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ESSENTIALS In its widest sense a drug is any chemical entity that can perturb a biological system. For the purposes of drug therapy the biological system is the human body and the perturbation is exploited to aid the diagnosis, treatment, or even cure of a disease process. Historically, chemical entities have been plant derived or synthetic small (organic) molecules (<1000 of Dalton in size). However, increasingly new drugs are large biomolecules (up to 100 000 Dalton; e.g. monoclonal antibodies or recombinant proteins). These biologics are expected to exceed small molecules in the drug pipelines of the pharmaceutical industry in the coming decades. The role of clinical pharmacology is to provide the scientific basis for rational prescribing: 'patients may recover in spite of drugs . . . or because of them' (Gaddum). This sums up the dilemma facing any doctor who prescribes a drug to a patient: it may be the explicit in- tention to do the patient some good, but the drug may actually harm and on rare occasions even kill them. Principles of clinical pharmacology Drug therapy can be considered under four headings: (1) pharmaceutical—is the drug getting from the formulation into the patient?; (2) pharmacokinetic—how does the drug dose, formulation, frequency, and route of administration affect the drug concentration in the body, and the way that this concentration changes with time?; (3) pharmacodynamic—how does a drug produce its pharmaco- logical effects?; (4) therapeutic—is the pharmacological effect trans- lated into a therapeutic effect? Adverse drug reactions Definition and causes—an adverse drug reaction is any unwanted or harmful reaction experienced following administration of a drug, or combination of drugs, under normal conditions of use that is sus- pected of being related to the drug (or combination). If a causal connection with a drug cannot be established, then the injury is referred to as an adverse drug event. An adverse drug reaction may be (1) dose-related—usually due to an exaggeration of a known pharmacological effect of the drug and to an extent predictable; or (2) non-dose-related—often caused by immunological or pharma- cogenetic mechanisms and hence largely unpredictable. Clinical importance—adverse drug reactions are responsible for 1 to

4% of acute hospital admissions, affect 5 to 20% of inpatients at some time during their admission, and are responsible for up to 3% of inpatient deaths. Pharmacovigilance is the subspecialty of clinical pharmacology devoted to the detection and evaluation of adverse drug reactions. Drug interactions A drug interaction occurs when the effects of one drug are altered by the effects of another drug, usually resulting in an adverse drug re- action. Drugs likely to precipitate interactions typically (1) are highly protein bound (e.g. aspirin and sulphonamides); or (2) induce drug metabolism (e.g. phenytoin, carbamazepine, and rifampicin); or (3) inhibit drug metabolism (e.g. cimetidine, metronidazole, anti-HIV protease inhibitors, and triazole antifungals). The drugs most likely to be affected by drug–drug interactions are those with a steep dose– response curve and a low therapeutic index. A rational basis for prescribing To maximize a drug's therapeutic potential and minimize its side ef- fects, a series of checks and balances is needed. The following should be considered before any drug is prescribed: (1) does the patient need a drug at all?—do the risks outweigh its benefits?; (2) are the benefits of the drug well established, preferably by randomized con- trolled trials?; (3) what drug action is being sought, and what class of drug can best provide it?; (4) what is the most appropriate drug in that class, and in what formulation?; (5) what is the appropriate dose and how long should the drug be prescribed for— a single course or for indefinite use?; (6) will this drug interact with other drugs the patient is taking?; (7) can this drug replace other drugs the patient is taking?; (8) what does the patient need to understand about this drug—and who will communicate this?; (9) will it be necessary to review the prescription of this drug—and if so, when, how, and by whom?; (10) does the patient need anything else to derive the most benefit from this drug? Practical prescribing Guidelines and formularies—in practice, the question checklist here is not completed before every drug is prescribed, as many of the questions are addressed by using appropriate therapeutic guidelines 2.6 Principles of clinical pharmacology and drug therapy Kevin O'Shaughnessy

72 section 2 Background to medicine and formularies. Guidelines provide prerehearsed decision paths for many of the issues raised in the checklist, and formularies tackle the specific question of which drug to prescribe (from within a thera- peutic class). The patient's drug history—it is essential to obtain a thorough drug history from the patient before prescribing. Key information that should be obtained includes details of: (1) all the medicines currently being prescribed, including their doses; (2) any previous medical treatments; (3) any 'alternative' treatments (e.g. herbal and homeo- pathic remedies); (4) any self-prescribed medicines; (5) any history of allergy or adverse reactions to drugs. Prescribing for the individual patient—guidelines, formularies, and other prescribing aids are not a substitute for an intelligent clin- ical approach. The prescriber needs to establish what the patient's
experience and expectations of drug therapy are, and the patient needs to know the likely consequences—both good and bad—of taking any drug that is prescribed. This dialogue is important, since it will often de- cide whether the patient actually takes the drug as prescribed. Patient compliance (or, more correctly, adherence) is a key variable in the pre- scribing process, and one over which the doctor often has least control. Balancing a drug's therapeutic benefit with its side effects The prescriber checklist implies that balancing the expected bene- fits of a drug against the expected harm is a straightforward process. It is not. By the time a drug reaches the clinic we know a lot about the size of its therapeutic effect, its relation to drug dose, and the proportion of patients likely to show this effect. Measuring harm is a less precise and much slower process. Terms such as 'risk:benefit ratio' are widely used but can be very misleading. Benefit is often measured in terms of amount and not its probability or frequency. It can also be measured

accurately by a single therapeutic endpoint; harm from a drug encompasses a spectrum of side effects that differ in both their frequency and severity. Some side effects are predictable from the pharmacology of the drug (so-called type A) and are relatively common and dose- dependent. Others are rare and unpredictable (so-called type B or idiosyncratic). Type B side effects are usually more severe with a higher burden of mortality and morbidity and, because of their low frequency, will only come to light after a drug is licensed for clinical use. It is important to remember that only a few thousand patients are exposed to a drug before a license is granted (and for drugs with orphan status, the patient exposure may be very much smaller). The duration of dosing is also inevitably short when the intention is to give the drug to patients indefinitely. Hence, crucial important information about side effects has to be gathered after the drug is licensed, and it may take many millions of patient-years of dosing before some drug side effects emerge. Perhaps the best way of comparing a drug's benefit with its harm is to define them in terms of the number of patients needed to be treated to observe a certain benefit and cause specific harm. These are referred to as the number needed to treat (NNT) and number needed to harm (NNH), respectively. Take, for example, the drug clopidogrel. It is currently given to patients for 12 months after suffering an acute coronary syndrome (non-ST elevation myocardial infarction, NSTEMI) to prevent myocardial infarction. Because of its antiplatelet action it also causes gastrointestinal bleeding. Used in this way to prevent nonfatal myocardial infarction, the NNT for clopidogrel is about 67 and the NNH to cause a major bleeding epi- sode is 100. So, if 100 patients are treated for 1 year, 1.5 nonfatal myocardial infarctions will be prevented at the expense of causing one major bleeding episode. This is a much more transparent pres- entation than the relative risk reduction that is often used to high- light drug benefit in clinical trials. These percentage measures inevitably boost the psychological impact of a drug's effect—the NNT for clopidogrel equates to a 22% reduction in the frequency of nonfatal myocardial infarction. But even with reliable measures of harm and benefit, how do we decide where the final balance lies? It will depend on other factors such as the severity of the disease and whether there are safer al- ternative drugs. Hence, if we want to treat a disease with a high fa- tality rate using a drug which is highly effective and carries little risk of harm, the balance is clearly in favour of the drug. But if the dis- ease itself carries no mortality or morbidity and we propose using a drug whose effectiveness is low and carries a high risk of harm, the balance is clearly against using the drug. Most clinical decisions to use a drug or not will be in the grey area between these two extremes. Efficacy, effectiveness, and efficiency of drugs These terms are not synonymous and can be easily confused. Efficacy is a pharmacological term. It refers to the ability of a drug to bring about a certain size of an effect at a given concentration or dose. The effect may not be applicable to clinical practice or is only ac- curately measured in a clinical trial. Hence the term is best reserved for the performance of a drug in this setting. Effectiveness refers to the performance of a drug in everyday clinical use, and is defined as the likelihood and extent of the therapeutic effect in a given patient. Efficiency weights drug performance against cost: it is the ratio of effectiveness to cost. Clearly, it is more efficient to use the cheaper of two drugs that are equally effective and safe. The therapeutic index of a drug The therapeutic index is a term taken from animal pharmacology. It is the dose needed to harm over the dose needed to produce the therapeutic response. However, as harm is usually measured by a drug's lethality, it is not a useful clinical measure. Instead, the index is employed clinically in a very loose and entirely qualitative way. Drugs that produce side effects at doses well outside the clinical dose range are said to have a high therapeutic index and those where the ranges are much closer or even overlap are said to have a low therapeutic index. Hence penicillins have a high therapeutic index; large doses can be given without the worry of adverse effects unless the patient is allergic to penicillins.

In contrast, digoxin has a low therapeutic index; the doses causing toxicity overlap with those producing therapeutic benefit. Drugs with a low therapeutic index in- clude: aminoglycoside antibiotics, anticoagulants, anticonvulsants, antihypertensives, some antiparasitic and antiviral drugs, cardiac glycosides, and cytotoxic and immunosuppressant drugs. To increase the margin of safety for drugs with a low index, dosing can be guided by measuring drug levels in plasma or serum. Such therapeutic monitoring is mandatory for drugs such as lithium and aminoglycoside antibiotics because of additional pharmacokin- etic problems with their use. Anticoagulants are unusual in being

2.6 Principles of clinical pharmacology and drug therapy 73 monitored by their effect on clotting rather than as a plasma drug concentration. Formularies Formularies are lists of medicines for prescribers and pharmacists, intended to guide the choice and facilitate the dispensing of medicines. Many give details of the formulation and doses of drugs. Each formulary is produced primarily for a particular group, usually the prescribers in one country or region or institution, or even one prac- tice. Most formularies are restrictive (i.e. they make a narrow choice of medicines from all those available). This is typical for the formu- lary of a hospital, or of a health maintenance organization. A hospital formulary lists only the preparations that are stocked in the hospital pharmacy; a health maintenance organization formulary only those that the organization will pay for. The British National Formulary (BNF) is probably the best known and most widely used formulary of all, but is unusual in including all medicines available for prescrip- tion in the United Kingdom, whether they are good choices or not. However, every section of the BNF has concise and critical ‘notes to facilitate the selection of suitable treatment’ that precede the list of available agents. This invaluable resource is revised biannually and available online (https://www.medicinescomplete.com/about/). The WHO ‘Model List of Essential Drugs’ In many developing countries, having limited health budgets means that large sections of the population have no access to drugs or healthcare, and governments cannot afford to provide necessary drugs. To help them to use their limited funds in the best ways, the World Health Organization (WHO) has since 1977 published a regularly updated Model List of Essential Drugs. It is updated every two years and currently in its 18th edition (http://www.who.int/medicines/publications/essentialmedicines/en/index.html). Essential drugs on the list are intended to ‘provide safe, effective treatment for the majority of communicable and noncommunicable diseases’. The WHO list is a ‘model’ list that can be adapted to meet the needs of the local health economy. Hence, over 150 countries have an es- sential list based on the WHO model. It is a salient fact that the first WHO list contained 208 drugs and, in the intervening 30 years, it has not doubled in size. There may be some clear lessons here for the drug lists of developed countries. Medicines management Rapidly escalating costs of providing drugs within healthcare sys- tems and the need to maximize drug safety mean that the concept of medicines management is now widespread. By bringing together clinical, pharmacy, and financial skills, drugs that are considered es- sential can be prescribed in the most cost-effective and safest way. In the United Kingdom, drugs are assessed at a national level by the National Centre for Health and Clinical Excellence (NICE) before deployment within the National Health Service (NHS). NICE con- siders in detail the evidence for a drug’s alleged benefit and weights this against known side effects and economic modelling of its total cost versus benefit within the NHS. The principles of clinical pharmacology Drug therapy can be considered under four headings—pharmaceutical, pharmacokinetic, pharmacodynamic, and therapeutic—each of which addresses a pertinent question about drug therapy (Fig. 2.6.1). The pharmaceutical process The pharmaceutical step is concerned with the

question, ‘Is the drug getting from the formulation into the patient?’ The route of drug administration is usually a more crucial choice than how it is formulated. Nevertheless, formulation can greatly af- fect the rate and extent of drug absorption. Repackaging short-acting drugs into ‘sustained’ or ‘modified’ release formulations to slow re- lease of the drug into the gut allows them to be taken once daily. Morphine, calcium channel blockers (e.g. diltiazem and nifedipine), theophylline, and l-dopa have been widely reformulated in this way. Other drugs are formulated for specific routes of administration: glyceryl trinitrate is available for sublingual (as a spray and tablets), buccal, and transdermal (as a paste or patch) use. To understand the differences between these various routes, it is necessary to under- stand the concept of systemic availability. Systemic availability Systemic availability, commonly called bioavailability, is the pro- portion of administered drug that reaches the systemic circulation and is available for distribution to the site of drug action. If a drug is given intravenously, it will enter the systemic circulation directly (i.e. it is said to be 100% bioavailable). The same drug given orally, or by any other route, must be absorbed first (which may be an in- complete process), and possibly metabolized, before entering the systemic circulation. Metabolism can occur in the gut wall and liver following oral ad- ministration, although it can occur at any site of drug administra- tion. The cells lining the gut also express drug efflux pumps (e.g. P-glycoprotein) and transporters that can actively reduce the extent of absorption of a drug. These processes, together with incomplete absorption, ensure that most drugs have a bioavailability of less than 100% when given orally. In some cases, the reduction is so large that a drug has zero bioavailability and is clinically ineffective. Oral in- sulin or benzylpenicillin are good examples of this problem, with their instability in the stomach preventing significant absorption. Complete presystemic metabolism also explains why glyceryl tri- nitrate and buprenorphine are orally effective only if given sublin- gually or as a buccal patch. Absorption from the mouth allows the drug to bypass gut wall and liver metabolism. Special drug formulations Most drugs are given orally; oral formulations include syrups, or- dinary (instant release) tablets, capsules, and modified release for- mulations. However, drugs can be given by other routes, including sublingually, buccally, rectally, transdermally, by inhalation, and by injection intravenously, subcutaneously, intramuscularly, or locally. Modified release formulations Most conventional instant release tablets are designed to disintegrate in the stomach or proximal small bowel, so that absorption is com- plete within a few hours on ingestion. Modified or sustained release

 formulations are oral formulations that allow a drug to be released over long periods (12–24 h typically) relative to the half-life of the drug. The intention of the prolonged and slowed release is to smooth out the concentration profile of the drug in the blood and extend its duration of action. They include formulations of theophylline, ni- fedipine, diltiazem, morphine, and lithium. Prescriptions of these drugs should specify the exact formulation, as formulations differ in systemic availability and may not be interchangeable. Sublingual, buccal, rectal formulations Drugs that are absorbed through the oral or rectal mucosa avoid first-pass metabolism in the liver by uptake into veins that drain directly into the systemic circulation. For example, sublingual gly- ceryl trinitrate is rapidly effective as a sublingual tablet, but if the tablet is swallowed, the remainder is not bioavailable because of high presystemic metabolism. Rectal administration achieves a direct ef- fect on the local bowel wall (e.g. corticosteroids in ulcerative colitis), but is also useful for achieving high blood levels rapidly when intra- venous access is difficult (e.g. diazepam for seizure control). Transdermal formulations Some lipid-soluble drugs are well absorbed through the skin, and their transdermal delivery via ‘patches’ allows controlled re-

lease over many hours or days. Examples are glyceryl trinitrate in the long-term treatment of angina pectoris, transdermal hyoscine for travel sickness, oestradiol as hormone replacement therapy, buprenorphine for pain control, and nicotine for smoking cessation. Inhaled formulations The lung provides a huge surface area (c. 100 m2) for drug absorp- tion, but to reach the distal airways, a drug for delivery by inhal- ation must be associated with particles in the 2 to 5 μm range. These can either be solid particles (dry powder devices) or dissolved in small droplets (aerosol devices). For hand-held aerosol inhalers the drug is dissolved in a volatile hydrocarbon, but in nebulizers the drug is in an aqueous solution that is aerosolized by a jet of air or oxygen. Both aerosols and dry powders are widely used to deliver inhaled corticosteroids and bronchodilators used in the manage- ment of asthma and chronic obstructive pulmonary disease. Even peptides can be delivered by this route, as demonstrated by the li- censing of inhaled insulin. The efficiency of inhalation as a route of administration also explains the ‘success’ of some drugs of abuse (e.g. nicotine and crack cocaine). Subcutaneous, intramuscular, and local injections The rate of absorption of insulin from the site of subcutaneous in- jection is controlled by its physical state (e.g. monomer, crystalline, or noncrystalline), pH, and the presence of zinc ions or protamine PHARMACEUTICAL PROCESS ‘Is the drug getting into the patient?’ Formulations Routes of administration (compliance) PHARMACOKINETIC PROCESS ‘Is the drug getting to its site of action?’ PHARMACODYNAMIC PROCESS ‘Is the drug producing the required pharmacological effect?’ THERAPEUTIC PROCESS ‘Is the pharmacological effect being translated into a therapeutic effect?’ Biliary excretion Rectal or sublingual administration Parenteral administration Disintegration etc. Dissolution ‘First pass’ Elimination Therapeutic/toxic effects Absorption Distribution Plasma proteins Tissues Elimination Hepatic metabolism Renal excretion Other Molecular pharmacology Cell and tissue pharmacology Cell and tissue physiology Organ physiology Clinical effects Extracellular fluids Tissues (sites of action) d n u o b n U Drug in solid dosage form Drug in particulate form Drug in solution Metabolism in gut lumen and gut wall Hepatic metabolism Pharmacological effects Protein-bound Fig. 2.6.1 The four processes of clinical pharmacology in relation to drug therapy.

