The drug dilemma—benefits and hazards

Drug interactions and lethal drug combinations

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Although the development of drugs of greater potency and efficacy confers on the physician increasing power to treat serious diseases, it also increases the number and seriousness of potential adverse effects and drug interactions which can occur. Most hospital patients receive more than one drug at a time, the average number often being greater than five (Smith, Seidl, and Cluff, 1966). The incidence of drug reactions rises with the number of drugs prescribed simultaneously. In patients prescribed one to five drugs the incidence of reactions is 18.6%, while in patients prescribed six or more it rises to 81.4% (Hurwitz and Wade, 1969).

The Boston Collaborative Drug Surveillance Program (1972) surveyed the incidence of drug reactions in 9900 patients admitted to nine acute disease hospitals and one chronic disease hospital. There were 83 200 drugs administered, and 3600 adverse reactions occurred of which 6.9% were due to drug interactions. The most serious interactions included depression of the central nervous system, severe hypotension, gastrointestinal bleeding, psychotic behaviour and superinfection. Although the clinical importance of drug interactions has been exaggerated in some reports, the number which end in a fatal outcome is disproportionately high. In a survey of 6199 medical inpatients in five general hospitals and one chronic disease hospital, 744 patients died in hospital, and of these deaths 27 were considered to be due to drug treatment, of which nine were caused by drug interactions (Shapiro, Slone, Lewis, and Jick, 1971).

The physician should be alert to the danger of drug interactions in a number of circumstances.

1 When the pharmacological effect of a drug is harmful in excess and when the therapeutic ratio is low. Examples are hypoglycaemic drugs, anticoagulants, digoxin, depressants of the central nervous system, cytotoxic drugs.

2 When a drug produces an altered state of receptor sensitivity in the sympathetic nerve terminals, eg, monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants, hypotensive drugs.

3 When interactions occur with medicines that can be bought over the chemist's counter. For

example, aspirin can displace oral anticoagulants from their plasma-protein-binding sites, and indirectly acting sympathomimetics contained in cough mixtures can cause a hypertensive crisis in patients on monoamine oxidase inhibitors. Self-medication is common, and often involves drugs obtained on prescription for a previous illness.

4 When several clinics or doctors are involved in the care of a patient, one doctor may not be aware of what another has prescribed.

5 When preparations which contain more than one ingredient are prescribed by their trade names.

There are a number of ways in which drugs may interact. These will be outlined and illustrated in the remainder of this paper.

Interactions before Administration

Some drugs are chemically or physically incompatible in the forms in which they are presented for administration. For example, thiopentone sodium injection is strongly alkaline and will cause hydrolysis of suxamethonium if both drugs are drawn up into a syringe together for combined anaesthetic induction and muscle relaxation. The excess of protamine zinc in protamine zinc insulin will combine with soluble insulin if the two preparations are mixed in the syringe before injection, resulting in a change in the rate of absorption of the latter preparation. As a general rule drug solutions should not be mixed, nor added to intravenous infusions, particularly whole blood, unless it is known that the components are chemically and physically compatible.

Interactions in the Gut

Drugs are absorbed largely in the upper part of the small intestine because of the enormous mucosal surface area and blood supply present there. Drugs which alter the rate of gastric emptying can affect the delivery of the drug to this site and can thereby influence either the rate or the extent of absorption. The anticholinergic properties of propantheline reduce the rate of gastric emptying and therefore slow down the absorption of a drug such as paracetamol (Prescott, 1974). However, the extent of absorp-

tion, particularly of poorly soluble drugs like digoxin, may be increased. As many drugs possess anticholinergic effects, eg, antihistamines, tricyclic antidepressants, phenothiazines and anti-Parkinsonian drugs, this type of interaction probably occurs commonly. Metoclopramide increases the rate of gastric emptying, particularly in patients in whom it is delayed, and has been shown to shorten the time to peak plasma concentration of paracetamol and aspirin (Prescott, 1974; Volans, 1974).

