CLINICAL PHARMACOLOGY AND THERAPEUTICS

Lecture Notes

Gerard A. McKay
Matthew R. Walters

9th Edition

LN

with self-assessment MCQs

WILEY-BLACKWELL

Clinical Pharmacology and Therapeutics

Lecture Notes

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Edited by

Gerard A. McKay

BSc (Hons) FRCP
Consultant Physician and Honorary Clinical Associate Professor
Glasgow Royal Infirmary and University of Glasgow

Matthew R. Walters

MD FRCP MSc
Professor of Clinical Pharmacology
Director, Clinical Pharmacology and Therapeutics
Institute of Cardiovascular and Medical Sciences
University of Glasgow

Ninth Edition

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The Atrium, Southern Gate, Chichester, West Sussex, PO19 8SQ, UK
111 River Street, Hoboken, NJ 07030-5774, USA

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Contributors

The following have contributed substantially to the writing, revision and rewriting of the chapters for this ninth edition.

Peter Higgins Institute of Cardiovascular and Medical Sciences, University of Glasgow
Chapter 1, Pharmacodynamics and pharmacokinetics

Jesse Dawson Institute of Cardiovascular and Medical Sciences, University of Glasgow
Chapter 2, Clinical trials and drug development

Beth Reed NHS Greater Glasgow and Clyde
Chapter 3, Drugs and gastrointestinal disease

Shona Jenkins NHS Greater Glasgow and Clyde
Chapter 4, Management of coronary artery disease and its complications
Chapter 5, Primary and secondary prevention of cardiovascular disease

Manish Patel NHS Lanarkshire
Chapter 6, Drugs used to treat respiratory disease

Edward Newman Institute of Neuroscience and Psychology, University of Glasgow
Chapter 7, Drugs used to treat neurological disease

Tom McPhee NHS Greater Glasgow and Clyde
Chapter 8, Treatment of psychiatric disorders

Andrew Seaton Brownlee Centre, Gartnavel General Hospital, Glasgow
Chapter 9, Antimicrobial therapy

Nick Kennedy NHS Lanarkshire
Chapter 10, HIV and antiretroviral treatment

Alisdair MacConnachie Brownlee Centre, Gartnavel General Hospital, Glasgow
Chapter 11, Travel medicine and tropical disease

David Carty Institute of Cardiovascular and Medical Sciences, University of Glasgow
Chapter 12, Drugs and endocrine disease

Claire Higgins School of Medicine, University of Glasgow
Chapter 13, Drugs and the reproductive system

Prabhakar Rajan Institute of Cancer Sciences, University of Glasgow
Chapter 14, Drugs and the urological system

Charles Gourlay University of Edinburgh
Chapter 15, Cancer therapeutics

Islay Morrison NHS Greater Glasgow and Clyde
Chapter 16, Drugs and inflammatory joint disease

Jagtar Nijjar Institute of Infection, Inflammation and Immunity, University of Glasgow
Chapter 17, Immunopharmacology

Nick Heaney Beatson Oncology Centre, Glasgow
Chapter 18, Drugs and the blood including anticoagulants and thrombolytic drugs

Rachel Harrison NHS Greater Glasgow and Clyde
Chapter 19, Drugs used for pain relief and anaesthesia

Kathleen Collins NHS Greater Glasgow and Clyde
Chapter 22, Prescribing for the young and the elderly

Shazya Huda NHS Greater Glasgow and Clyde
Chapter 23, Drugs in pregnant and breastfeeding women

Ailsa Brown Scottish Medicines Consortium
Chapter 24, Pharmacoeconomics

Kenneth Paterson Scottish Medicines Consortium
Chapter 24, Pharmacoeconomics: the economic evaluation of new drugs

Iain Keith NHS Greater Glasgow and Clyde
Chapter 26, Drugs you may need in a hurry

Preface

The ability to use drugs safely and effectively is a defining characteristic of a good doctor. This ability is predicated upon an up-to-date knowledge of the ever-expanding pharmacopeia available to modern clinicians. In recent years the advent of translational and stratified approaches to the development of new medicines has accelerated the pace of change and resulted in a profusion of new knowledge across a wide range of therapeutic areas.

The extensive changes made to the text of this the ninth edition of *Clinical Pharmacology and Therapeutics Lecture Notes* reflect the enormous progress made in recent years. The new edition has been extensively revised and updated with significantly expanded sections covering areas which are developing rapidly such as immunopharmacology and cancer therapeutics. A particular emphasis has been placed upon practical aspects and clinical relevance throughout each chapter. Although the content of the text has been revised and refreshed, the objective of this book remains as set out in the preface to its first edition more than 30 years ago: to provide a brief, clearly written and up-to-date review of clinical pharmacology. As in earlier editions we have not attempted to be comprehensive, but have tried to emphasise the principles of clinical pharmacology, and topics which are of particular clinical importance.

Recognition of the importance of prescribing skills has prompted a focus on their assessment in UK medical schools. Key prescribing points are emphasised in each chapter, and a series of questions covering commonly examined topics is included to allow self-assessment.

This is the first edition of *Clinical Pharmacology and Therapeutics Lecture Notes* to have been prepared without Professor John Reid, former Regius Professor of Medicine and Therapeutics at the University of Glasgow. John's immense contribution to Clinical Pharmacology extends far beyond his founding role and expert stewardship of this textbook over decades. Both of the current Editors gratefully acknowledge his expert mentorship and guidance which continues to influence the preparation of this text. We hope that the ninth edition will continue to succeed in the provision of a clear understanding not only of how but also when to use drugs.

Gerry McKay
Matthew Walters
Glasgow

Foreword

Over 30 years ago we were (then) three young clinical academics responsible for teaching medical students to prescribe medicines at one of the UK's largest medical schools.

The curriculum at the time consisted of two years of preclinical teaching – mainly anatomy, physiology, biochemistry and pharmacology – increasingly delivered by non-clinicians. From the third year, students were based in hospital and through a four-term course of weekly lectures and seminars were introduced to applied or clinical pharmacology and therapeutics.

By the late 1970s, in recognition of the dramatic developments and innovation in drugs available, our programme aimed to close the gap between the basic scientific principles of drug action and practical therapeutics at the bedside or in the clinic. As we said in the Preface to the first edition '… clinical pharmacology has as its primary aim the promotion of safe and effective drug use: to optimise benefits and minimise risks' – an update on the classical objective 'primum non nocere' or 'firstly do no harm'!

