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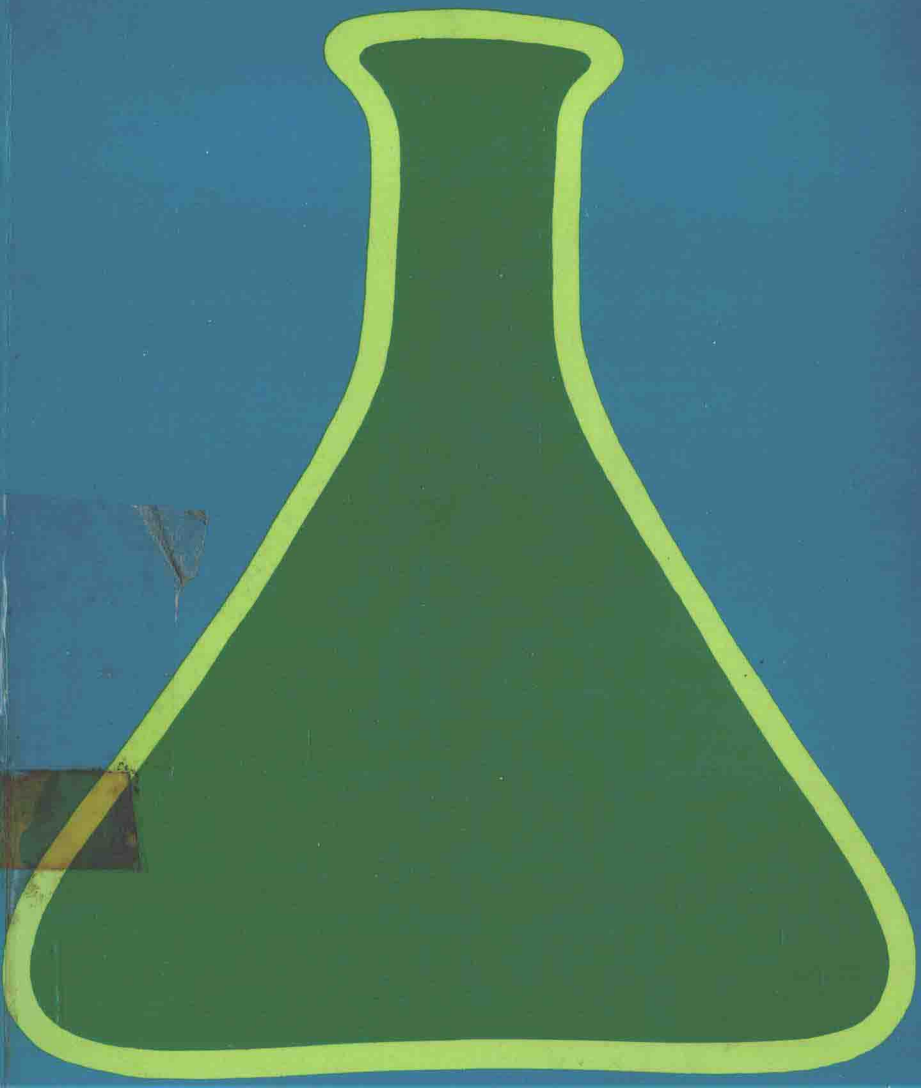
DENTAL PHARMACOLOGY

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

Third Edition



Dental Pharmacology

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Third Edition
Second Printing

Blackwell Scientific Publications
Oxford · London · Edinburgh · Melbourne

Osney Mead, Oxford, OX2 OEL
8 John Street, London, WC1N 2ES
9 Forrest Road, Edinburgh, EH1 2QH
P.O. Box 9, North Balwyn, Victoria, Australia.

First published 1965
Second edition 1969
Third edition 1977
Reprinted 1978

Pennington, George Williams
Dental pharmacology. – 3rd ed.
Bibl. – Index.
ISBN 0-632-00249-2
1. Title 2. Calvey, Thomas Norman
3. O'Neil, Terence Cuthbert Anthony
617.6'061 RK701
Dental pharmacology

Distributed in the United States of America by
J.B. Lippincott Company, Philadelphia,
and in Canada by
J.B. Lippincott Company of Canada Ltd, Toronto.

