behavioural problems in siblings. Separation of mother and baby also interferes with the establishment of breast feeding,¹⁶ and an unnecessarily prolonged stay on a special care baby unit increases the risk of serious cross infection.¹⁷

Many units have insufficient trained nursing staff because of either difficulties in recruitment or underfunding.^{18,19} Babies requiring the most basic neonatal care need four hours of nursing time a day,¹⁴ so earlier discharge of healthy babies frees limited nursing resources.

In 1985 the average cost of the Community Special Care Baby Service was £123 for each patient referred. Sandhu *et al* have calculated the costs of providing various levels of care for very low birthweight (<1500 g) infants in a regional neonatal intensive care unit.²⁰ The most basic nursing care costs £71 a day at 1984 prices. If, as our experience suggests, providing the community service results in infants weighing under 2250 g being discharged on average two weeks earlier considerable savings can be made. In 1985 337 babies weighing under 2250 g were discharged into the care of the service. If we assume that because of their smaller size these infants were visited more often and that the cost of providing the service for them was twice the average cost—that is £246—then the savings associated with their shortened stay on the neonatal unit would have been roughly £250 000 in 1985 ((337 × 14 × 71) – (337 × 246)).

The results of this study suggest that a community specialist nursing service for low birthweight infants and infants at high risk has many advantages for babies and their families. It allows more efficient use of overstretched hospital neonatal services and is therefore highly cost effective. This service is not unique to Manchester, nor is the way in which it is organised the only way of providing support for small infants, but we hope that our experience will stimulate debate about the way in which the special needs of these vulnerable infants can best be met.

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New Drugs

Practical clinical pharmacology: drug handling and response

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Throughout this series we have presented important new drugs and reconsidered some older ones where recent information has led to a reappraisal of efficacy or toxicity. Over 500 pharmacological agents have come on to the market in the past 25 years, and more than 100 are currently being developed. The production of hormones and regulatory peptides through recombinant deoxyribonucleic acid technology heralds another therapeutic revolution. Despite the

increasing adoption of postmarketing surveillance we rely heavily on perceptive observations by practising doctors not only for the early detection of adverse events but also for the recognition of unanticipated additional benefits that come to be regarded as secondary indications—for example, intraocular β blockers for glaucoma, topical minoxidil for baldness.

An increasing amount of assessment of new drugs will be undertaken by family doctors. This development is important, as many drugs are used almost entirely in general practice. In the final analysis the prescriber has to judge from available information whether or not to try a new treatment for the patient. For many, the interpretation of the clinical data, often presented in indigestible pharmacokinetic terms and as complicated clinical trials, is hindered by a lack of familiarity with the jargon and methods. These two articles will consider some basic principles in clinical pharmacology, an appreciation of which will facilitate better use of the available drugs and proper evaluation of newly introduced therapeutic agents.

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Pharmacokinetics

Pharmacokinetics, or how the body handles drugs, is the quantitative study of the time course of drug absorption, distribution, metabolism, and excretion and is by necessity a mathematical description. Some of the terms seem at first sight to have little relevance to everyday clinical practice, but they can enhance the prescribers' ability to recognise the cause of a therapeutic problem and to alter dosage schedules in a wide variety of clinical settings.

ABSORPTION

The absorption of most orally administered drugs takes place in the upper gastrointestinal tract, by and large, by passive diffusion.

FIG 1—Simple one compartmental model of drug distribution in humans and concentration-time curve in plasma. Volume of distribution (V_d) is calculated from extrapolated concentration at time 0 (C_0), assuming homogeneous and instantaneous mixing of drug. Elimination half life ($t_{1/2}$) may be "eyeballed" from curve or derived mathematically from its slope. Relation between clearance, $t_{1/2}$, and V_d is shown.

FIG 2—Typical two compartmental model (—) after intravenous administration of a drug. Profile after a single oral dose (....) is also shown. C_{max} = Maximum concentration. T_{max} = Time to achieve C_{max} .