Some drugs may interact chemically in the gut, leading to impaired absorption of both drugs. Calcium, magnesium and aluminium ions contained in antacid preparations cause the formation of a metal-tetracycline chelate which is poorly absorbed (Kunin and Finland, 1961). Iron salts given simultaneously for anaemia will have a similar effect (Neuvonen and Turakka, 1974). These interactions may result in an inadequate serum concentration of the antibiotic being reached, with consequent failure of therapy. Chemical interaction in the gut appears to account also for the failure of griseofulvin's antifungal action in patients receiving a barbiturate drug (Riegelman, Rowland, and Epstein, 1970), and the reduction in plasma rifampicin concentrations by concurrent administration of *para*-aminosalicylate (Boman, Hanngren, Malmberg, Borgå, and Sjöqvist, 1971). Although barbiturates are known to induce the hepatic metabolism of oral anticoagulants, it has been suggested that an interaction in the gut lumen might also contribute to the lowering of the serum level of the anticoagulant (O'Reilly and Aggeler, 1969).

A deficiency of vitamin K in a patient treated with oral anticoagulants will exaggerate the effect of these latter compounds. Commensal organisms in the gut produce vitamin K and therefore gut sterilization with broad-spectrum antibiotics may disturb anticoagulant control. Ingestion of liquid paraffin may have the same effect because of the fat-soluble nature of the vitamin.

Interactions during Absorption

Drugs which are absorbed from the gut enter the portal venous system and are therefore exposed to drug-metabolizing enzymes in the hepatic cells before they enter the systemic circulation. This results in a considerable loss of drugs that are metabolized rapidly on first passage through the liver—the so-called 'first pass effect'. Examples of drugs for which this is important are isoprenaline, ephedrine, levodopa, propranolol, aspirin and nortriptyline. Drug interactions may alter the extent of first pass metabolism. This is likely to be most important when a normally high rate of first pass

metabolism is substantially reduced by inhibition of the metabolic enzyme. It is probable that this partly accounts for the hypertensive crisis which can result from the administration of directly acting sympathomimetic amines, eg, tyramine, ephedrine, levodopa, to patients on chronic MAOI therapy. An interaction at the sympathetic nerve terminal is also important in causing the crisis (see below).

The administration of dopa decarboxylase inhibitors, eg, carbidopa in Sinemet, or benserazide in Madopar, probably increases the quantity of levodopa which reaches the systemic circulation unmetabolized, as well as reducing its peripheral metabolism in tissues which contain the enzyme, such as sympathetic nerve terminals. In this case the interaction is used to advantage because the amount of levodopa which has to be administered daily to the Parkinsonian patient can be reduced to between a quarter and a fifth by the addition of the enzyme inhibitor.

It is likely that long-term therapy with liver-enzyme-inducing drugs such as barbiturates can reduce the quantity of other drugs reaching the systemic circulation by increasing their first-pass metabolism, although it is not easy to distinguish this type of interaction from one involving a reduction in absorption from the gut.

Plasma-protein-binding Interactions

Many drugs are loosely bound to plasma proteins, usually albumin. Only the unbound drug molecules are available for pharmacological action, although as they are removed from the circulation by distribution or elimination they are replaced by other molecules detaching themselves from protein-binding sites. A number of drugs are extensively bound to plasma proteins and therefore competition for binding sites can be a cause of drug interaction, although it is not easy to predict which drugs are likely to interact in this way because different types of binding sites may be used by different drugs. On the whole, it is probable that competition for binding sites is not often a cause of a clinically important interaction.

Although displacement of a proportion of a drug bound to plasma proteins will increase the concentration of free drug in the serum and therefore its pharmacological effect, the extent to which it is increased is dependent upon the drug's distribution volume. Centrally acting drugs, eg, phenytoin, are usually highly lipid soluble and have a large distribution volume. A small quantity displaced from binding sites will therefore rapidly redistribute to other tissues and will not cause an important increase in the effects of the drug. Warfarin, however,

is both highly bound to plasma proteins (98-99%) and has a relatively small distribution volume. Displacement from its binding sites by phenylbutazone (Aggeler, O'Reilly, Leong, and Kowitz, 1967) and chloral hydrate (Sellers and Koch-Weser, 1971) may cause a sudden increase in the anticoagulant response with an attendant danger of bleeding. With phenylbutazone, however, inhibition of the metabolism of warfarin may be more important than displacement from its binding sites (Lewis, Trager, Chan, Breckenridge, Orme, Rowland, and Schary, 1974).