2.6 Principles of clinical pharmacology and drug therapy 75 (isophane) in the buffer in which it is suspended. It is also affected by altering the amino acid sequence of insulin; allowing recom- binant insulins, which are rapidly (lispro and aspart) or slowly re- leased (Glargine or Detemir) after injection. Soluble insulins have a rapid onset (15–30 min) and short duration of action (4–6 h), so they are usually given together with intermediate or long-acting insulin. Long-acting insulins act for more than 24 h and can provide the in- sulin background as a once daily injection. The isophane insulins have an intermediate duration of action and are usually given twice daily mixed with soluble insulin. Absorption of a drug after subcutaneous injection is affected by blood flow. Hence, the duration of action of local anaesthetics can be prolonged by vasoconstriction. Adrenaline or felypressin is added to the subcutaneous formulations for this purpose. Smoking also re- duces subcutaneous insulin absorption by causing cutaneous vaso- constriction. Reduced absorption also explains why subcutaneous adrenaline is not advised for the treatment of anaphylaxis. The intramuscular route is a popular parenteral route but can be erratic. Hence, phenytoin and diazepam should not be given by this route for emergency use. Absorption following intramuscular in- jection may be retarded by esterifying a drug to a large lipid mol- ecule. This gives oily formulations that provide long-lived drug depots in muscle, which are used in the treatment of male hypo- gonadism (testosterone enanthate or undecanoate) and schizo- phrenia (fluphenazine or flupentixol decanoates). Combination formulations in oral therapy Combination products are attractive and may aid compliance (see following paragraphs), but should be used only when at

least two criteria are met: • The frequency of administration of the two drugs is the same. • The fixed doses in the combination product are therapeutically and optimally effective in most cases (i.e. it is not necessary to alter the dose of one drug independently of the other). Acceptable combination products include: • Aspirin plus codeine (co-codaprin) or paracetamol plus dihydro codeine (co-dydramol), pairs of drugs that have different analgesic ac- tions (which synergize) and different adverse effects (which do not). • l-Dopa plus a peripherally-acting dopa decarboxylase inhibitor (benserazide or carbidopa); the peripheral action of the decarb- oxylase inhibitor blocks peripheral metabolism of l-dopa, which is free to enter the central nervous system, where it is converted to dopamine, producing the therapeutic effect in Parkinson's disease. • Combined oral contraceptives, which contain an oestrogen and a progestogen. • Ferrous sulphate plus folic acid, used to prevent anaemia in pregnancy. • Co-amoxiclav (amoxicillin plus clavulanic acid); the β-lactamase inhibitor, clavulanic acid, prevents the breakdown of amoxicillin by bacterial penicillinase, so broadening its spectrum. The patient's use of a drug: Compliance and concordance Compliance is the extent to which a patient follows a prescribed drug regimen. Some prefer the term 'concordance' or 'adherence', to make it clear that therapeutic decisions are best arrived at jointly between prescriber and patient and avoiding a patronizing relationship. Rates of adherence are difficult to measure and can be surprisingly low, even in conditions where the drug has a very obvious benefit, such as epilepsy and asthma. Possibly as few as 1 in 6 patients take a drug exactly as prescribed and 1 in 6 take none at all; the remainder take a different dose and/or a different frequency from that prescribed. Poor adherence is still not well recognized by doctors as a cause of therapeutic failure. The effect of the prescribing regimen Apart from the financial cost to the patient (which in some countries is substantial), the two factors that determine adherence to drug therapy are the complexity of the regimen and the likelihood of side effects. The complexity of the prescribed regimen reflects frequency of administration and the number of drugs prescribed. Generally speaking, the more frequently a drug is prescribed per day, and the more drugs in total are prescribed, the lower is the rate of compli- ance. For most chronic diseases, drugs that can be taken once daily are preferred. Obviously, using several drugs (polypharmacy), where one may be adequate, should be avoided wherever possible. Side effects that a patient attributes to a drug may lead them to stop taking the drug completely. It may be necessary then to persuade them to persevere or switch to an alternative drug. However, giving another drug to simply reduce the side effects of the first drug has to be thought through carefully. For example, giving furosemide to a patient who develops ankle oedema on nifedipine, causing in turn gout or hypokalaemia, is poor practice. But giving omeprazole to a rheumatoid patient who develops acid reflux on their nonsteroidal anti-inflammatory (NSAID) is appropriate. The effect of the illness People with severe mental health problems (e.g. patients with schizophrenia or manic-depressive psychosis), often take medicines unreliably. Physical disability may cause difficulty even in patients who want to take their medicine. For example, patients with rheumatoid arth- ritis who cannot reach the tablets, or cannot remove the top of a childproof container, cannot take them without help. Sometimes, a good response to treatment leads patients to stop. For example, patients with tuberculosis need long courses of several drugs to eradicate the infection; once the symptoms have resolved, motivation to continue treatment may decline, risking reactivation and the emergence of resistant tuberculosis. Some diseases may promote compliance. Patients with insulin- dependent diabetes easily become very ill quite quickly if they forget to take their insulin, and that is likely to make them comply, al- though they may not use it precisely as advised. Patients in whom a β-blocker or vasodilator has prevented anginal attacks will also be more likely to have good compliance. The patient's behaviour People tend to forget to take drugs,

or cannot be bothered; they may feel no need for treatment (e.g. in asymptomatic hypertension); they may be unclear about the prescribing instructions; they may not want to feel dependent or be thought to be dependent on ‘drugs’. There may be social or physical reasons why they cannot reach a pharmacist, financial difficulties, or everyday inconveniences in carrying and taking the medication.

76 section 2 Background to medicine The doctor’s behaviour The enthusiasm and confidence with which a drug is prescribed, and the extent to which these attitudes are transmitted to the patient, may influence not only compliance but also the response to therapy. This is related to the placebo effect of drug taking. Methods of assessing adherence It is important to assess adherence both in everyday practice and in clinical trials. The most obvious and usually the easiest approach is to ask the patient whether he or she has been taking the drugs, and whether there have been any problems. If the doctor is non- judgemental and indicates that difficulties are common, the patient is encouraged to be open. Less directly, one can ask to see the patient’s tablets: this at least confirms that the prescription has been filled. Counting the tablets left in the bottle is a guide to how many have been taken, but some may have been thrown away. Recording devices fitted in the caps of medication containers can record the frequency and exact timing of the opening of the container, and are useful in research. If a patient is vague or untrustworthy, measurement of the drug level in plasma or urine may give some reassurance—at least on the day they visit the doctor. The list of drugs for which assays are rou- tinely available is small, but a surrogate marker can be used (e.g. the level of thyroid stimulating hormone (TSH) to ensure compli- ance with thyroxine or the international normalized ratio (INR) for patients on warfarin). Alternatively, a pharmacological effect such as heart rate can be measured directly (to assess β-blocker compliance). Methods of improving adherence Adherence can be improved by supervised administration of the drug, by removing barriers, by simplifying the therapeutic regimen, and by educating the patient on the need to take the medicine, with reinforcement whenever possible. Supervised administration Administration of a drug by the doctor or nurse ensures compli- ance. This is possible in hospital or when occasional administration is required (e.g. intramuscular injections of vitamin B12, long-acting intramuscular depot injections of neuroleptics, and supervised twice-weekly antituberculosis therapy). A relative or other carer can give the drug at home and this may be aided by using dosimeter boxes prefilled by a pharmacist. Removing barriers to adherence Adherence may be encouraged by prescribing pleasant-tasting syrups rather than tablets for children and older people, and by using a drug or formulation that minimizes side effects. Simplification of the therapeutic regimen The therapeutic regimen can be simplified by reducing both the number of drugs a patient has to take and the frequency of administration. Modified release or com- bination formulations may be useful here. Education and reminders Educating the patient about why treat-ment is necessary (e.g. treating hypertension or diabetes reduces the risk of serious complications) is time-consuming but improves com- pliance. In the treatment of certain infections (e.g. tuberculosis) and in typhoid carriers, the wider importance to the community should also be explained. Even in the well-motivated, reminders to take the treatment may improve compliance. Many drugs for long-term use are also now dispensed in a ‘calendar pack’ to help compliance. The pharmacokinetic process Pharmacokinetics concerns the complicated question ‘How does the drug dose, formulation, frequency and route of administration affect the drug concentration in the body, and the way that this concentra- tion changes with time?’ The answer will depend on the absorption, distribution, metabolism, and excretion of that drug (otherwise known as ADME). This naturally lends itself to complex mathemat- ical modelling, but the key points can be understood

without being overwhelmed by the mathematics. The size and chemistry of biologics poses special problems for both the measurement and understanding of their ADME. Generally they are metabolized to small peptide fragments or amino acids that can be renally cleared or recycled through cellular protein syn- thesis. This process can be very rapid for small peptides and proteins (c.hours), but very slow for large proteins such as IgG that can have a half-life of 7–28 days. The uptake of biologics from the subcutaneous injection sites frequently used for biologics is also slow and affected by lymphatic drainage and binding of any Fc-domains to FcRn re- ceptors on endothelial cells. Small proteins may also be deliberately modified by, for example, PEGylation, glycosylation, or coupling to larger proteins such as albumin to reduce their degradation. Basic pharmacokinetic terms and concepts Before considering the various components of ADME, a few pharma- cokinetic terms need to be explained. Consider a time after admin- istering a drug when its absorption and distribution throughout the various compartments of the body are complete. At this time, there are no concentration gradients across compartments and any fur- ther decline in drug concentration reflects drug elimination, that is, excretion and metabolism of the drug. Several parameters charac- terize this elimination phase of a drug: Volume of distribution (Vd) This can be a confusing term, since it is really a mathematical device and not a true physical volume. Hence, it rarely relates to any par- ticular water compartment (e.g. plasma, 3 litres; extracellular water, 16 litres; total body water, 42 litres). It simply allows the amount of drug remaining in the body to be inferred from the drug concen- tration (concentration = amount/volume). Drugs have a wide range of values for their Vd and sometimes they are much greater than the total water space. This is typical for drugs that bind to tissues or partition into lipid. Amiodarone is an extreme example of this behaviour with a Vd of approximately 5000 litres. Biologics in sharp contrast usually have a small Vd (e.g. 2–4 litres) reflecting their con- finement to the blood space. Clearance In the same way that the volume of distribution is a proportion- ality term, so clearance is used to relate the rate of drug excretion

 to the concentration of the drug in the body. It is expressed in units of flow (volume per unit time) and is effectively the volume of the Vd cleared of drug per unit time. A drug can be elimin- ated (or cleared) from the plasma by one or more mechanisms (e.g. through the kidney by filtration and the liver by metabolism). The total clearance of the drug is simply the sum of these different organ-based clearances. Plasma half-life During the elimination phase, the drug concentration falls in a predictable way: in a fixed time called the half-life it falls by 50%, and by a further 50% after another half-life and so on. Thus, it takes between four and five half-lives for 95% of the drug to be elimin- ated (see Fig. 2.6.2). For most drugs, the half-life is constant (except if the kinetics becomes nonlinear—see following paragraphs). The half-life is not affected by the starting concentration or amount of the drug, but it is directly affected by the volume of distribution and clearance of a drug (actually proportional to their ratio). Repeated dosing and the ‘plateau principle’ A drug can be given once but it is more common for a drug to be given repeatedly (even indefinitely). After the first dose, the plasma level will rise to its maximum (Cmax) and fall as shown in Fig. 2.6.2. If the dose is not repeated until all the drug has been eliminated (which means the dose interval must be long, e.g. 10 half-lives), the drug level will oscillate between the Cmax after a single dose and a trough value of zero. The problem with this regimen is that to give a plasma level that is therapeutic (but not toxic), a large part of the dosing interval is spent with a nontherapeutic drug level. To get around this, the drug is given at smaller doses separated by short dose intervals compared to the drug’s half-life. Because the dose interval is similar to the drug’s half-life, the first dose of drug is not completely eliminated

before the second dose is given. The third dose is given before either the second dose, or the remaining fraction of the first dose is eliminated and so on. Hence, the drug plasma level accumulates and eventually it comes to a steady state where it oscillates between a new peak and trough (substantially greater than zero); ideally, the peak is below the toxic threshold and the trough above the therapeutic threshold throughout the dose interval. This is what is known as the plateau principle and the therapeutic and toxic threshold levels for the drug define its 'thera- peutic window'. Loading doses The half-life also dictates the time it takes for a drug to reach its plateau with repeated dosing. In the same way that it takes almost 5 half-lives to eliminate a drug, it takes almost 5 half-lives to reach plateau. The delay imposed by the drug's half-life in reaching steady state can be unacceptable clinically. Consider, for example, the use of digoxin to treat fast atrial fibrillation. Because of the long half- life of digoxin (40 h), it takes over a week to reach plateau, and over twice this if the patient has renal failure because of the increased half-life. The solution is to give a loading dose of a drug. The loading dose is intended to take the blood concentration rapidly into the 0 6 12 18 [mg/litre] 12 11 10 9 8 7 6 5 4 3 2 1 0 24 30 36 42 48 54 60 Time after dosing (h) Drug concentration in the plasma Therapeutic threshold Toxicity threshold Drug elimination with a t½ of 12 h Cmax 66 72 78 84 90 96 102 108 114 120 Therapeutic window Fig. 2.6.2 Plateau principle. Plasma concentrations of a hypothetical drug after a single oral dose (black line) versus repeated dosing (red line). A smaller dose is used for repeated dosing, but the half-life is the same. Both approaches give levels within the 'therapeutic window', but only with repeat dosing are the levels within the window throughout the dose interval.

78 section 2 Background to medicine therapeutic window. Dosing then resorts to the usual maintenance dose, which is chosen to replace the drug eliminated in each subse- quent dose interval. Absorption and systemic availability Systemic availability, introduced earlier in this chapter, is meas- ured by plotting the blood concentration at various times after dosing. Typical curves are shown in Fig. 2.6.3 for three different formulations (containing the same dose) of a hypothetical drug. The area under each of these curves (abbreviated to AUC) reflects the bioavailability of the formulation and it is actually the same in this simulation. However, it is clear that they produce very different profiles in terms of the maximum concentration (Cmax) and the time to reach Cmax after dosing (tmax). This reflects the decreasing rate of absorption from left to right for the three formulations, and hence the duration over which absorption occurs. Hence the fastest absorption gives the highest Cmax, but this would cause transient toxicity as crosses into the toxic range for this drug. The middle curve takes the drug level above the therapeutic threshold for as long as the first curve but remains below the toxicity threshold. The slowest rate of absorption here gives a Cmax that is too low because the drug concentration is subtherapeutic throughout. Choosing the optimum concentration profile, and hence the for- mulation, depends on the therapeutic effect being sought. Hence, a rapid (instant release) formulation of nifedipine would be needed to treat an episode of angina and is typified by the left-hand curve in Fig. 2.6.3. The transient flushing and headache this would cause would be an acceptable side effect. However, when drugs are intended to be given repeatedly, and the therapeutic effect is related to a steady state concentration, the flatter profile of the slowest ab- sorption formulations are preferred (right-hand curve in Fig. 2.6.3). So, for chronic angina prophylaxis, a slow release formulation of ni- fedipine would be preferred to achieve the smoothest profile of drug level in the blood after dosing. The rate of absorption Gastrointestinal motility Drugs are absorbed mainly in the upper small intestine, so altered gastric emptying can affect absorption. For example, in migraine, the rate of absorption of analgesics is reduced because of reduced gastric motility,

delaying the response to an oral analgesic. In fact, the shift in the drug concentration–time profile is similar to the rightward shift produced by reformulation discussed in Fig. 2.6.3. This delay can be reduced by giving metoclopramide to accel- erate gastric emptying. Erythromycin can have a similar effect on gastric emptying. The converse of delayed emptying occurs with antimuscarinics or older antihistamines (e.g. promethazine and di- phenhydramine) or tricyclic antidepressants (e.g. amitriptyline) that have substantial antimuscarinic actions. This can be particularly im- portant in drug overdoses involving these drugs. If a drug dissolves more slowly than the stomach empties, in- creased gastrointestinal motility reduces both the rate and extent of absorption. This effect is exaggerated for sustained release formula- tions, such that in severe diarrhoea enteric-coated formulations can pass through the gut intact. Proximal ileostomies are also a problem for these formulations. 1 0 10 9 8 7 6 5 4 3 2 Drug concentration in the plasma 0 2 4 6 8 10 12 Time after dosing (h) Therapeutic threshold Toxicity threshold 14 16 18 20 22 24 [h] [mg/litre] Cmax Cmax Cmax Fig. 2.6.3 Effect of slowed absorption on drug kinetics. Plasma concentration profiles for a hypothetical drug formulated to progressively slow absorption (slows left to right). As the absorption is slowed, the peak concentration (Cmax) falls and is delayed.