We are particularly interested in the extent to which a drug is absorbed. This is sometimes referred to as bioavailability, which also takes into account presystemic elimination or first pass metabolism. The speed of drug absorption, expressed as T_{max} (see fig 2), may be important when a rapid effect is needed—for example, with analgesics and antibiotics. The rate is not a critical factor in long term treatment provided that a consistent amount of drug is absorbed from each dose to maintain adequate steady state concentrations.

A delay in absorption may result from concomitant disease (for example, migraine) or drug administration (for example, narcotic

analgesics), which reduce transit time through the gastrointestinal tract. The effect of food is complex. As a general rule the absorption of lipid soluble drugs will be enhanced by a meal, but this is of marginal benefit as, for most of these, the process is rapid and complete. A few drugs such as captopril, digoxin, and rifampicin are better absorbed on an empty stomach. Gastric irritants, such as non-steroidal anti-inflammatory agents and iron, should be taken with a meal. Capsules and tablets should be washed down with a glass of water with the patient in an upright position, either sitting or standing, as this enhances passage into the stomach and more rapid dissolution. Giving drugs orally to a recumbent patient should be avoided if possible, particularly those agents that have the potential to damage the oesophageal mucosa—for example, tetracyclines, iron salts, and slow release potassium preparations.

DISTRIBUTION

After absorption a drug passes through the circulation into body water and into cells. The extent of this distribution is largely determined by the physicochemical characteristics of the compound. Drugs that are highly soluble in lipid—the vast majority—tend to have large volumes of distribution (V_d , measured in hundreds of litres), whereas those that are highly protein bound, such as warfarin, remain largely within the plasma and have a volume similar to that of the vascular compartment—about seven litres.

Though the simplest model of distribution assumes the body to be a single homogeneous compartment (fig 1) most drugs are best described by a two compartmental system (fig 2). The drug initially enters a central compartment (V_1), primarily the circulation and highly vascular organs, where rapid diffusion leads to a sharp decline in drug concentration (α phase). A larger peripheral compartment (V_2) incorporates many tissues, including muscle, fat, bone, and so on. Though drugs do pass between these compartments, entry and elimination is through the central one only. Concentrations decrease more slowly in the elimination (β) phase owing to irreversible removal by hepatic metabolism or renal excretion, or both.

Where the apparent volume of distribution seems to exceed the total volume of body water (about 42 litres)—for example, with tricyclic antidepressants—there is substantial uptake and binding within tissues, such as muscle or brain, where the concentration may be considerably higher than that in plasma. Drugs that have a large volume of distribution and a long elimination half life—for example, digoxin—may be given initially in a loading dose to saturate these tissue binding sites. The maintenance dose will then depend on the rate of elimination.

HALF LIFE

The elimination half life of a drug is the time taken for the circulating concentration to fall by half (fig 1). For most drugs the rate of decline in their plasma concentration is constant and directly proportional to the amount present (that is, first order kinetics), with progressively more being removed at higher concentrations. This exponential decay, when plotted on a log arithmetic scale, produces a straight line whose slope represents the rate of elimination. Where there is a particularly good concentration-effect relation the half life may be useful in predicting a drug's duration of action. The half life in this case may also help to decide on the appropriate frequency of dosing—for example, twice daily dosing of a drug with an elimination half life of about 12 hours. For most drugs, however, the half life does not easily equate with response, as there is substantial accumulation in tissues and avid binding to receptor sites. The presence of active metabolites may also alter the time course of the effect. Some drugs act by influencing biological systems, such as enzymes or cell membranes, that have their own inherent duration of action.

The half life can be used to predict the time to achieve the steady

state concentration in the circulation. It takes around five half lives to achieve equilibrium, where the amount of drug eliminated is equivalent to that absorbed (fig 3). The half life can be used in the same way to calculate the time required for the drug concentration to decrease to a desired concentration or to be cleared almost completely from the circulation—again five half lives.

