Home visiting

Patients who are discharged from hospital are always asked if they would like me to visit them at home; if so the general practitioner will be contacted by the consultant and his permission sought for a home visit. In turn, I discuss the patient, his treatment, and care with the community nurse. When and if the patient is discharged and later readmitted my service is mainly one of counselling and liaison between home and hospital; and by having time to offer, I can provide special nursing care within a district general hospital. Patients may prefer their own china cup and saucer, their own pillow, and even their own sheets. This is a novel idea in a general hospital—but it is not wrong to help a patient to die in comfort and dignity. In past years hospital staff have not had the time to think about such policies because they have put all their energies into the care of patients who will live.

Need for honesty

Dying patients require a confidant. Quite often they are unwilling or unable to communicate with their loved ones. I find that it is totally futile to be dishonest at this time. Though

I always accede to the wishes of the individual doctor if questioned about diagnosis or prognosis, I also try to be honest, for to tell lies destroys any trust between the patient and myself. The patient soon realises that his body is getting weaker and his pain or vomiting more prolonged; if he has been told anything other than the truth in answer to his question "Am I going to die?" he has no one in whom to trust or confide and must face the reality and fear of death in total isolation.

There is no more rewarding phrase than to hear a patient or relative say, "We feel safe as long as we know that you are around and we can get you." The emotional cost is high to the special care nurse; the counsellor must herself be able to be counselled when necessary. I am fortunate that my senior nursing staff are as enthusiastic and interested in the special care service as I am. Without their support I could not even start to provide this type of service.

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Today's Treatment

Clinical pharmacology

Adverse drug interactions

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In this article we shall discuss the incidence and mechanisms of adverse drug interactions, give examples of clinically important interactions, and mention other sources of information. We shall not discuss beneficial interactions.

In considering the incidence of adverse interactions one must distinguish between potential interactions—that is, the concurrent prescription of two drugs known to interact—and interactions that result in clinically obvious adverse effects. In one study¹ of 2422 patients studied prospectively during two months 113 (4.7%) were taking drugs with the potential for interaction but in only seven cases was there any clinical evidence of interaction (0.3% of all the patients; 6.2% of those potentially affected). With certain combinations of drugs, however, clinically important effects may occur more often. For example, in one survey of 1554 prescriptions for potassium chloride and 245 for spironolactone² 104 prescriptions were issued for the combination of those two (6.1%), and in a sample of 25 patients taking

such a combination three developed hyperkalaemia (0.7% of all patients; 12% of those taking the combination). In a study of the use of oral anticoagulants³ in 277 patients 94 were receiving other drugs that might have interacted (33.9%) and clinically significant interactions were thought to have occurred in six (2.2% of all patients; 6.4% of those taking combinations).

Unfortunately there are problems in collecting incidence figures of this type. For example, it may often be difficult to determine whether an adverse effect of a drug occurs as a result of a drug interaction rather than as a result of, say, misuse of the drug or of an interaction between the drug and some peculiarity of the patient, such as renal or hepatic dysfunction. What is certain, however, is that the chance of an adverse drug interaction increases with the number of drugs the patient is taking.⁴

Most drug interactions concern only two drugs, although there are published examples of interactions among more than two drugs. In general, when two drugs interact one *precipitates* the interaction by one or more of several different mechanisms (see below) while the other is the *object* of the interaction, and its effects are either increased or reduced. We propose, therefore, for ease of discussion, that the drug that precipitates the interaction be called the *precipitant* drug while that whose effect is altered be called the *object* drug. Occasionally, two drugs may each alter the effects of the other (as in the complex interaction of

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phenytoin with phenobarbitone). In these few cases our proposed terms lose their significance.

The drugs most likely to be the object drugs in adverse interactions are those that have a steep dose-response curve—that is, drugs for which a small change in dose results in a relatively large change in effect, important in interactions causing decreased efficacy of the object drug; and those that have a low toxic:therapeutic ratio—that is, drugs for which the dose at which toxic effects start to occur is very little more than the therapeutic dose, important in interactions causing toxic effects of the object drug. Drugs fulfilling these criteria include anticoagulants, hypoglycaemics, anticonvulsants, antiarrhythmics and cardiac glycosides, drugs acting on the central nervous system, and antihypertensives. Those drugs most likely to be precipitant drugs may often be predicted on the basis of the various mechanisms of interaction—for example, drugs that are highly protein-bound (for example, sulphonamides, salicylates); alter hepatic metabolism either by stimulation (for example, phenytoin) or inhibition (for example, metronidazole, cimetidine); or have effects that either mimic that of the object drug (for example, central nervous depressants) or have some effect that interacts with an effect of the object drug (for example, aspirin, which causes gastric erosions and diminishes platelet aggregability, both of which increase the chance of gastrointestinal bleeding in patients taking oral anticoagulants).