2.6 Principles of clinical pharmacology and drug therapy 79 Malabsorption Drug absorption is often impaired in patients with malabsorption, but not always. For example, the absorption of propranolol and some antibiotics (co-trimoxazole and cefalexin) is increased in pa- tients with coeliac disease. Untreated coeliac disease patients have a higher intraluminal pH that can affect the ionization of a drug, while the villous atrophy removes CYP 3A4 that can significantly reduce the first-pass metabolism of some drugs (e.g. simvastatin). Digoxin, however, is less well absorbed from tablets in patients with coeliac disease, radiation-induced enteritis, and other gastrointestinal dis- ease, and thyroxine absorption is impaired in coeliac disease. Food Food alters the rate and extent of absorption of many drugs. For ex- ample, eggs impair iron absorption, and milk (or any calcium, alu- minium, magnesium, or ferrous salt) impairs tetracycline absorption by the formation of an insoluble chelate. Such effects are rarely im- portant clinically, unless the drug has a very limited bioavailability, when the effect can be highly significant. Hence, bisphosphonates are only bioavailable in the complete absence of food. Grapefruit juice, and some other citrus juices such as Seville orange and pomelo, can markedly increase the bioavailability of some drugs (Fig. 2.6.4). These include antihistamines (terfenadine), simvastatin, calcium channel blockers (e.g. felodipine, nifedipine, and verapamil), im- munosuppressive drugs (ciclosporin A, sirolimus, and tacrolimus), and PDE5 inhibitors (e.g. sildenafil and vardenafil). Coadministered drugs Drugs affecting gastric emptying can affect absorption of coad ministered drugs as mentioned earlier. Anion exchange resins (bile acid sequestrants) used for lipid management avidly bind certain drugs. The resulting reduction in drug absorption is clinically sig- nificant for warfarin, thyroxine, thiazides, and digoxin when taken with cholestyramine. The newer resin, colesevalam, also affects ciclosporin and sulphonylurea absorption. Hence it is usually re- commended these resins are taken at least an hour after the drugs or the interacting drugs taken at least 4 hours after the resin. This strategy can of course be put to good effect in drug overdose, where absorption can often be prevented by adsorbing the drug to swal- lowed activated charcoal (see Chapter 10.4.1). First-pass metabolism First-pass metabolism is metabolism that occurs before the drug en- ters the systemic circulation. This may happen in the gut lumen itself (e.g. with benzylpenicillin or insulin), the gut wall (tyramine, chlor- promazine), the lungs (various amines and inhaled glucocorticoids), and the liver, which is the most important site. Many drugs undergo first-pass metabolism in the liver. It is substantial for certain drugs, including cocaine, desipramine, lig- nocaine, pethidine, morphine,

nicotine, nitroglycerin (and other organic nitrates), propranolol, and verapamil. When first-pass metabolism results in the formation of com- pounds with less pharmacological activity than the parent com- pound, the drug's efficacy is lower after oral than intravenous administration. In some cases, metabolism is so extensive that oral therapy is impossible. However, such a drug given sublingually, rec- tally, or transdermally, can bypass the liver (see earlier paragraphs). Distribution Protein binding Many drugs are bound to circulating proteins, usually albumin (acidic drugs), but also globulins (hormones), lipoproteins, and α1-acid glycoprotein (basic drugs). Only free drugs (i.e. not protein bound) can bind to cell surface receptors, cross cell membranes to access intracellular drug targets, or distribute to other tissues where they may be metabolized and excreted (e.g. by the kidney). Thus, changes in protein binding can sometimes cause changes in drug distribution. However, such changes are only important if the drug is extensively bound to plasma proteins (>90%) and not widely dis- tributed to other tissues. Phenytoin and warfarin are the two drugs most frequently affected. The binding of drugs to albumin may be changed in renal im- pairment (the explanation for this is unknown), hypoalbuminaemia (drug binding is reduced when the plasma albumin concentration falls below 25 g/litre), the last trimester of pregnancy (during which protein binding is reduced partly because of hypoalbuminaemia), and displacement by other drugs. Because α1-acid glycoprotein is an acute-phase protein, its levels are affected by trauma, surgery, inflammatory diseases (e.g. Crohn's disease and rheumatoid arthritis), and infections. Hence, the binding of quinine is increased in malaria. Tissue distribution The extent of drug distribution to the tissues of the body varies widely. The drugs with the widest distributions will have the lar- gest volumes of distribution (see earlier paragraphs). Some water- soluble drugs are limited to one or more of the water compartments (vascular and extra- and intracellular), while others are bound 30 25 20 15 10 5 0 0 2 4 6 8 10 12 24 Time (h) Simvastatin (ng/ml) Fig. 2.6.4 Effect of grapefruit juice (closed symbols) or water (open symbols) taken daily for 3 days on the plasma levels after a single 40 mg dose simvastatin. The effect relies on furanocoumarin components of grapefruit juice that directly reduce P450 protein expression (CYP 3A4 principally) in the gut wall. From Lilja JL, Neuvonen M, Neuvonen PJ (2004). Effects of regular consumption of grapefruit juice on the pharmacokinetics of simvastatin. Br J Clin Pharmacol, 58, 56–60,

 extensively in tissues. The distribution of drugs to different tissues is influenced by plasma-protein binding, specific receptor sites in tissues (e.g. the binding of cardiac glycosides to the Na+,K+-ATPase in cell membranes throughout the body), regional blood flow (well- perfused organs, such as the heart, kidneys, and liver accumulate drugs more than poorly perfused organs, such as fat and bone), lipid solubility (lipid-soluble drugs enter tissues more readily than charged compounds with poor lipid solubility), and active transport across cell membranes (adrenergic neuron-blocking drugs such as guanethidine accumulate in noradrenergic nerve terminals through the noradrenaline transporter, uptake-1) or active transport across epithelia. The importance of epithelial transport has been appreciated with the discovery of specific transporters. These fall into two families: ei- ther solute carriers (SLC) or ATP-binding cassette (ABC) trans- porters. P-glycoprotein is the best understood ABC transporter and was first identified in tumour cells where it confers multidrug resist- ance (MDR) by promoting the extrusion of many structurally unre- lated anticancer drugs. But this drug efflux pump is widely expressed in normal tissues such as small intestine (brush border membrane of enterocytes), kidney (brush border membrane of proximal tubule cells), liver (canalicular membrane of the hepatocytes), and at the blood–brain barrier (capillary endothelial cells). The latter explains, for example, why drugs such as

ivermectin, digoxin, loperamide, and domperidone are rapidly pumped out of the cerebrospinal fluid, so effectively excluding them from the brain. In some diseases, drug distribution is altered for unknown reasons. In renal failure, for example, the distribution of drugs such as insulin and digoxin is decreased as well as their protein binding. In cardiac failure, the distribution of some antiarrhythmic drugs, such as disopyramide, is also reduced. Obesity and malnutrition influence the distribution of drugs that are highly fat soluble (e.g. inhalational anaesthetics). Metabolism Most drugs are metabolized in the liver. Examples of other sites are suxamethonium in the plasma; insulin and vitamin D in the kid- neys; and acetylcholine and catecholamines at their corresponding synapses and nerve endings. Drug metabolism occurs in two phases: • Phase I metabolism involves chemical alteration of the basic structure of the drug (e.g. by oxidation, reduction, or hydrolysis). This results in free groups such as –OH or –NH2 that are con- jugated in phase II. Many phase I reactions are catalysed by en- zymes from the P450 family (see following paragraphs). Examples of phase I reactions include the N-demethylation of diazepam to desmethyldiazepam, an active metabolite with a long duration of action, and the oxidation of ethanol to acetaldehyde. • Phase II metabolism involves conjugation (e.g. by sulphation, glucuronidation, methylation, or acetylation). Some drugs are conjugated without prior phase I transformation, while others undergo phase I metabolism before conjugation can occur. The products of conjugation are more water soluble and therefore more easily cleared by the kidney or biliary system. They are usually, although not always, pharmacologically inactive (e.g. morphine-6-glucuronide is an active metabolite of morphine that accumulates in renal failure). Examples of phase II reactions are the glucuronidation of paracetamol and the N-acetylation of hydralazine and procainamide.
A conjugated product may some- times be further metabolized. For example, oestrogens are ex- creted via the bile, deconjugated in the gut by bacteria, and then reabsorbed (so-called enterohepatic recycling). The end result of drug metabolism is inactivation, but during the process, compounds with pharmacological activity are often formed. Alternatively, inactive drugs (prodrugs) may be metabol- ized to active ones. The antiparkinsonian drug l-dopa, for example, is a typical prodrug. It has no action on dopamine receptors until it enters the central nervous system and is metabolized to dopamine. Other examples include diamorphine and codeine (which are rap- idly metabolized to diacetylmorphine and morphine, respectively) and many angiotensin-converting enzyme (ACE) inhibitors (e.g. enalapril is converted to its active form enalaprilat). Some drugs also have toxic metabolites. For example, norpethidine is a metabolite of pethidine that can cause fits, and acrolein is a bladder irritant formed from cyclophosphamide. The normally minor metabolic pathway for paracetamol forming N-acetyl-p- benzoquinone imine (NABQI) is important in overdose because of the saturation of other detoxification pathways; this metabolite causes the hepatotoxicity that follows paracetamol overdose. Most of the phase I reactions in the liver are carried out by en- zymes of the large cytochrome P450 superfamily of proteins. They are all prefixed by ‘CYP’ and tens of different isoforms are recog- nized in the human liver. The commonest is the CYP3A4 isoform through which over 50% of marketed drugs are metabolized. Others such as CYP2D6 have special importance because they are poly- morphic, that is, they are encoded by CYP genes that have common variants that affect enzyme activity. The 10 major isoforms and some of the commoner drugs that are substrates for them are shown in Table 2.6.1. Certain drugs also selectively block CYP isoforms, which re- duce the elimination of drugs through these enzymes. Examples of these are cimetidine (1A2 and 2D6), amiodarone (2C9, 2D6, and 3A4), fluoxetine (2D6), ketoconazole (3A4 and 2C19), and ritonavir (3A4). Conversely, drug elimination through some CYP pathways is enhanced by drugs that act as inducers that increase enzyme activity by directly activating transcription of the corres- ponding CYP genes. The classical inducers

include phenobarbitone (2B6, 3A4), rifampicin (2B6, 2C9, and 3A4), and antiepileptics such as phenytoin and carbamazepine (both 3A4). Tobacco and ethanol are also inducers, albeit for minor CYP isoforms (1A2 and 2E1, respectively). A full list of CYP inhibitors and inducers (so-called Flockhart table) is available at this link: https://drug-interactions. medicine.iu.edu/Main-Table.aspx Other factors that affect hepatic drug metabolism are hep- atic blood flow (for drugs that are rapidly cleared), liver disease (only important in extensive liver disease or when there is ar- teriovenous shunting), and age. The metabolism of some drugs is impaired in old people and in babies younger than about 6 months, particularly premature babies. In both cases, this is due to reduced activity of the microsomal enzymes that includes CYP and nonCYP enzymes. For example, in neonates uridine diphosphoglucuronosyl transferase (EC 2.4.1.7), which conju- gates chloramphenicol, is relatively inactive; neonates eliminate chloramphenicol slowly, and may suffer peripheral circulatory

2.6 Principles of clinical pharmacology and drug therapy 81 collapse (the ‘grey syndrome’) when given the drug in weight- related doses that do not harm adults. Excretion The kidney is a major route of drug excretion. Other, usually minor, routes include the lungs (important for paraldehyde and gaseous anaesthetic gases), breast milk, sweat, tears, and genital secretions (alarming if the orange-red discoloration caused by rifampicin is not mentioned), saliva, and bile. Excretion in bile can be prominent for some drugs and this can lead to the reabsorption of some of the excreted compounds from the gut—a process called enterohepatic recycling. This recycling affects drugs such as oestradiol, rifampicin, and tetracyclines, and can substantially prolong their duration in the body. Drugs excreted in bile as water-soluble conjugates (after phase II metabolism—see earlier) may also be deconjugated by gut bacteria to release parent drug so facilitating enterohepatic recycling (e.g. chloramphenicol, digitoxin, indomethacin, and valproic acid). Renal excretion of drugs involves three separate processes: glomerular filtration, passive tubular reabsorption, and active tubular secretion (often through an SLC transporter). Thus: Total Table 2.6.1 The main cytochrome P450 isoforms (in bold) and their common substrate drugs 1A2 2C9 2D6 3A4,5,7 Clozapine NSAIDs β-Blockers Macrolide antibiotics Imipramine Diclofenac Metoprolol Clarithromycin Mexiletine Ibuprofen Propafenone Erythromycin Naproxen Naproxen Timolol NOT azithromycin Theophylline Celecoxib Antidepressants Antiarrhythmics 2B6 Sulphonylureas Amitriptyline Quinidine Bupropion Glibenclamide Clomipramine Benzodiazepines Cyclophosphamide Glipizide Desipramine Diazepam Efavirenz Tolbutamide Duloxetine Midazolam Ifosfamide Angiotensin II blockers Fluoxetine Triazolam Methadone Irbesartan Imipramine Immune modulators 2E1 Losartan Paroxetine Ciclosporin Anaesthetics NOT valsartan Venlafaxine Tacrolimus Enflurane NOT candesartan Antipsychotics HIV protease inhibitors Halothane Phenytoin Haloperidol Indinavir Isoflurane Sulfamethoxazole Risperidone Ritonavir Methoxyflurane Tamoxifen Opiates Saquinavir Sevoflurane Warfarin Codeine Antihistamines 2C19 oxycodone Astemizole Paracetamol Proton pump inhibitors Tramadol Chlorpheniramine Ethanol Omeprazole Dextromethorphan Calcium channel blockers 2C8 lansoprazole Flecainide Amlodipine Paclitaxel Pantoprazole Mexiletine Diltiazem Torsemide Antiepileptics Ondansetron Felodipine Amodiaquine Diazepam Tamoxifen Nifedipine Repaglinide Phenytoin Verapamil Phenobarbitone Statins Atorvastatin Simvastatin NOT pravastatin Others Amitriptyline Citalopram Clomipramine Clopidogrel Cyclophosphamide proguanil NOT rosuvastatin Imatinib Methadone Pimozide Quinine Sildenafil
Source: http://www.medicine.iupui.edu/CLINPHARM/ddis/clinical-table

82 section 2 Background to medicine renal clearance = Clearance by filtration + Clearance by secretion −
Retention by reabsorption. If a drug is mainly metabolized to inactive compounds, renal func- tion will have little impact on its elimination. However, if the drug itself or an active metabolite is excreted unchanged via the kidneys, changes in renal function will substantially affect its elimination. Glomerular filtration All drugs are filtered at the renal glomerulus, although molecules larger than 2 kDa are not freely filtered (e.g. insulin concentration in the ultrafiltrate is 0.89 × plasma) and proteins as large as albumin (69 kDa) are not filtered at all by a normal glomerulus. The extent of filtration is directly proportional to the glomerular filtration rate (GFR = 120 ml/min) and to the fraction of unbound drug in the plasma (fu), that is, rate of clearance by filtration = fu × GFR. If the total renal clearance of a drug is equal to fu × GFR, then it is cleared principally by filtration (it could be affected by the other two mechanisms, secretion and reabsorption, but they would have to cancel each other out). Examples of drugs whose clearance is similar to the GFR (after correction for protein binding) are digoxin, gen- tamicin, vancomycin, methotrexate, and ethambutol. As creatinine is cleared mainly by filtration, the creatinine clearance is useful in estimating the clearance rates of these drugs; although there is some secretion, which explains its tendency to overestimate GFR. Passive tubular reabsorption Drugs are passively reabsorbed by the renal tubules. The elimination of drugs with very low rates of renal clearance (i.e. approaching urine flow rate, or about 1–2 ml/min) will be significantly affected by changes in urine flow rate (because a doubling of flow rate will in- crease their rate of clearance by 1–2 ml/min, i.e. twofold). However, for weak acids and weak bases that are nonpolar in their union- ized form, the main factor affecting passive reabsorption is the pH of the renal tubular fluid (which can vary between 4.5 and 8), be- cause the extent of their ionization (and therefore of their passive reabsorption) depends on the urine pH in relation to the pKa of the drug. For example, in an alkaline urine, weak acids with a pKa below 7.5, such as salicylate (pKa 3), are more highly ionized, and there- fore less well reabsorbed. The reverse is true for weak bases with a pKa greater than 7.5, such as methamphetamine (pKa 10), whose re- absorption is reduced, and whose clearance is therefore enhanced, by an acid urine. These principles are put to good use in the treat- ment of overdose (see Chapter 10.4.1). Renal failure alters passive reabsorption indirectly, by changing both urine flow rate and pH. Active tubular secretion If the renal clearance of a drug exceeds GFR then there must be active secretion of the drug into the renal tubule. The active trans- port of organic anions and cations is dependent on specific trans- porter proteins (SLC and ABC transporters) in the cells lining the proximal tubule (detailed in https://www.ncbi.nlm.nih.gov/pubmed/28210973). There are broadly two functional groups: or- ganic anion and organic cation transporters. The organic anion transporters are responsible for the secretion of many β-lactam antibiotics, NSAIDs, antivirals, and ACE inhibitors, as well as acidic glutathione and glucuronide-conjugated drug metabolites. Probenecid is a generic inhibitor of anion transport and anionic transport capacity can be measured by p-aminohippuric acid (PAH) excretion. Substrates for the organic cation transporters include en- dogenous cations (e.g. guanidine, choline, N-methylnicotinamide, and monoamine neurotransmitters), cationic toxins (e.g. 1-methyl- 4-phenylpyridinium, MPP+), and cationic drugs (e.g. cimetidine, procainamide, quinidine, vecuronium, cardiac glycosides). Both ci- metidine and trimethoprim can affect cationic transport. Blockade of kidney drug transporters explains several drug–drug interactions (see following paragraphs). Nonlinear kinetics Most drugs show linear kinetics (i.e. an increase in dose will cause a similar-fold increase in plasma concentration). There are excep- tions, however, and when a drug shows nonlinear behaviour (e.g. a twofold increase in dose produces a tenfold increase in plasma

level) it implies that some aspect of the drug's elimination pathway has saturated. Some tricyclic antidepressants and the selective serotonin reuptake inhibitor (SSRI) paroxetine show this behaviour. But the best-known example is phenytoin (see Fig. 2.6.5), whose oxidation through CYP 2C19 in the liver is saturated within the therapeutic range. Inspection of the curves in Fig. 2.6.5 shows how small in- crements in the dose of phenytoin can produce large increments in its plasma level and hence neurotoxicity. In fact, many drugs taken in overdose saturate their elimination pathways, and this is clearly shown by drugs such as ethanol, salicylate, and paracetamol. The pharmacodynamic process Pharmacodynamics addresses the question 'How does a drug pro- duce its pharmacological effects?' Of course, this concerns both ad- verse as well as therapeutic effects. Drugs have many different mechanisms of action but the overwhelming majority are mediated through receptors, which they either block or activate. 0 0 100 200 300 Daily dose of PHENYTOIN (mg) 400 500 600 25 50 75 Serum [PHENYTOIN] (μmol/litre) 100 125 150 175 200 Fig. 2.6.5 Nonlinear kinetics. The plasma level achieved after repeated phenytoin dosing is shown versus the corresponding phenytoin dose for three hypothetical patients. The plots are not straight lines but rise steeply within the therapeutic range (between the dashed lines) as the CYP2C19 metabolic pathway for phenytoin saturates.

