Lecture Notes on Clinical Pharmacology

THIRD EDITION

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Preface

Clinical pharmacology is a 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 optimize benefits and minimize 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 optimization of drug use.

For many years we have taught clinical pharmacology to medical practitioners and undergraduate students. We were persuaded by our students that there was a need for a brief, clearly written and up to date review of clinical pharmacology. *Lecture Notes on Clinical Pharmacology* was prepared to meet this need in 1981 and now enters its third edition. The book has been extensively revised and updated: several chapters have been re-written and a new chapter dealing with thrombolytic therapy has been added. We have not attempted to be comprehensive, but have tried to emphasize the principles of clinical pharmacology, areas which are developing rapidly and topics which are of particular clinical importance. The book is based on the 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 organizing 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.

Glasgow
April 1989

John Reid
Peter Rubin
Brian Whiting

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We owe a great debt of gratitude to Mrs Mary Wood, Miss Eleanor Newell and Miss Nan Scott for their considerable efforts in typing and collating the original text and revisions. Miss Randa Pharaon prepared the index. Mr Per Saugman, Mr Robert Campbell and Mr Nigel Palmer of Blackwell Scientific Publications have advised, guided and encouraged us throughout and to them we also offer our thanks.

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

John Reid
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Section 1

Chapter 1
Principles of Clinical Pharmacology

1.1 Principles of drug action
1.2 Principles of pharmacokinetics
1.3 Principles of drug elimination

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 dveloped. The chemical synthesis of agents with well characterized, specific actions on cellular mechanisms has led to the introduction of many powerful and effective drugs.

1.1 PRINCIPLES OF DRUG ACTION

Pharmacological agents are used in therapeutics to:

1 Cure disease:
   (a) Chemotherapy in cancer or leukaemia.
   (b) Antibiotics in specific bacterial infections.
2 Alleviate symptoms:
   (a) Antacids in dyspepsia.
   (b) Non-steroidal anti-inflammatory drugs in rheumatoid arthritis.
3 Replace deficiencies:
   Restoration of normal function by the replacement of a deficiency in an 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

Action on a receptor

A receptor is a specific macromolecule, usually a protein, to which a specific group of drugs or naturally occurring substances such as neurotransmitters or hormones can bind.

An *agonist* is a substance which stimulates or activates the receptor to produce an effect.

An *antagonist* prevents the action of an agonist but does not have any effect itself unless it also possess *partial agonist* activity.

The biochemical events which result from an agonist–receptor interaction and which produce an effect are still to be determined.

There are many types of receptors and in several cases subtypes have been identified which are also of therapeutic importance (Table 1.1).

Table 1.1 Some receptors involved in the action of commonly used drugs

Receptor	Subtype	Main actions of natural agonist	Drug agonist	Drug antagonist
Adrenoceptor	α_1	Vasoconstriction		Prazosin
	α_2	Hypotension, sedation	Clonidine	
	β_1	↑ Heart rate	Dopamine, Dobutamine	Atenolol Metoprolol
	β_2	Bronchodilation, Vasodilation, Uterine relaxation	Salbutamol, Terbutaline, Ritodrine	
Cholinergic	Muscarinic	↓ Heart rate ↑ Secretion ↑ Gut motility Bronchoconstriction		Atropine Benzotropine Orphenadrine Ipratropium
	Nicotinic	Contraction of striated muscle		Suxamethonium Tubocurarine
Histamine	H_1	Bronchoconstriction, Capillary dilation		Chlorpheniramine, terfenadine
	H_2	↑ Gastric acid		Cimetidine Ranitidine
Dopamine		CNS neurotransmitter	Bromocriptine	Chlorpromazine Haloperidol Thioridazine
Opioid		CNS neurotransmitter	Morphine, pethidine, etc.	Naloxone

Action on an enzyme

Enzymes, like receptors, are protein macromolecules with which substrates interact to produce activation or inhibition. Drugs in common clinical use which exert their effect through enzyme action generally do so by inhibition.

Digoxin inhibits the membrane bound Na^+/K^+ ATPase.

Aspirin inhibits platelet cyclo-oxygenase.

Captopril inhibits angiotensin converting enzyme.

Phenelzine inhibits monoamine oxidase.