FIG 3—Repeated twice daily oral dosing of a drug with half life ($t_{1/2}$) of 12 hours showing concentration-time curve to steady state. ▨=Area under plasma concentration-time curve (AUC) after one dose. This can be used to calculate clearance (administered dose/AUC).

CLEARANCE

Clearance denotes the volume of blood or plasma from which the drug is completely removed per unit time. Most drugs are biodegraded through the action of liver enzymes to produce more water soluble metabolites. A few are excreted unchanged into urine. Doctors are familiar with the concept of clearance with regard to renal function. If the renal clearance of a water soluble drug is around 120 ml/min this suggests that the glomerular filtration rate is the main limiting factor. Where clearance is more rapid than this additional tubular secretion of the drug can be assumed to be occurring. Information on the kinetics of such a drug is required in cases where renal function can be expected to be altered—for example, in the newborn, elderly, or patients who have renal disease.

For some drugs clearance after intravenous dosing is equivalent to blood flow through the liver (500-1500 ml/min)—for example, with lignocaine and morphine. The liver is so efficient at excreting these drugs from the blood that the rate of delivery to that organ is the rate limiting factor in its metabolism. Occasionally the calculated clearance after oral administration of a drug is even greater than the blood flow through the liver—for example, 2-5 litres/min for propranolol and tricyclic antidepressants—suggesting that there is appreciable presystemic metabolism in the gut wall or liver, or both. Such an occurrence can be confirmed when the clearance value is lower after an intravenous dose (systemic clearance) than that obtained after oral administration, as is the case with verapamil and salbutamol.

A few drugs, notably ethanol, phenytoin, and theophylline, do not obey simple first order kinetic laws. For these the rate of elimination at high concentrations is independent of the drug concentration and is described by “zero order” (or saturation) kinetics, where a constant amount is cleared per unit time. Thus first order kinetics apply at lower doses, and zero order metabolism takes over at higher concentrations, explaining why increments need to be progressively reduced with increasing dosage.

DRUG METABOLISM

Most lipid soluble compounds are metabolised in the liver to more water soluble products. This is often a two phase process, with

initial oxidation primarily carried out by a family of enzymes (mono-oxygenase or mixed function oxidases) found in the endoplasmic reticulum of hepatocytes. Their cellular content can be measured in vitro as cytochrome P450 because of the production of a characteristic wave band at 450 nm on spectrophotometry. Many drugs also undergo a second step (phase 2) by conjugation, where an endogenous substance such as glucuronic acid or sulphate is attached to the drug or its metabolite. Larger molecules are then eliminated in the bile, whereas smaller ones (molecular weight less than 300) are excreted through the kidney.

Though most lipid soluble drugs are rendered inactive by metabolism, there are a few prodrugs whose activation takes place by oxidative processes—for example, cyclophosphamide, sulindac, enalapril. Some metabolites are of interest because they have a longer duration of action than the parent compound (for example, those from flurazepam and clobazepam). Paracetamol hepatotoxicity is produced by an evanescent oxidative metabolite that binds irreversibly to liver cell macromolecules. In an overdose the normal cellular defensive mechanism of conjugation with glutathione is overwhelmed.

A large variety of endogenous substances, exogenous toxins, and lipid soluble drugs are metabolised in the liver by a limited number of enzyme systems. The rate at which drugs are metabolised depends on a combination of interlinked factors—namely, the genetically determined enzyme complement, the physiological and pathological state of the major organs, and environmental factors including the presence of other drugs, alcohol consumption, and cigarette smoking (fig 4). The variability in enzyme content and the differential effect of those genetic and environmental factors makes a single dosage regimen with a lipid soluble drug unrealistic.

FIG 4—Overlapping variables that influence rate and extent of drug metabolism in liver.

