemically pure compounds that have been synthesised and prepared by pharmaceutical firms. Many thousands of new compounds are synthesised every year, although the majority are discarded during subsequent pharmacological and toxicological testing. Others may have undesirable effects that are only apparent after initial trials in volunteers or patients. New drugs must now meet stringent criteria before they can be generally used for medical or dental treatment.

Some drugs of animal origin still play an indispensible part in clinical practice. Thus, although many hormones can be synthesised, they are often derived from animal sources. The hormone insulin, for instance, is extracted from the pancreatic

islets of Langerhans of pigs and cattle, and is used in the treatment of diabetes mellitus.

Plants have also been the source of many important drugs. Digoxin, atropine, tubocurarine, reserpine, and quinine were all originally obtained from plants. Although the pharmacological properties of crude extracts containing these drugs have been known for centuries, the isolation and identification of their active constituents is a relatively recent development.

Minerals are occasionally administered in the form of salts. Thus, magnesium sulphate (Epsom salts) is sometimes used as a purgative; ammonium chloride as an acidifying agent; and ferrous sulphate is used in the treatment of iron-deficiency anaemia. Elements are only rarely used in medicine, except as radioactive isotopes.

Drug administration, distribution, and elimination

In order to produce pharmacological effects, drugs must be present in an adequate concentration at their site of action. In general, the concentration of drugs at their site of action is determined by several factors: these are

1 Drug administration
2 Drug dissolution
3 Drug absorption
4 Drug distribution
5 Drug metabolism
6 Drug excretion

The relation between these processes is shown in Fig. 1.1.

1 DRUG ADMINISTRATION

Drugs are usually administered by one of the following four methods. Firstly, by oral administration; secondly, by injection (either subcutaneous, intramuscular, or intravenous); thirdly, by inhalation; and finally, by local application to mucosal surfaces. Many drugs used in dentistry are given by local application or injection.

The method of drug administration is determined by several considerations. Oral administration is usually the most acceptable

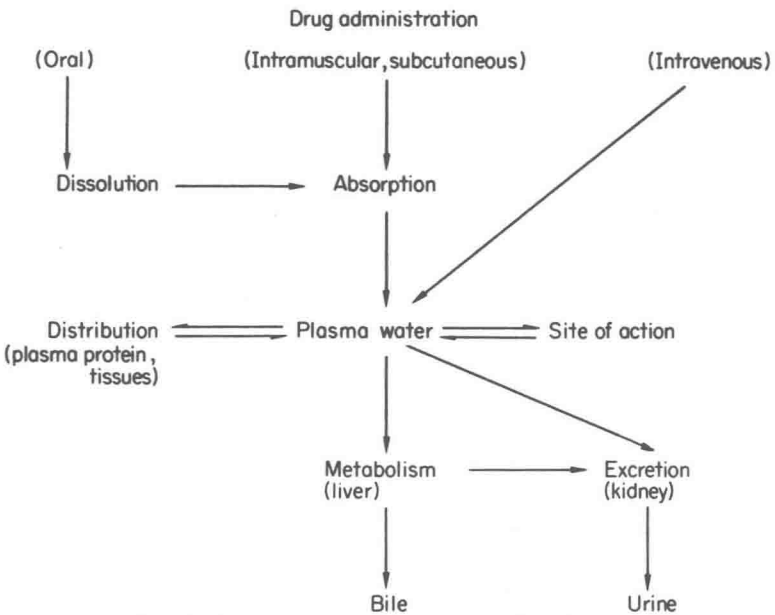

Fig. 1.1 The relation between the factors affecting the concentration of drugs at their site of action.

and convenient for the patient. However, there are several disadvantages with oral administration when used for certain drugs. Thus, some compounds are broken down by hydrochloric acid secreted by the stomach (for instance, benzylpenicillin). Other drugs are poorly or unpredictably absorbed (for example, streptomycin and all quaternary amines). In addition, certain drugs may irritate the stomach and cause nausea, vomiting, or gastro-intestinal haemorrhage. Orally administered drugs do not usually have an immediate action; there is a latent period (30 minutes–2 hours) before absorption and the onset of drug action. After oral administration and absorption, certain drugs are extensively metabolised by the liver ('first pass effect') before they gain access to the systemic circulation. For these reasons, some drugs are not administered by mouth but given by parenteral (i.e. non-oral) administration.

