John L. Reid, Peter C. Rubin, Brian Whiting Lecture Notes on Clinical Pharmacology

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Clinical Pharmacology

JOHN L. REID
DM FRCP
Regius Professor of Materia Medica

PETER C. RUBIN
DM MRCP
Senior Registrar in Clinical Pharmacology

BRIAN WHITING
MD FRCP
Senior Lecturer in Clinical Pharmacology

Department of Materia Medica
University of Glasgow

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Preface

Clinical pharmacology is a new and rapidly expanding specialty which has grown in importance with the increase in both the number and the complexity of drugs. Bridging the gap between laboratory science and the practice of medicine at the bedside, clinical pharmacology has as its primary aim the promotion of safe and effective drug use: to optimise benefits and minimise risks.

Developments in medicine, pharmacology and physiology have led to a better understanding of disease processes and a more rational use of drugs. Recent years have seen the development of drugs designed to interact with specific receptors or enzyme systems. In addition the application of biochemical and immunological techniques has led to a clearer appreciation of the mechanisms involved in adverse drug reactions and interactions. With this understanding has come the potential to reduce greatly the number of unwanted drug effects. The intensity of drug action is often related to plasma concentration, and recent advances in analytical techniques have enabled rapid and accurate determination of the plasma concentrations of many drugs. This provides an added dimension to the optimisation of drug use.

For many years we have taught clinical pharmacology to medical practitioners and undergraduate students. We have now been persuaded by our students that there is a need for a brief, clearly written and up to date review of clinical pharmacology. *Lecture Notes on Clinical Pharmacology* has been prepared to meet this need. We have not attempted to be comprehensive, but have tried to emphasise the principles of clinical pharmacology, areas which are developing rapidly and topics which are of particular clinical importance. The book is based on the four term course of

lectures and seminars in clinical pharmacology and therapeutics for medical students at the University of Glasgow. In addition, we have drawn on our experience of organising courses for postgraduate students, general practitioners and medical specialists. Thus, while intended primarily for medical students, we believe this book will also be of use to those preparing for higher examinations and doctors in established practice who wish to remain well informed of current concepts in clinical pharmacology.

For all who use it, we hope this book will provide a clear understanding not only of *how* but also of *when* to use drugs.

John Reid
Peter Rubin
Glasgow, December 1981 Brian Whiting

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We ourselves accept full responsibility for the contents of the volume and for any mistakes or misunderstandings.

John Reid
Peter Rubin
Brian Whiting

Contents

CHAPTER 1

Principles of clinical pharmacology

Until the twentieth century, medical practice depended largely on the administration of mixtures of natural plant or animal substances. These preparations contained a number of pharmacologically active agents in variable amounts. Their actions and indications were empirical and based on historical or traditional experience. Their use was rarely based on an understanding of the mechanism of disease or careful critical measurement of effect.

During the last 80 years, an increased understanding of biochemical and pathophysiological factors in disease has developed. The chemical synthesis of agents with well characterised, specific actions on cellular mechanisms has led to the introduction of many powerful and effective drugs.

1.1 PRINCIPLES OF DRUG ACTION

Application of drug treatment

Pharmacological agents are used in therapeutics to:

(1) Cure disease:
chemotherapy in cancer or leukaemia,
antibiotics in specific bacterial infections.

(2) Alleviate symptoms:
antacids in dyspepsia,
non-steroidal anti-inflammatory drugs in rheumatoid arthritis.
(3) Replace deficiencies:
restoration of normal function by the replacement of a deficiency in endogenous hormone, enzyme or transmitter.

A *drug* is a single chemical entity that may be one of the constituents of a medicine.

A *medicine* may contain one or more active constituents (drugs) together with additives to facilitate administration (colouring, flavouring, and other excipients).

Mechanism of drug action

Drugs may act in several different ways and our understanding of the mechanism of drug action advances hand-in-hand with developments in basic and clinical science.

Action on a specific receptor

Receptors are macromolecular structures linked to effector mechanisms which interact with drugs to form a drug–receptor complex. This interaction may be reversible or irreversible.

Agonist drugs stimulate or activate the receptor to produce an effect. Antagonist drugs block the effects that usually result from stimulation of the receptor by agonists. Antagonism is either *competitive* if the drug–receptor interaction is reversible, or *non-competitive* if the drug–receptor complex is irreversible.

Blockade by a competitive antagonist *can be overcome* by large amounts of agonist.

Competitive antagonism is generally of short duration and depends on the presence of drug. For examples, Beta-receptor antagonists, such as propranolol block the chronotropic and inotropic effects of increased catecholamine release. Opiate receptor antagonists, such as naloxone reverse the respiratory depressant and sedative effects of morphine.