Printed and bound in Great Britain by
Billing & Sons Limited
Guildford, London and Worcester

DENTAL PHARMACOLOGY

Preface to the Third Edition

Since the publication of the second edition, several new drugs have been introduced into medical and dental practice. Some traditional remedies have been superseded by safer alternatives, and the mode of action of several established drugs on cellular and biochemical processes has been clarified. A thorough revision of the text has therefore been necessary. Many chapters have been rewritten to take account of recent advances in pharmacology and therapeutics. The subdivision of the book into General and Systematic Pharmacology has been modified, and a new chapter on drug hypersensitivity has been included. Certain subjects (in particular, the sections on the development and clinical testing of new drugs, and the legal implications of the Misuse of Drugs Act) have been omitted from this edition; it was felt that these subjects were outside the scope of the book and were adequately covered in other publications. The suggestions for further reading at the end of each chapter have also been omitted.

The primary purpose of this book is to provide the scientific basis for the logical use of drugs by the dental practitioner. It is not a textbook of basic pharmacology nor one of clinical therapeutics, although it contains certain elements of both subjects. As in previous editions, particular emphasis has been placed on the adverse effects of drugs, including the various interactions between drugs which may occur. Although the book is primarily designed for undergraduate use, it is hoped that it will also be of interest to the practising dental surgeon.

Our sincere thanks are due to our many colleagues in both Sheffield and Liverpool with whom we have discussed sections of the book. We are also greatly indebted to Miss Sheila Ashton, Mrs Angela Allison, Mrs Myrna Bennett, Mrs Yvonne Foster and Miss Sharon Gosling for their skill in preparing the typescript.

Preface to the 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.

Preface to the Second Edition

The contents of this edition have again been primarily selected to meet the needs of the dental student. It is hoped, however, that the approval of the practising dental surgeon will be forthcoming.

It has not been our intention to provide a textbook of therapeutics, but rather that this book will provide a springboard for the rational application of therapeutics.

A fairly extensive revision has been carried out, chapters have been rewritten while others have been remodelled to include recent advances in pharmacological knowledge.

The index of Proprietary Preparations has been omitted as it was felt that this field is now well covered by a number of commercial publications.

A short additional chapter has been added, which it is hoped will remind the dental student of the effects of vitamin-lack.

The book is divided into two parts. A short first section which is devoted to the principles of action and the effects of drugs, and which also covers such general fields as the pharmacological evaluation of drugs, clinical testing and clinical trials. A further chapter is devoted to various medical conditions which impinge upon the practice of dentistry, for it is important that the dentist is able to recognize the patient who is not fit enough for treatment particularly if this involves minor surgery or a general anaesthetic.

In Part II a systematic study has been made of the effects of drugs with similar actions and effects.

The effects of modern drugs are multiple and special precautions may have to be taken prior to dental treatment. Throughout the book particular emphasis has been placed on the untoward effects which may arise and the various interactions between drugs which might take place.

Our sincere thanks are due to the many practising clinicians with whom we have discussed sections of the book and in particular to Mr Dick McGhee. We are also greatly indebted to Miss Anne Sharman for her skill in preparing the typescript.

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 recognized 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 synthesized and prepared by pharmaceutical firms. Many thousands of new compounds are synthesized every year, although the majority are discarded during subsequent pharmacological and toxicological testing. New drugs must meet stringent criteria, including the scrutiny of the Medicines Commission, before they can be generally used for medical or dental treatment.

Some drugs of animal origin still play an indispensable part in clinical practice. Thus, the hormone insulin is extracted from the pancreatic islets of Langerhans of pigs and cattle; it is used

in the treatment of diabetes mellitus. Other hormones can be synthesized (for instance corticotrophin), although they are more usually derived from natural sources (for example, the pituitary hormone vasopressin).

Plants have also been the source of many important drugs. Indeed, some pharmaceutical houses are currently engaged in the extraction and identification of active principles from plants. Digoxin, atropine, tubocurarine, reserpine, and quinine were all originally obtained from plants and their pharmacological properties have been known for centuries.

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

The aim of local or systemic drug administration is the production of an adequate concentration of the drug at its site of action. Several factors may affect the concentration of the drug at its site of action: these are:

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

The relation between these factors is shown in Fig. 1.1

1 Drug administration

In general, drugs are administered by 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.