Subcutaneous or intramuscular administration is generally used for non-irritant drugs that are poorly or unpredictably

absorbed from the gut, and when an immediate action is not essential. With subcutaneous administration, the onset of action is slower and the duration of action is longer than with intramuscular injection. Subcutaneous administration is sometimes used to slow the rate of drug absorption and thus prolong the duration of drug action (for instance, with preparations of insulin).

Intravenous administration is used for extremely irritant drugs (thiopentone sodium or aminophylline) or when an immediate action is required (heparin or tubocurarine). This route of administration does not require absorption, since the drug is introduced directly into the plasma compartment.

Inhalation is the method of administration of many general anaesthetics that are gases (e.g. nitrous oxide) or volatile liquids (e.g. halothane). Due to the large surface area of the pulmonary epithelium, general anaesthetics are rapidly absorbed and gain almost immediate access to the circulation.

Local application to mucous surfaces is used when the local rather than the general actions of a drug are required (for instance, with surface anaesthesia).

2 DRUG DISSOLUTION

Drugs are only absorbed in solution. Thus, the dissolution of oral dosage forms (i.e. tablets or capsules) is essential before drug absorption can take place. Drug dissolution usually occurs in the stomach, and may be dependent on the presence of acid conditions; by contrast, absorption mainly takes place in the upper small intestine. Variations in the dissolution of tablets and capsules, and the rate and extent of gastric emptying, can thus affect drug absorption and bioavailability (i.e. the proportion of the dose present in the systemic circulation). Many pharmaceutical factors may influence dissolution of tablets and capsules (for instance, particle size, the chemical formulation, the presence of inert fillers and the outer coating applied to the tablet core). It is therefore not surprising that different proprietary preparations of the same drug may have differing dissolution characteristics and thus produce different plasma concentrations and bioavailability after oral administration.

Variations in drug dissolution mainly occur with relatively insoluble drugs that are administered orally; the subsequent differences in bioavailability may be of considerable clinical significance. For instance, in recent years differences in the potency of digoxin tablets in man that were based on clinical observations were eventually traced to variations in the rate of dissolution of different preparations of the drug.

3 DRUG ABSORPTION

When drugs are given orally, intramuscularly, subcutaneously, or by inhalation, absorption into plasma is essential before drug action can take place. Indeed, in some instances the method of administration is determined by the rate of absorption of the drug from different sites. Most orally administered drugs are absorbed from the upper small intestine, since the total mucosal surface area is far greater than in the stomach.

After oral administration, absorption is primarily determined by the physicochemical properties of the drug (in particular, by its molecular weight and relative lipid solubility). In the small intestine, the mucosal cell membrane (like most other cellular membranes) is approximately 10 nanometres wide, and consists of a bimolecular layer of lipid with intercalated molecules of protein on both its inner and outer aspects. The double lipid-protein membrane is interspersed with fine pores 0.5 nanometres in diameter. (In some tissues, for instance in capillary endothelium, these pores are substantially wider.)

Some drugs are absorbed by simple diffusion; this is a passive process that is solely dependent on the difference in concentration between the outer and the inner aspects of the membrane. Due to the nature of the cell membrane, highly lipid-soluble drugs (for instance, ethyl alcohol) are readily absorbed by simple diffusion. Drugs that are less lipid-soluble diffuse less readily, while ionised drugs (for instance, all quaternary amines) barely penetrate the lipophilic barrier. However, some highly polar, low molecular weight compounds can penetrate the small pores in the cell membrane.

Alternatively, drugs may be absorbed by non-ionic diffusion (Fig. 1.2). Certain drugs are present in the gut in both an ionic and non-ionic form. Only the non-ionised, lipid-soluble fraction

