Clinically Important Drug Interactions

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A Morass of Irrelevant Information

Much attention has been focused on adverse drug interactions during the last 15 years or so, and as a result many drug-drug interactions are now predictable and many of the unwanted consequences of using drug combinatious can be avoided by simply adjusting the dosage of one or more of the interactants. As a result of this, there has been a considerable improvement in the safety and efficacy of therapy with drug combinations.

Unfortunately, however, because much has been written and published with a lack of clinical perspective, the literature has become clogged with a sticky and inpenetratble morass of irrelevant information much of which has been generated in animal studies or in single-dose pharmacokinetic studies in healthy subjects usually drawn from a young adult age group. Such studies can be of predictive value, but only if they mimic the clinical situation and if they relate to drug combinations and dosage regimes that are normally used in sick patients. Likewise a large number of uncorroborated or anecdotal observations on individual patients have appeared. These are useful if they stimulate other clinicians to report similar experiences in their own patients. However, if other reports are not forthcoming then the original report should be regarded as idiosyncratic and be accepted with some reservation as to its generality.

Currently much information is appearing in the literature usually from pharmaceutical research sources on drug-interactions **in vitro**; these can be useful and may indeed indicate possible mechanisms by which drugs or formulation components interact; they may indeed act as an 'early-warning' system and prevent interactions occurring in the clinic. **Per se**, however, they are of limited value unless confirmed **in vivo**, preferably in man.

There is a need therefore to focus attention on those drug-drug interactions which really do influence the efficacy or safety of human drug therapy in all age groups, especially the elderly or very old patients. Fortunately only a relatively small number of drugs enter into those interactions which present clinical importance or life-threatening clinical emergencies. The drugs in these two categories include: anti-arrhythmic agents (especially quinidine), anti-coagulants (especially warfarin), anticonvulsants (notably phenytoin), beta-blockers,H -receptor blockers (especially warfarin), anticonvulsants (notably (mainly digoxin), lithium salts, oral contraceptives, hypoglycaemics, psychotropics (antidepressants and neuroleptics), theophylline, and the immunosuppressants (notably cyclosporin).

It may be noted from this list that most of the drugs involved in clinically relevant interactions are those on which patients are carefully stabilised for relatively long periods. It may also be deduced that many of these patients will be in the older age bracket. Past-experience has clearly shown that it is these drug-stabilised patients who are at special risk of any changes in therapy or environment which will influence the potency or availability of their normal medication. It should also be clearly understood that removal of a drug from a stabilised regimen of treatment may also initiate a serious interaction sequel.

It is not possible within the space allocated to this presentation to discuss all the clinically relevant interactions that occur with the list of drugs that has been detailed. Instead it is intended to concentrate on interactions involving four of the groups of drugs that have been mentioned: the anticoagulants, H -receptor blockers, oral contraceptives, and the immunosuppressants. These will serve to illustrate the types of problems that can occur and how these may be prevented or managed in the clinical situation. Information on the other drugs and their interactions is listed in The Griffin, D'Arcy and Speirs 'Manual of Adverse Drug Interactions'.

Anticoagulants

Warfarin interactions may take place at virtually all stages of its pharmacokinetic progress through the body including absorption, distribution, and metabolism, as well as at the receptor site (the pharmacodynamic phase). In addition, since the main action of the anticoagulants is an inhibition of the vitamin K-induced sythesis of blood clotting factors, it follows that any other drugs (e.g. oral contraceptives) affecting these clotting factors will modify the overall response to warfarin as well. The result of these interactions (see Table 1) may be to potentiate the therapeutic response to warfarin (a drug with a narrow therapeutic 'window') which may lead to uncontrollable haemorrhage. A comparatively mild symptom of moderate overdosage of warfarin can be excessive bruising which should alert the clinician that something is starting to go wrong with the patient's anticoagulation status. Alternatively, the efficacy of warfarin may be decreased (Table 1) and a thromboembolic condition may develop or worsen. It should be noted from the drugs listed in the table that the non-steroidal anti-inflammatory agents are well represented among treatments that are capable of potentiating the anticoagulant effects of warfarin, while enzyme inducers will antagonise the therapeutic action of the anticoagulant. Many of these drugs are commonly used in the elderly patient and it may well be this age group that is likely to suffer the greatest hazard from such interactions.