Non-competitive antagonism *is not reversed* by any amount of agonist, is usually long-lasting (days or weeks) and may persist after the drug has been withdrawn. Recovery depends on the synthesis of new receptors.

For example, phenoxybenzamine, which irreversibly blocks alpha adrenoceptors.

Action on specific enzymes

Enzymes, like receptors, are protein macromolecules with which substrates interact to activate or inhibit enzymatic activity. Inhibition of enzyme activity may be *competitive* (reversible) and relatively short-lasting. For example allopurinol, a xanthine oxidase inhibitor and carbidopa a decarboxylase inhibitor.

Alternatively it may be *non-competitive* (irreversible) and long-lasting, persisting until new enzyme protein has been synthesised. For example, prostaglandin synthetase inhibitors such as aspirin, and monoamine oxidase inhibitors such as phenelzine.

Action on membranes

The electrophysiological processes that form the basis of nerve and muscle function depend on ion fluxes to alter transmembrane potential. Various drugs can influence these ionic movements:

Antiarrhythmic drugs,
Anticonvulsant drugs,
General anaesthetics.

Cytotoxic actions

Drugs used in cancer or in the treatment of infections may kill malignant cells or micro-organisms. Often the mechanisms have been defined in terms of effects on specific receptors or enzymes. In other cases chemical action (alkylation) damages DNA or other macromolecules and results in cell death or failure of cell division.

1.2 PRINCIPLES OF DRUG ABSORPTION

Bioavailability

Some drugs are applied directly to their sites of action. Examples of such topical administration include the application of fungicides to

TABLE 1.1 Modes of drug administration

Parenteral	Enteral	Topical
Intravenous	Oral	Determatological
Intramuscular	Sublingual	Ocular
Subcutaneous	Rectal	Inhalational
Intrathecal		
Intra-articlar		

infected skin and steroid or bronchodilator aerosols in the treatment of asthma. However, in most cases a drug must be transported to its site of action by the systemic circulation.

Bioavailability is the term used to describe the *proportion of administered drug that reaches the systemic circulation in unchanged form.*

In the case of intravenous administration bioavailability will clearly be 100%, but most drugs are given orally and numerous factors can prevent complete absorption. Among the more important are the presence of food, the barrier presented by the lipid membranes of the gut and first-pass metabolism.

First-pass metabolism

First-pass or pre-systemic metabolism refers to *metabolism of a drug that occurs en route from the gut lumen to the systemic circulation.*

Some drugs, e.g. chlorpromazine and levodopa, are metabolised in the gut wall, but in most cases first-pass metabolism occurs in the liver. This is so complete with lignocaine and glyceryl trinitrate that bioavailability following oral administration is zero. However, drugs normally given orally can have extensive first-pass metabolism: e.g. propranolol is about 80% metabolised before it reaches the systemic circulation.

The importance of first-pass metabolism is twofold:

(1) It is a major reason for apparent differences in drug absorption between individuals. Even healthy people show considerable variation in liver metabolising capacity.

(2) In patients with severe liver disease, a far greater proportion of drugs that normally undergo extensive first-pass metabolism is absorbed *unchanged*. This is discussed in detail in Chapter 2.3.

1.3 PRINCIPLES OF DRUG DISTRIBUTION

Volume of distribution

Most drugs are not wholly confined to the blood but are distributed throughout the body to other tissues. Many factors determine the extent of distribution; the most important are:

The ability of a drug to cross lipid membranes. For example, drugs that are ionised at physiological pH tend to distribute poorly because ionisation tends to preclude passage across lipid membranes.

The extent of binding to plasma proteins. Drugs that are highly protein bound distribute less extensively than those with low binding.

A knowledge of the extent of drug distribution is important because:

(1) When a drug is extensively distributed outside the blood, it is not easily removed from the body by techniques such as haemodialysis, which remove drug from blood. For example, well over 95% of digoxin in the body is distributed outside the blood. Thus, if a person has taken an overdose of the drug there is no advantage in trying to speed elimination by dialysis.

(2) A drug that is distributed outside the circulation provides a reservoir from which the blood is continuously replenished as drug elimination from the body occurs. If this reservoir is large, i.e. distribution is extensive, fluctuations of drug concentration in blood are damped. In other words, swings from peak to trough concentration between doses are less dramatic than for drugs less widely distributed.

The extent of distribution is expressed in numerical terms as: *Apparent volume of distribution*, which is *the volume that would be occupied by the drug if all the drug in the body had the same concentration as the drug in blood.*

This is an *abstract* concept. Volumes of distribution often *far exceed* the total body volume because drug may be concentrated in certain tissues such as fat. However, it is useful to have a numerical means of describing the extent of distribution. Examples are shown in Table 1.2.