2.6 Principles of clinical pharmacology and drug therapy 83 Actions via direct effects on receptors Receptors are proteins situated either in cell membranes or within the cellular cytoplasm. For each receptor type there is usually an en- dogenous molecule (or ligand) that binds to the receptor. There are broadly four types of receptors: G protein-coupled receptors, ion channels, nuclear receptors, and tyrosine kinase receptors. Drug mol- ecules target the same binding site on the receptor as the endogenous ligand and may activate the receptor, block the binding of the en- dogenous ligand, or a have mixture of both effects. These actions are referred to as agonism, antagonism, and partial agonism, respectively. This terminology is made clearer by considering these actions in terms of the μ opioid receptor. Morphine acts as an agonist at μ opioid receptors to cause analgesia. This μ receptor activation mimics the ac- tion of endogenous analgesic peptides such as enkephalin and endor- phin. Compare this with naloxone, which behaves as an antagonist at the same receptor and blocks its activation by either morphine or other opiates. Importantly, in the absence of an agonist, a pure antag- onist such as naloxone has no pharmacological action through the μ opiate receptor. This contrasts with buprenorphine that behaves as a partial agonist at the μ receptor. Hence, in the absence of an agonist such as morphine, buprenorphine is able to activate the μ receptor, but it is not able to produce an analgesic effect as large as morphine (this explains the 'ceiling' effect seen clinically). Yet, in the presence of a full agonist such as morphine, buprenorphine can block μ receptor activa- tion (this explains why buprenorphine can trigger opiate withdrawal). Receptor subtypes In many cases, a receptor will have subtypes, and drugs may have sub- type selectivity. For example, there at least three subtypes of opioid receptors: μ, κ, and δ. The μ and δ are both involved in analgesia, gastrointestinal motility, and respiratory depression, and κ is involved in analgesia, sedation, and miosis. These receptors are variably distrib- uted in the nervous system. Most opiates act at μ receptors, but none is completely selective and they may act at other subtypes. Long-term effects of drugs at receptors During long-term therapy, the effects of a drug may be altered by adaptive responses, usually accompanied by either increases ('upregulation') or decreases ('downregulation') in receptor num- bers. Such changes may explain both the therapeutic and adverse effects of drugs. Examples include: • The therapeutic response to antidepressants (e.g. an SSRI) that may involve changes in receptors within the central nervous system secondary to the increased synaptic levels of neurotransmitter

caused by these drugs. This probably explains why the therapeutic response to antidepressants takes a few weeks to emerge. • The way in which the response to l-dopa in Parkinson's disease changes during long-term administration (e.g. producing the 'on–off' effect). • Withdrawal syndromes that may occur because long-term changes become unopposed when the drug is withdrawn (e.g. after the long- term use of opiates or benzodiazepines). Actions via direct effects on second messengers When an agonist stimulates a membrane-bound receptor, its effect is usually signalled in one of two ways: either through a so-called second messenger (e.g. cAMP, diacylglycerol, or inositol trisphosphate) or by changing the activity of an ion channel linked to the receptor. Some drugs may act by affecting second messen- gers directly. For example, some drugs block phosphodiesterases that normally metabolize the second messengers cAMP and cGMP. Several types of phosphodiesterases regulate cAMP levels and theo- phylline and caffeine work by inhibiting them nonspecifically. In contrast, type 5 phosphodiesterase (EC 3.1.4.17) specifically de- grades cGMP in smooth muscle and is selectively inhibited by drugs such as sildenafil and vardenafil. Actions via indirect alterations of the effects of endogenous receptor ligands Drugs may oppose the physiological effects of the endogenous ligand. For example, glucagon is a physiological antagonist of the actions of insulin; hence its use to treat hypoglycaemia. Other drugs act indirectly on a receptor by altering the levels of the endogenous ligand for that receptor. They can do this in a number of ways: Increase in endogenous release Some drugs enhance release of the endogenous ligand. For example, amphetamine and tyramine increase the release of dopamine and noradrenaline, respectively, from nerve terminals. Prevention of endogenous release or synthesis The release of many neurotransmitters from nerve terminals is regulated by inhibitory receptors activated by the neurotransmitter itself. Hence, α2-receptors on noradrenergic nerve terminals re- duce noradrenaline release into the synapse. Clonidine and α- methyldopa reduce the release of noradrenaline by activating these receptors (α-methyldopa actually works through its metabolite α-methylnoradrenaline) and is the basis of their antihypertensive action. Drugs can also reduce the production of the endogenous ligand rather than affect release of a preformed store of the ligand. For ex- ample, angiotensin II (which activates the angiotensin II receptor to cause vasoconstriction and aldosterone release) is produced enzymatically from angiotensin I. ACE inhibitors block the con- verting enzyme (cleaving angiotensin I to angiotensin II) and renin inhibitors (e.g. aliskiren) block the enzymatic cleavage of angio- tensin I from angiotensinogen. Inhibition of endogenous reuptake Many neurotransmitters are pumped back into their corresponding nerve terminals. The transporters that carry out this reuptake are targeted by certain psychoactive drugs. Many antidepressants, for example, block the reuptake of noradrenaline (such as amitrip- tyline), or 5-hydroxytryptamine (serotonin, 5HT) (such as fluox- etine), or both (such as venlafaxine). Reuptake of γ-aminobutyric acid (GABA) is blocked by the anticonvulsant tiagabine. Inhibition of endogenous metabolism Drugs can also increase the effect of an endogenous ligand by blocking its metabolism. Examples of these include: cholinesterase inhibitors for acetylcholine (e.g. neostigmine), vigabatrin for GABA, and monoamine oxidase inhibitors (MAO) inhibitors for catechol- amines and 5HT (e.g. tranylcypromine).

 The MAO inhibitors have some selectivity for the two forms of MAO (types A and B), which explains their use both as antidepres- sants and antiparkinsonian agents. For example, selegiline select- ively inhibits monoamine oxidase type B. This results in blockade of dopamine metabolism in the central nervous system and enhances the action of l-dopa in parkinsonism. However, because MAO in the gut and liver is predominantly type A, selegiline does not pro- duce the 'cheese reaction' (due to tyramine and other amines, see following

paragraphs) seen with nonselective MAO inhibitors (e.g. tranylcypromine). In contrast, the antidepressant moclobemide se- lectively inhibits MAO A. Moclobemide is also unusual in being a reversible inhibitor of MAO. All other MAO inhibitors block MAO irreversibly, so that recovery requires synthesis of new enzyme. This explains the slow offset of their action (7–10 days) and why moclobemide does not produce a ‘cheese reaction’. Actions by inhibiting the movement of ions Since cations (such as sodium, potassium, and calcium) and anions (such as chloride and iodide) have so many important roles in the maintenance of normal cellular function, inhibition of their trans- port is an important mechanism of drug action. This movement of cations and anions across membranes can be either through trans- porters or channels. Diuretics Most diuretics reduce sodium reabsorption in the renal tubules by targeting specific transporters or ion channels. Hence, loop diuretics (e.g. furosemide and bumetanide) block the Na–K–Cl transporter (NKCC2) in the ascending limb of Henle’s loop. Thiazide diuretics inhibit Na–Cl cotransporter (NCC) in the distal convoluted tubule and potassium-sparing diuretics (amiloride and triamterene) block the epithelial sodium channels in the collecting ducts (ENaC). Calcium channel antagonists The calcium antagonists, such as verapamil, diltiazem, and the dihydropyridines (e.g. nifedipine), inhibit the transport of calcium via voltage-operated calcium channels (of the l-type). They are able to exert different effects in different tissues (e.g. verapamil slows atrio- ventricular nodal conduction in the heart but nifedipine does not) because of separate binding sites within the l-type calcium channel. Drugs acting on potassium channels The potassium permeability of cell membranes affects their mem- brane potential and is controlled by potassium (K) channels. They are a very large and diverse group of ion channels and drugs may either open or close (or block them). Drugs that open potassium channels include vascular smooth muscle relaxants, such as minoxidil and nicorandil (targeting KATP channels). The same KATP channels are closed by sulphonylureas such as gliclazide. Of the many potassium channels in the heart, the iKr channel plays a key role as it is involved in repolarization of the myocyte. Blockade of the iKr channels explains why many drugs cause prolongation of the QT interval and are hence arrhythmogenic (e.g. terfenadine). Drugs acting on chloride channels Intracellular chloride plays a key role in neuronal excitability. Hence, the inhibitory effect of the neurotransmitter GABA on neurons is due to chloride entry into neurons through GABA-activated chloride channels. Progabide behaves as a GABA agonist and GABA-activated chloride currents are increased by benzodiazepines and barbiturates. The antiseizure activity of these drugs is directly attributed the neuronal hyperpolarization that results. Some anaesthetic agents also probably rely on effects on chloride currents for their general anaesthetic effect. They form a diverse group of agents, such as the halogenated hydrocarbons (halothane, trichloroethylene), and nonhalogenated agents (nitrous oxide, ether, cyclopropane), and were previously thought to influence neuronal excitability by non-specific effects on the lipid phase of the cell membrane, changing its biophysical properties and hence the kinetics of ion channels. More recent evidence has shown that they specifically affect currents through GABA/glycine-coupled ion channels. Others (such as ketamine and nitrous oxide) antagonize the excitatory NMDA-coupled ion channel. Actions via enzyme inhibition Drugs often act by directly inhibiting enzymes. Inhibitors of cholin- esterase and MAO (see earlier paragraphs), for example, have been in therapeutic use for more than half a century. The metabolism of purines involves the oxidation of xanthine and hypoxanthine to uric acid by xanthine oxidase. Hence, blockade of this enzyme with allopurinol prevents excessive uric acid produc- tion during tumour lysis and reduces the frequency of gout. The cardiac glycosides act by inhibiting the Na/K pump. This changes the distribution of sodium across excitable membranes es- pecially in the heart: and the secondary change in intracellular cal- cium causes the cells’ contractility to increase. Other drugs that act via

enzyme inhibition include warfarin (vitamin K epoxide reductase), aspirin, and other NSAIDs, targeting the cyclo-oxygenase (COX) enzymes involved in prostaglandin synthesis, ACE inhibitors, disulfiram (alcohol dehydrogenase), some anticancer drugs such as cytarabine (DNA polymerase), and imatinib (chronic myelogenous leukaemia-specific tyrosine kinase), and some anti-infective drugs (bacterial or viral enzymes; e.g. tri- methoprim inhibits bacterial dihydrofolate reductase, the quin- olones inhibit bacterial DNA gyrase, and zidovudine and didanosine inhibit the reverse transcriptase of HIV). Danazol and stanozolol are examples of drugs that inhibit an en- zyme indirectly—they stimulate the production of an inhibitor of C1 esterase and are used to treat hereditary angio-oedema, in which there is reduced plasma activity of the inhibitor. Actions via enzyme activation or direct enzymatic activity Some drugs either activate enzymes or are enzymes themselves. The clotting and fibrinolytic factors are enzymes, and certain drugs that act on clotting and fibrinolysis do so by increasing their activity. Heparin acts by activating antithrombin III. The thrombolytic drugs streptokinase, alteplase, and tenecteplase activate plasminogen. Deficiencies of clotting factors can be treated by replacing defi- cient enzymes of the clotting pathway (e.g. factor VIII in patients with haemophilia and fresh frozen plasma in warfarin toxicity). Pancreatic enzymes are used in treating malabsorption in patients with chronic pancreatic insufficiency. Rasburicase is used to prevent the hyperuricaemia that accom- panies the tumour lysis syndrome during the treatment of acute

2.6 Principles of clinical pharmacology and drug therapy 85 leukaemias and lymphomas. It is recombinant urate acid oxidase that directly catalyses the breakdown of uric acid to the more soluble allantoin. Actions via other miscellaneous effects Chelating agents Drugs that chelate metals can be used to hasten their removal from the body (see Chapter 10.4.1). Calcium sodium edetate chelates many divalent and trivalent metals and is used to treat poisoning, particularly with lead. Dimercaprol chelates some heavy metals and is used to treat mercury and gold poisoning. Desferrioxamine chelates iron and is used in treating iron poisoning and the iron overload that occurs with repeated blood transfusion (as in thal- assaemia). Penicillamine chelates copper and is used in treating hepatolenticular degeneration (Wilson’s disease); it is also used to complex cystine and thus prevent renal damage in cystinuria. Osmotic diuretics Mannitol is freely filtered at the glomerulus but the renal tubules reabsorb relatively small amounts. It therefore increases the concen- tration of osmotically active solute in the tubular fluid, the subse- quent influx of water massively augments urine flow rates. Replacement of vitamins and minerals Some drugs are used simply to replace deficiencies (e.g. ferrous salts in iron deficiency anaemia and hydroxocobalamin (vitamin B12) in vitamin B12 deficiency). Stereoisomerism and drug action Stereoisomerism (chirality) of organic compounds is due to asym- metry in one or more of their atoms (usually carbon), resulting in two or more three-dimensional structures (enantiomers) that cannot be superimposed on each other. Several different terminologies are used to describe the two chiral partners: R and S (from the Latin rectus = right and sinister = left), (+) -d and (–)-l and d and l (from the Latin dexter = right and laevus = left). Examples of drug enantiomers are R-warfarin and S-warfarin, d-glucose (dextrose) and l-glucose (laevulose), and d- propranolol and l-propranolol. Of all synthetic drugs used in clinical practice, almost 50% are chiral and about 90% of those are marketed in their racemic form (i.e. as an equal mixture of the two enantiomers). Examples include d,l- propranolol and R,S-warfarin. Naproxen is one of the few examples of a synthetic compound that is marketed as a single enantiomer (hence an enantiopure drug). In contrast, naturally occurring and semisynthetic compounds are almost all chiral and almost all are marketed as a single isomer. Examples include d-glucose (dextrose) and the naturally occurring

amino acids (e.g. l-dopa), l-thyroxine, and l-noradrenaline. Enantiomers often have different pharmacological actions. For example, l-propranolol is a β-blocker, whereas d-propranolol has membrane-stabilizing activity like that of local anaesthetics; l- sotalol is a β-blocker, whereas d-sotalol has antiarrhythmic effects like those of amiodarone. Sometimes these differences between the pharmacology of en- antiomers can separate the therapeutic and adverse effects of a ra-cemate. For example, R-thalidomide is responsible for the sedative effects of R,S-thalidomide, while the teratogenic effect resides in the S enantiomer. However, this cannot be exploited clinically to limit thalidomide toxicity, because the two enantiomers spontaneously interconvert in the body. This so-called 'chiral inversion' also occurs in some NSAIDs such as ibuprofen. The interaction of a drug with its target (such as a receptor or en- zyme) is often stereo-selective, so enantiomers may show marked differences in potency. For example, S-warfarin is some five times more potent an anticoagulant than R-warfarin, and S-citalopram is 30 times more potent as an SSRI than R-citalopram. In some cases, one enantiomer is completely inactive therapeutically (e.g. levofloxacin is the active antimicrobial enantiomer in ofloxacin with dextrofloxacin being completely inactive). The enantiomers may have different pharmacokinetics. For ex- ample, the half-lives of S-warfarin and R-warfarin average around 30 h and 50 h and they are metabolized to 7-hydroxywarfarin and warfarin alcohols, respectively. This is important in some drug interactions with warfarin, because drugs inhibiting warfarin me- tabolism (such as metronidazole) primarily affect the more potent enantiomer, S-warfarin. Omeprazole provides a further example. The single enantiomer of omeprazole, S-omeprazole, has almost twice the bioavailability of R-omeprazole. Hence, esomeprazole (S-omeprazole) gives plasma levels of omeprazole 70 to 90% higher than racemic omeprazole. However, both enantiomers are converted to the same active intermediate and since this lacks a chiral centre the enantiomers are equiactive if they achieve the same plasma level. Because of these caveats, despite the appeal of prescribing single- drug enantiomers, in most instances the single enantiomer has failed to show a substantial clinical advantage over the racemate. When comparing racemates to single enantiomers in clinical trials, it is critical they are compared at comparable doses of the active enantiomer. The therapeutic process The question associated with the therapeutic process is, 'Is the pharmacological effect being translated into a therapeutic effect?' Translation of pharmacological effect into therapeutic effect during short-term therapy The short-term therapeutic and toxic effects of drugs occur as a re- sult of the pharmacological actions discussed earlier. However, the translation of molecular and cellular pharmacological effects into the therapeutic or toxic effect is not a simple process, and involves several translational stages at different pharmacological and physio- logical levels. Take, for example, the action of salbutamol, a β2-adrenoceptor agonist, in the treatment of asthma. Salbutamol stimulates bronchial β2-adrenoceptors, and so increases the activity of adenylate cyclase; this is its pharmacological effect at the molecular level. The increase in adenylate cyclase activity raises the intracellular concentration of cAMP that leads to relaxation of the bronchial smooth muscle cells; this is the cellular effect. This leads to dilatation of the bronchioles, reduces the resistance to air flow in the bronchial tree, and improves gas exchange; this is the effect on tissue and whole organ function.