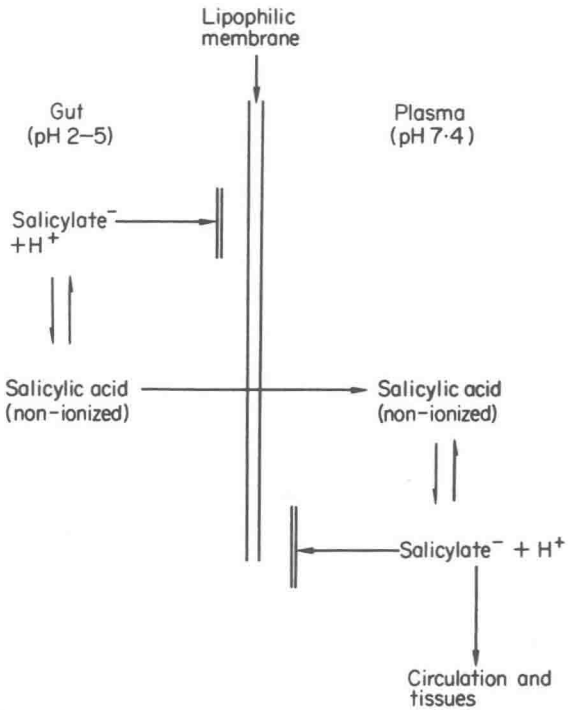

Fig. 1.2 The absorption of salicylates by non-ionic diffusion. Only the non-ionized salicylic acid can freely diffuse the lipophilic cell membrane. The diffusion gradient is provided by the immediate conversion of salicylic acid to salicylate^{--} in the relatively alkaline plasma. The salicylate^{-} anion cannot back-diffuse and remains in the circulation.

can readily diffuse across mucosal cells (hence the term 'non-ionic diffusion'). The ionised moiety cannot penetrate the lipophilic mucosal membrane. For example, sodium salicylate is present in the gut as both ionised salicylate (salicylate^{-}) and non-ionised salicylic acid. After oral administration of salicylates, only the non-ionised salicylic acid diffuses from the stomach and intestine into blood (Fig. 1.2). In the relatively alkaline plasma (pH 7.4) non-ionised drug is rapidly converted to the salicylate anion (salicylate^{-}) which cannot back-diffuse, but is rapidly removed by tissue perfusion; more than 99.9 per cent of the drug

is present as salicylate$^-$ in plasma. The difference in pH between the gut and the plasma provides a continuous gradient for the diffusion of non-ionised drug by rapidly removing it as salicylate$^-$. The absorption and excretion of other acid drugs (for instance, phenylbutazone, probenecid, barbiturates, and some sulphonamides) is also dependent on non-ionic diffusion.

Reverse arguments can be applied to many basic drugs, which attract hydrogen ions in the acid environment of the stomach; these compounds are poorly absorbed by the gastric mucosa, but are rather better absorbed in the relatively alkaline small intestine.

Finally, some drugs may be absorbed by carrier transport (for instance, simple sugars). This involves the active participation of the cell in the transfer of the drug from the gut to plasma, and requires the expenditure of cellular energy. Carrier transport is usually unidirectional and specific, but it can be saturated by large amounts of the drug. In addition, carrier transport can be readily inhibited (either competitively or non-competitively).

The absorption of drugs after subcutaneous or intramuscular administration is also dependent on these processes (particularly diffusion and non-ionic diffusion). Small lipid-soluble molecules are rapidly and completely absorbed after parenteral administration; larger, ionised drugs are absorbed less rapidly.

Although the physico-chemical properties of drugs are the major determinant of drug absorption, other factors may play a less important role. Thus drug absorption may be restricted by diminished circulation to the site of absorption. Vasoconstrictor drugs (for example, adrenaline) reduce the systemic absorption of local anaesthetics. The circulation to the absorption site is mainly responsible for differences between subcutaneous and intramuscular administration. In addition, surface area influences the rate of absorption and drugs are rapidly absorbed from sites with a large surface area. Thus, after intraperitoneal administration of drugs in experimental animals their pharmacological actions are almost immediate.

4 DRUG DISTRIBUTION

The distribution of drugs in the body after oral or intravenous administration is extremely variable. In general, lipid-soluble

drugs with a relatively low molecular weight are widely distributed in tissues. For example, ethyl alcohol, urea, and some sulphonamides are evenly distributed throughout body water. By contrast, ionised compounds (for instance, lithium and most quaternary amines) cannot readily penetrate most cell membranes, and are largely confined to extracellular fluid. Dyes such as Evans blue and Trypan blue are mainly distributed in plasma, and have been used to measure the total plasma volume. Some drugs cannot cross the blood-brain barrier, and so do not gain access to, or affect, the central nervous system. Other compounds tend to be localised in certain tissues or organs; for example, bromsulphthalein is concentrated in the liver, iodine in the thyroid gland, and tetracyclines in developing teeth and bone. The concentration of the drugs in these tissues may be much greater than in plasma. Some drugs are redistributed from well-perfused tissues to poorly perfused tissues as the plasma concentration falls, and this may have important practical implications. After the intravenous administration of thiopentone and methohexitone, these drugs are initially taken up by the brain, due to its extensive blood supply. Subsequently, they are redistributed to other tissues via the plasma; redistribution is responsible for the short duration of action of these general anaesthetics (Chapter 5).

After oral absorption or intravenous administration, drugs are initially distributed in plasma, where they may be present in two forms.