TABLE 1.2 Volumes of distribution of some commonly used drugs

Drug	Volume of distribution (litres/70 kg)
Nortriptyline	1200
Digoxin	600
Propranolol	250
Lignocaine	120
Phenytoin	40
Theophylline	25
Gentamicin	20
Warfarin	9
Tolbutamide	8

Protein binding

A proportion of any drug circulating in blood is usually attached by physicochemical forces to plasma proteins, and a proportion is free or unbound in solution. Only the unbound drug is available for pharmacological action at receptors. Protein binding becomes clinically important when it involves a high proportion, i.e. > 90% of drug in the blood. Drugs that are highly protein bound are listed in Table 1.3. One consequence of high protein binding is that it limits distribution of drug to other body tissues, as indicated above. A second consequence is that it limits the amount of free drug available for pharmacological effect, and clinically relevant effects may become apparent when the extent of binding is altered by:

Disease. Plasma proteins are altered both in quantity and chemical characteristics in renal and hepatic disease: there is a decrease in drug binding. This is discussed in Chapter 2.2 and 2.3.

TABLE 1.3 Drugs that are highly (> 90%) protein bound

Phenytoin	Frusemide
Tolbutamide	Warfarin
Diazoxide	Phenylbutazone
Propranolol	Chlorpromazine
Prazosin	Tricyclic antidepressants

Drugs competing for protein-binding sites. Theoretically competition for binding sites may result in an increase in the free concentration of one drug, but rapid redistribution and clearance of this fraction precludes the risk of toxicity.

The major plasma protein involved in drug binding has long been thought to be albumin. However, certain basic drugs also bind to alpha-1-acid glycoprotein, e.g. propranolol, prazosin and chlorpromazine. This is an acute phase protein whose concentration rises in acute inflammation with a resulting decrease in free-drug concentration. The clinical significance is uncertain.

1.4 PRINCIPLES OF DRUG ELIMINATION

Drug metabolism

Drugs are eliminated from the body by two principal mechanisms: (1) liver metabolism and, (2) renal excretion. Drugs that are already water soluble are generally excreted unchanged by the kidney. Lipid-soluble drugs are not easily excreted by the kidney because, following glomerular filtration, they are largely reabsorbed from the proximal tubule. The first step in the elimination of such lipid-soluble drugs is metabolism to more polar (water-soluble) compounds. This is achieved mainly in the liver, and generally occurs in two phases:

(1) Mainly oxidation (sometimes reduction or hydrolysis) to a more polar compound,

(2) Conjugation, usually with glucuronic or sulphuric acid.

Phase 1 metabolism

Oxidation can occur in various ways: hydroxylation, oxygenation at carbon, nitrogen or sulphur atoms, *N*- and *O*-dealkylation or deamination. These reactions are catalysed by the mixed function oxidases of the endoplasmic reticulum which comprise at least four types of enzymes: cytochrome P–450 and b5 with their corresponding reductases. The biochemistry of the mixed function oxidase system has not been fully elucidated. It is known, however, that there are multiple forms of cytochrome P–450, which can act on numerous substrates.

Phase 1 metabolites usually have only minor structural differences from the parent drug but may exhibit totally different pharmacological actions. For example, the aromatic hydroxylation of phenobarbitone abolishes its hypnotic activity, while metabolism of azathioprine produces the powerful antimetabolite 6-mercaptopurine.

Phase 2 reactions

These involve the addition of small endogenous molecules to the phase 1 metabolite, and almost always lead to abolition of pharmacological activity. Like phase 1 reactions, the liver is the major site but conjugation can occur in the gut wall where it can contribute to first-pass metabolism.

For most drugs, the rate of metabolism is directly proportional to the concentration of drug at the enzyme receptor site, and the concentration of drug in blood is proportional to the dose given. In these circumstances, elimination from the body is referred to as a first-order process. If the capacity of drug metabolising enzymes is exceeded, however, there is an accumulation of drug as elimination proceeds by a zero-order process. This implies that drug concentration in the blood increases out of proportion to increases in dose. Fortunately this occurs infrequently, the most important clinical example being the anticonvulsant phenytoin (p. 44). The enzymes that metabolise phenytoin can become saturated at therapeutic drug concentrations, and small increases in dose can produce large increases in phenytoin concentration. Therapeutic drug monitoring in these circumstances is vital (Chapter 5.1).

Metabolic drug interactions

The wide range of drugs metabolised by the mixed function oxidase system provides the opportunity for interactions of two types:

(1) *Induction.* Enzyme activity increases as the concentration of substrate increases. If two drugs which are metabolised by the same enzyme are given together, each can influence the metabolism of the other. For example, the anticonvulsants phenytoin, carbamazepine and phenobarbitone are all metabolised by the same enzymes that metabolise the constituents of oral contraceptives. If a woman receiving an oral contraceptive starts taking one of these