 Finally, the patient feels less breathless and oxygen saturation may improve; this is the desired clinical effect. This analysis of the short-term effects of a drug teaches us sev- eral things about drug action: how drug action may be modified; how therapeutic and adverse effects may be mediated via different pharmacological effects; the relation between the pharmacological effects of a drug and the rate of onset or duration of its

therapeutic action; and drug–disease interactions. How to modify drug action It is often possible to modify drug action positively or negatively. For example, a methylxanthine derivative, such as theophylline, which blocks cAMP breakdown by its inhibition of phosphodiesterase, should potentiate the action of salbutamol. This turns out to be both a beneficial and an adverse interaction—beneficial because theo- phylline enhances the therapeutic action of salbutamol, adverse because it enhances the hypokalaemia (by stimulating Na+/K+- ATPase) and tachycardia (by activating cardiac β-adrenoceptors) that salbutamol causes. Different pharmacological actions may mediate therapeutic and adverse or other effects Some drugs have more than one molecular mechanism of action, and different therapeutic effects of a drug may result from different actions. For example, tetracycline acts against bacteria by interfering with their protein synthesis, but in acne, it helps by interfering with sebum production in sebaceous glands. Similarly, a therapeutic effect may be brought about by one pharmacological action and an adverse effect by another. For ex- ample, the antibacterial action of erythromycin is due to inhibition of bacterial ribosomal function, but its gastrointestinal side effects are due to activation of motilin receptors in the human gut. Other macrolides such as azithromycin are much weaker motilin mimetics and hence produce much less vomiting and diarrhoea. A drug may also produce therapeutic and adverse effects through the same molecular mechanism but in different tissues. For example, the inhibition of β2-adrenoceptors within muscle spindles by pro- pranolol reduces benign essential tremor, but blocking the same receptors in the lung causes bronchoconstriction in susceptible in- dividuals and impairs glycogenolysis in the liver (which can delay a diabetic's recovery from hypoglycaemia). The relation between the pharmacological actions of a drug and the rate of onset and duration of its effects The rate of onset of a drug's effects depends not only on its pharma- cokinetics (i.e. the time it takes for a therapeutic concentration of drug to build up at its site of action), but also on how long it takes for the full pharmacodynamic sequence of events to unroll. In the case of salbutamol, the time between β2-adrenoceptor stimulation and bronchodilatation is of the order of a few minutes. However, for other drugs, the sequence of events takes much longer. For ex- ample, corticosteroids bind to an intracellular receptor protein in the cytoplasm of target cells to form a steroid–receptor complex. This complex translocates to the nucleus, where it binds to regu- latory sequences on target genes to cause RNA transcription. The induction of de novo protein synthesis by RNA transcription and translation takes several hours, explaining the slow onset of cortico- steroid effects. Similarly, the duration of action of a drug is related not only to the time it takes for the drug to be cleared from the body, but also to the duration of its pharmacological effects. For example, aspirin inhibits COX-1 by acetylating a serine moiety at the active site of the enzyme. As platelets cannot synthesize new protein, the re- covery from aspirin requires the appearance of new platelets from the marrow. This process can take 7 to 10 days to restore peripheral platelet function. Drug–disease interactions Because of the complex links between the pharmacological effects of a drug and its therapeutic or adverse effects, the pathophysiology of the disease being treated, or of other coincidental diseases, can vari- ously impact the way in which the pharmacological effect is trans- lated into a therapeutic effect. The use of digoxin in cardiac failure exemplifies this. Digoxin inhibits the activity of the membrane-bound Na+,K+-ATPase. Pump inhibition increases the intracellular concentration of so- dium, which secondarily raises intracellular calcium to produce a positive inotropic effect. The various steps in this process are af- fected by drug–disease interactions. Hypokalaemia, for example, is a common side effect of diuretic use to manage fluid overload in heart failure. Low extracellular potassium increases pump block by raising the affinity of digoxin for the sodium pump. This risks cal- cium overload and hence digoxin toxicity. Coincident diseases also affect digoxin's therapeutic effect. In hyperthyroidism,

the Na+,K+- ATPase is upregulated, resulting in resistance to the inhibitory ef- fects of digoxin. So, increasing the dose may cause digoxin toxicity without ever producing a therapeutic effect. In patients with chronic cor pulmonale, tissue hypoxia may also lead to Na/K pump inhib- ition and cardiac arrhythmias without increasing myocardial con- tractility. In patients with hypertrophic obstructive cardiomyopathy, although digoxin increases the rate of myocardial contractility, a rise in cardiac output is prevented because left ventricular outflow re- mains obstructed. Thus even when it can be shown that a drug is having its ex- pected action at a particular pharmacological or physiological level, it cannot automatically be assumed that it will have a thera- peutic effect. Interactions with circadian rhythms (chronopharmacology) Most physiological functions follow a circadian rhythm, so some drug effects are liable to differ at different phases of the rhythm. In some instances, the difference is dramatic. The timing of cortico- steroid dosing is a good example. Peak ACTH release from the pi- tuitary occurs at night leading to plasma cortisol peaks at around 08.00 a.m. when ACTH levels are at trough. So, exogenous cortisol in the morning will have no impact on ACTH release. But given in the evening it will completely inhibit night-time ACTH. For this reason, cortisol given once daily in the morning causes much less pi- tuitary inhibition than the same dose given in the evening, or spread throughout the day. The cholesterol-lowering effect of some statins is also affected by the time of administration because cholesterol synthesis has a cir- cadian rhythm with most synthesis occurring at night. Short-acting statins are hence more effective if given at night (e.g. simvastatin, half-life c.3 h). For longer-acting statins there is no discernible dif- ference, as the drug level will still be high enough during the night

2.6 Principles of clinical pharmacology and drug therapy 87 even with morning dosing (e.g. atorvastatin half-life c.20 h with even longer-lived active metabolites). Translation of pharmacological effect into therapeutic effect: Long-term therapy During prolonged therapy, adaptation may develop to the short- term pharmacological effects of the drug with several consequences. Therapeutic effects through adaptation In immunization, by adapting to an initial immunological challenge, the immune system develops the ability to respond to a subsequent similar challenge (e.g. tetanus immunization). Although tricyclic antidepressants rapidly inhibit reuptake of noradrenaline and 5-HT in the brain, the therapeutic effect of these drugs takes 1 to 2 weeks to become evident. In certain brain regions, there is adaptation to the increased concentrations of neurotransmit- ters in the synaptic cleft with reduction in numbers of postsynaptic receptors. Part of this adaptive downregulation probably explains their therapeutic effects. Tolerance: Increasing ineffectiveness of therapy Tolerance is a state of decreased responsiveness to a drug, resulting from previous exposure, either to the same drug or to one with similar short-term effects. For example, it can develop to the vasoconstricting effects of ephedrine nose drops, used to treat vasomotor rhinitis: as ephedrine acts by releasing noradrenaline from sympathetic nerve endings, noradrenaline depletion will reduce the effectiveness of ephedrine. Patients taking long-term glyceryl trinitrate, particularly from transdermal patches, become tolerant to its acute effects. To avoid this, a patch should be applied for no longer than 18 h. This effect probably reflects depletion of tissue sulphydryl groups by oxida- tion to disulphide groups. Some oral preparations of isosorbide mononitrate are formulated to release their contents over 18 h for the same reason. Physiological tolerance by homoeostatic mechanisms Secondary hyperaldosteronism is a physiological response to so- dium loss produced by loop or thiazide diuretics. The enhanced potassium excretion that it causes may be reduced by using a potassium-sparing diuretic (e.g. amiloride) or the aldosterone an- tagonist spironolactone. Another type of physiological tolerance occurs in patients given the carbonic anhydrase inhibitor acetazolamide.

This causes both a diuresis and a kaluresis. However, these effects are only sustained for a matter of days, because the large amounts of bicarbonate lost from the kidney causes a metabolic acidosis. Interestingly, topical carbonic anhydrase inhibitors do not show the same tolerance when they are used in chronic glaucoma. Metabolic tolerance Metabolic tolerance results from faster metabolic clearance of the drug. The commonest cause is induction of hepatic P450 en- zymes by drugs such as barbiturates, phenytoin, carbamazepine, or rifampicin. Occasionally, drugs may induce their own metabolic clearance—a phenomenon called 'autoinduction' (e.g. carbamaze- pine and artemisinin). Withdrawal syndromes A common, but not inevitable, outcome of an adaptive response to long-term drug use is a withdrawal response either when the drug is withdrawn or when an antagonist is given. A withdrawal syndrome occurs in opiate users when the opiate is withdrawn or an antagonist, such as naloxone, is given. The symp- toms consist of yawning, rhinorrhoea, and sweating, followed by shivering and goose flesh ('cold turkey'); later, nausea, vomiting, diarrhoea, and hypertension may occur. The acute syndrome sub- sides within a week, but the anxious and disturbed sleep patterns may last for several weeks or months. This syndrome can be avoided by introducing increasing doses of methadone as the opiate is with- drawn; methadone has a longer half-life than opiates such as heroin and causes much less withdrawal when it is eventually discontinued. Delirium tremens is a feature of alcohol withdrawal in chronic alcohol abusers. This syndrome consists of disorientation and visual hallucinations. Withdrawal of benzodiazepines after long-term therapy may result in a disturbance of sleep pattern (rebound in- somnia associated with abnormal sleep patterns), agitation, restless- ness, and occasionally epileptic convulsions. The risk of angina pectoris, myocardial infarction, and ar- rhythmias is increased in patients with ischaemic heart disease when β-adrenoceptor antagonists are withdrawn after long-term use. This may be due to upregulation in the number of cardiac β-adrenoceptors, with increased sensitivity to the β-adrenergic effects of sympathetic stimulation. Long-term therapy with corticosteroids suppresses pituitary secretion of ACTH, leading to adrenal cortical atrophy. When treatment is suddenly withdrawn, ACTH secretion may take sev- eral weeks or months to recover. During this time patients risk an Addisonian crisis if stressed (e.g. if they have a myocardial infarction or are operated on). Adverse effects directly due to adaptation Patients taking a neuroleptic drug (e.g. fluphenazine or haloperidol) continuously for a period of years commonly develop abnormal movements (known collectively as tardive dyskinesia). The face, mouth, and tongue are often affected, with stereotyped sucking and smacking of the lips, lateral jaw movements, and darting move- ments of the tongue. Occasionally more widespread dyskinesia may resemble choreoathetosis. The long-term blockade of central dopa- mine receptors is thought to lead to increased central sensitivity to the effects of dopamine; this partly reflects increases in the number of dopamine receptors. The risk of tardive dyskinesia is much lower in the newer atypical agents such as quetiapine and risperidone; the atypical clozapine has even been suggested to ameliorate established tardive dyskinesia. Adverse drug reactions An adverse drug reaction can be defined as 'an unwanted or harmful reaction experienced following administration of a drug, or com- bination of drugs, under normal conditions of use and is suspected as being related to the drug (or combination)'. Sometimes, the term is broadened to include all adverse reactions whether the drug is dosed appropriately or not. Hence the term 'adverse drug event',

 which includes drug prescription and dispensing errors and failures of patient compliance, is also used. Incidence The scale of the problem is probably still underestimated. Data suggests that: • 1 to 4% of acute hospital admissions are due to an adverse drug reaction • 5 to 20% of inpatients suffer an adverse drug reaction at some point in their

admission • up to 3% of deaths in hospital inpatients are due to an adverse drug reaction In addition to the morbidity and mortality, adverse drug reactions are hugely expensive for healthcare systems. In the United Kingdom the cost probably exceeds several billion pounds annually, and in the United States of America some estimates have exceeded 100 billion dollars annually. Classification Dose-related adverse reactions Dose-related adverse reactions are usually due to an exaggeration of a known pharmacological effect of the drug. The pharmacological effect that produces the adverse reaction may be responsible for the therapeutic effect (e.g. hypoglycaemia following insulin administra- tion), or be a parallel effect (e.g. the anticholinergic action of tri- cyclic antidepressants, producing a dry mouth or urinary retention). Dose-related adverse reactions may occur because of variations in the pharmaceutical, pharmacokinetic, or pharmacodynamic properties of a drug, often due to a drug–disease interaction or a pharmacogenetic characteristic of the patient. These mechanisms are illustrated in the following paragraphs. Pharmaceutical problem Adverse reactions can be caused by a contaminant (e.g. pyrogens or even bacteria in intravenous formulations). This is obviously a hazard for illicit drugs that are used intravenously: not only are they dissolved under nonsterile conditions, they may also be ‘cut’ with other drugs (e.g. quinine, caffeine, and procaine). Febrile reactions can occur routinely with some manu- factured drugs given intravenously (e.g. amphotericin B and bisphosphonates), but otherwise fever should be treated very sus- piciously and the drug and giving set should be sent for microbio- logical screening. Out-of-date formulations may sometimes cause adverse reac- tions because of degradation products. For example, outdated tetra- cycline may cause Fanconi’s syndrome, because it is degraded to anhydrotetracycline and epiandrotetracycline. The omission of the preservative citric acid from tetracycline formulations has reduced the risk of this effect, but has not removed it completely. Very occasionally a drug has been incorrectly labelled by the manu- facturer. Of more concern is the rise of counterfeit medicines (see Chapter 2.10). They are thought to account for 15% of drug sales world- wide and in parts of Asia and Africa the figure probably exceeds 50% of sales. Counterfeit agents frequently contain none of the active drug, or subtherapeutic doses, and may also contain additional chemicals or drugs that are harmful. For example, ethylene glycol has been used in the manufacture of fake paracetamol syrups (for its sweetness and vis- cosity) and caused a number of deaths, especially in children. Pharmacokinetic variation There is often enormous variation in rate of drug elimination be- tween individuals. This variation is greatest for drugs cleared by hep- atic metabolism and is determined by several factors, which may be genetic, environmental (diet, smoking, alcohol), or hepatic (blood flow and intrinsic drug-metabolizing capacity). On top of this vari- ability, pharmacogenetic or hepatic abnormalities may be associated with specific adverse reactions. In addition, renal and cardiac dis- ease can change drug pharmacokinetics. The impact of pharmaco- genetics is discussed in the following paragraphs. The reserve of the liver parenchyma is large, so adverse reactions due to impaired hepatic metabolism are uncommon. Nevertheless, in patients with severe liver disease caution is needed when a drug has a low therapeutic index or is subject to extensive first-pass me- tabolism. For example, severely impaired hepatocellular function can reduce the clearance of drugs such as phenytoin, theophylline, and warfarin. The portosystemic shunting seen in advanced cirrhosis can also dramatically increase the bioavailability of drugs normally cleared rapidly by the liver (e.g. morphine and other narcotic anal- gesics, propranolol, and chlormethiazole). Drugs that the kidneys excrete unchanged, or whose active metabolites are excreted, will accumulate in renal failure. Important examples include digoxin, atenolol, lithium, aminoglycoside antibiotics, and vancomycin. Pharmacodynamic variation The variability in pharmacodynamic response to a drug may be compounded by concomitant disease. The patient

with cirrhosis is a good example: impaired hepatocellular function can reduce the synthesis of clotting factors; the presence of oesophageal and gastric varices imposes a further risk of upper gastrointestinal bleeding and patients with alcoholic liver disease may have additional thrombo- cytopenia and impaired platelet function. Judging the response to an anticoagulant, antithrombotic, or antiplatelet drug in this setting is very difficult, and the risk of haemorrhage is high. A cirrhotic patient is also at risk of exaggerated sedation and en- cephalopathy from opiates or long-acting benzodiazepines that are cleared by the liver. The hypokalaemic effects of diuretics or amphotericin carry a similar risk. Patients with cirrhosis also have inappropriate salt and water retention that can be worsened by drugs such as NSAIDs, corticosteroids, and carbamazepine. The pharmacodynamic effects of some drugs may be altered by changes in fluid and electrolyte balance. For example, both hypo- kalaemia and hypercalcaemia potentiate the toxic effects of di- goxin. Hypocalcaemia prolongs the action of muscle relaxants such as tubocurarine. Fluid depletion and hypovolaemia enhances the hypotensive effects of antihypertensive drugs. Non-dose-related adverse reactions Non-dose-related adverse drug reactions are caused by immuno- logical and pharmacogenetic mechanisms. Allergic drug reactions are unrelated to the usual pharmacological effects of the drug, and frequently show a delay between the first ex- posure to the drug and the subsequent adverse reaction. Very small doses of the drug may elicit the reaction once allergy is established.