Interactions at Site of Metabolism

Most drugs which are used therapeutically in man are metabolized by enzyme systems in the liver, the object being to convert lipid-soluble drugs into more polar water-soluble metabolites which can be rapidly cleared by the kidneys. Many drugs use common microsomal enzyme systems, for example, the cytochrome P450-dependent oxidase system by which drugs are hydroxylated, dealkylated, deaminated or sulfoxidized. Substrates of the system, for example, phenobarbitone, phenytoin, primidone, glutethimide, rifampicin, can cause enzyme induction if they are administered repeatedly. Six to eight weeks of treatment is required for this effect to become maximal. Not only is the metabolism of the inducing drug stimulated, but many other drugs and endogenous substances will be turned over much more rapidly (Richens, 1974). This can lead to a reduction in the anticoagulant effect of dicoumarol (Hansen, Siersbaek-Nielsen, Kristensen, Skovsted, and Christensen, 1971), the anti-asthmatic effect of corticosteroids (Brooks, Werk, Ackerman, Sullivan, and Thrasher, 1972), the contraceptive effect of the 'pill' (Laengner and Detering, 1974), the anti-depressant effect of nortriptyline (Alexanderson, Evans, and Sjöqvist, 1969; Braithwaite, Flanagan, and Richens, 1975) and the antibiotic effect of doxycycline (Neuvonen and Penttilä, 1974).

Perhaps even more important than these therapeutic failures is the potential danger which is created when an enzyme-inducing drug is stopped in a patient receiving a second drug with a narrow therapeutic ratio, eg, warfarin. A gradual reduction in its rate of metabolism following withdrawal of a barbiturate hypnotic can turn a therapeutic dose into a lethal one. In these circumstances the coagulability of the patient's blood will need to be carefully monitored.

Some drugs will inhibit, rather than induce the metabolism of a second drug, and it appears that a biphasic response is sometimes seen, first inhibition (presumably by substrate competition) then stimula-

tion (by enzyme induction). This latter type of interaction may account for the conflicting reports on the effect of phenobarbitone therapy on steady-state serum phenytoin levels in epileptic patients (Kutt, 1972). Inhibition of drug metabolism is of clinical importance when the pharmacological effect of the drug is dangerous or toxic in excess. At serum levels above 20 or 25 $\mu\text{g/ml}$ phenytoin frequently produces symptoms of cerebellar dysfunction, namely, coarse nystagmus, ataxia and slurred speech. If sulthiame is added as a supplementary antiepileptic drug, the serum concentration of phenytoin is likely to increase by an average of 75% (Houghton and Richens, 1974), leading to phenytoin intoxication in a substantial proportion. It is possible that sulthiame has anti-convulsant activity only by its ability to inhibit the metabolism of other drugs given in combination.

Because phenytoin metabolism is saturable it is easily inhibited. A number of other drugs can cause inhibition, such as isoniazid, pheneturide, disulfiram, chloramphenicol, dicoumarol and phenylramidol (Kutt, 1972).

Other examples of inhibition of drug metabolism are the increase in the anticoagulant action of warfarin by oxyphenbutazone (Fox, 1964), nortriptyline and various other drugs (Koch-Weser and Sellers, 1971), and the hypoglycaemia which can result from adding dicoumarol (Kristensen and Hansen, 1967), chloramphenicol (Christensen and Skovsted, 1969) or sulphaphenazole (Christensen, Hansen, and Kristensen, 1963) to tolbutamide therapy in the diabetic patient.

Interaction at Site of Excretion

Many acidic drugs and their metabolites are secreted actively by the renal tubules, and competition for secretion can occur. For example, probenecid competes with penicillin, greatly prolonging its plasma half-life. Similarly, phenylbutazone competes with chlpropamide and acetohexamide, and may potentiate the hypoglycaemic effect of these drugs (Field, Ohta, Boyle, and Remer, 1967).

Weakly acidic drugs are cleared faster in an alkaline than in an acid urine, which is the reason for promoting a forced alkaline diuresis in patients overdosed with aspirin or phenobarbitone. Administration of carbonic-anhydrase-inhibited drugs, eg, acetazolamide, may have a similar action.