The second half of the twentieth century had been a bonanza period for drug discovery. Understanding of basic physiological mechanisms and insights into pathology led to screening and testing of small molecules which had specific (or relatively specific) interactions with cellular processes: beta blockers for heart disease, antibiotics and effective anticancer drugs became available.

It became easier to demonstrate efficacy and possible to confirm profiles of adverse side effects.

The potential for serious harm (for example birth defects after thalidomide) led internationally to rigorous protocols to establish efficacy and safety not only for new drugs but also long available remedies with little or no evidence of usefulness (or safety).

In the 1970s, we felt that the available textbooks to support student learning were less than optimal. In Glasgow, staff had been preparing their own 'lecture notes' for individual lectures. These were generally very popular with the students and largely replaced textbooks in this area. These notes were usually two or three pages of summary information but were individually prepared by lecturers and varied greatly in quality as well as length. In addition, the preparation and copying of several pages of notes for over 200 students – before the widespread availability of photocopiers – was a major task for the secretarial support staff!

Following encouragement from our students we explored alternative means of making the notes available. The obvious approach was to publish and the most obvious vehicle to us was the already existing and popular series of *Lecture Notes* published by Blackwell Scientific Publications, a series which already included a successful *Lecture Notes on Pharmacology* by J.H. Burn. We were encouraged by Blackwell to prepare a book based on the notes for students prepared by us and our colleagues. This manuscript became the first edition of *Lecture Notes in Clinical Pharmacology* in 1981

We have been very fortunate in the enormous help and support we have had over the years. In the early days most of the contributions both in writing specialist chapters and reviewing draft texts came from colleagues in Glasgow, often those individuals who gave the lectures to our students. As time has passed, with retirements and promotions/transfers, we have broadened the specialties and locations of our collaborators.

Time has also taken a toll on the editorial team. For this edition, although none of the original team is directly involved, we have all taken a close interest in the contents, particularly the newer styles and approaches to learning in the electronic age.

As we noted in the Prefaces to earlier editions 'whether learning is problem based or more traditional, it must be underpinned by a clear understanding of the principles of the pathophysiology of disease, the molecular mechanisms of drug action in humans and an appreciation of drug therapy in the context of overall health care' The style and innovative layout of this book provides the core information and encourages self learning.

We strongly believe that the book now named *Clinical Pharmacology and Therapeutics Lecture Notes* continues, as we have believed for over 30 years, to 'provide a clear understanding not only of how but also when to use drugs'.

John Reid
Peter Rubin
Brian Whiting

Part 1

Principles of clinical pharmacology

1

Pharmacodynamics and pharmacokinetics

Clinical scenario

A 50-year-old obese man with type 2 diabetes, hypertension and hyperlipidaemia has made arrangements to see his general practitioner to review his medications. He is on three different drugs for his diabetes, four different anti-hypertensives, a statin for his cholesterol and a dispersible aspirin. These medications have been added over a period of 2 years despite him not having any symptoms and he feels that if anything they are giving him symptoms of fatigue and muscle ache. He has also read recently that aspirin may actually be bad for patients with diabetes. He is keen to know why he is on so many medications, if the way he is feeling is due to the medications and whether they are interfering with the action of each other. What knowledge might help the general practitioner deal with this?

KEY POINTS – WHAT IS PHARMACODYNAMICS AND PHARMACOKINETICS?

- The variability in the relationship between dose and response is a measure of the sensitivity of a patient to a drug. This has two components: dose – concentration and concentration – effect
- The latter is termed **pharmacodynamics**. The description of a drug concentration profile against time is termed **pharmacokinetics**
- In simple terms pharmacodynamics is what the drug does to the individual taking it and pharmacokinetics what the individual does to the drug
- Clinical pharmacology seeks to explore the factors that underlie variability in pharmacodynamics and pharmacokinetics for the optimization of drug therapy in individual patients

Introduction

A basic knowledge of the mechanism of action of drugs and how the body deals with drugs allows the clinician to prescribe safely and effectively. Prior to the twentieth century prescribing medication was based on intelligent observation and folklore with medical practices depending largely on the administration of mixtures of natural plant or animal substances. These preparations contained a number of pharmacologically active agents in variable amounts (e.g. powdered bark from the cinchona tree, now known to contain quinine, being used by natives of Peru to treat 'fevers' caused by malaria).

During the last 100 years an increased understanding has developed of biochemical and pathophysiological factors that influence disease. The chemical synthesis of agents with well-characterised and specific actions on cellular mechanisms has led to the introduction of many powerful and effective drugs. Additionally, advances in the detection of these compounds in body fluids have facilitated investigation into the relationships between the dosage regimen, the profile of drug concentration against time in body fluids, notably the plasma, and corresponding profiles of clinical effect. Knowledge of this concentration–effect relationship, and the factors that influence drug concentrations, underpin early stages of the drug development process.

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More recently the development of genomics and proteomics has provided additional insights and opportunities for drug development with new and more specific targets. Such knowledge will replace the concept of one drug and/or one dose fitting all.

Principles of drug action (pharmacodynamics)

Pharmacological agents are used in therapeutics to:

1 Alleviate symptoms, for example:
   - Paracetamol for pain
   - GTN spray for angina
2 Improve prognosis – this can be measured in number of different ways – usually measured as a reduction in morbidity or mortality, for example:
   - Prevent or delay end stage consequences of disease, e.g. anti-hypertensive medication and statins in cardiovascular disease, levodopa in Parkinson's disease
   - Replace deficiencies, e.g. levothyroxine in hypothyroid
   - Cure disease, e.g. antibiotics, chemotherapy

Some drugs will both alleviate symptoms and improve prognosis, e.g. beta-blockers in ischaemic heart disease. If a prescribed drug is doing neither one must question the need for its use and stop it. Even if there is a clear indication for use the potential for side effects and interactions with any other drugs the patient is on also needs to be taken into account.

Mechanism of drug action

Action on a receptor

A receptor is a specific macromolecule, usually a protein, situated either in cell membranes or within the cell, to which a specific group of ligands, drugs or naturally occurring substances (such as neurotransmitters or hormones), can bind and produce pharmacological effects. There are three types of ligands: agonists, antagonists and partial agonists.

An **agonist** is a substance that stimulates or activates the receptor to produce an effect, e.g. salbutamol at the β_2-receptor.

An **antagonist** prevents the action of an agonist but does not have any effect itself, e.g. losartan at the angiotensin II receptor.

A **partial agonist** stimulates the receptor to a limited extent, while preventing any further stimulation by naturally occurring agonists, e.g. aripiprazole at the D2 and 5-HT1A receptors.