2.6 Principles of clinical pharmacology and drug therapy 89 The reaction disappears on withdrawal; and the illness is often rec- ognizable as a form of immunological reaction (e.g. rash, serum sickness, anaphylaxis, asthma, urticaria, angio-oedema). Factors associated with an increased risk of allergic drug reac- tions include a history of allergic disorders (patients with a history of atopic disease and those with hereditary angio-oedema) and HLA status (e.g. the risk of severe skin reactions to carbamazepine and allopurinol is strongly associated with specific alleles of the HLA B locus). Drug allergy and its manifestations are classifiable according to the classification of hypersensitivity reactions (i.e. into four types, I–IV). Type I reactions (anaphylaxis; immediate hypersensitivity) In type I reactions, the drug or metabolite interacts with IgE mol- ecules fixed to cells, particularly tissue mast cells and basophil leucocytes. This triggers a process that leads to the release of pharma- cological mediators (a cocktail of histamine, 5-HT, kinins, and ara- chidonic acid derivatives including leukotrienes), which cause the allergic response. Clinically, type I reactions manifest as urticaria, rhinitis, bron- chial asthma, angio-oedema, and anaphylactic shock. Drugs likely to cause anaphylactic shock include penicillins, local anaesthetics, and iodide-containing radiographic contrast media. Type II reactions (cytotoxic reactions) In type II reactions, a circulating antibody of the IgG, IgM, or IgA class interacts with a hapten (drug) combined with a cell membrane constituent (protein), to form a hapten–protein/antigen–antibody complex. Complement is then activated and cell lysis occurs. Most examples are haematological: thrombocytopenia from quinidine or its enantiomer quinine (‘gin and tonic purpura’), and occasionally rifampicin; ‘immune’ neutropenia, which can be difficult to distin- guish from neutropenia occurring as a direct toxic effect on the bone marrow—phenylbutazone, carbimazole, tolbutamide, anticonvul- sants, chlorpropamide, and metronidazole have all been incrimin- ated; and the haemolytic anaemias that penicillins, cephalosporins, rifampicin, and quinidine can also produce by this mechanism. Type III reactions (immune-complex reactions) In type III reactions, antibody (IgG) combines with antigen to form immune complexes that deposit in tissues; complement is then ac- tivated, causing capillary endothelial damage. Serum sickness, with fever, arthritis, enlarged lymph nodes, urticaria, and maculopapular rashes, is the typical drug reaction of this type. Penicillins, sulphonamides, and

antithyroid drugs may cause it. Another type III reaction is the acute interstitial nephritis caused by penicillins, some NSAIDs, and some diuretics. Type IV reactions (cell-mediated or delayed hypersensitivity reactions) In type IV reactions, T lymphocytes are sensitized by a hapten– protein antigenic complex. When the lymphocytes meet the antigen, an inflammatory response ensues. Examples are the contact derma- titis caused by topical local anaesthetics and antihistamines, and topical antibiotics and antifungal drugs. Rashes caused by a type IV mechanism in response to sulphonamides and thiacetazone are more common in people infected with HIV. Anaphylactoid and pseudoallergic reactions Anaphylactoid reactions resemble type I allergic reactions clinic- ally, but the mast cell and basophil activation is not IgE-dependent. Instead, the cells are triggered directly, and drugs capable of doing this include: succinylcholine, morphine, d-tubocurarine, vanco- mycin (hence 'red man' syndrome on rapid intravenous admin- istration), and N-acetylcysteine. They are generally less severe than allergen-mediated anaphylaxis, and emergency treatment is the same. Aspirin can also trigger an attack of asthma by a nonimmune mechanism. The inhibition of airway COX-1 enzyme by as- pirin is thought to remove the inhibitory effect of prostaglandin E2 and divert arachidonic acid towards production of cysteinyl- leukotrienes (especially LTC4). This is a very powerful constrictor of airway smooth muscle (c. 1000-fold the potency of histamine), and this mechanism explains why aspirin-sensitive asthmatics are often sensitive to other NSAIDs (although COX-2 selective drugs may be relatively safe). It does not appear to explain why half of aspirin-sensitive asthmatics are also sensitive to the yellow food dye tartrazine (E102). In some patients, ampicillin, and its derivative amoxicillin, causes a maculopapular erythematous rash resembling the toxic erythema that can occur in penicillin hypersensitivity. However, this ampi- cillin rash is not immunological in origin. It can be distinguished from true penicillin hypersensitivity by its later onset after the first dose (typically 10–14 days compared with 7–10 days in penicillin hypersensitivity, though they overlap) and nonrecurrence if re- exposed to ampicillin. Unlike penicillin hypersensitivity, it carries no increased risk of anaphylaxis to penicillin. An ampicillin rash oc- curs in about 1% of the normal population, but at a much higher fre- quency in some groups of patients: it occurs almost invariably (and can be a useful diagnostic pointer) in patients with some viral in- fections (e.g. infectious mononucleosis, cytomegalovirus infection, measles), lymphomas, and leukaemias. The risk is also increased in patients taking allopurinol. Other manifestations of allergic reactions Drugs may cause other adverse reactions that do not fit clearly into the earlier hypersensitivity classification, but where there is a strong suspicion of an immune basis. Drug fever as an isolated phenomenon can occur with anti- biotics (penicillins, cephalosporins, isoniazid, sulphonamides, and vancomycin), anticonvulsants (phenytoin and carbamazepine), α- methyldopa, hydralazine, and quinidine. The height or periodicity of the fever is not a useful clue that it is drug-induced, but all drug- induced fevers defervesce rapidly on drug withdrawal (c.24–48 h). Fever is also a manifestation of neuroleptic malignant syndrome, a rare and serious idiosyncratic adverse reaction to neuroleptic therapy (either initiation or dose-escalation). In neuroleptic malig- nant syndrome, the fever is accompanied by rigidity, reduced con- sciousness, and autonomic disturbance. It resembles another rare syndrome, malignant hyperpyrexia, although here the fever and ri- gidity follow sensitization to volatile halogenated anaesthetic gases (e.g. halothane) or suxamethonium. The aetiology of neuroleptic malignant syndrome is still unclear, but patients with malignant hyperthermia have mutations either in the ryanodine receptor or skeletal muscle l-type calcium channel.

 A syndrome mimicking systemic lupus erythematosus, often involving joints and skin but generally sparing the kidneys, may follow long-term treatment with

hydralazine, procainamide, pheny- toin, or ethosuximide. Drug-induced lupus is partly dose-related and, in the case of procainamide and hydralazine, is affected by the acetylator status of the patient. Both drugs are metabolized by N- acetylation which is controlled by the polymorphic enzyme NAT2 (see following paragraphs). The two variants cause either slow or fast clearance of the drug and slow acetylators are at increased risk of drug-induced lupus. Asthma occurring as a pseudoallergic reaction to NSAIDs and tartrazine is noted in the earlier paragraph. Other adverse drug reac- tions in the lung include pneumonitis associated with drug-induced lupus (see earlier paragraph), pulmonary eosinophilia, and fibrosing alveolitis. Eosinophilic granulomatosis with polyangiitis has been associated with the use of cysteinyl-leukotriene receptor antagonists (e.g. montelukast), but it now seems unlikely that the syndrome is actually caused by them. Rather their introduction was frequently accompanied by withdrawal of corticosteroids that probably un- covered a pre-existing disease. Jaundice may occur as an allergic response to some drugs through either cholestasis (e.g. with phenothiazines, erythromycin, and chlorpropamide) or generalized liver damage (e.g. with halothane, isoniazid, and monoamine oxidase inhibitors). Long-term effects causing adverse drug reactions Some adverse effects during long-term therapy are related to both the duration of treatment and the dose. Adaptive changes These are the basis of some adverse reactions such as the develop- ment of tolerance and physical dependence to opiates, and tardive dyskinesia in patients receiving long-term neuroleptic therapy for schizophrenia.
Rebound phenomena When adaptive changes occur during long-term therapy, sudden withdrawal of the drug may result in rebound reactions. Examples include the typical syndromes that occur after the sudden withdrawal of opiates or of alcohol (delirium tremens). Sudden withdrawal of barbiturates may result in restlessness, confusion, and convulsions, and a similar syndrome in which anxiety features predominate may occur after the sudden withdrawal of benzodiazepines. Similarly, pa- tients who abruptly stop an SSRI may complain of a constellation of symptoms 3 to 4 days later, which include headache, insomnia, diz- ziness, paraesthesia, sweating, and flu-like symptoms. The withdrawal of some antihypertensive drugs may result in rebound hypertension, but is especially common with clonidine. Sudden withdrawal of β-adrenoceptor antagonists may result in re- bound tachycardia and arrhythmia, sometimes precipitating myo- cardial ischaemia. Acute adrenal insufficiency can occur when corticosteroids are stopped abruptly. The risk depends on the potency and duration of corticosteroids used, but not the route of administration—it has even been reported after stopping high-dose topical or inhaled glucocorticoids. Reversal of the effects of unfractionated heparin with protamine sulphate may be associated with rebound hypercoagulability and an increased risk of thromboembolism. However, this risk may be justi- fied if heparin overdosage has caused life-threatening haemorrhage. Importantly, protamine sulphate will not reverse the effect of low- molecular-weight heparin and stopping or reversing oral anticoagu- lants (such as warfarin) does not lead to rebound hypercoagulability. Other long-term effects Chloroquine may accumulate in the corneal epithelium (causing a keratopathy) and in the retina (causing a pigmentary retinopathy and blindness). The former occurs in most patients on long-term therapy; the latter is less common but more serious. The risk in- creases with daily doses of more than 2.5 mg/kg (as the free base) and chloroquine should only be used in inflammatory arthropathies where the safer hydroxychloroquine has failed. Amiodarone also accumulates extensively in tissues. Almost all patients on long-term amiodarone develop photosensitization from skin deposition. They also develop microdeposits in the cornea, al- though these are rarely symptomatic. It also accumulates in other tissues but pulmonary alveolitis, neuropathy, and hepatocellular im- pairment are relatively uncommon. Delayed effects causing long-term adverse drug reactions Carcinogenesis The long-term effects of oestrogen therapy on cancer risk are

complex and depend on whether they are administered to pre- or postmenopausal women. Long-term oestrogen exposure through the oral contraceptive pill probably increases the risk of breast cancer but the effect is not consistent across all studies. The administration of hormone replacement therapy (HRT) to postmenopausal woman also increases their risk of breast cancer, although it appears that the breast cancer risk from combined oestrogen–progesterone HRT is greater than from oestrogen-only HRT (used in women after hyster- ectomy). The incidence of endometrial carcinoma is also increased in women taking oestrogen HRT for menopausal symptoms. In contrast, the oral contraceptive pill protects against endometrial cancer and the effect persists for many years after taking it. The risk of colon cancer may also be reduced by HRT but not the oral contraceptive pill. Anabolic steroids carry a risk of both benign and malignant hepatic tumours on long-term administration. The risk is greatest for the 17-alkylated derivatives such as oxymetholone. The latter is now largely restricted for palliative use in cachectic states such as HIV wasting syndrome, but is still used illicitly by bodybuilders. Various anticancer drugs increase the risk of secondary solid tu- mours and haematological malignancy. For example, cyclophosphamide containing chemotherapy regimens increase the risk of bladder cancer. The risk of secondary acute myeloid leukaemia and myelodysplastic syndromes is substantially increased in patients re- ceiving chemotherapy for Hodgkin's or non-Hodgkin's lymphoma and testicular cancers. Alkylating agents, especially older regimens using the mustard mechlorethamine, carry the highest risk from lymphoma chemotherapy, and etoposide is the greatest risk from testicular cancer chemotherapy. Immunosuppressive drug regimens are also widely associated with an increased risk of lymphoma and solid tumours in organ trans- plant recipients. These regimens are typically based on calcineurin inhibitors, such as ciclosporin. Recent data suggests that regimens

 based on a noncalcineurin inhibitor, sirolimus, may reduce the risk of lymphoma and solid tumours in these patients. Adverse drug reactions associated with reproduction Some drugs impair fertility. For example, cytotoxic drugs can cause permanent ovarian failure with amenorrhoea. Sperm pro- duction may be reversibly impaired by sulphasalazine (espe- cially in slow metabolizers), gonadotropin hormone antagonists, methotrexate, and androgens. In fact, the reversible azoospermia achieved with depot formulations of testosterone esters and pro- gestogens is being developed for male contraception. Cytotoxic drugs (especially alkylating agents) can reversibly or irreversibly affect sperm production depending on the age of administration (the prepubertal testis is relatively insensitive), the doses used, and duration of exposure. Teratogenesis Teratogenesis occurs when a drug taken early in pregnancy causes a developmental abnormality in a fetus. Exposure to a teratogen in the first trimester of pregnancy, and particularly the period of organogenesis (weeks 2–8 of gestation), is most likely to cause structural abnormalities. The central nervous system is vul- nerable throughout pregnancy. For a drug to be teratogenic it must first cross the placenta. As a general rule, the drugs that do this have a low molecular weight, are poorly ionized at physiological pH, and are very lipophilic. Hence, heparin (even low-molecular-weight heparin) is a large, highly charged molecule and d-tubocurarine is a small, ionized, and hydrophilic molecule; neither crosses the placenta. The placenta also expresses large numbers of transporter proteins including the ABC efflux pump P-glycoprotein (MDR-1). The efflux pumps are expressed predominantly on the maternal-facing surface of the pla- cental villi and form part of the maternal–fetal barrier. So, whether a drug crosses the placenta depends not just on physiochemical properties, but also its affinity for the efflux pump. The existence of functional polymorphisms in these pumps probably explains the wide variability observed in fetal drug concentrations, inci- dence of teratogenesis,

and drug failure in pregnancies exposed to therapeutic drugs. Since most drugs that are proven teratogens in animals will not enter human development, it is unclear how well animal teratogenicity testing predicts human teratogenicity. A drug will have been tested for teratogenicity in rodents and one other nonprimate species before it can be registered. However, negative results from animal testing should not reassure anyone that the drug is safe in human pregnancy. Indeed, thalidomide itself is not teratogenic in rodents and the New Zealand rabbit is the only common labora- tory mammal that shows similar sensitivity to humans. Women of childbearing age are excluded from preregistration testing, so the teratogenic risk for humans of a drug at the time of its regis- tration is usually unknown. This explains the comments that exist in package inserts and other literature on new drugs, discouraging their use in pregnancy. It also explains why obstetricians often em- ploy drugs that seem to other clinicians to be obsolete. For example, in pregnancy-related hypertension and pre-eclampsia, hydralazine and α-methyldopa are still first-line drugs. In nonpregnant hyper- tension, they would not even be fourth-line choices. Both drugs have, however, been in obstetric use for a half century without asso- ciated teratogenicity. Adverse drug reactions on the fetus during the later stages of preg- nancy Some drugs that are not teratogenic may have adverse effects on the fetus if given later in pregnancy. Table 2.6.2 lists some important drugs that should be avoided or used with care during later pregnancy (some throughout the whole duration of pregnancy). Given the uncertainty about teratogenic risk, what should be done if a woman of childbearing potential is given a drug, and then finds out days or weeks later that she is pregnant? First, it is important to identify the drug and the exact time of exposure to it. If it is a known or a likely teratogen, the relation between the time of ex- posure and the likely time of conception should be determined. Even if the precise date of conception is known, dating the preg- nancy by ultrasound is advisable if a suspected teratogen has been taken. If exposure to a known teratogen has occurred during the first 8 weeks of pregnancy, detailed ultrasound examination of the fetus may detect structural abnormalities, and serum and amniotic α-fetoprotein concentrations measured to screen for neural tube de- fects. Any advice on termination of a pregnancy should be based on a consideration of the risk of fetal abnormality from both published information and investigation of the individual case. Adverse reactions to drugs in breast milk Some drugs cause ad- verse reactions in babies after ingestion by the mother and excretion in her breast milk. Excretion of drugs into breast milk is important because 90% of women take at least one prescribed drug during the first week after delivery. This may discourage many women from breastfeeding unless they can be reassured that the benefits for the baby of being breastfed far outweigh any risks for the overwhelming majority of drugs (see Table 2.6.3). The factors affecting drug excretion into breast milk are the same as those that govern drug transfer across the placenta. The only important difference is that breast milk has a lower pH and higher lipid content than plasma. Like the placenta, this passive transfer only explains a fraction of the total transport capacity. Active drug transport also oc- curs through transporters and efflux pumps expressed in the breast epithelium, which explains why some drugs are present in breast milk at levels higher than expected (e.g. atenolol and benzylpenicillin). Table 2.6.2 Drugs with proven or very high teratogenic risk in human pregnancy Drug Associated risk ACE inhibitorsa Fetal renal toxicity/oligohydramnios Alcohol Fetal alcohol syndrome Carbamazepine Neural tube defects?/Features of hydantoin syndrome Diethylstilboestrol Vaginal adenocarcinoma in female offspring Isotretinoin Craniofacial and cardiac anomalies Lithium Cardiac defects including Ebstein’s anomaly Methotrexate Fetal aminopterin syndrome Misoprostol Moebius syndrome Phenytoin Fetal hydantoin syndrome Tetracycline Decidual teeth staining Thalidomide Phocomelia Valproic acid Neural tube defects Warfarin Stippled epiphyses/nasal hypoplasia a ATII receptor antagonists carry

similar risk.

92 section 2 Background to medicine Neonates and young babies may be at risk of adverse drug reactions because clearance pathways for a drug are immature. The GFR is only 25% of the adult value at birth (based on body weight) and only reaches the adult range at 3–6 months. Tubular secretion measured by PAH clearance is also impaired (10% of adult capacity until 6 months), which explains the slow elimin- ation of frusemide in neonates (it is secreted by the PAH trans- porter). Phase I metabolism through CYP enzymes are isoform dependent: 3A7 is the predominant isoform in utero; it is replaced by 3A4 postpartum, but it takes more than 1 month to reach adult levels; CYP 1A2 does not appear until 3 months; CYP2D6 and E1 appear after birth but rapidly achieve adult levels within hours of delivery. Drugs that should be given to breastfeeding mothers with caution are included among the drugs in Table 2.6.3. A more extensive list can be found in the British National Formulary and the Physician's Desk Reference. If the safety of a drug is in serious doubt and it is not possible to identify an alternative, breastfeeding can be temporarily suspended while the drug is given. Detecting adverse drug reactions: Pharmacovigilance The importance of adverse reactions for drug regulatory bodies and the pharmaceutical industry has led to the evolution of a subspecialty of clinical pharmacology devoted to the detection and evaluation of adverse drug reactions. This specialization is called pharmacovigilance. Because drugs reach the market based on the experience of dosing just a few thousand patients, capturing as many adverse drug reac- tions as possible afterwards is of crucial importance. This activity is called postmarketing surveillance, which usually relies on self- reporting by health professionals and in some countries, the gen- eral public as well. In the United Kingdom, reporting by healthcare workers operates through the yellow card scheme run by the Medicines and Healthcare Products Regulatory Agency (MHRA) and the Commission on Human Medicines (CHM). It is a spon- taneous reporting scheme in the sense that it is voluntary and used to rely on the 'yellow card' in the back of every BNF being filled out by the healthcare worker. This can now be done online (https:// yellowcard.mhra.gov.uk/). The scheme aims to collect (1) serious or fatal adverse drug reactions from all drugs; (2) all adverse drug re- actions from newly licensed drugs (designated with a black triangle in the BNF); and (3) all adverse drug reactions in children under 18. Spontaneous reporting schemes rely on goodwill and are prone to considerable underreporting. Rare or unusual side effects are easily detected with them (e.g. the withdrawal of cerivastatin because of rhabdomyolysis and pergolide because of valvular heart disease). On the other hand, serious adverse reactions involving effects that occur frequently in the population receiving the drug are not so easily de- tected. The thrombotic risk of COX-2 selective NSAIDs (coxibs), es- pecially rofecoxib (Vioxx), is a timely reminder of this serious flaw in spontaneous reporting schemes. If used over long periods, coxibs cause an excess of stroke and myocardial infarction, but both of these are common events in patients receiving NSAIDs. Most physicians, for example, would not immediately conclude that a 65-year-old pa- tient who died from a stroke or myocardial infarction while on a coxib was the victim of an adverse drug reaction. It is a sobering reminder that rofecoxib was only withdrawn after some 20 million people were exposed to it and many thousands had probably died from taking it. Despite the limitations of spontaneous reporting, it is a cru- cial part of the World Health Organization's efforts to coordinate pharmacovigilance on a global scale as opposed to local efforts such as the yellow card scheme. Its database (http://www.who-umc.org/) currently contains some 11 million reports (May 2015), and 122 countries had signed up to the scheme by September 2015. There is also a Europe-wide (or rather European Union-wide) pharmacovigi lance programme run by the European Medicines Agency, called EudraVigilance

(https://www.ema.europa.eu/en/human-regulatory/ research-development/pharmacovigilance/eudravigilance). The dif- ference in this scheme is that adverse drug reaction notification by the pharmaceutical companies operating within the European Union is not voluntary, by a statutory requirement of their marketing authorization. It is too early to say how the performance of these two systems compares in terms of the early detection of ad- verse drug reactions. The probity of the pharmaceutical industry itself has also been seriously questioned in recent years in the process of alerting the regulatory authorities about suspected adverse drug reactions. Large Table 2.6.3 Effects of common maternal drugs on breastfed infants or milk production Acebutolol/atenolol Cyanosis, hypotension, bradycardia Amoxicillin None Aspirin Metabolic acidosisa Bendrofluazide May reduce milk production Bromocriptine Suppresses lactation Caffeine Irritability if >2–3 cups of coffee/day Carbamazepine None Carbimazole Goitre Ciprofloxacin None Digoxin None Diltiazem None Fluconazole None Isoniazid None Labetalol None Levothyroxine None Lithium Plasma level up to 50% mother Nalidixic acid/nitrofurantoin Haemolysis in G6PD deficient infanta Morphine None Oestrogen (in oral contraceptive pill) May reduce milk production Pethidine None Phenobarbitone/primidone Sedation Phenytoin Methaemoglobinaemiaa Prednisolone None Propylthiouracil None Valproic acid None Verapamil None Warfarin None a Single case reports. From American Academy of Pediatrics (2001). Policy statement. (http://aappolicy. aappublications.org/cgi/content/full/pediatrics;108/3/776).