Initial estimates of drug clearance and half life are usually derived from studies in healthy subjects, often young men because of the possibility of teratogenesis. Metabolism is less efficient in patients, particularly those with liver disease or cardiac failure, and in the elderly. Clearance values often extend over a wide range. Unfortunately the influences on metabolism are too diverse and unpredictable to allow precise recommendations for dosage to be adjusted in the individual patient. They do, however, help to explain the considerable variability seen in response to treatment and allow general predictions of the likely effects of aging, organ failure, and concomitant drug treatment. This background knowledge, combined with a careful appraisal of efficacy and toxicity, will facilitate drug use in these groups of patients at high risk.

PHARMACOGENETICS

There is increasing recognition of the potentially pivotal role of genetics in determining the rate at which drugs are metabolised. Several primary routes of metabolism such as acetylation and hydroxylation are subject to strong genetic control. This may explain individual or ethnic susceptibility to enhanced toxicity or poor efficacy with particular agents. About 8% of the European population show a reduced capacity to oxidise certain drugs. A poor capacity for hydroxylation helps to explain why some patients develop profound hypotension with debrisoquine and considerable β blockade with metoprolol and why phenformin and perhexiline were withdrawn from clinical practice because they produced lactic acidosis and hepatotoxicity, respectively, in an unacceptable proportion of patients.

Throughout the world there is a much larger variation in acetylation among ethnic groups. Fast acetylators make up 90% of Eskimos, 40% of Europeans, but only about 20% of Egyptians. Such people are less likely to have tuberculosis cured by the intermittent administration of isoniazid. Slow acetylators, on the other hand, more often develop peripheral neuropathy when treated with isoniazid and systemic lupus erythematosus when treated with procainamide and hydralazine. Similarly, evidence is now accumulating that the serious "idiosyncratic" toxicity (blood dyscrasias, rash, nephrotic syndrome) seen after treatment with penicillamine and gold is more common in patients whose ability to sulphoxidate is comparatively low. The metabolism of certain environmental toxins may be associated with metabolic polymorphisms—for example, primary liver cancer in Nigerians is predominantly seen in fast hydroxylators, and bladder cancer in people who work with dye is more commonly found in slow acetylators.

STEREISOMERISM

Many pharmaceuticals, perhaps one quarter, exist in mirror image forms as optically active stereoisomers (or enantiomers). The drug on the market is often a racemate, or equal mixture of left (L or S) and right (R or D) isomers. Isomers may differ in metabolism, pharmacological effect, and toxicity. For example, propranolol is marketed as the racemate DL, but only L-propranolol is responsible for the β blockade—D-propranolol has little activity. Other β blockers such as timolol and sotalol and the calcium antagonist verapamil also show stereoselective differences in drug action. These isomers may be cleared by the body at different rates.

One of the better known examples concerns warfarin. Most pharmacological activity resides within the S isomer, whose clearance is faster than that of R-warfarin. Interactions with other drugs such as sulphinpyrazone and co-trimoxazole show stereoselective inhibition of the S enantiomer only. Phenylbutazone inhibits the breakdown of the S isomer and induces the metabolism of R-warfarin. The result is potentiated anticoagulation with no change in total warfarin concentrations. The commercial production of individual isomers could result in more specific and safer drugs. One isomer of thalidomide, for example, is hypnotic while the other is teratogenic.

DRUG PROTEIN BINDING

Drugs may be bound to several proteins in the circulation, particularly albumin and the acute phase reactant α_1 acid glycoprotein. In general, acidic and neutral drugs bind to albumin, and basic drugs bind to α_1 acid glycoprotein. Low concentrations of albumin—for example, in the nephrotic syndrome or hepatic cirrhosis—or increased α_1 acid glycoprotein concentrations—for example, in rheumatoid arthritis or Crohn's disease—will alter the binding of drugs such as warfarin and lignocaine, respectively. As the free (unbound) fraction is pharmacologically active such a change may affect distribution and accessibility to hepatic metabolic sites and renal excretion mechanisms. It is the free component that is transferred into the cerebrospinal fluid, transplacentally to the fetus, and into breast milk.