Carbidopa inhibits decarboxylase

Allopurinol inhibits xanthine oxidase.

Drug receptor antagonists and enzyme inhibitors can act as *competitive, reversible, antagonists* or as *non-competitive irreversible antagonists*. The

duration of the effect of drugs of the latter type is much longer than that of the former. Effects of competitive antagonists can be overcome by increasing the dose of endogenous or exogenous agonist while effects of irreversible antagonists cannot usually be overcome.

Propranolol is a competitive beta-adrenoceptor antagonist used in hypertension and angina. Its effects last for hours and can be overcome by administering an appropriate dose of a beta-receptor agonist like isoprenaline.

Phenelzine is an irreversible non-competitive monoamine oxidase inhibitor used in depression. Its action and adverse effects may persist for 2 to 3 weeks.

Action on membrane ionic channels

The conduction of impulses in nerve tissues and electromechanical coupling in muscle depends on the movement of ions, particularly sodium, calcium and potassium, through membrane channels. Several groups of drugs interfere with these processes:

Antiarrhythmic drugs (Chapter 6).
Calcium slow channel antagonists (Chapter 8).
General and local anaesthetics (Chapter 18).
Anticonvulsants (Chapter 20).

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.

Dose–response relationship

Dose–response relationships in clinical practice rarely follow the classical sigmoid pattern of experimental studies. It is uncommon for the upper plateau or maximum effect to be reached in man or to be relevant therapeutically. Dose–response relationships may be steep or flat. The former implies a marked increase in response with modest increases in dose while the latter implies little increase in response over a wide dose range (Fig. 1.1).

The *potency* of a drug is relatively unimportant — what matters is its *efficacy* or the maximum effect that can be obtained.

In clinical practice the maximum therapeutic effect may often be unobtainable because of the appearance of adverse or unwanted effects: few, if any, drugs cause a single pharmacological response. The dose–adverse response relationship is often different in shape and position to that of the dose–therapeutic response relationship. The difference between the dose which will produce the desired effect and that which will cause adverse effects is called the *therapeutic index* and is a measure of the selectivity of a drug (Fig. 1.2).

The shape and position of *dose–response* curves in a group of patients is variable because of genetic, environmental and disease factors. But this variability is not solely an expression of differences in response to drugs. It has two important

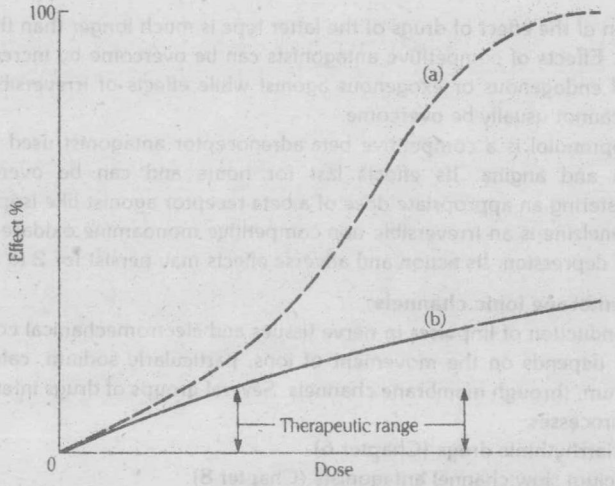

Fig. 1.1 Schematic examples of a drug (a) with a steep dose–response relationship in the therapeutic range, e.g. warfarin as an oral anticoagulant, and (b) a flat dose–response relationship within the therapeutic range, e.g. thiazide diuretics in hypertension.