2.6 Principles of clinical pharmacology and drug therapy 93 observational studies commissioned by the pharmaceutical com- panies to capture adverse reactions have been deliberately hidden (by Bayer in the case of aprotinin) or methodologically questioned (by Merck in the case of Vioxx) when they confirmed suspected ad- verse reactions. These and other cases have highlighted the need for regulatory agencies to be able to compel pharmaceutical companies to: (1) carry out the necessary controlled trials to investigate the safety of a new drug; and (2) make disclosure of these studies man- datory. Alternatively, healthcare systems should probably commis- sion the necessary studies. These would certainly be cost-effective considering how much they will have been spent (e.g. managing the excess of strokes and myocardial infarction that followed the intro- duction of coxibs). Prevention of adverse drug reactions: The role of the patient Most people who take either a prescribed drug or one purchased over the counter do not usually expect unwanted effects from it, al- though they may have been alerted to potential adverse reactions by the doctor, pharmacist, or packet insert. The information from any of these sources should warn about all potential adverse drug reac- tions, so that the patient can: • assess the potential disadvantages of the drug, before deciding to take it; • connect an adverse reaction with the taking of the drug and take appropriate action. However, what is usually lacking is advice about how to minimize or avoid adverse drug reactions. This advice is as relevant for the patient as it is for the prescriber. The prescriber in particular should consider the following: 1. Are there dose-dependent effects? If there are, they can be pre- vented or minimized by keeping the drug dosage as low as possible. It is always worth considering whether dosing below the pharmaceutical company's recommended range may be ap- propriate for individual patients. This is especially the case in older people or for nonwhite ethnic groups (who may metab- olize the drug differently) as both are often underrepresented in preregistration drug trials. If adverse reactions are more likely with continued use of the drug, then the duration of use should be limited (e.g. with neuroleptic drugs). 2. Are drug interactions likely? If there are known interactions, they may be prevented by ensuring interacting drugs are avoided. This list should include agents that could be taken by the patient but are not prescribed. For example, it may be necessary to avoid con- sumption of grapefruit juice or herbal remedies such as

St John’s wort if the drugs are substrates for CYP 3A4 or P-glycoprotein (and the patient is taking simvastatin bought over the counter). 3. There may be serious adverse reactions that are unknown and/ or undetected during preregistration trials. Drugs that have been prescribed over many years have an established margin of safety and should be used in preference to newer drugs. If there is a compelling reason to use a new drug, the patient should be aware that it is a new drug and there should be closer monitoring for adverse reactions. 4. Adverse reactions are more likely when a prescriber is using a drug they are not familiar with. The prescriber might consider asking for a second opinion about the appropriateness of the drug and problems with its use if they are not sure. 5. Some individuals are predisposed to adverse drug reactions. This is usually a genetic susceptibility. They may, for example, be poor drug metabolizers, porphyriacs, or have G6PD deficiency. If this is known, patients should be aware of drugs they should avoid, and they should tell other prescribers of the problem before they take any new drug. Drug interactions A drug interaction occurs when the effects of one drug are altered by the effects of another drug. Usually this results in an adverse reac- tion, but in a few cases, it may actually prove beneficial. Interactions form up to 10% of all adverse drug reactions, but crucially, among patients who die from an adverse drug reaction, about one-third of deaths are due to interactions. Drugs likely to precipitate interactions often have one or more of the following properties: • They are highly protein bound (e.g. aspirin and sulphonamides). • They induce drug metabolism (e.g. phenytoin, carbamazepine, and rifampicin). • They inhibit drug metabolism (e.g. cimetidine, metronidazole, and triazole antifungals). The drugs most likely to be affected by drug–drug interactions are also those with a steep dose–response curve and a low therapeutic index, which includes aminoglycoside antibiotics, warfarin, and other coumarins, anticonvulsants, antihypertensive drugs, cardiac glycosides, cytotoxic and immunosuppressant drugs, oestrogen- containing oral contraceptives, and some centrally acting drugs. The most frequent interactions occur with warfarin and other coumarins. Drug interactions fall into three basic types (see Table 2.6.4).
Pharmaceutical interactions These involve physiochemical effects between a drug and the solu- tion it is mixed with or between two drugs when they are mixed together (usually for injection). The interaction results in the drug either precipitating from solution or being inactivated in some other way. There are numerous examples, but some general principles can help to avoid many of them: give intravenous drugs by bolus injec- tion if possible or via an infusion pump; do not add drugs to infu- sion solutions other than dextrose or saline; only mix drugs in the same infusion solution if they are known to be safe (e.g. potassium chloride with insulin).
Pharmacokinetic interactions Pharmacokinetic interactions occur when a drug alters the ab- sorption, distribution, or elimination (metabolism or excretion) of another drug.
Absorption interactions One drug substantially altering the absorption of another is rela- tively uncommon but there are important examples. Anion ex- change resins, for example, bind warfarin, digoxin, and thyroxine very avidly (see earlier paragraphs). Other examples are given in Table 2.6.4.

 This type of interaction may occasionally be beneficial. Hence, metoclopramide increases gastric emptying and speeds the absorp- tion of analgesics (such as ibuprofen and paracetamol) used to treat acute migraine. Activated charcoal also binds many drugs in the gut lumen, so preventing their absorption or enterohepatic recycling. This is widely exploited in drug overdoses (see earlier paragraphs and Chapter 10.4.1). It is also used to accelerate excretion of the antirheumatoid drug leflunomide if it causes a serious adverse re- action because of the extremely long half-life (2 weeks) of its active metabolite. Protein-binding

displacement interactions Displacement of one drug by another from its binding sites on plasma proteins will cause an increase in the circulating concentra- tion of unbound drug. This is only important if the displaced drug is highly protein bound (>90%) and has a small volume of distribution (that will exaggerate the rise in free drug concentration). The drugs concerned are warfarin, phenytoin, and tolbutamide. The most common precipitant drugs in protein-binding dis- placement interactions are sulphonamides, salicylates, and chloral hydrate and some of its congeners (because of their metabolite, trichloroacetic acid). In addition, valproate specifically displaces phenytoin. However, displacement interactions are generally relatively un- important. This is because the rise in free drug concentration in- creases the drug's clearance, so that the total concentration actually falls if the displacing drug is given chronically. Displacement is only a problem if the initial rise in free drug concentration itself causes toxicity; fortunately, if this is not serious it will be transient. Interactions through induction of metabolism Induction of P450 enzymes is a major source of drug inter- actions. Drugs that induce drug metabolism include barbiturates, carbamazepine, griseofulvin, phenytoin, and rifampicin (see Table 2.6.4). The herbal preparation of St John's wort also induces P450 isoforms. Table 2.6.4 Mechanisms of drug interactions, with important examples Mechanism Example Outcome Physiochemical Calcium gluconate plus sodium bicarbonate Precipitation of calcium carbonate in infusion solution Pharmacokinetic Altered absorption Reabsorption of oestrogens reduced by antibiotics Contraceptive failure Gastric emptying increased by metoclopramide Increased rate of absorption of simple analgesics Fluoroquinolones (e.g. ciprofloxacin) and agents containing divalent/trivalent cations (e.g. antacids or Fe salts) or sucralfate Reduced absorption Altered protein binding Displacement of phenytoin by aspirin (not low-dose aspirin) Phenytoin toxicity (transient) Increased metabolism Oestrogen metabolism increased by carbamazepine, phenytoin, rifampicin Contraceptive failure Reduced metabolism Warfarin metabolism inhibited by amiodarone, metronidazole, cimetidine Warfarin toxicity Theophylline metabolism inhibited by erythromycin or fluoroquinolones (e.g. ciprofloxacin) Theophylline toxicity Phenytoin/carbamazepine metabolism inhibited by cimetidine, erythromycin, fluconazole, or isoniazid Phenytoin/carbamazepine toxicity Amine metabolism inhibited by monoamine oxidase inhibitors (includes tyramine in foods and phenyl-propanolamine in cold cures) Acute severe hypertension Reduced renal elimination Penicillin/cephalosporin excretion reduced by probenecid Prolonged duration of antibiotic action Lithium excretion reduced by diuretics or NSAIDs Lithium toxicity Digoxin excretion reduced by amiodarone, quinidine, verapamil Digoxin toxicity Pharmacodynamic Shared mechanisms Vitamin K competes with warfarin for epoxide reductase Reversal of the effect of warfarin Naloxone displaces opioids from opioid receptors Reversal of opioid toxicity PDE5 inhibitors (e.g. sildenafil) and nitrates Profound hypotension Statin and niacin, fibrates (especially gemfibrozil) Risk of rhabdomyolysis/renal failure SSRIs and tramadol, triptans (e.g. sumatriptan) or monoamine oxidase inhibitors (e.g. selegiline) Risk of serotonin syndrome Parallel mechanisms Psychoactive drugs and alcohol Increased sedation Cytotoxic drugs acting at different stages of the cell cycle Therapeutic potentiation in cancer chemotherapy Warfarin and antiplatelet drugs (aspirin and other NSAIDs or clopidogrel) Increased risk of bleeding and impaired haemostasis

 Interactions through inhibition of metabolism Most of the interactions under this heading involve drugs that in- hibit specific P450 pathways, for example, through CYP3A4 or 2D6. Some examples are shown in Table 2.6.4. Metabolism through non-CYP metabolic pathways can also be af- fected. Hence, the interaction of

allopurinol with azathioprine and 6-mercaptopurine results from its inhibition of xanthine oxidase. Both 6-mercaptopurine and azathioprine (which is metabolized to 6-mercaptopurine) are metabolized by xanthine oxidase. The interaction of MAO inhibitors with dietary tyramine is another example of a non-CYP pathway. Tyramine in the diet usu- ally has very low bioavailability because of degradation by MAO in the gut wall and liver. MAO inhibitors inactivate the enzyme both here and within sympathetic nerve endings, which increase their noradrenaline content. Hence, tyramine ingested after an MAO in- hibitor has substantially increased bioavailability, and the resulting plasma levels are sufficient to displace the enhanced noradrenaline stores from sympathetic nerve terminals. The hypertensive crisis this causes is referred to as the 'cheese reaction'. These interactions may again be sometimes useful. The protease inhibitor ritonavir, for example, is a potent CYP3A4 inhibitor and is added to antiretroviral drug regimens containing other protease inhibitors to specifically inhibit their metabolism and so increase bioavailability (which may otherwise be low). This is referred to as PK-enhanced drug formulation. Excretion interactions Most interactions involving drug excretion occur in the kidneys, although secretion into the gut through P-glycoprotein is im- portant for some drugs (e.g. digoxin, cyclosporin). The latter explains drug interactions with substances such as St John's wort and grapefruit juice. Interactions due to the alteration of active renal drug secretion are shown in Table 2.6.4. Some drugs that are weak acids or bases are passively reabsorbed along the nephron. The extent of reabsorp- tion is pH-dependent and can be exploited following overdose to increase drug elimination in the urine (see earlier paragraphs). Pharmacodynamic interactions Pharmacodynamic interactions are very common and occur when one drug alters the effect of another. This can arise because the two drugs act on the same drug target or pathway. Alternatively, the interacting drugs may produce the same effect but by entirely sep- arate mechanisms. Some examples are shown in Table 2.6.4. Interactions through a shared mechanism When there is a shared drug target (such as a receptor) the inter- action may arise because of antagonism or combined agonism at this site. Many antagonistic interactions are therapeutically benefi- cial. Examples are the reversal of the effects of benzodiazepines with flumazenil or warfarin with vitamin K. In contrast, synergistic inter- actions are often adverse. Hence, nitroglycerin and sildenafil are useful drugs to treatment angina and erectile failure, respectively; nitroglycerin being metabolized to nitric oxide (NO) and sildenafil augmenting the effect of endogenous NO. Combining the two, how- ever, causes devastating hypotension. Interactions through parallel mechanisms Two drugs may have similar pharmacological or toxic effects but they are achieved through different mechanisms. For example, the bleeding risk of warfarin is increased by drugs that affect platelet function (e.g. NSAIDs, clopidogrel, or glycoprotein IIb/IIIa antag- onists), reduce platelet number (drug-induced thrombocytopenia) or cause gastrointestinal ulceration (e.g. NSAIDs). Exploiting parallel pathways can also be beneficial. Many chemo- therapy regimens exploit pharmacodynamic interactions of their component drugs. And combinations of antibiotics are used rou- tinely even when a single organism is being targeted (e.g. penicillin plus an aminoglycoside in bacterial endocarditis and multiple-drug regimens for tuberculosis). Pharmacogenetics and pharmacogenomics The variability between individuals in terms of both the pharmaco- kinetics and pharmacodynamics of a drug is partly determined by genetic variation. The variability can occur in a single gene (hence pharmacogenetics) or arise from the interplay of a variety of genes (pharmacogenomics). The realization that the human genome is an important player has fuelled expectation that drug prescription may in future be 'personalized' based on the patient's genotype.

Pharmacokinetic variability Several important pathways of drug metabolism can affect drug pharmacokinetics through polymorphic variation in the enzymes involved. These include oxidation,

acetylation, S-methylation, and suxamethonium hydrolysis (Table 2.6.5). Oxidation About 80% of oxidative drug metabolism occurs through the cyto- chrome P450 or CYP enzyme family of enzymes (see earlier para- graphs). There are some 57 genes in humans encoding these enzymes and they are named with a number and letter for the family and sub- family to which they belong (e.g. 3A4 or 2D6). Many of these genes are polymorphic, with the common wild-type gene being mutated to produce a change in gene function; usually a reduction. The alleles for these different polymorphisms or gene variants are designated by a number after an asterisk (e.g. 2D6*4 for the commonest variant of 2D6 that reduces enzyme function). Drugs that are metabolized through polymorphic CYP enzymes show drug metabolism in the population that has a bimodal (or occasionally trimodal) distribution. An example of this is shown in Fig. 2.6.6, where the metabolic ratios for debrisoquine are shown in the urine of over 1000 patients (debrisoquine is an ob- solete antihypertensive but is still used as a 'probe' drug to define metabolic phenotype for CYP enzymes). Most are extensive met- abolizers with low-to-intermediate drug:metabolite ratios in their urine, but a significant minority are poor metabolizers with high ratios. In this case, the poor-metabolizer status is due to 2D6 gene variants that reduce 2D6 enzyme activity. Genetically, the defect is very heterogenous with around 100-point mutations, promoter variants, and deletions now recognized (see http://www.imm.ki.se/ cypalleles). The frequency of the poor-metabolizer phenotype

 varies across different ethnic groups: it is around 5 to 10% in northern Europeans but only approximately 1% in the Chinese. Drugs that are commonly metabolized through 2D6 include co- deine, dextromethorphan, flecainide, metoprolol, nortriptyline, propafenone, timolol, and tramadol (see Table 2.6.1). The dose- related adverse reactions of these drugs (e.g. central nervous system toxicity with nortriptyline or bradycardia and hypo- tension with the β-blockers) are more likely in patients with the poor-metabolizer phenotype. Quinidine is an inhibitor of the 2D6 enzyme and is able to convert an extensive to a poor metabolizer. Some patients even have a super- or ultrametabolizer pheno- type. This phenotype occurs through duplication of the 2D6 gene and shortening of the half-life of 2D6-metabolized drugs in these patients is directly related to the degree of duplication (Fig. 2.6.7). They are relatively uncommon compared to the poor metabol- izers (see Fig. 2.6.6), but their status has important clinical conse- quences. A 2D6 drug will appear to be relatively ineffective in an ultrametabolizer unless very large doses are used, and they may even be suspected of poor compliance. In contrast, if the drug is a prodrug, ultrametabolizers are characteristically very sensitive to its effects. Hence, they may show opiate intoxication from what appear to be low therapeutic doses of codeine because of its rapid and complete metabolism to morphine. Although they are rare in Europe, 30% of East Africans may be ultrametabolizers. The other CYP enzymes are not as well studied as 2D6, but poor metabolizers have been identified for 2C9 (metabolizing losartan, phenytoin, tolbutamide, and warfarin) and 2C19 (metabolizing omeprazole). There is a commercial microarray available to geno- type individuals for the commoner variations in the 2D6 and 2C19 genes (it is called the AmpliChip P450) that has been approved by the FDA, but the technology in this area is evolving rapidly Table 2.6.5 Pharmacogenetic variation affecting drug metabolism Metabolizer phenotype Enzyme responsible Common deficiency gene variant Frequency in white people Comments Suxamethonium apnoea Butyrylcholinesterase (CHE) CHE*70 D>G 1:3000 Many other variants encoding CHE with reduced or no activity Poor metabolizer CYP2D6 2D6*4* (premature stop codon) 5–10% Commonest allele for PM phenotype Slow acetylator N-acetyltransferase (NAT2) NAT2*5B c.40% carry it but compound heterozygotes as likely as *5B