The biochemical events that result from an agonist–receptor interaction to produce an effect are complex. There are many types of receptors and in several cases subtypes have been identified which are also of therapeutic importance, e.g. α and β-adrenoceptors and nicotinic and muscarinic cholinergic receptors.

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, for example:

1 Aspirin inhibits platelet cyclo-oxygenase
2 Ramipril inhibits angiotensin-converting enzyme

Drug receptor antagonists and enzyme inhibitors can act as competitive, reversible antagonists or as non-competitive, irreversible antagonists. Effects of competitive antagonists can be overcome by increasing the dose of endogenous or exogenous agonists, while effects of irreversible antagonists cannot usually be overcome resulting in a longer duration of the effect.

Action on membrane ionic channels

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

1 Nifedipine inhibits the transport of calcium through the slow channels of active cell membranes
2 Furosemide inhibits Na/K/Cl co-transport in the ascending limb of the loop of Henle

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 may be steep or flat. A steep relationship implies that small changes in dose will produce large changes in clinical response or adverse effects, while flat relationships imply that increasing the dose will offer little clinical advantage (Figure 1.1).

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 effect.

The concentration–adverse response relationship is often different in shape and position to that of the concentration–therapeutic response relationship. The difference between the concentration that produces the desired effect and the concentration that causes adverse effects is called the therapeutic index and is a measure of the selectivity of a drug (Figure 1.2).

The shape and position of dose–response curves for a group of patients is variable because of genetic, environmental and disease factors. However, this variability is not solely an expression of differences in response to drugs. It has two important 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 characterise dose–plasma concentration relationships so that this component of the variability in response can be taken into account when drugs are prescribed for patients with various disease states. For drugs with a narrow therapeutic index it may be necessary to measure plasma concentrations to assess the relationship between dose and concentration in individual patients (see Chapter 20 Therapeutic Drug Monitoring)

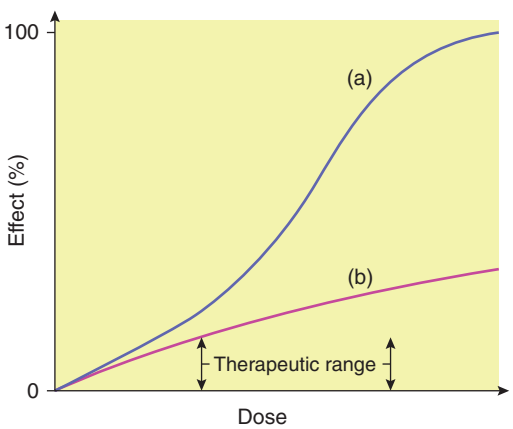

Figure 1.1 Schematic examples of a drug (a) with a steep dose– (or concentration–) response relationship in the therapeutic range, e.g. warfarin an oral anticoagulant; and (b) a flat dose– (or concentration–) response relationship within the therapeutic range, e.g. thiazide diuretics in hypertension.

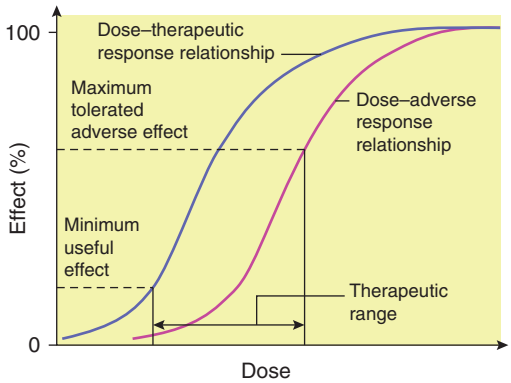

Figure 1.2 Schematic diagram of the dose–response relationship for the desired effect (dose–therapeutic response) and for an undesired adverse effect. The therapeutic index is the extent of displacement of the two curves within the normal dose range.

Principles of pharmacokinetics

Absorption

Drug absorption after oral administration has two major components: absorption rate and bioavailability. Absorption rate is controlled partially by the physicochemical characteristics of the drug but in many cases is modified by the formulation. A reduction in absorption rate can lead to a smoother concentration–time profile with a lower potential for concentration-dependent adverse effects and may allow less frequent dosing.

Bioavailability is the term used to describe the fraction of the dose that is absorbed into the systemic circulation. It can range from 0 to 100% and depends on a number of physicochemical and clinical factors. Low bioavailability may occur if the drug has low solubility or is destroyed by the acid in the stomach. Changing the formulation can affect the bioavailability of a drug and it can also be altered by food or the co-administration of other drugs. For example,

antacids can reduce the absorption of quinolone antibiotics, such as ciprofloxacin, by binding them in the gut. Other factors influencing bioavailability include metabolism by gut flora, the intestinal wall or the liver.

First-pass metabolism refers to metabolism of a drug that occurs en route from the gut lumen to the systemic circulation. For the majority of drugs given orally, absorption occurs across the portion of gastrointestinal epithelium that is drained by veins forming part of the hepatoportal system. Consequently, even if they are well absorbed, drugs must pass through the liver before reaching the systemic circulation. For drugs that are susceptible to extensive hepatic metabolism, a substantial proportion of an orally administered dose can be metabolised before it ever reaches its site of pharmacological action, e.g. insulin metabolism in the gut lumen is so extensive that it renders oral therapy impossible.

The importance of first-pass metabolism is twofold:

1. It is one of the reasons for apparent differences in drug bioavailabilty between individuals. Even healthy people show considerable variation in liver metabolising capacity
2. In patients with severe liver disease first-pass metabolism may be dramatically reduced, leading to the appearance of greater amounts of active drug in the systemic circulation

Distribution

Once a drug has gained access to the bloodstream it begins to distribute to the tissues. The extent of this distribution depends on a number of factors including plasma protein binding, lipid solubility and regional blood flow. The volume of distribution, V_D, is the *apparent volume* of fluid into which a drug distributes based on the *amount* of drug in the body and the *measured concentration* in the plasma or serum. If a drug was wholly confined to the plasma, V_D would equal the plasma volume – approximately 3 L in an adult. If, on the other hand, the drug was distributed throughout the body water, V_D would be approximately 42 L. In reality, drugs are rarely distributed into physiologically relevant volumes. If most of the drug is bound to tissues, the plasma concentration will be low and the apparent V_D will be high, while high plasma protein binding will tend to maintain high concentrations in the blood and a low V_D will result. For the majority of drugs, V_D depends on the balance between plasma binding and sequestration or binding by various body tissues, for example, muscle and fat. Volume of distribution can therefore vary considerably.