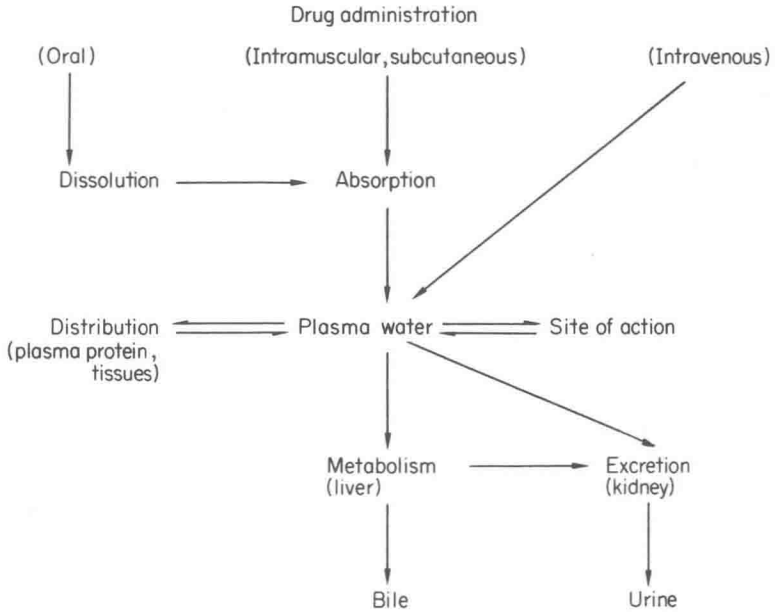

Fig. 1.1 The relation between the factors affecting the concentration of drugs at their site of action.

Oral administration is usually the most acceptable and convenient for the patient. However, there are several disadvantages with oral administration as applied to 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 and vomiting. Orally administered drugs do not usually have an immediate action; there is a latent period (30 min–2 hr) before drug action is apparent. Furthermore, certain drugs are extensively metabolized by the liver 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 the semi-lente, lente and ultra-lente 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. Due to the large surface area of the pulmonary epithelium, 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, while absorption takes place in the upper small intestine; variations in the drug dissolution of tablets can thus affect their absorption and their 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 different dissolution characteristics, and thus produce differing plasma concentrations after oral administration.

Variations in drug dissolution mainly occur with relatively insoluble drugs that are administered orally, and may be of considerable clinical significance. For instance, in recent years differences in the potency and bioavailability of digoxin tablets in man 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 takes 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 physico-chemical 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 nm wide, and consists of a bimolecular layer of lipid with intercalated molecules of protein on both its inner and its outer aspects. There are about 70 molecules of lipid for every molecule of protein. The double lipid-protein membrane is interspersed with fine pores approximately 0·5 nm 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, alcohol) are readily absorbed by simple diffusion. Drugs that are less lipid-soluble diffuse less readily, while ionized 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 a non-ionic form. Only the non-ionized, lipid-soluble fraction can readily diffuse across mucosal cells (hence the term 'non-ionic diffusion'). The ionized moiety cannot penetrate the lipophilic mucosal membrane. For example, sodium salicylate is present in the gut as both ionized salicylate ($salicylate^-$) and non-ionized salicylic acid. After oral administration of salicylates, only the non-ionized salicylic acid diffuses from the stomach and intestine into blood (Fig. 1.2). In the relatively alkaline plasma (pH 7·4) non-ionized drug is rapidly converted to the salicylate anion ($salicylate^-$) which

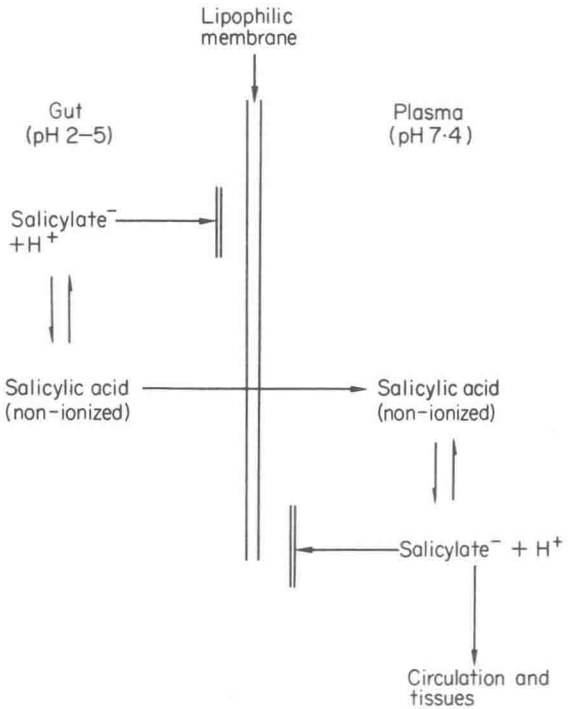

Fig. 1.2 The absorption of salicylates by non-ionic diffusion. Only the non-ionized salicylic acid can freely diffuse the lipophilic cell membrane. The diffusion gradient is provided by the immediate conversion of salicylic acid to salicylate$^-$ in the relatively alkaline plasma. The salicylate$^-$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

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-ionized 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 quantities of the drug. In addition carrier transport can be readily inhibited (either competitively or non-competitively).