Types and mechanisms of interactions

The types of drug interactions are pharmaceutical, pharmacokinetic and pharmacodynamic.

PHARMACEUTICAL INTERACTIONS

We have not hitherto considered those interactions that may be termed “pharmaceutical”—that is, those of a drug either with another drug in the same infusion solution or with the infusion solution itself. Interactions between drugs and infusion (saline or dextrose) solutions often take the form of loss of activity of the drug because of instability in solution. Table I lists the most important examples. Interactions between drugs and infusion

TABLE I—Stability of some drugs in saline and dextrose solutions

Unstable—infuse within 2 hours
Ampicillin
Stable for 6-8 hours
Frusemide
Benzylpenicillin
Diazepam
Stable for 12 hours
Flucloxacillin
Oxytetracycline
Tetracycline
Light-sensitive
Nitroprusside
Amphotericin B

solutions other than saline or dextrose are often due to other mechanisms⁵ and may be avoided by avoiding such solutions for drug infusion. Interactions between two drugs in solution are far too numerous for individual discussion. In one study⁶ of 67 different drugs all 2211 possible combinations of any two drugs were studied in both 0.9% saline (pH 7) and 5% dextrose (pH 4.3). Only effects that were visible after three hours (precipitation, turbidity, or colour change) were studied. Only 23 of the 67 drugs gave no visible positive results in all com-

binations and in one in 30 cases there was visible precipitation. Such interactions should be avoidable, and the following principles should be followed.

(a) Read the manufacturer's publications for specific warnings and to check that the drug is suitable for intravenous administration.

(b) Give intravenous drugs by bolus injection whenever possible.

(c) Never use infusion solutions other than dextrose or saline for drug infusion.

(d) Avoid mixing drugs in the same infusion solution unless you know the mixture to be safe—for instance, potassium chloride and insulin.

(e) Mix the drug thoroughly in the infusion solution and check soon after and later during infusion for visible changes (turbidity, precipitation, colour change). Absence of such changes does not, however, guarantee the absence of an interaction.

(f) Prepare solutions only when needed (exceptions to this rule include drugs that are available in prepacked infusion solutions, such as KCl, lignocaine, metronidazole, chlormethiazole.)

(g) Label all infusion bottles clearly with the name and dose of drug added and the times of starting and ending the infusion.

(h) Use two separate infusion sites if it is necessary to infuse two drugs simultaneously unless it is known that there is no interaction.

(j) Consult your local hospital pharmacist if in doubt.

Other points are discussed in the 1976 DHSS report on this matter,⁷ and extensive lists of potential interactions are given by Riley⁸ and Grayson.⁸

PHARMACOKINETIC INTERACTIONS

By pharmacokinetic interactions we mean those interactions in which the disposition of the object drug is altered in some way by the precipitant drug. Such interactions are best considered according to which facet of drug disposition is affected.

Absorption

Although there are several mechanisms whereby the absorption of a drug may be altered by another drug—for example, the decrease in gastrointestinal motility caused by morphine-like drugs and anticholinergic drugs such as tricyclic antidepressants and chelation of calcium, aluminium, magnesium, and iron salts by tetracyclines—such effects are rarely of clinical importance.

Exceptions are the interactions of cholestyramine with oral anticoagulants and digitoxin. Reduction of initial absorption and of reabsorption after biliary excretion increases requirements of the object drugs.