Table 1 Drug interactions involving anticoagulants

Mechanisms	Effect	Examples
Inhibiton of vitamin K absorption from gastrointestinal tract	Potentiation of oral anticoagulant	Cholestyramine, liquid paraffin
Inhibition of vitamin K synthesis by gut flora	Potentiation of oral anticoagulant	Aminoglycoside antibiotics cephalosporins, penicillins, sulphonamides, tetracyclines
Alteration of absorption of coumarin anticoagulants from gastrointestinal tract	Reduces the efficacy of oral anticoagulants	Antacids
Displacement of coumarin from plasma-binding sites	Potentiation of oral anticoagulant	Non-steroidal anti-inflammatory agents, e.g. aspirin, indomethacin, ketoprofen, naproxen, phenylbutazone, sulphonylureas, e.g. chlorpropamide, metachlorpropamide, tolbutamide
Enzyme induction reducing coumarin plasma half-life	Reduces the efficacy of oral anticoagulant	Barbiturates, glutethimide, griseofulvin, meprobamate, phenytoin, tybamate
Inhibition of the metabolic breakdown of coumarin	Potentiation of oral anti-coagulant	Tricyclic antidepressants, xanthine oxidase inhibitors, e.g. allopurinol
Interacting drug increases the synthesis of blood-clotting factors	Reduces the efficacy of oral anticoagulant	Oral contraceptives, xanthines e.g. choline theophyllinate (Choledyl), theophylline containing medicines (Franol)
Interacting drug reduces the synthesis or increases the catabolism of blood-clotting factors	Potentiation of oral anti-coagulant	Anabolic steroids, cholestyramine, propylthiouracil, quinidine, quinine, thiouracil, thyroxine
Potentiation of inherent fibrinolytic activity	Potentiation of oral anti-coagulant	Biguanides, e.g. metformin
Multiple mechanism of interaction	Variable	Clofibrate, dichloralphenazone

H -receptor blockers

The histamine H -receptor blocker, cimetidine, has well established clinical use mainly in the treatment of peptic ulcer disease. This clinical use has also clearly indicated the extent to which cimetidine may participate in drug interactions. Early work by clinical investigators showed that cimetidine potentiated the anticoagulant effects of warfarin and suggested that it did so by inhibiting hepatic microsomal enzyme oxidase activity. It was also predicted from this that cimetidine might also interact with other drugs that were metabolised by liver microsomal enzymes.

That this prediction was justified has been well shown by subsequent reports in the literature and it is now certain that cimetidine has the potential to interact with a wide range of drugs including some benzodiazepines (diazepam, chlordiazepoxide, prazepam, nitrazepam, alprazolam), carbamazepine (conflicting reports), chlormethiazole, morphine (conflicting reports), metronidazole, phenytoin, theophylline, flecainide, and digitoxin/quinidine (a double interaction) due to inhibition of liver enzymes. It has also become evident that cimetidine will potentiate the actions of the beta-blockers propranolol, labetalol, and metoprolol, but not atenolol, by mechanisms that may be related to reduced liver blood flow. Cimetidine is also reported to inhibit the tubular secretion of both procainamide and n-acetylprocainamide in man and this interaction may necessitate dosage adjustments of procainamide in patients being treated concomitantly with both drugs. The more commonly reported interactions involving cimetidine are summarised in Table 2.

The literature on interactions involving cimetidine has become almost voluminous and to save space in this present context the reader is referred to primary reference sources that are cited in the following reviews: Bauman and Kimelbatt (1982), Sorkin and Darvey (1983), Griffin, D'Arcy and Speirs (1988), and Penston and Wormsley (1986).

In view of the conflicting therapeutic indications for cimetidine and the anticoagulants, it is not altogether surprising that, apart from the early studies on the cimetidine-warfarin interaction, there have been relatively few cases of prolongation of prothrombin time by cimetidine in patients taking warfarin. Indeed of 9907 patients identified in an American, post-marketing, outpatients surveillance programme as receiving cimetidine, only nine cases of haematological problems were reported. Of these only a single case was considered to be related to a cimetidine-anticoagulant (Gifford **et al.**, 1980). Furthermore, evaluation of a world-wide spontaneous reporting system indicated that 0.4 per 100,000 patients, who had previously been stabilised with oral anticoagulants, required re-titration after the start of cimetidine therapy (Davis **et al.**, 1980). It is therefore of interest that Kerley and Ali (1982) have reported that this type of interaction was responsible for the development of a huge retroperitoneal haematoma which was life-threatening to their 19-year-old patient.