Clinical relevance of volume of distribution

Knowledge of volume of distribution (V_D) can be used to determine the size of a *loading dose* if an immediate response to treatment is required. This assumes that therapeutic success is closely related to the plasma concentration and that there are no adverse effects if a relatively large dose is suddenly administered. It is sometimes employed when drug response would take many hours or days to develop if the regular maintenance dose was given from the outset, e.g. digoxin.

In practice, weight is the main determinant to calculating the dose of a drug where there is a narrow therapeutic index.

Plasma protein binding

In the blood, a proportion of a drug is bound to plasma proteins – mainly albumin (acidic drugs) and α_1-acid glycoprotein (basic drugs). Only the unbound, or free, fraction distributes because the protein-bound complex is too large to pass through membranes. It is the unbound portion that is generally responsible for clinical effects – both the target response and the unwanted adverse effects. Changes in protein binding (e.g. resulting from displacement interactions) generally lead to a transient increase in free concentration but are rarely clinically relevant. However, a lower total concentration will be present and the measurement might be misinterpreted if the higher free fraction is not taken into account. This is a common problem with the interpretation of phenytoin concentrations, where free fraction can range from 10% in a normal patient to 40% in a patient with hypoalbuminaemia and renal impairment.

Clearance

Clearance is the sum of all drug-eliminating processes, principally determined by hepatic metabolism and renal excretion. It can be defined as the theoretical volume of fluid from which a drug is completely removed in a given period of time.

When a drug is administered continuously by intravenous infusion or repetitively by mouth, a balance is eventually achieved between its input (dosing rate) and its output (the amount eliminated over a given period of time). This balance gives rise to a constant amount of drug in the body which depends on the dosing rate and clearance. This amount is reflected in the plasma or serum as a steady-state

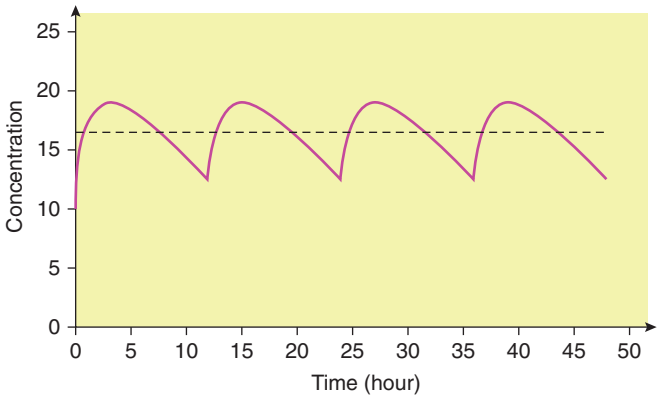

Figure 1.3 Steady-state concentration–time profile for an oral dose (—) and a constant rate intravenous infusion (- - - - -).

concentration (*C*ss). A constant rate intravenous infusion will yield a constant *C*ss, while a drug administered orally at regular intervals will result in fluctuation between peak and trough concentrations (Figure 1.3).

Clearance depends critically on the efficiency with which the liver and/or kidneys can eliminate a drug; it will vary in disease states that affect these organs, or that affect the blood flow to these organs. In stable clinical conditions, clearance remains constant and is directly proportional to dose rate. The important implication is that if the dose rate is doubled, the $Css_{average}$ doubles: if the dose rate is halved, the $Css_{average}$ is halved for most drugs. 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.

Single intravenous bolus dose

A number of other important pharmacokinetic principles can be appreciated by considering the concentrations that result following a single intravenous bolus dose (see Figure 1.4) and through a number of complex equations the time at which steady state will be achieved after starting a regular treatment schedule or after any change in dose can be predicted.

As a rule, in the absence of a loading dose, steady state is attained after four to five half-lives (Figure 1.5).

Furthermore, when toxic drug levels have been inadvertently produced, it is very useful to estimate how long it will take for such levels to reach the therapeutic range, or how long it will take for the entire drug to be eliminated once the drug has been stopped. Usually, elimination is effectively complete after four to five half-lives (Figure 1.6).

The elimination half-life can also be used to determine dosage intervals to achieve a target

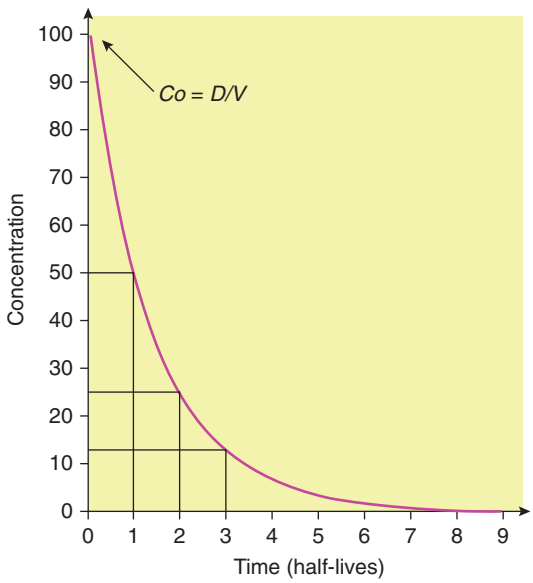

Figure 1.4 Plot of concentration versus time after a bolus intravenous injection. The intercept on the y- (concentration) axis, C_0, is the concentration resulting from the instantaneous injection of the bolus dose.

concentration–time profile. For example, in order to obtain a gentamicin peak of 8 mg/L and a trough of 0.5 mg/L in a patient with an elimination half-life of 3 hours, the dosage interval should be 12 hours. (The concentration will fall from 8 mg/L to 4 mg/L in 3 hours, to 2 mg/L in 6 hours, to 1 mg/L in 9 hours and to 0.5 mg/l in 12 hours.) However, for many drugs, dosage regimens should be designed to maintain concentrations within a range that avoids high (potentially toxic) peaks or low, ineffective troughs. Excessive fluctuations in the concentration–time profile can be prevented by giving the drug at intervals of less than one half-life or by using a slow-release formulation.

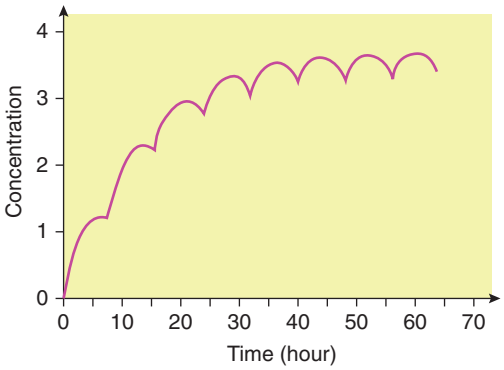

Figure 1.5 Plot of concentration versus time illustrating the accumulation to steady state when a drug is administered by regular oral doses.