Protein binding

If a drug is highly protein bound (greater than 90%) in the plasma then displacement by a precipitant drug will result in a relatively large increase in the free concentration of object drug in the plasma and therefore to an increased effect. If the precipitant drug is withdrawn the reverse will occur. That the object drug must be highly protein bound is important—displacement of 5% of a drug that is 20% bound results in a change in free concentration from 80% to 85%, a negligible effect; on the other hand, a change in binding of 1% of a drug that is 99% bound (such as warfarin), leads to a change in free concentration from 1% to 2% of total, a doubling of the free concentration. That change is important, however, only if a large amount of the drug is in the plasma—if most of the drug is in the tissues even total displacement from plasma proteins will make little differ-

ence; hence only drugs with a low apparent volume of distribution (V_d) will be affected. The important drugs that fulfil these criteria for object drugs are oral anticoagulants, such as warfarin, bound 99%, V_d 9 l; oral hypoglycaemics, such as tolbutamide, bound 96%, V_d 10 l; and phenytoin (bound 90%, V_d 35 l). For the precipitant drug it is enough that it be highly protein bound to the same binding site as the object drug; the commonest precipitant drugs in such interactions are the sulphonamides, salicylates, derivatives of chloral (because of their metabolite trichloroacetic acid), phenylbutazone, and oxyphenbutazone.

The importance of protein-binding-displacement interactions, however, has been exaggerated, and such interactions are usually of no clinical importance. The reason is that for drugs such as warfarin, phenytoin, and tolbutamide the total clearance rate is proportional to the fraction of drug unbound in the plasma and after displacement of the object drug its rate of clearance from the body is increased. Thus at steady state the total concentration of drug in the plasma will have fallen to a new equilibrium value such that the free concentration is the same as it was before the introduction of the precipitant drug. In some cases the change in free concentration occurs so slowly that the compensatory increase in clearance reduces the transient increase in free concentration of the object drug to negligible proportions. Thus, provided the patient can "weather" the increase, if any, in free concentration of object drug for as long as it takes to reach a new steady-state, such an interaction will not be of clinical importance. Indeed, only for warfarin has it been reported that such interactions may be important in causing adverse clinical effects, and those adverse effects may be avoidable by slow introduction of the precipitant drug. There is, however, another effect, important for phenytoin, in regard to the "therapeutic" plasma concentration range. It is best discussed with an illustrative example. Suppose a patient has a therapeutically effective total plasma phenytoin concentration of 60 $\mu\text{mol/l}$ ("therapeutic" range 40-80) of which 10% is free—that is, free concentration is 6 $\mu\text{mol/l}$. If the free fraction is doubled to 20% of total, although the free concentration at the new equilibrium will be, as before, 6 $\mu\text{mol/l}$, it will represent 20% of the total concentration, which will have fallen to 30 $\mu\text{mol/l}$ —that is, below the so-called "therapeutic" range. In fact for that patient the effective "therapeutic" range is lowered during the interaction.

Metabolism

If a drug is extensively metabolised it may become the object drug in an interaction if its metabolism by hepatic microsomal, or other, enzymes is either increased (enzyme induction) or inhibited by a precipitant drug. The precipitant drugs that commonly increase drug metabolism (enzyme inducers) are phenytoin, phenobarbitone, primidone, carbamazepine, rifampicin, griseofulvin, and alcohol (chronic use). Such interactions are of clinical importance. For example, an unwanted pregnancy may occur in patients taking oral contraceptive agents in the now conventional low-dose (oestrogen) preparations and an enzyme inducer. Warfarin metabolism may be increased by an enzyme inducer leading to higher dosage requirements; if the inducer is then withdrawn haemorrhagic complications may occur. Enzyme induction increases the hepatotoxic effects of paracetamol in overdose. The time course over which enzyme induction occurs is a few weeks.

Inhibition of hepatic microsomal enzymes may be caused by several drugs (metronidazole, phenylbutazone and oxyphenbutazone, chloramphenicol, isoniazid, cimetidine, and alcohol in acute intoxication) and the commonest object drugs are the oral anticoagulants and phenytoin. Some of the effects of inhibitors of warfarin metabolism are stereospecific—for example, phenylbutazone inhibits the metabolism of the S(–) enantiomer but induces the metabolism of the R(+) enantiomer; the overall effect on the racemic mixture is no apparent change in metabolism but since S(–)warfarin is more potent than R(+)warfarin

the inhibitory effect predominates and a clinically important potentiation of warfarin effect occurs. Phenylbutazone interacts with warfarin in four other ways—directly by protein-binding displacement and indirectly by inhibition of platelet aggregation and by increasing the likelihood of gastrointestinal ulceration and thrombocytopenia. Also important are the interactions of phenytoin with isoniazid (in slow acetylators) and chloramphenicol, in which the effects of phenytoin are increased. Other important examples of inhibition of specific metabolic processes include the interaction of monoamine oxidase inhibitors with tyramine-containing foods (such as cheese, red wine—tyramine metabolism by gut-wall monoamine oxidase is inhibited and hypertension results) and that of allopurinol with 6-mercaptopurine and azathioprine (whose metabolism is mediated by xanthine oxidase which is inhibited by alloxanthine, the active metabolite of allopurinol).