Pharmacodynamic Interactions

The interactions described above have been the result of a change in the kinetics of one drug by another. Some important interactions occur, however, by a change in the sensitivity of a tissue to the

actions of a drug. A simple additive effect of central nervous system depressant drugs would be a good example. It has been said that nitrazepam will rarely, if ever, cause death when taken alone in overdosage, but when alcohol or a barbiturate is taken at the same time the suicidal attempt may be successful.

Drugs which modify the function of sympathetic nerve terminals can change the pharmacological effects of other drugs acting on the system. For example, antihypertensive drugs which act by blocking the release of noradrenaline from the terminals, eg, guanethidine, bethanidine, debrisoquine, cause a 'denervation supersensitivity' of the receptor sites, leading to an exaggerated pressor response to directly acting sympathomimetic amines such as adrenaline and noradrenaline (Dollery, 1965). An enhanced pressor response is also seen with tricyclic antidepressant therapy, although in this case it is probably the result of an impaired uptake of the amine into the sympathetic nerve terminal, leading to excessive concentrations at the receptor sites. With both of these groups of drugs it is probably wise to avoid the use of local anaesthetic agents containing adrenaline or noradrenaline as a vasoconstrictor during dentistry (Boakes, Laurence, Teoh, Barar, Benedikter, and Prichard, 1973). The use of felypressin, a directly acting polypeptide vasoconstrictor, appears to be safe, however (Boakes *et al*, 1973).

Because tricyclic antidepressants block the uptake mechanism into sympathetic neurones they reverse the hypotensive effect of sympathetic neurone-blocking drugs (Mitchell, Cavanaugh, Arias, and Oates, 1970). This is probably a common cause of failure of anti-hypertensive therapy, particularly as these latter drugs sometimes produce depression. Chlorpromazine can also block the effects of these drugs (Fann, Janowsky, Davis, and Oates, 1971), as can indirectly acting sympathomimetics contained in cough mixtures (Misage and McDonald, 1970).

The dangerous interactions between monoamine oxidase inhibitors and various drugs and foodstuffs are well known. The antidepressant effect of these compounds is thought to result from an accumulation of noradrenaline and 5-HT in monoamine-producing nerve terminals in the brain. A similar effect occurs in peripheral sympathetic nerve terminals resulting in a greater store of transmitter available for release by nerve impulses or by indirectly acting sympathomimetic amines. Interaction with these latter compounds will cause a hypertensive crisis, which may end fatally. This constitutes the chief danger of monoamine oxidase-inhibiting therapy because these amines are contained in proprietary medicines which can be bought

over the chemist's counter, and are also present in various foodstuffs (Sjöqvist, 1965). The following medicines should be strictly avoided in patients receiving a monoamine oxidase inhibitor:

Cough mixtures, which often contain indirectly acting sympathomimetic amines as bronchodilators, such as ephedrine or phenylpropanolamine;

Nasal decongestants, which usually contain ephedrine or phenylephrine. Proprietary 'cold cures' often contain similar substances.

Anti-obesity preparations, which are usually indirectly acting sympathomimetic amines or related drugs.

Indirectly-acting sympathomimetic amines used for any other purposes, eg, amphetamine derivatives, methylphenidate.

Levodopa used for Parkinsonism.

In addition to the above drugs, tricyclic antidepressants and pethidine should be used with great caution in patients receiving monoamine oxidase inhibitors. The former are likely to produce excitation, hyperpyrexia, delirium and coma. Despite these alarming adverse effects, tricyclics are sometimes cautiously used in combination with monoamine oxidase inhibitors in patients with resistant depression. Pethidine can also produce alarming effects resembling an overdosage of the drug, probably because its metabolism is inhibited by monoamine oxidase inhibitors. Morphine and pentazocine appear not to carry the same risks.

Certain foodstuffs contain indirectly acting sympathomimetic amines such as tyramine. The following have been reported to contain substantial amounts of this amine and should therefore be avoided: cheeses, yeast extracts, eg, Marmite, pickled herring, Chianti. Although there are many other foods which appear on warning lists, there is no clear evidence with most that a hazardous interaction can occur.

It should be noted that directly acting sympathomimetic amines do not interact with monoamine oxidase inhibitors, in contrast to the tricyclic antidepressants (Boakes *et al*, 1973).