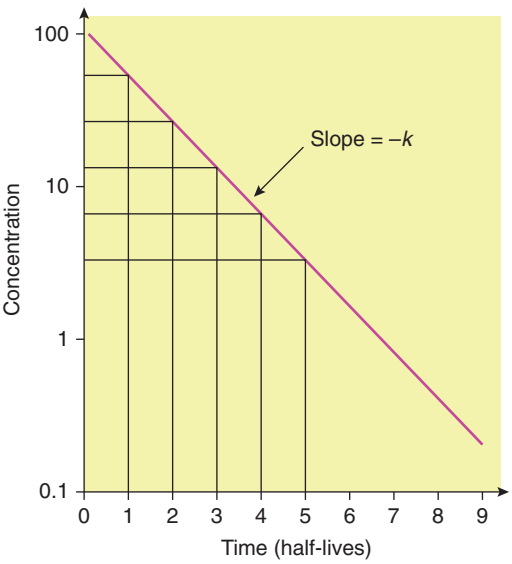

Figure 1.6 Semi-logarithmic plot of concentration versus time after a bolus intravenous injection. The slope of this line is –k; the elimination rate constant and the elimination half-life of the drug can be determined from such a plot by noting the time at which the concentration has fallen to half its original value.

Linear versus non-linear kinetics

In the discussion on clearance, it was pointed out that the hallmark of linear pharmacokinetics is the proportionality between dose rate and steady-state concentration. This arises because the rate of elimination is proportional to the amount of drug in the body, while the clearance remains constant. This is not, however, always the case for a few drugs such as phenytoin, alcohol and heparin. When the enzymes responsible for metabolism reach a point of saturation, the rate of elimination, in terms of amount of drug eliminated in a given period of time, does not increase in response to an increase in concentration (or an increase in the amount of drug in the body) but becomes constant. This gives rise to non-linear or zero-order kinetics.

The clinical relevance of non-linear kinetics is that a small increase in dose can lead to a large increase in concentration. This is particularly important when toxic side effects are closely related to concentration, as with phenytoin.

Principles of drug elimination

Drug metabolism

Drugs are eliminated from the body by two principal mechanisms: (i) liver metabolism and (ii) 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, but can also occur in the gut and may contribute to first-pass elimination. Metabolism generally occurs in two phases:

Phase 1 – Mainly oxidation, but also reduction or hydrolysis to a more polar compound: ***Oxidation*** can occur in various ways at carbon, nitrogen or sulphur atoms and N- and O-dealkylation. These reactions are catalysed by the cytochrome P450-dependent system of the endoplasmic reticulum. Knowledge of P450, which exists as a superfamily of similar enzymes (isoforms), has increased greatly recently and is divided into a number of families and subfamilies. Although numerous P450 isoforms are present in human tissue, only a few of these have a major role in the metabolism of drugs. These enzymes, which display distinct but overlapping substrate specificity, include CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A4. Induction or inhibition of one or more of these enzymes may form the basis of clinically relevant drug interactions. Phase 1 metabolites usually have only minor structural differences from the parent drug,

but may exhibit totally different pharmacological actions. For example, the metabolism of azathioprine produces the powerful antimetabolite 6-mercaptopurine.

Phase 2 – Conjugation usually by glucoronidation or sulphation to make the compound more polar: This involves the addition of small endogenous molecules to the parent drug, or to its phase 1 metabolite, and almost always lead to abolition of pharmacological activity. Multiple forms of conjugating enzymes are also known to exist, although these have not been investigated to the same extent as the P450 system.

Metabolic drug interactions

The wide range of drugs metabolised by the P450 system provides the opportunity for interactions of two types, namely enzyme induction and inhibition.

Clinical scenario

A 24-year-old woman goes to a family planning clinic for advice about contraception. The patient has a history of epilepsy which is stable on carbamazepine 200 mg bd. What options are available to the general practitioner?

Induction

Enzyme induction, which may be defined as the increase in amount and activity of drug-metabolising enzymes, is a consequence of new protein synthesis resulting from prolonged exposure to the inducing drug. While a drug may induce its own metabolism, it can also accelerate the metabolism and clearance of unrelated compounds. Many compounds are known to act as enzyme inducers in animals at toxicological dose levels, but relatively few drugs produce clinically significant induction in humans when used at therapeutic dose levels. For practical purposes anticonvulsants (carbamazepine, phenytoin) and rifampicin are the most potent enzyme inducers in clinical use and have produced numerous clinically significant drug interactions, related primarily to increases in the metabolism of CYP2C9, CYP2C19 and CYP3A4 substrates (including for example oestrogen and progesterone, the constituents of a combined oral contraceptive pill). Enzyme induction is not, however, limited to administration of prescription drugs. St John's wort, a herbal remedy, can also cause enzyme induction as can cigarette smoking (induction of CYP1A2 substrates, e.g. theophylline) and ethanol (induction of CYP2E1 but unlikely to be clinically relevant).

KEY POINTS – ENZYME INDUCTION AND INHIBITION

Enzyme induction produces clinical changes over days or weeks, but the effects of enzyme inhibition are usually observed immediately. In most circumstances, these changes are manifest as:

- Therapeutic failure resulting from induction
- Adverse effects resulting from inhibition

Clinical relevance occurs when drug therapy needs to be altered to avoid the consequences of the drug interaction and this is most common and most serious in compounds that have a narrow therapeutic index.

Clinical scenario

A 58-year-old man with chronic obstructive pulmonary disease is admitted to hospital with an infective exacerbation. He is on three different inhalers and additionally takes simvastatin for hypercholesterolaemia. He is allergic to penicillin. The admitting doctor prescribes nebulised salbutamol, prednisolone and clarithromycin along with the patient's usual medications. The next day the patient complains of general aches and pains. Could this be due to a drug interaction?

Inhibition

Concurrently administered drugs can also lead to inhibition of enzyme activity, with many P450 inhibitors showing considerable isoform selectivity. Some of the most clinically relevant inhibitors are listed in Table 1.1, together with the isoform inhibited. In some cases this can lead to potentially dangerous adverse events, e.g ketoconazole decreases the metabolism of the CYP3A4 substrate, terfenadine, leading to QT interval prolongation and torsades de pointes.