Active transport

Some drugs are transported by active systems that may be inhibited by a precipitant drug. A clinically important example is the effect of tricyclic antidepressants in blocking the transport of adrenergic neurone blockers (guanethidine, bethanidine, debrisoquine) to within nerve endings, thus attenuating their antihypertensive effects.

Excretion

Occasionally a precipitant drug may alter the urinary excretion of a compound that is excreted unchanged. An important example is the effect of quinidine in reducing digoxin excretion by the kidneys and thus increasing its plasma concentration (by, on average, a factor of two). The interaction, however, may also entail displacement from tissue-binding sites. Phenylbutazone reduces the renal clearance of chlorpropamide with consequent increase in the risk of hypoglycaemia. Frusemide and ethacrynic acid decrease excretion of gentamicin, thus enhancing its potential for ototoxicity and nephrotoxicity; it is not known whether or not bumetanide has a similar effect.

PHARMACODYNAMIC INTERACTIONS

Pharmacodynamic interactions may be either direct or indirect.

Direct interactions

The most common direct pharmacodynamic interactions are those resulting from drugs acting on the central nervous system. Since most such drugs—for instance, benzodiazepines, alcohol, phenothiazines—have effects that result in the depression of central nervous function their concomitant use results in a combination of their separate effects. Other important examples of such additive effects are antihypertensive drugs (which in combination may be harmful or beneficial) and the following combinations: frusemide (or ethacrynic acid) with gentamicin (ototoxicity); non-depolarising muscle relaxants with aminoglycoside antibiotics or quinidine (increased muscle relaxation); verapamil with propranolol (increased incidence of arrhythmias and possibly cardiac arrest); potassium-sparing diuretics either with each other or with potassium chloride (hyperkalaemia). An example of a more subtle potentiating interaction is that of warfarin with clofibrate, anabolic steroids, tetracyclines, or thyroxine (increased warfarin effect, possibly because of altered affinity of vitamin K for clotting factor receptors).

In passing it is worth while clearing up a misconception about

TABLE II—Some adverse drug interactions of clinical importance

Object drug(s)	Precipitant drug(s)
<i>Interactions in which effects of object drug are potentiated</i>	
Acetohexamide	Phenylbutazone
Alcohol	CNS drugs, disulfiram, metronidazole
Amine-containing foods	Monoamine oxidase inhibitors
Amphetamines	CNS drugs, monoamine oxidase inhibitors
Azathioprine	Allopurinol
Beta-adrenoceptor blockers	Verapamil
Cardiac glycosides	Hypokalaemia (diuretics, purgatives, carbenoxolone, corticosteroids, amphotericin B), hypercalcaemia (vitamin C, calcium), quinidine
Cephaloridine	Potent diuretics (frusemide, ethacrynic acid)
Chlorpropamide	Phenylbutazone
CNS drugs	Other CNS drugs
Coumarin anticoagulants	Anabolic steroids, chloral hydrate, chloramphenicol, cimetidine, clofibrate, dextropropoxyphene, dipyrindamole, disulfiram, D-thyroxine, indomethacin, mefenamic acid, metronidazole, oxyphenbutazone, phenylbutazone, salicylates, sulphapyrazole, tetracyclines
Diuretics (potassium-sparing)	Diuretics (potassium-sparing), potassium chloride
Gentamicin	Potent diuretics (ethacrynic acid, frusemide)
Lithium	Diuretics (sodium-wasting)
Mercaptopurine	Allopurinol
Non-depolarising muscle relaxants	Aminoglycoside antibiotics, quinidine
Pethidine	Monoamine oxidase inhibitors
Phenytoin	Chloramphenicol, coumarin anticoagulants, disulfiram, isoniazid, phenylbutazone, sulthiame
Potassium chloride	Diuretics (potassium-sparing)
Tolbutamide	Chloramphenicol, clofibrate, coumarin anticoagulants, phenylbutazone, salicylates, sulphonamides
Verapamil	Beta-adrenoceptor blockers
<i>Interactions in which effects of object drug are diminished</i>	
Adrenergic neurone blockers (bethanidine, debrisoquine, guanethidine)	Chlorpromazine, tricyclic antidepressants
Antiarrhythmics	Hypokalaemia (diuretics, purgatives, carbenoxolone, corticosteroids, amphotericin B)
Carbenoxolone	Spironolactone
Cardiac glycosides (digitoxin)	Cholestyramine
Chlorpromazine	Barbiturates, orphenadrine
Cortisol	Barbiturates, phenylbutazone, phenytoin
Coumarin anticoagulants	Alcohol (chronic use), barbiturates, chloral hydrate, cholestyramine, cortisol, dichloralphenazone, diuretics, glutethimide, griseofulvin, nortriptyline, oestrogens, phenytoin, rifampicin
Oral contraceptives	Barbiturates, phenytoin, rifampicin
Oral hypoglycaemics	Diazoxide, diuretics
Phenytoin	Alcohol, barbiturates, carbamazepine
Tolbutamide	Rifampicin