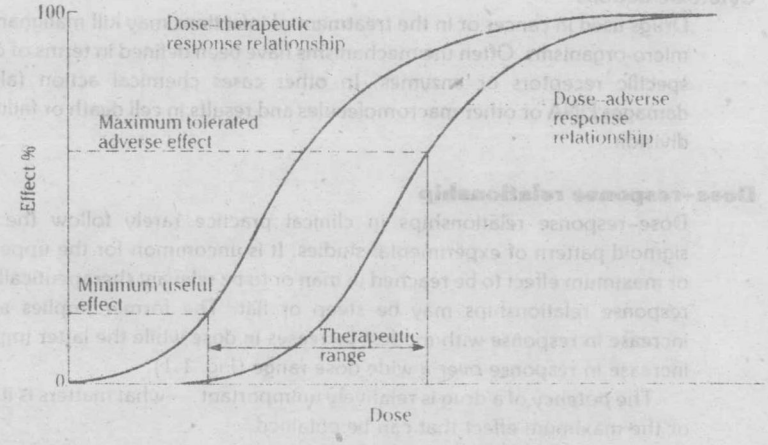

Fig. 1.2 Schematic diagram of the dose–response relationship for the desired effect (dose–therapeutic response) and for an undesired adverse effect. The therapeutic index is the extent of displacement of the two curves within the therapeutic dose range.

components, the *dose–plasma concentration* relationship and the *plasma concentration–effect* relationship:

Dose → Concentration → Effect

With the development of specific and sensitive chemical assays for drugs in body

fluids, it has been possible to characterize the dose–plasma concentration relationships in individual patients so that this component of the variability in response can be largely accounted for. This is *pharmacokinetics* (Chapter 1.2), and its application in clinical practice is *clinical pharmacokinetics* (Chapter 2). The residual variability in the dose–response relationship — characterized by the concentration–effect component — is a true expression of drug response, or in quantitative terms, a good measure of the *sensitivity* of a patient to a drug. This is the province of *pharmacodynamics* and the exploration of the factors which underlie the variability in both pharmacokinetics and pharmacodynamics is the basis of clinical pharmacology.

1.2 PRINCIPLES OF PHARMACOKINETICS

Clearance

When a drug is given continuously by intravenous infusion or repetitively by mouth, a balance is eventually achieved between input (dose rate) and output (the amount eliminated over a given period of time). This balance gives rise to a constant amount of drug in the body, reflected in the plasma as a *steady-state* concentration (Cp_{ss}). During a constant rate infusion the Cp_{ss} will remain constant; with repetitive oral dosing, it will fluctuate between peaks and troughs.

The relationship between Cp_{ss}, drug input and output can be written

$$Cp_{ss} = \frac{\text{input}}{\text{output}} = \frac{\text{dose rate}}{\text{clearance}} \qquad \text{(Eqn. 1.1)}$$

where 'clearance' is the net result of all eliminating processes, principally determined by the liver and/or kidneys. Since the dose rate has units of amount/time (e.g. mg/h) and Cp_{ss} has units of amount/volume (e.g. mg/l), clearance has units of volume/time, thus:

$$\text{Clearance} = \frac{\text{dose rate}}{Cp_{ss}} \qquad \text{(Eqn. 1.2)}$$

and represents the theoretical *volume* of fluid from which a drug is completely removed in a given period of time.

Clearance depends critically on the efficiency with which the liver and/or kidneys can eliminate a drug; it will vary in disease states which affect these organs. Equation 1.1 shows that the Cp_{ss} will vary inversely with clearance if the dose rate is not altered to compensate for a change in clearance. In stable clinical conditions, however, clearance remains *constant* and Eqn. 1.1 shows that the Cp_{ss} is directly proportional to dose rate. The important clinical implication is that if the dose rate is doubled, the Cp_{ss} doubles: if the dose rate is halved, the Cp_{ss} is halved. This is illustrated in Fig. 1.3. If each Cp_{ss} is plotted against its corresponding dose rate, the direct proportionality becomes obvious (Fig. 1.4) and the slope of the line (a constant) is the reciprocal of clearance (Cp_{ss}/dose rate). In pharmacokinetic terms, this is referred to as a first-order or linear process, and results from the fact that the *rate* of elimination is proportional to the amount of drug present in the body.