As with induction, P450 inhibition is not limited to drug administration. Grapefruit juice is an inhibitor of CYP3A4 activity and produces clinically significant interactions with a number of drugs, including midazolam, simvastatin and terfenadine. This type of information, together with some knowledge of the enzymes involved in a particular drug's clearance, makes it much easier to understand and predict drug interactions.

Clearly, pronounced enzyme inhibition, which may result in plasma concentrations of the inhibited

Table 1.1 P450 inhibitors involved in drug interactions.

Major human P450s	Typical inhibitors
CYP1A2	Furafylline, fluvoxamine, ciprofloxacin
CYP2C9	Fluconazole, ketoconazole, sulfaphenazole
CYP2C19	Omeprazole, ketoconazole, cimetidine
CYP2D6	Quinidine, fluoxetine, ritonavir
CYP2E1	Disulfiram
CYP3A4	Ketoconazole, itraconazole, ritonavir, clarithromycin, diltiazem

drug being many times higher than intended, can be a major safety issue. For example, co-administration of ketoconazole or ritonavir with the hypnotic drug midazolam increases the midazolam plasma exposure (AUC – area under the curve) by 15–20 times, a situation which should be avoided.

Genetic factors in metabolism

The rate at which healthy people metabolise drugs is variable. Although part of this variability is a consequence of environmental factors, including the influence of inducers and inhibitors, the main factor contributing to interindividual variability in metabolism is the underlying genetic basis of the drug-metabolising enzymes. Although there is probably a genetic component in the control of most P450 enzymes, some enzymes (e.g. CYP2C19 and CYP2D6) actually show genetic polymorphism. This results in distinct subpopulations of poor and extensive metabolisers, where the poor metabolisers are deficient in that particular enzyme. There are a number of enzymes under polymorphic control and some clinically important examples are shown in Table 1.2. As with enzyme inhibition, genetic polymorphism is primarily a concern for drugs that have a narrow therapeutic index and that are metabolised largely by a single polymorphic enzyme. In such cases, the phenotype of the patient should be determined and lower doses of the drug used, or alternative therapy should be considered.

Renal excretion

Three processes are implicated in renal excretion of drugs:

1. *Glomerular filtration*: This is the most common route of renal elimination. The free drug is cleared by filtration and the protein-bound drug remains in the circulation where some of it dissociates to restore equilibrium.
2. *Active secretion in the proximal tubule*: Both weak acids and weak bases have specific secretory sites in proximal tubular cells. Penicillins are eliminated by this route, as is about 60% of procainamide.
3. *Passive reabsorption in the distal tubule*: This occurs only with un-ionised, i.e. lipid-soluble, drugs. Urine pH determines whether or not weak acids and bases are reabsorbed, which in turn determines the degree of ionisation.

If renal function is impaired, for example by disease or old age, then the clearance of drugs that normally undergo renal excretion is decreased.

Table 1.2 Major enzymes displaying genetic polymorphism.

Enzyme	Typical substrates	Characteristics
CYP2C19	*(S)*-Mephenytoin, diazepam, omeprazole	About 2–5% of white people are poor metabolisers, but 18–23% of Japanese people have this phenotype
CYP2D6	Propafenone, flecainamide, desipramine	About 7% of white people are poor metabolisers, but this frequency is only about 2% in black Americans and <1% in Japanese/Chinese
N-Acetyl-transferase	Hydralazine, sulphonamides, isoniazid, procainamide	About 50% of white people are slow acetylators

2

Clinical trials and drug development

Clinical scenario

A chemist in a major pharmaceutical company has been performing research into a compound that appears to provide neuronal protection from ischaemia in *in vitro* models. This discovery has caused some excitement – if it is shown to have efficacy in humans then it might be a useful treatment for patients with acute stroke. What are the various stages that this compound has to go through in development before it can be licensed as a drug to be used in patients?

KEY POINTS

- Many compounds are screened as potential drugs but few make it through to being used in patients
- Drug development is a lengthy process with high costs, particularly in the later stages
- Rigorous regulatory requirements have to be met before a drug can be tested in humans
- To get a licence a drug has to be shown to be safe and efficacious

Introduction

Drug regulation in the UK and elsewhere arose following the use of thalidomide in the late 1950s and early 1960s. Thalidomide was marketed as a sedative that had little hangover effect, and was also used in treatment of morning sickness in pregnancy. In 1961 it became clear that thalidomide use in early pregnancy resulted in the congenital defect phocomelia, where the long bones of the fetus fail to develop properly. This resulted in the formation of the Committee on Safety of Drugs and the passing of the Medicines Act in 1968, providing for a system of licensing affecting manufacture, sale, supply and importation of medicinal products into the UK. Drug regulation in the UK was initially under the control of the Medicines Control Agency. This was merged in 2003 with the Medical Devices Agency to form the Medicines and Healthcare products Regulatory Agency (MHRA). Other countries in Europe had similar systems to regulate drug development and as early as 1965 there was a European directive to try and harmonise the processes within Europe. This has now evolved and European legislation now takes precedence over the Medicines Act. The MHRA contributes to the work of the European Medicines Agency (EMA). At a European level, new drugs can now either be reviewed and licensed across all members states simultaneously, i.e. in partnership, or the drug can get a licence from one member state first, and undergo a shortened 'mutual recognition' review and approval in the other member states.

Developing a new drug takes, in general, more than 10 years from patent filing, through the development process to marketing. There are many stages that a drug has to go through to be approved for use. Many drugs will enter development but few will reach the end of the process and gain regulatory approval. Even then approximately only one in seven new products will become a commercial success, recouping the investment in its development. Once a drug is licensed for use there are means by which the safety in the longer term can be monitored. With the increasing complexity of diseases, society and drug development the pharmaceutical companies

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are moving towards alternative research strategies, such as translational research, to try and improve the speed by which drugs make it from 'bench to bedside'.

Drug development and regulation

Combinatorial chemistry, involving the rapid synthesis and computer simulation of a large number of different but structurally related molecules, has allowed pharmaceutical research companies to routinely produce and screen tens of thousands of compounds each year. This library of compounds can be tested for specific activities, using high-throughput screening techniques providing the starting point for taking promising compounds forward to the more traditional preclinical and animal studies. This approach has been embraced by pharmaceutical research companies as a means of increasing the productivity of drug development. In general, this has meant a move away from a serendipitous approach to drug discovery to a more focused one.