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

After drugs are absorbed, they may be present in plasma 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. Many drugs, particularly lipid-soluble compounds, are rapidly transferred from plasma water to tissues. Transfer from plasma water to interstitial or intracellular fluid is usually essential for a drug to reach its site of action (heparin is an exception). Most drugs are transferred to tissues by passive diffusion.

Secondly, drugs may be bound to plasma proteins. Many acidic drugs (for example, salicylates, phenylbutazone, indomethacin, penicillin, sulphonamides, hydrocortisone and oral anticoagulants) are present in plasma as anions and are bound to plasma albumin. The extent of protein binding varies greatly, even among closely related drugs. For example, 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 to plasma albumin is an electrostatic (reversible) rather than a covalent (chemical bond) phenomenon and is therefore readily dissociable. As the free level of drug in plasma falls due to distribution into tissues, protein-bound drug is released into plasma water and is thus made available for diffusion. There is some evidence that anionic drugs are bound to positively charged amino groups on lysine residues of albumin. However, cationic drugs and non-ionic drugs may also be bound to plasma protein.

The plasma protein binding of drugs is important for several reasons.

Protein-bound drugs usually have a slow onset of action and a long duration of action. Diffusion into tissues from plasma is slow, since the free concentration of the drug in plasma is low; protein-bound drug acts as a reservoir, progressively dissociating and replacing the small amounts of free drug lost by diffusion from plasma water. Renal clearance of the drug may also be low, since only the free drug is eliminated by glomerular filtration.

Protein-bound drugs may compete for and displace each other from the same binding site on plasma albumin. If two drugs A and B are bound at related sites on albumin, and drug B is given to a patient on drug A, increased amounts of drug A may be displaced into plasma and tissue water, thus increasing its pharmacological and toxic properties. Competition for plasma protein binding is the explanation for certain examples of drug interaction, for instance, the potentiation of the action of oral anticoagulants by phenylbutazone and mefenamic acid (Chapter 10).

In some instances the rate of drug metabolism is related to the concentration of free drug in plasma rather than to the concentration of protein-bound drug. If the concentration of a drug in plasma is sufficient to 'saturate' the binding sites on albumin, further increasing the dose may merely increase the rate of metabolism without influencing therapeutic effectiveness. The best example is the anti-inflammatory drug phenylbutazone.

Finally, antibiotic therapy may be inadequate in spite of the fact that the plasma concentrations achieved *in vivo* are greater than the minimum inhibitory concentration (MIC) measured *in vitro*. The concentration of antibiotics in tissue fluid is related to the free and not the total plasma concentration; this may well be less than the MIC *in vitro*.

The concentration of drugs in plasma is usually highest during or immediately after oral absorption. Even higher levels are present after intravenous administration of equivalent doses. The distribution of drugs varies greatly; ethyl alcohol, urea, and some sulphonamides are evenly distributed throughout the body water, while lithium and quaternary amines are largely confined to extracellular water. Dyes such as Evans blue and Trypan blue are mainly distributed in plasma while other drugs tend to localize in a particular tissue; for example, iodine is localized in the thyroid gland, and lead in bone.

The half-life of drug elimination may vary from minutes to days; it can be used to calculate the mean plasma concentration of a drug during intermittent oral administration. As long as drug absorption is complete, the elimination half-life after oral administration should be identical with the terminal half-life after intravenous administration.

The redistribution of drugs from one tissue to another may have important practical implications. After the intravenous administration of thiopentone and methohexitone, the 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 anaesthetics (Chapter 5).

5 Drug metabolism

Drug metabolism mainly occurs in the liver, and is usually the main 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 renal parenchyma, to a limited extent.

In general, drug metabolism reduces biological activity. However, some drugs are relatively inactive on administration and require metabolism in order to produce their pharmacological effects (for example, chloral hydrate, cyclophosphamide, cortisone, prednisone and proguanil).