Alterations in binding are likely to be of clinical relevance only for drugs that are more than 90% protein bound. A decrease of 1% in warfarin binding (normally 99% bound) will result in a 100% increase in concentrations of the free drug. The effect of this will be offset by increased hepatic metabolism (first order process). The result is a more subtle variation in the concentration-time curve—that is, higher peaks and lower troughs but a similar steady state. For the same reason drug interactions caused by the displacement of binding sites on circulating proteins are not regarded as a great cause of toxicity (see earlier article).

RENAL ELIMINATION

The kidney is responsible for excreting water soluble drugs and metabolites. Lipid soluble substances are also filtered by the glomerulus, but these will diffuse back into the circulation further down the nephron. The extent of back diffusion is less for drugs that are highly ionised or dissociated. This situation can be exploited in the management of overdose, where the rates of renal excretion can be substantially increased by altering urinary pH—for example, alkalinisation in overdose of aspirin and barbiturates, acidification in overdose of amphetamines.

The tubules actively secrete several weak acids such as penicillin, cephalosporins, salicylates, probenecid, and thiazides and bases such as amiloride, cimetidine, and procainamide by two separate systems. Interactions may occur owing to competition between drugs for these sites of tubular transport. Thus probenecid has been usefully used for many decades to increase circulating concentrations of penicillin. Some drugs, including digoxin and aminoglycosides, are excreted unchanged by the kidney, and information on their handling in patients who have disorders of renal function is of obvious importance. Unfortunately, serum urea, largely determined by protein intake, and creatinine, reflecting formation in muscle, are not sufficiently sensitive indices to assess changes in the glomerular filtration rate and renal drug clearance. Measuring creatinine clearance provides the most accurate guideline for adjusting dosage. This can be estimated from a simple equation such as: creatinine clearance (ml/min) = $((140 - \text{age}) \times \text{weight (kg)}) / \text{plasma creatinine } (\mu\text{mol/l})$. Though this calculation may overestimate creatinine clearance in grossly overweight or oedematous patients and where serum creatinine concentration is rising rapidly, it is accurate enough for most patients whose renal function is stable. In patients who have renal failure lower doses of water soluble drugs are necessary, often at extended intervals.

Pharmacodynamics

Pharmacodynamics is the description of the pharmacological properties of a drug. Many drugs depend for their action on binding to a receptor protein in the cell or its membrane to produce a direct effect (agonist) or to block the effect of an endogenous agonist (antagonist). An increasing number of highly specific receptors have been identified—for example, for adrenaline, acetylcholine, histamine, dopamine, opioids, benzodiazepines, and so on. Subclasses of most receptors—for example, β_1 - β_2 adrenoceptors—have been recognised. A few drugs have been shown to be partial agonists (antagonist at low concentrations and agonist at high)—for example, buprenorphine, pindolol. Drugs may act on more than one receptor site, particularly in the central nervous system. Some influence the transduction process (or coupling) between receptor occupancy and drug effect, which is usually mediated by an internal energy releasing system such as cyclic adenosine monophosphate. Others affect general processes such as nerve conduction or muscle contraction.

Receptors exist in a dynamic state. Their number and functional state—the avidity with which they will bind agonists—vary with disease state and drug treatment. Continued exposure to an agonist leads to the internalisation of receptors, thus limiting or reducing efficiency ("down regulation"). This may be seen with the long term use of a selective β_2 agonist in asthma. Tolerance, or decreased

responsiveness, may develop when an increased dose is required to produce the same effect. This may be a consequence of the down regulation of receptors, a homeostatic adaptive response, or the stimulation of the drug's metabolism. Recently tolerance to the antianginal effect of nitrates has been explained by a deficiency of reduced sulphhydryl groups which they induce in vascular smooth muscle. Intermittent treatment may allow replenishment and restore efficacy. In some disease processes such as insulin resistance defects exist not only at the receptor but also within the mechanism of coupling or at a post receptor site.