homozygotes *4 is the fast allele and behaves dominantly Thiopurine sensitivity Thiopurine S-methyltransferase (TPMT) TPMT*3A (154A>T, 240T>C) 5% are carriers (homozygous rate c.1:250) 20 other variants but 95% of cases due to *2 or *3(A–D) Irinotecan sensitivity UDP-glucuronyl transferase 1 (UGT1A1) (TA)7–TATA c.40% Promoter variant reduces UGT1A1 expression 0 0 0.01 0.10 1 10 100 40 Ultrarapid metabolism Poor metabolism Extensive metabolism Cutoff 80 120 Debrisoquin:4-Hydroxydebrisoquin metabolic ratio No. of subjects Fig. 2.6.6 Pharmacogenetics of CYP2D6. Urinary metabolic ratios of debrisoquin to its metabolite, 4-hydroxydebrisoquin, for more than
1000 Swedish subjects. Poor metabolizers with no or reduced CYP2D6 activity are separated by the cut-off box from extensive metabolizers. Adapted from Bertilsson L, et al. (1992). Pronounced differences between native Chinese and Swedish populations in the polymorphic hydroxylations of debrisoquin and S-mephenytoin. Clin Pharmacol Ther, 51, 388–97. Morphine Morphine-3-glucuronide 0 0 10 20 30 40 50 60 70 80 90 2 4 6 8 10 12 14 16 18 20 22 24 0 0 1 2 3 4 2 4 6 8 10 12 14 16 18 20 22 24 Concentration [µg/litre] Concentration [µg/litre] PM EM UM Fig. 2.6.7 Effect of 2D6 genotype on the plasma concentration of morphine and its active metabolite following a 30 mg dose of codeine. Ultrametabolizers with duplication of the 2D6 wild-type gene show higher levels compared to extensive metabolizers carrying single
copies. Poor metabolizers for comparison have only loss-of-function or nonfunctional copies. Reprinted by permission from Springer Nature: The Pharmacogenomics Journal. Kirchheiner J, et al. (2007). Pharmacokinetics of codeine and its metabolite morphine in ultra-rapid metabolizers due to CYP2D6 duplication. Pharmacogenomics J, 7, 257–65, Copyright © 2006, Springer Nature.

2.6 Principles of clinical pharmacology and drug therapy 97 Acetylation Some drugs are cleared by acetylation. These include dapsone, hydralazine, isoniazid, procainamide, and some sulphonamides. The enzyme involved is the hepatic enzyme N-acetyltransferase (NAT2, EC 2.3.1.5) and if drug:metabolite ratios for a drug cleared by acetylation are measured, they distribute bimodally in the population. Subjects producing the highest ratios are described as being fast acetylators (cf. extensive metabolizers for the 2D6 pathway). Again, the genetic basis for the biochemical phenotype is very heterogenous, and the frequency of fast acetylators varies across different ethnic groups: 40% in northern Europeans, 85% in Japanese, and 5% among the Inuit. Slow acetylators require lower doses of drugs that are cleared by acetylation than fast acetylators. Slow acetylators are also more likely to develop the lupus erythematosus-like syndrome caused by isoniazid, hydralazine, and procainamide, and the peripheral neuropathy caused by isoniazid (isoniazid actually causes deg- radation of pyridoxine). The interaction between isoniazid and phenytoin, in which isoniazid inhibits phenytoin metabolism causing phenytoin toxicity, is also more frequent among slow acetylators. Disease associations with polymorphic metabolism As some diseases may be related to the effects of environmental chemicals that have carcinogenic metabolites, it is of interest that polymorphic acetylation, hydroxylation, and sulphoxidation have other clinical associations. The evidence linking acetylator status with the risk of bladder cancer is probably the best- established association; slow acetylators having increased risk. Other weaker associations may exist between debrisoquine metabolizer status (2D6) and risk of parkinsonism in poor debrisoquine hydroxylators, of bronchogenic carcinoma in exten- sive debrisoquine hydroxylators, and of primary biliary cirrhosis in poor sulphoxidizers. Glucuronidation The antitumour agent irinotecan is a prodrug. Its active metabolite, SN-38, has about 1000-fold higher activity than irinotecan itself and is inactivated by glucuronidation through UGT1A1. Patients homozygous for a polymorphism in the promoter of UGT1A1 are much more likely to develop

severe neutropenia after irinotecan because of defective glucuronidation of SN-38. The same polymorphism is also involved in Gilbert's syndrome. Methylation The thiopurines (6-mercaptopurine and 6-thioguanine) are me- tabolized by S-methylation through the enzyme thiopurine S-methyltransferase (TPMT, EC 2.1.1.67). The metabolism of azathioprine is also affected by this enzyme as azathioprine is re- duced to 6-mercaptopurine after dosing (i.e. it is a prodrug). High levels of TPMT are found in red cells, and the activity is trimodal in the population with high, intermediate, and low levels of TPMT detectable. Because low levels of TPMT (present in c.1:300 whites) reduces metabolic clearance of thiopurines, these subjects are ex- posed to high levels of 6-thioguanine nucleotides. This leads to severe myelosuppression if they are given standard doses of these drugs. Hence, thiopurines can only be used safely in subjects with low TPMT if they are given very low doses. There are some 20 gene variants that affect the activity of TPMT and carriers for TPMT variants are common—overall frequencies are typically 5 to 10%. The commonest variant (TPMT*3A) is ac- tually a double mutant that switches two amino acids and produces an unstable enzyme that explains the low level of TPMT in homo- zygotes. There is considerable ethnic variation in the frequency of variants (e.g. the *3A is not seen among the Chinese). Suxamethonium hydrolysis Suxamethonium (succinylcholine) is metabolized in the plasma by the nonspecific esterase pseudocholinesterase (EC 3.1.1.8; also called butyrylcholinesterase). Normally this happens quickly, which explains why neuromuscular blockade with this drug lasts only a few minutes. Some patients, however, have very slow clear- ance of suxamethonium due to low plasma pseudocholinesterase activity. This manifests as prolonged neuromuscular blockade or apnoea after the use of suxamethonium, which can last several hours or longer. Suxamethonium apnoea is usually very rare, but is common in Inuit (up to 10%). Several different gene defects can cause pseudo- cholinesterase deficiency: the dibucaine-resistant, fluoride-resistant, and 'silent' gene types. Patients with reduced pseudocholinesterase also show increased sensitivity to the nondepolarizing blocker mivacurium. Interestingly, pseudocholinesterase deficiency does not appear to affect the conversion of the prodrug bambuterol (which is also a substrate for pseudocholinesterase) to its active me- tabolite terbutaline. Pharmacodynamic defects Some biochemical abnormalities make individuals peculiarly sensi- tive or resistant to the effects of certain drugs. All have a genetic basis. Red cell enzyme defects (see Chapter 22.6.11) Adverse drug reactions may affect people whose red cells are de- ficient in glucose-6-phosphate dehydrogenase (G6PD). If their red cells are exposed to an oxidizing drug, they lose their oxygen-carrying capacity as haemoglobin is oxidized to methaemoglobin and they eventually haemolyse. Drugs commonly implicated are doxorubicin, nalidixic acid, nitrofurantoin, primaquine, and sulphamethoxazole. There is a longer list of drugs that may cause haemolysis in some G6PD-deficient individuals, depending on their genotype. This is because the common African variant gives higher red cell G6PD levels than the Mediterranean form, so mild oxidative stress is better tolerated. This list includes aspirin (low dose is usually safe), chloramphenicol, l-dopa, isoniazid, quinine and related com- pounds, trimethoprim, and vitamin K. Porphyria (see Chapter 12.5) The hepatic porphyrias, acute intermittent porphyria and porphyria cutanea tarda, are characterized by abnormalities of haem biosyn- thesis. Certain drugs may precipitate an attack of porphyria especially cytochrome P450 inducers (e.g. barbiturates, carbamazepine, and rifampicin). The quality of data as to the safety (or not) or other drugs is variable. There is a useful web database that rates drug safety on a five-point scale (http://porphyriadrugs.com/).

 Malignant hyperthermia This potentially fatal complication of general anaesthesia follows ex- posure to halogenated anaesthetic gases and suxamethonium (see

earlier paragraphs). Vitamin D-resistant rickets Three varieties of rickets are resistant to the effects of vitamin D (cholecalciferol): familial hypophosphataemic rickets, vitamin D dependency, and Fanconi's syndrome (see Chapter 21.16). Warfarin sensitivity Sensitivity to warfarin varies widely in the general population. This has been explained on the basis of common gene variants in its target enzyme vitamin K epoxide reductase (EC 1.1.4.2, encoded by VKORC1) and the CYP2C9 gene responsible for its metabolism. Pharmacogenomics and the prospect of 'personal prescribing' The realization that the pharmacokinetics and pharmacodynamics of a drug may be genetically determined has raised the prospect of tailoring the drug to the patient. Predefining the generic variants that a patient has before a drug is given could, in principle, avoid many adverse drug reactions and interactions. The sequencing technology to perform the necessary genotyping is now available, and many drug trials now incorporate this technology to identify genotypic signatures that both affect the therapeutic response to the drugs and predict adverse reactions. However, we are some way off truly 'personalized prescribing'. Monitoring drug therapy Monitoring drug therapy usually involves trying to measure the clin- ical response directly. If this is difficult, or is not related directly in time to a dose of the drug, a surrogate measure of the response may be required. In some cases, it may be necessary to resort to measure- ment of the plasma concentration of the drug. Monitoring the therapeutic effects of drugs Some events can be directly monitored in the individual patient. Examples of therapeutic events that can be monitored in the indi- vidual include frequency of seizures during anticonvulsant drug therapy, muscle power during treatment of myasthenia gravis, the frequency of attacks of angina pectoris, and body weight during di- uretic therapy. Preventive measures in medicine often cannot be monitored in the individual patient and their impact has to be predicted from popula- tion studies (usually a clinical trial). Examples include the frequency of infections after immunization, the reduction in NSAID-induced peptic ulceration with a proton pump inhibitor, or the prevention of the complications of myocardial infarction by the use of thromb- olysis and aspirin. Monitoring the pharmacodynamic effects of drugs In some circumstances, the pharmacological effect of a drug can be carefully measured, followed sequentially, and used as a guide to drug therapy even though it may not be correlated precisely with the therapeutic effect. Examples include the effect of insulin on the blood glucose concentration in diabetes mellitus, anticoagulants on the prothrombin time, bronchodilators on FEV1 and peak flow rate in asthma, and cancer chemotherapy on tumour markers. Monitoring drug pharmacokinetics (therapeutic drug monitoring) This is useful for drugs where: • the clinical evidence of therapeutic or toxic effects is difficult to measure or interpret • the relation between dose and plasma concentration is unpredictable • the drug has a low therapeutic index • the plasma concentration of the drug is a good predictor of response There are only a handful of drugs that meet these requirements (see Table 2.6.6). For these drugs, monitoring drug levels can be used to individualize therapy (e.g. at the start of drug dosing, when the relation between dose and plasma concentration in the individual is uncertain or rapid changes in renal function alter the relation between dose and plasma concentration), to monitor toxicity and to assess compliance (see earlier section, 'The patient's use of a drug: Compliance and concordance'). Phenytoin Plasma concentrations of phenytoin in the toxic range are quite well related to its acute neurotoxic effects, but not to its long-term adverse reactions, such as gingival hyperplasia, hirsutism and acne, and folate and vitamin D deficiencies. At low dosages it takes about 2 weeks of maintenance therapy to reach steady state after a change in dose, but because of its nonlinear kinetics (Fig. 2.6.5), the half-life lengthens at higher plasma concentrations; so it can take up to 3 weeks or longer in some patients to reach steady state. For this reason the dosage should not be changed frequently. Provided the

sample is not taken too soon after a dose (i.e. within 1 to 2 h), the time of sampling for phenytoin is not critical, as peak–trough fluctuation is small between doses. Digoxin Plasma digoxin concentrations correlate well with toxic effects but not with the therapeutic effect within the therapeutic dosage range. The time of blood sampling should be at least 6 h after the last dose. During regular maintenance dosage without a loading Table 2.6.6 Drugs that commonly require therapeutic concentration monitoring and their reference ranges Drug Concentration below which a therapeutic effect is unlikely Concentration above which a toxic effect is more likely Gentamicina 5 µg/ml (peak) 12 µg/ml (peak), 2 µg/ml (trough) Digoxin 1.0 nmol/litre 3.8 nmol/litre Ciclosporinb 80–200 nmol/litre 170–300 nmol/litre Lithium 0.4 mmol/litre 1.0 mmol/litre Phenytoin 40 µmol/litre 80 µmol/litre Theophylline 55 µmol/litre 100 µmol/litre a Conventional dosage regimens. b Actual range will vary between laboratories.

2.6 Principles of clinical pharmacology and drug therapy 99 dose, steady state is reached after about 7 days (normal renal func- tion) to more than 14 days (functionally anephric). The pharma- cological response to a given plasma level of digoxin is dependent on thyroid function (hyperthyroidism decreases responsiveness and hypothyroidism increases it) and the plasma potassium (hypo- kalaemia increases responsiveness and hyperkalaemia reduces it). Children younger than 6 months have lower plasma digoxin con- centrations at a given dose than older children and adults, and they are also more resistant to the pharmacodynamic actions of digitalis; so plasma digoxin concentrations cannot be clearly interpreted in this age group. Lithium The therapeutic range is 0.4 to 1 mmol/litre. In the range of 1 to 1.5 mmol/litre, the incidence of both acute toxicity and long-term adverse effects is increased. Concentrations above 1.5 mmol/litre should be avoided. Blood samples should be taken at least 12 h after the last dose. It takes about 3 days for steady state to be reached during regular maintenance therapy, but patients vary widely. It may take up to a week. Monitoring the plasma lithium concentration is necessary for several reasons. Lithium is nephrotoxic and excreted by the kid- neys, so if toxicity occurs it is self-perpetuating. Systemic avail- ability varies from person to person and is altered by diarrhoea. It also varies widely between formulations, which cannot be used interchangeably. Sodium balance also affects renal excretion of lithium. For example, diuretic-induced renal sodium loss reduces renal lithium excretion and can precipitate toxicity. Aminoglycoside antibiotics Gentamicin is the most widely used aminoglycoside antibiotic, but the principles hold for other aminoglycosides. The relation between the plasma concentration of gentamicin and its therapeutic efficacy is complicated by the fact that different organisms have different sensitivities to the antibiotic. Gentamicin is renally excreted, so in renal impairment it accumulates unless the dose frequency (and eventually the dose itself) is reduced. The toxic effects of gentamicin on the inner ear and kidneys are related to the ‘peak’ concentration (usually taken 1 h after an intramuscular injection or the start of an intravenous infusion) and the ‘trough’ concentration (taken just before the next dose). These should be measured after three or four doses, or sooner if there is renal impairment. A peak plasma concentration of 5 to 9 mg/litre is generally considered necessary, although when gentamicin is used together with benzylpenicillin to treat bac- terial endocarditis, lower plasma gentamicin concentrations may be effective. Bacteriological measurement of in vitro inhibitory concentrations will help to guide therapy. If there is uncertainty, expert advice on dosing and target plasma concentrations should be sought. Theophylline Plasma theophylline concentrations correlate well with therapeutic and toxic effects. Measurement is essential in any patient who has been taking oral theophylline before it is given intravenously. It is also important in smokers who usually have increased theophylline clearance and hence require higher maintenance doses. Ciclosporin Ciclosporin is generally measured in whole blood, and the result of the assay may

depend on whether the measurement technique is by immunoassay or high-performance liquid chromatography. The time to steady state is about 2 days and samples should be taken at trough (just before the next dose). The whole-blood concentra- tion of ciclosporin can be affected by reduced absorption (due to diarrhoea or reduced bile-salt production) or altered bioavailability (due to liver disease, coadministered drugs such as ketoconazole and rifampicin, grapefruit juice, or St John’s wort). FURTHER READING Clinical pharmacology Brown MJ, Sharma P, Mir FA, Bennett PN (2019). Clinical pharma- cology, 12th Edition. Elsevier, North Holland. Ritter JM, et al. (2008). A textbook of clinical pharmacology, 5th edition. Arnold, London. Pharmacological effects of drugs Brunton LL, et al. (2012). Goodman & Gilman’s the pharmacological basis of therapeutics, 12th edition. Mc-Graw Hill, London. Rang HP, et al. (2019). Rang & Dale’s pharmacology, 9th edition. Elsevier, Amsterdam. Pharmacokinetics Gibaldi M, Perrier D (1982). Pharmacokinetics, 2nd edition. Marcel Dekker, New York. Rowland M, Tozer TN (1995). Clinical pharmacokinetics. Concepts and applications, 3rd edition. Lea & Febiger, Philadelphia, PA. Adverse effects of drugs Aronson JK (ed) (2015). Meyler’s side effects of drugs, 16th edition. Elsevier, Amsterdam. Websites Medicines and Healthcare Products Regulatory Agency (MHRA). https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency/ UL Cochrane Centre. http://www.cochrane.co.uk/ World Health Organization (1994). Guide to Good Prescribing. http://whqlibdoc.who.int/hq/1994/WHO_DAP_94.11.pdf

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