Various other interactions can occur at a tissue level which in broad terms can be described as pharmacodynamic interactions. The most important of these are the potentiation of cardiac glycosides by thiazide-induced hypokalaemia, the exaggerated hypoglycaemia produced by propranolol in diabetic patients treated with oral agents, and the antagonism of these latter agents by thiazide diuretics, corticosteroids, and the contraceptive pill.

Conclusion

The interactions which have been mentioned in this

paper are only a selected few of those that have been reported. They have been chosen for special mention because they are among the more serious that can occur clinically. Unfortunately, the lists of potential interactions are growing longer each day, partly because we are becoming more aware of this problem as a real risk in clinical practice, but partly because lists are compiled by one author, added to by another, recompiled by a third and so on, with the result that the inference from a single case report may become perpetuated as if it were a proven interaction. Reference back to the original source can often be quite revealing.

No physician can remember long lists. Fortunately, this is unnecessary if the principles underlying drug interactions are understood, and the broad groups of drugs likely to interact in one of the ways described in this paper are borne in mind. Nevertheless, there is a clear need for improving the effectiveness of communication of information about drug interactions if unnecessary iatrogenic disease is to be avoided (Petrie, Howie, and Durno, 1974) and this is, perhaps, one of the future roles of the clinical pharmacologist.