Preclinical studies

Preclinical studies include in vitro studies and animal studies that are designed to find out if a drug is likely to be useful before any testing in humans is done.

In vitro studies

Drugs can now be assessed relatively extensively by in vitro work using cell cultures, bacteria, enzymes, isolated tissues and perfused organ systems. Additionally certain aspects of drug development that traditionally have been tested in healthy volunteers, such as drug interactions in the liver, can now be largely tested using cell cultures, so even when a drug moves into clinical testing, in vitro work still has an ongoing role.

Animal studies of efficacy and toxicity

New chemical entities are tested in animals to look for desirable pharmacological effects and to assess toxic effects. Acute and in most cases chronic toxicity studies will be carried out in animals, using increasing doses, until clear toxic effects are noted, including a proportion of the animals dying. These studies provide 'pointers' to focus the safety assessments in human studies. In Europe the guidelines require that the toxic effects of the drug should be assessed in two mammalian species (one non-rodent) over 2 weeks of dosing before a single dose is administered to a human (see later). In addition, mutagenicity, carcinogenicity and the impact of drugs on reproduction will be assessed and pharmacokinetic studies in animals can be used to help predict the doses needed when the drug is first used in humans.

Clinical trials

Clinical trials have to be performed under highly regulated processes in order to minimise the risk to participants. This principle of protecting the rights of the trial subjects comes from the Declaration of Helsinki (initially agreed by the World Medical Association in 1964, with six revisions since, the last being in October 2008). The International Conference on Harmonization (ICH) is a project that brings together the regulatory authorities of the three main regions, Europe, Japan and the United States, with the aim of producing common guidelines relating to quality, e.g. manufacturing, safety and efficacy requirements. Their Good Clinical Practice Guidelines were established to provide a unified standard for the three major regions undertaking clinical trials as a means of ensuring more economical use of human, animal and material resources, and the elimination of unnecessary delay in the global development and availability of new medicines. This also ensures maintaining safeguards on quality, safety and efficacy, and regulatory obligations to protect public health. It should be noted, however, that ICH has not produced global harmonisation in all matters. The three main regions still have some differences in their requirements for drug development, which manufacturers must take into account in their planning.

Phase I clinical trials

These usually involve healthy volunteers. They are designed to find out how the drug affects the human body and vice-versa. This will be a combination of assessing the pharmacodynamics of the drug, including detailed safety screens and the pharmacokinetics. The results of Phase 1 clinical studies will determine whether there is potential for the drug to move towards the next stage of development. At this stage the drug has to be shown to be relatively safe and, where feasible, for a reasonable signal of efficacy to have been established. This is easier in some disease areas (e.g. hypertension) than others (e.g. oncology). Usually less than 100 individuals are involved.

Specific types of Phase I clinical studies

First in man studies

A medicine may work well in the laboratory, but a clinical trial will find out if it works well in people and is safe to use. Phase I studies can only start to answer these questions, but their main benefit is the highly controlled environment, and relatively clean baseline. Studies will start with low, single doses, in just a couple of volunteers. The serious side effects experienced by volunteers taking part in the trial of TGN1412 in March 2006 at Northwick Park Hospital in London are extremely rare but highlights the need for thoroughly testing a treatment before widespread use. First in man studies may also provide evidence for proof of concept, for example a demonstration of inhibition of relevant enzyme systems.

Dose ranging studies

Healthy volunteer phase I clinical studies can be used to start the process of predicting the optimal dose of a medication before it gets tested in large clinical trials. The doses will start low and single dose, and then be escalated and move to multiple dosing with bloods taken for plasma concentrations of drug, and dose–concentration curves plotted. Pharmacodynamic responses to the drug, both desired and side effects, will be noted with the aim of selecting a dose range that will give you the desired effect but with few side effects. This range will then be taken into Phase 2 trials. Selecting the dose is a critical part of the drug development process. Too low a dose taken into large clinical trials may mean that a good drug will fail. Too high a dose and the same good drug may fail because of unwanted side effects. In most disease areas it is difficult to select the optimal dose based on the response in healthy individuals, and Phase 2 studies are more valuable for this aim.

Interaction studies

There is a lot of potential for drugs to interact with other drugs or dietary factors. A lot of the potential for interaction occurs through the effect of drugs on enzymes in the liver, both induction and inhibition. A lot of these interactions can now be predicted from in vitro studies but if such studies suggest a clinically relevant interaction may exist, many regulatory authorities will require that the effect be quantified more accurately via a clinical interaction study. An example of this is when there are concerns that a drug may cause an interaction mediated through an effect on cytochrome P450 3A4. Midazolam is almost exclusively metabolised by this enzyme. If a drug in development is thought to interact through an effect on cytochrome P450 3A4 then dosing the drug with and without midazolam will allow you to quantify the effect. If the drug is an enzyme inducer then the amount of midazolam measured in the plasma will be less and if an enzyme inhibitor the amount of midazolam measured in the plasma will be greater.

Safety studies

Phase I studies can be used to look at specific safety issues in drug development. For example, based on pharmacology or toxicology results a drug may be thought to have potential to cause prolongation of the QT interval on the ECG which may predispose to cardiac arrhythmias. A simple Phase I study using an escalating dose of drug with ECG recording can show whether there is any relationship between concentration of drug in the plasma and QT interval. Such studies in healthy individuals can however only be seen as an initial screen, and cannot provide the definitive answer. Patients, who are often older and have additional co-morbidities, are likely to be more predisposed to safety issues and therefore the large Phase III and IV studies are required for fully assessing safety profiles.

Phase II clinical trials

These crucial studies, often called 'proof of concept', look at whether a drug works in the patient population that might benefit from the treatment. They are usually conducted by specialists in the field, in a relatively controlled environment, and are designed to assess efficacy or markers of efficacy and the dose–response relationship, taking the dose range suggested from Phase I. A key goal is to decide whether the odds are acceptably good that the compound is effective, may have an acceptable benefit/risk ratio and, if so, to define a single dose to be taken into the Phase III trials. However, some disease areas have very limited markers of efficacy which can be measured in a short, small trial; therefore, in these cases dose selection is significantly more difficult and sometimes more than one dose will be taken into Phase III. In addition to looking at markers of efficacy this stage of development allows the identification of side effects in the target patient population. Phase II would normally involve designing a double blind randomised control trial against placebo and possibly also a study against a standard reference drug therapy as control. If the exploratory type II studies suggest good efficacy and acceptable results concerning safety, tolerance and pharmacokinetics

then the larger Phase III clinical trials can be planned. This decision has potentially huge cost implications as the costs rise exponentially once you start phase III clinical trials. In general, pharmaceutical companies aim to balance the 'development risk' profile of their development portfolio, i.e. to have a mix of higher and lower risk products. High risk products have a greater chance of failing before they reach patients, while the lower risk development programmes may bring less benefit to patients and face more competition.