the potentiating interactions of warfarin with some antibiotics. Such interactions are commonly attributed to the inhibitory effect of antibiotics on the gut flora responsible for synthesising vitamin K. Dietary vitamin K, however, will prevent a potentiation of warfarin effect even if vitamin K synthesis by gut flora (which in any case takes place mostly in the large bowel) is completely inhibited. Antibiotics such as chloramphenicol, metronidazole, and tetracycline, which do potentiate the action of warfarin, do so by other mechanisms. Thus, unless there is dietary deficiency of vitamin K, antibiotics such as those of the penicillin, cephalosporin, and aminoglycoside groups should be safe to use.

Interactions in which the precipitant drug antagonises the effects of the object drug are common but are often beneficial—for instance, naloxone reversal of opiate effects, the treatment of poisoning with anticholinergic drugs using physostigmine. Important exceptions are the interaction of diuretics (thiazides or frusemide) or diazoxide with oral hypoglycaemic drugs (reduction in hypoglycaemic effects) and the attenuation of the therapeutic effects of carbenoxolone by spironolactone and of warfarin by oestrogens (increased clotting factor synthesis).

Indirect interactions

Indirect pharmacodynamic interactions are of two kinds. The first is the interaction in which the precipitant drug causes some alteration of fluid or electrolyte balance which influences the effect of the object drug. Important examples are: the enhancement of the effects of cardiac glycosides or the attenuation of the effects of antiarrhythmic drugs such as quinidine or lignocaine because of hypokalaemia secondary to diuretics; the attenuation

of the effects of warfarin by diuretics because of relief of hepatic congestion; and the increased retention of lithium due to sodium loss secondary to diuretics. This last example shows how a pharmacodynamic effect of precipitant drug may cause a change in the pharmacokinetics of the object drug.

The second variety of indirect interaction results between oral anticoagulants and drugs that either cause gastrointestinal erosion or ulceration (such as non-steroidal anti-inflammatory drugs, corticosteroids) or decrease platelet aggregability (such as salicylates, phenylbutazone, and indomethacin). In such cases there will be either an increased tendency to bleed or, if bleeding occurs, impaired haemostasis.

Sources of information

We have not tried here to be comprehensive, but have aimed simply at discussing the basis of some of the commoner adverse drug interactions of clinical importance. One cannot, in any case, hope to remember all those interactions that might result in an adverse reaction, and a knowledge of sources of information is useful. We have listed in table II the most common interactions of clinical importance or possible importance. There are two other forms of similar but more comprehensive listing available.

TEXTBOOKS

The following will be found helpful:

Drug Interactions and their Mechanisms by Ivan Stockley (published by the Pharmaceutical Press, London, and available from them at a give-away price).

Drug Interactions by P D Hansten (published by Lea and Febiger, Philadelphia).

Evaluations of Drug Interactions (published by the American Pharmaceutical Association, Washington DC).

CHARTS AND SLIDE-RULES

The information contained in Stockley's monograph mentioned above has been brought up to date and summarised in the form of a wall chart, a pocket folder, and a cardboard slide-rule. The first two are available free in their 4th edition from Boehringer Ingelheim, Berkshire. A new edition of the slide-rule will be issued later this year.

Alternatively there is an interaction disc based on the same slide-rule principle⁹ (MediscTM) published by Excerpta Medica, but it may be difficult to obtain in Britain.

No reprints will be available from the author.

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