References

- Aggeler, P. M., O'Reilly, R. A., Leong, L., and Kowitz, P. E. (1967). Potentiation of anticoagulant effect of warfarin by phenylbutazone. *New Engl. J. Med.*, **276**, 496-501.
- Alexander, B., Evans, D. A. P., and Sjöqvist, F. (1969). Steady-state plasma levels of nortriptyline in twins: influence of genetic factors and drug therapy. *Brit. med. J.*, **4**, 764-768.
- Boakes, A. J., Laurence, D. R., Teoh, P. C., Barar, F. S. K., Benedikter, L. T., and Prichard, B. N. C. (1973). Interactions between sympathomimetic amines and antidepressant agents in man. *Brit. med. J.*, **1**, 311-315.
- Boston Collaborative Drug Surveillance Program (1972). Adverse drug interactions. *J. Amer. med. Ass.*, **220**, 1238-1239.
- Boman, G., Hanngren, A., Malmberg, A. S., Borgå, O., and Sjöqvist, F. (1971). Drug interaction: decreased serum concentrations of rifampicin when given with P.A.S. *Lancet*, **1**, 800.
- Braithwaite, R. A., Flanagan, R. J., and Richens, A. (1975). Steady-state plasma nortriptyline concentrations in epileptic patients. *Brit. J. clin. Pharmacol.*, in press.
- Brooks, S. M., Werk, E. E., Ackerman, S. J., Sullivan, I., and Thrasher, K. (1972). Adverse effects of phenobarbital on corticosteroid metabolism in patients with bronchial asthma. *New Engl. J. Med.*, **286**, 1125-1128.
- Christensen, L. M., Hansen, J. M., and Kristensen, M. (1963). Sulphaphenazole-induced hypoglycaemic attacks in tolbutamide-treated diabetics. *Lancet*, **2**, 1298-1301.
- Christensen, L. K., and Skovsted, L. (1969). Inhibition of drug metabolism by chloramphenicol. *Lancet*, **2**, 1397-1399.
- Dollery, C. T. (1965). Physiological and pharmacological interactions of antihypertensive drugs. *Proc. roy. Soc. Med.*, **58**, 983-987.
- Fann, W. E., Janowsky, D. S., Davis, J. M., and Oates, J. A. (1971). Chlorpromazine reversal of the antihypertensive action of guanethidine. (Letter) *Lancet*, **2**, 436-437.
- Field, J. B., Ohta, M., Boyle, C., and Remer, A. (1967). Potentiation of acetohexamide hypoglycemia by phenylbutazone. *New Engl. J. Med.*, **277**, 889-894.
- Fox, S. L. (1964). Potentiation of anticoagulants caused by pyrazole compounds. *J. Amer. med. Ass.*, **188**, 320-321.
- Hansen, J. M., Siersbæk-Nielsen, K., Kristensen, M., Skovsted, L., and Christensen, L. K. (1971). Effect of diphenylhydantoin on the metabolism of dicoumarol in man. *Acta med. scand.*, **189**, 15-19.
- Houghton, G. W., and Richens, A. (1974). Phenytoin intoxication induced by sulthiame in epileptic patients. *J. Neurol. Neurosurg. Psychiat.*, **37**, 275-281.
- Hurwitz, N., and Wade, O. L. (1969). Intensive hospital monitoring of adverse reactions to drugs. *Brit. med. J.*, **1**, 531-536.
- Koch-Weser, J., and Sellers, E. M. (1971). Drug interactions with coumarin anticoagulants. *New Engl. J. Med.*, **285**, 487-498; 547-558.
- Kristensen, M., and Hansen, J. M. (1967). Potentiation of the tolbutamide effect by dicoumarol. *Diabetes*, **16**, 211-214.
- Kunin, C. M., and Finland, M. (1961). Clinical pharmacology of the tetracycline antibiotics. *Clin. Pharmacol. Ther.*, **2**, 51-69.
- Kutt, H. (1972). Diphenylhydantoin interactions with other drugs in man. In *Antiepileptic Drugs*, edited by D. M. Woodbury, J. K. Penry, and R. P. Schmidt, pp. 169-180. Raven Press, New York.
- Laengner, H., and Detering, K. (1974). Antiepileptic drugs and failure of oral contraceptives. (Letter) *Lancet*, **2**, 600.
- Lewis, R. J., Trager, W. F., Chan, K. K., Breckenridge, A., Orme, M., Rowland, M., and Scharly, W. (1974). Warfarin—stereochemical aspects of its metabolism and the interaction with phenyllobutazone. *J. clin. Invest.*, **53**, 1607-1617.
- Misage, J. R., and McDonald, R. H. (1970). Antagonism of hypotensive action of bethanidine by 'common cold' remedy. *Brit. med. J.*, **4**, 347.
- Mitchell, J. R., Cavanaugh, J. H., Arias, L., and Oates, J. A. (1970). Guanethidine and related agents. III. Antagonism by drugs which inhibit the norepinephrine pump in man. *J. clin. Invest.*, **49**, 1596-1604.
- Neuvonen, P. J., and Penttilä, O. (1974). Interaction between doxycycline and barbiturates. *Brit. med. J.*, **1**, 535-536.
- Neuvonen, P. J., and Turakka, H. (1974). Inhibitory effect of various iron salts on the absorption of tetracycline in man. *Europ. J. clin. Pharmacol.*, **7**, 357-360.
- O'Reilly, R. A., and Aggeler, P. M. (1969). Effect of barbiturates on oral anticoagulants in man. *Clin. Res.*, **17**, 153.
- Petrie, J. C., Howie, J. G. R., and Durno, D. (1974). Awareness and experience of general practitioners of selected drug interaction. *Brit. med. J.*, **2**, 262-264.
- Prescott, L. F. (1974). Gastric emptying and drug absorption. *Brit. J. clin. Pharmacol.*, **1**, 189-190.
- Richens, A. (1974). The clinical consequences of chronic hepatic enzyme induction by anticonvulsant drugs. *Brit. J. clin. Pharmacol.*, **1**, 185-187.
- Riegelman, S., Rowland, M., and Epstein, W. L. (1970). Griseofulvin-phenobarbital interaction in man. *J. Amer. med. Ass.*, **213**, 426-431.
- Shapiro, S., Slone, D., Lewis, G. P., and Jick, H. (1971). Fatal drug reactions among medical in-patients. *J. Amer. med. Ass.*, **216**, 467-472.
- Sellers, E. M., and Koch-Weser, J. (1971). Kinetics and clinical importance of displacement of warfarin from albumin by acidic drugs. *Ann. Amer. N.Y. Acad. Sci.*, **179**, 213-225.
- Sjöqvist, F. (1965). Psychotropic drugs. 2. Interaction between monoamine oxidase (MAO) inhibitors and other substances. *Proc. roy. Soc. Med.*, **58**, 967-978.
- Smith, J. W., Seidl, L. G., and Cluff, L. E. (1966). Studies on the epidemiology of adverse drug reactions. V. Clinical factors influencing susceptibility. *Ann. intern. Med.*, **65**, 629-640.
- Volans, G. N. (1974). Absorption of effervescent aspirin during migraine. *Brit. med. J.*, **4**, 265-268.