Phase III clinical trials

These are the expensive trials, often involving many thousands of patients, which definitively quantify the extent to which the drug is effective and in what patient groups. Given the increase in numbers of patients exposed less common side effects may be seen and the benefit/risk ratio can be more clearly estimated. These are the key regulatory studies, and as such inform the labelling and patient information for the drug when it is marketed. At the same time as these trials are underway the pharmaceutical company will be investing considerable efforts into scaling up the manufacturing process, and completing the stability studies on the dose form and packaging which will be taken to market. While various formulations can be tested in Phase II, Phase III studies must be conducted using the final formulation. A key challenge with biotechnology products, which are not manufactured using conventional chemistry, is to develop manufacturing processes and robust assay methods which can guarantee consistent levels of biological activity between batches.

During Phase III the regulatory affairs department within companies will be pulling together the large amount of manufacturing, preclinical and clinical data necessary for making a formal application to the relevant regional and national regulatory authorities for a product licence. Each major regulator requires the data structured in a different way, therefore first priority will usually be given to submissions to the FDA and the EMA. Review times by these regulators vary based on circumstances, but it usually takes approximately 1 year.

Based on the data submitted, each regulatory authority will produce a factual summary of the preclinical and clinical results, including the key safety information and dosing instructions. This document will also state whether the marketing approval is general or restricted, e.g. hospital use only. The relevant document issued by the EMA is called the summary of product characteristics (SPC) and provides the key information required to aid a decision by the prescriber as to whether the drug is indicated. A second valuable document is the European Public Assessment report (EPAR), found on the EMA website, which provides a more detailed summary of the Agency's review of the data submitted. Over time, the SPC will be updated by the company as key new information becomes available, but clinical publications and treatment guidelines are also invaluable in providing additional detail which will not be found in the SPC.

In the UK each new drug in the British National Formulary has an inverted triangle symbol next to it reminding doctors that it is a new product and that any suspected adverse effects should be reported to the Commission on Human Medicines (CHM) via the yellow card scheme.

Clinical scenario

The new drug compound for neuroprotection has now been tested in Phase III clinical trials and has shown good efficacy with an acceptable benefit: risk ratio. It gets approved by the regulatory authorities and the company wants to start marketing the drug. Is there a limit to what the company can do in its marketing strategy? How is its safety monitored? What happens if concerns about side effects become apparent?

Phase IIIb and IV studies

New drugs can only be marketed on the basis of its licensed indications. Even when a new drug gets a licence it does not necessarily mean that there is widespread use. In many countries including the UK drugs have to undergo a health economic evaluation before being available for use in patients (see Chapter 24). Companies will also have ongoing clinical studies to support their product. Phase IIIb studies are aimed to widen the licence, e.g. to populations not initially approved (e.g. children or elderly). Additionally, as well as a means of looking at longer term safety of drugs, some phase IV studies are undertaken by companies to investigate efficacy against comparators, as if better efficacy is shown for their product this might improve their market share.

Pharmacovigilance

The regulatory authorities including the EMA have greatly increased the obligation on pharmaceutical companies to set up risk-management plans. While these were initially limited to exceptional cases where a drug was thought to have a greater risk they

are becoming more common and expensive, e.g. for most of the new oncology drugs. They often require specific databases to be set up, e.g. web-based, and are run for years, with regular reports back to EMA.

Phase IV pharmacovigilance studies are performed after marketing approval and the granting of a product licence. They are usually observational studies utilising data collected on specific drugs. Sometimes these are studies run by the companies themselves who set up a database or utilise information collected elsewhere. Examples of the types of repositories used for such studies include the GP database in the UK which was used to confirm a link between the oral contraceptive and the risk of deep vein thrombosis. Other examples include registries for drugs used in certain conditions, e.g. anti-convulsant use in pregnancy. It was through this that the evidence emerged that sodium valproate was the most likely of the anti-convulsants to cause neural tube defects, in addition to causing long-term neurodevelopmental side effects on the offspring of mothers taking this drug.

Sometimes observational studies or meta-analysis of randomised control trials will raise concern about a particular medication, e.g. increased cardiovascular risk with the oral hypoglycaemic agent rosiglitazone. The options in situations like this are for the company to withdraw the drug or the regulatory authorities to suspend the licence until the concern is investigated further. In the UK if a drug is thought to cause concerns it is marked with a black triangle in the BNF with prescribers encouraged to report any problems through the yellow card scheme.

Yellow card scheme

In the UK all new drugs are labelled in the BNF asking prescribers to report any side effects that may be attributable to the drug. This is done by completing a yellow card which can also now be done online. The MHRA monitor all drugs through this scheme. Information is assessed by a team of medicine safety experts who study the benefits and risks of medicines. If a new side effect is identified, information is carefully considered in the context of the overall side effect profile for the medicine, and how the side effect profile compares with other medicines used to treat the same condition. The MHRA is advised by the Commission on Human Medicines (CHM), which is the Government's independent scientific advisory body on medicines safety. The CHM is made up of experts from a range of health professionals and includes lay representatives. Where necessary action is taken based on the balance of benefit and risk.

Translational research

Traditionally, research is divided into basic research and applied research. Often there was delay in getting the basic research into meaningful treatments for patients. Translational research is a way of thinking about and conducting scientific research to make the results of research applicable to the population under study and in medicine is used to translate the findings in basic research more quickly and efficiently into medical practice. Translational research has been invested in by pharmaceutical companies as a means of aiding the drug development process and by governments trying to provide health care to the populations they serve.

Patient populations that require treatment are increasingly complex. The process that explores needs, develops treatments in basic laboratory research, and tests safety and efficacy in clinical trials can be thought of as translational research – the so called 'bench to bedside' approach to research. There needs to be a means of ensuring that the findings from clinical trials are applicable in the population that is being treated requiring a move away from considering research evidence quality in a hierarchical way and a need to consider other evidence apart from randomised clinical trials in judging whether or not specific treatments work in real life. If research processes can be incorporated within this to evaluate the complex interacting factors such as environment, costs, health care policy, etc., this may allow at government level the provision of enduring evidence-based health-care policies. All of this requires a collaborative multi-disciplinary approach.

Part 2

Aspects of therapeutics