Long term treatment with an antagonist will lead to an increase in receptor binding sites ("up regulation"). This phenomenon may explain the syndrome associated with the rapid withdrawal of some drugs—for example, rebound angina after withdrawing propranolol. The sensitivity of patients to low doses of a particular drug may be a consequence of age, concomitant renal or hepatic disease, or the type and severity of the underlying condition. Thus the pathophysiology of the disorder—for example, renal hypertension or coronary artery spasm—may determine the extent of response to various antihypertensive or antianginal drugs. The sensitivity of the central nervous system to benzodiazepines and narcotic analgesics in patients who have hepatic encephalopathy is largely a pharmacodynamic process.

The homeostatic and biochemical milieu may also influence the response to treatment—for example, altering the electrolyte balance. A depletion of sodium predisposes a patient to lithium toxicity and hypokalaemia to digoxin toxicity. Synergism of drugs that have similar pharmacodynamic properties may be beneficial, as with the antibiotic components of co-trimoxazole or with combined levodopa and selegiline (selective monoamine oxidase inhibitor) treatment in Parkinson's disease.

VARIATION IN RESPONSE

Variation in response to the same dose of drug is the rule rather than the exception in clinical practice. Assuming that a patient is compliant and that there are no pharmaceutical problems, the main reasons for this variability include a combination of pharmacokinetic and pharmacodynamic factors. A multifactorial situation therefore exists, the individual factors of which may be difficult to dissect out. An understanding of the likely components, however, will allow the prescriber to make adjustments when something goes wrong. A lack of pharmacological effect or the development of toxicity may warrant an alteration in dosage or substitution by another drug.

Several issues need to be considered when assessing the choice of treatment. Information on efficacy and the magnitude of risk-benefit ratio are important, particularly when deciding between comparable drugs. Potency—that is, the relation between dose (concentration) and effect—is of little clinical relevance. The therapeutic ratio, or the closeness of the relation between the dose producing the pharmacological or beneficial effect and that associated with toxicity, is critical in risk-benefit analysis. For drugs that have a low or narrow ratio—for example, digoxin, warfarin, phenytoin—increments of dosage should be small and the response or concentration, or both, reviewed often. Another problem, long recognised but poorly studied, is the placebo effect, or how the patients' perception of treatment influences their response. In some organic disorders a substantial proportion of patients respond satisfactorily to placebo—for example, 40% who have peptic ulcer or angina. A new treatment must be shown to be at least as good as standard treatment and, wherever possible, better than placebo.

Compliance

Despite evidence to the contrary, it is generally assumed by most prescribers that patients take their drugs as directed. The incidence of non-compliance is difficult to estimate, but studies show that between 20% and 30% of patients receiving short term curative treatment and up to half of those taking long term prophylactic treatment do not fully comply. The impact of incomplete compliance on outcome will depend on both the drug and the disease as well as on the extent to which the drug is not taken. Some patients adjust their compliance in line with the side effects they experience. This information may be withheld in order not to upset the doctor! A few patients take (virtually) none of the treatment prescribed. Some doctors are not fully aware of what drugs their patients are taking, particularly when patients are attending hospital clinics as well as the general practitioner's surgery. Confusion with generic and proprietary names can occur, and combination preparations—for example, a β blocker and a thiazide diuretic—may not be recognised as such.

About 70% of the population receives at least one prescription a year; there is even greater use of drugs in the elderly. Most patients also buy additional non-prescription drugs. Compliance can be improved by minimising the number of drugs prescribed and the frequency of their administration. Such rationalisation should be accompanied by discussing with the patient the expected benefits and likely side effects of the treatment. A realistic approach to outcome must be shared by the doctor and the patient.

The pharmaceutical industry goes to considerable lengths to produce drugs to be taken once daily, slow release formulations, calendar packs, and other reminders, often without supportive evidence that these more expensive presentations actually do increase compliance. Doctors should regularly assess compliance, particularly where treatment seems to be inefficient (or toxic). This should include objectively assessing drug effect whenever possible, inquiring about common side effects, counting residual tablets, and measuring drug concentration where appropriate.

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