In the first place, they may be unbound (or 'free') in plasma water. Drugs can only diffuse from plasma into tissues when they are free in plasma water; if drugs are partly bound to protein, only the non-protein bound fraction is available for diffusion into tissues. In these conditions, the tissue concentration is likely to reflect the level of the non-protein bound drug in plasma.

Secondly, drugs may be bound by plasma proteins. Although some compounds (in particular, hormones, vitamins, and their synthetic derivatives) may be associated with plasma globulins, most drugs (for example, salicylates, phenylbutazone, indomethacin, penicillins, sulphonamides, and oral anticoagulants) are bound to plasma albumin. Some muscle relaxants (i.e. tubocurarine and pancuronium) are bound to both albumin and gamma globulin (IgG). The extent of protein binding may vary

greatly, even among closely related drugs. For instance, in spite of the chemical similarities between the semi-synthetic penicillins, binding to plasma albumin at therapeutic concentrations varies from 25 per cent (ampicillin) to 90 per cent (cloxacillin). Binding of drugs to plasma proteins is usually rapidly reversible. As the concentration of unbound drug in plasma falls due to distribution into tissues, protein-bound drug is released and is available for diffusion. Most drugs (particularly lipid-soluble compounds) rapidly diffuse from plasma to tissues. Indeed, transfer from plasma water to interstitial or intracellular fluid is usually essential for a drug to reach its site of action.

Many drugs are bound to plasma proteins to a limited extent. Plasma protein binding is probably only clinically significant when drugs are extensively (i.e. more than 80%) bound at therapeutic plasma concentrations. Nevertheless, the binding of drugs to plasma proteins may have a number of important practical implications. In particular, drugs that are extensively bound to plasma proteins may interact with each other, since they may compete for and be displaced from related binding sites on plasma albumin. If two drugs are normally bound at identical or closely related sites on albumin, and both drugs are given to patients simultaneously, increased amounts of either drug may be displaced into plasma and tissue water, thus increasing its pharmacological effects. Competition for plasma protein binding is responsible for the potentiation of the action of oral anticoagulants by phenylbutazone and mefenamic acid (Chapter 10). Oral anticoagulants are normally extensively (98–99%) bound by albumin, so that a minor degree of displacement by these drugs may cause a marked increase in concentration in plasma and tissue water.

Many antibiotics are partially bound by plasma albumin. In these conditions, antibiotic therapy may be inadequate, in spite of the fact that the plasma concentrations achieved *in vivo* are greater than the minimum inhibitory concentration measured *in vitro*. The concentration of antibiotics in tissue fluid is related to the free and not the total plasma concentration, and this may be less than the minimum inhibitory concentration.

Many (but not all) protein-bound drugs have a long duration of action, and are only eliminated from the body relatively slowly.

In these instances, diminished hepatic and renal elimination may or may not be causally related to the extensive binding of drugs by plasma proteins.

5 DRUG METABOLISM

Drug metabolism mainly occurs in the liver, and is usually the principal factor responsible for the termination of drug action. By removing the drug from plasma, metabolism encourages the back-diffusion of drugs from their site of action. The main purpose of drug metabolism is to convert lipid-soluble drugs into water-soluble derivatives, which can be readily filtered by the renal glomerulus or secreted into bile.

Although the liver is the main site of drug metabolism, some drugs are broken down in plasma by cholinesterase (for instance, suxamethonium and procaine). Possibly drugs are broken down by other tissues, in particular by the gut and by renal parenchyma, to a limited extent.

In general, drug metabolism reduces biological activity. However, some drugs are relatively inactive in the form they are administered, and require metabolism in order to produce their pharmacological effects (for example, chloral hydrate, cyclophosphamide, cortisone, prednisone, and proguanil). Some drugs may be extensively metabolised by the liver before they gain access to the systemic circulation. After oral absorption, they pass to the liver where they are removed from hepatic sinusoids and metabolised. This 'first-pass effect' is an important cause of the failure to respond to drugs after their oral administration.

Many drugs are metabolised in a specific part of the liver cell (the smooth endoplasmic reticulum). This can be separated from other subcellular particles by ultracentrifugation; in this form, the smooth endoplasmic reticulum is known as 'the microsomes'. Occasionally, drugs are metabolised by mitochondria (for instance, dopamine and tyramine) or in the cellular cytoplasm (alcohol).

Metabolic changes carried out by the liver can be divided into two types. Firstly, non-synthetic (phase 1) reactions are carried out by a mixed-function oxidase, and result in drug degradation by oxidation, reduction, or hydrolysis. Secondly, synthetic