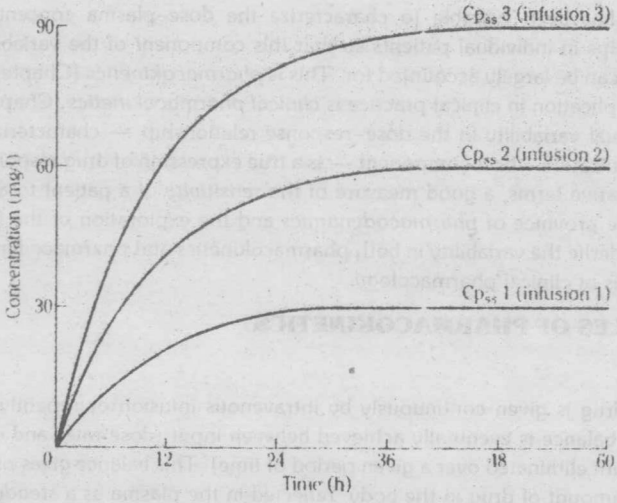

Fig. 1.3 Plots of concentration vs. time for three infusions allowed to reach steady-state. Infusion 2 is at a rate twice that of infusion 1. Infusion 3 is at a rate three times that of infusion 1. The three steady-state concentrations ($C_{p_{ss}}$ 1, 2 and 3) are directly proportional to the corresponding infusion rates.

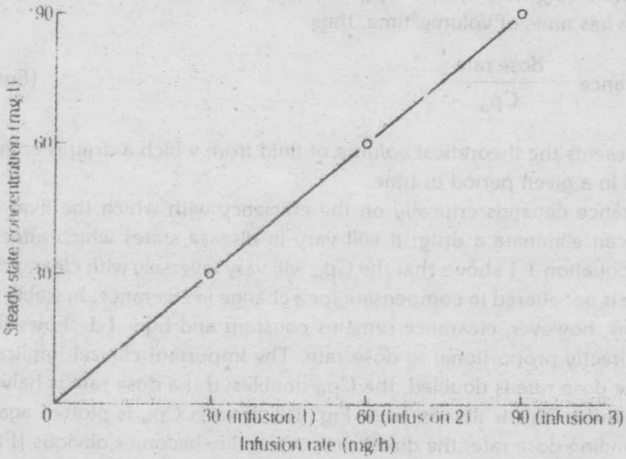

Fig. 1.4 Three steady-state concentrations plotted against corresponding infusion rates. The equation of the line is $Cp_{ss} = \frac{1}{Cl} \cdot$ infusion rate, so that the slope of the line is the reciprocal of clearance.

A constant rate intravenous infusion will clearly yield a constant Cp_{ss}, often referred to as the *average* steady-state plasma concentration. If a drug is administered orally at *regular* intervals, the *average* Cp_{ss} may be approximated by the concentration which is one-third of the way between a trough and a peak in any dosage interval.

Equation 1.1 also highlights the important fact if an estimate of clearance is available, it can be used to determine the maintenance dose rate for any desired Cp_{ss} thus,

$$\text{Dose rate} = \text{clearance} \times \text{desired } Cp_{ss} \qquad \text{(Eqn. 1.3)}$$

Volume of distribution

Once a drug has gained access to the bloodstream it is distributed to a greater or lesser extent to other tissues and the processes of metabolism and elimination begin. In the blood, a proportion of the drug is bound to plasma proteins — notably albumin. Only the unbound, or free, fraction distributes because the protein bound complex is too large to pass through all the membranes. Movement of the drug between the blood and other tissues proceeds until an equilibrium is established between the unbound drug in plasma and the drug in tissues. The volume of distribution, V, is conceived of as the volume of fluid into which a drug *apparently* distributes. If a drug was wholly confined to the plasma, then V would assume a value equal to that of the volume of the plasma — approximately 3 l in an adult. If on the other hand it was distributed throughout all body water, then V would have a value approximately 42 l. In reality, drugs are rarely distributed into volumes which have these precise physiological values. Indeed, some drugs have volumes of distribution far in excess of total body water and this emphasizes that distribution is not only a matter of dilution throughout fluid but also of sequestration or binding by various body tissues, for example, muscle and fat. The pK_a of a drug, its partition coefficient in fatty tissue and regional blood flow also play a part. Volume of distribution can vary, therefore, from relatively small values, e.g. an average of 0.14 l/kg body weight for aspirin to large values, e.g. an average of 7.0 l/kg body weight for digoxin (Table 1.2).

Table 1.2 Average volumes of distribution of some commonly used drugs

Drug	Volume of distribution (l/kg)
Nortriptyline	20
Digoxin	7
Propranolol	4
Lignocaine	1.5
Phenytoin	0.65
Theophylline	0.5
Gentamicin	0.23
Aspirin	0.14
Warfarin	0.1