Ranitidine is thought not to have an inhibitory effect on hepatic microsomal enzymes and would therefore not enter into interactions with

Table 2 Drug interactions involving cimetidine

By inhibiting hepatic microsomal enzyme oxidase activity, cimetidine potentiates the activity of the following drugs:
Anticoagulants, e.g. warfarin
Benzodiazepines, e.g. chlordiazepoxide, diazepam, prazepam but not lorazepam or oxazepam.
Carbamazepine (neurological toxic symptoms)
Chlormethiazole (significant increase in sedation)
Digitoxin/quinidine combination (resulting in cardiotoxicity)
Morphine (a potentially lethal interaction)
Phenytoin (rash or signs of intoxication)
Theophylline (half-life increased, potential toxicity)
By reducing hepatic blood flow (?), cimetidine potentiates the activity of the following drugs:
B-blockers, e.g. propranolol, metoprolol, labetalol, but not atenolol
The activity of cimetidine is reduced by the following drugs:
Antacids (reduced bioavailability with Al/MgOH containing preparations)
Metoclopramide (bioavailability of cimetidine reduced by 20-30%)
Propantheline (bioavailability of cimetidine reduced by 22%)

warfarin or other drugs that are metabolised by the liver. However, ranitidine may enter into interactions by mechanisms other than enzyme inhibition since, like cimetidine, it reduces blood flow in the liver, and could impair the hepatic elimination of a small number of drugs like propranolol or lignocaine which are highly extracted by the liver and whose systemic clearance is highly dependent upon liver blood flow. Exploratory studies in healthy subjects have, however, been controversial and conflicting in their results.

Oral contraceptives

Interactions involving the combined type (oestrogen plus progestogen) oral contraceptives are often ususpected and even unestablished. The sequel, an unplanned pregnancy, is often mistakenly blamed by the consulting physician on to poor subject compliance with medication instructions. Evidence has started to accumulate that neither the patient nor the "pill" is at fault in some contraceptive failures. It may be because the patient is taking other medicines and these may be preventing the pill from suppressing ovulation.

Most drug interactions reducing or negating contraceptive activity are due to concomitant use of drugs having microsomal-enzyme inducing activity (e.g. some antibiotics, especially rifampicin, and anticonvulsants, including phenytoin, phenobarbitone and primidone. Other antibiotics (e.g. tetracycline) may also interact by interruption of the enterohepatic circulation of contraceptive steroids.

Less well appreciated, oral contraceptive steroids may themselves modify the metabolism and pharmacological activity of various other drugs (e.g. anticoagulants, benzodiazepines, beta-blockers, corticosteroids, and antidepressants); in this respect the oral contraceptives are acting as enzyme inhibitors.

Contraceptive steroids may also interact with drugs that cause enzyme inhibition and this delays the metabolism of the hormonal agents. Interactions of this type would be expected to potentiate the action of the contraceptive steroids. It is suggested that the effects of such interactions might be presented in terms of increased incidence of side-effects, including water retention, diabetogenic effects, hypertension, and an increased risk of thromboembolic disorders.

The spectrum of interactions with oral contraceptives is summarised in Table 3. A more detailed account is given in a recent review on drug interactions with oral contraceptives (D'Arcy, 1986).

Table 3 Drug interactions involving oral contraceptives

Drugs implicated (or suspected of implication) in oral contraceptive failure	
Class of drug	**Individual drugs implicated**
Antibiotics	Ampicillin, rifampicin, tetracycline
Anticonvulsants	Phenobarbitone, phenytoin, primidone
Cholesterol-lowering agents	Clofibrate
Non-steroidal anti-inflammatory agents	Phenylbutazone
Hypnotics and sedatives	Barbiturates, chloral hydrate and derivatives, ethchlorvynol, methaqualone
Drug activities modified by oral contraceptives	
Aminocaproic acid	Possible hypercoagulable state; oestrogen augments blood levels of clotting factors VII, VIII, IX, and X
Anticoagulants	Reduced anticoagulant efficacy; oestrogen increases plasma concentration of clotting factors. NB. patients on oral contraceptives should not be anticoagulated and no patient on anticoagulants should take OCs
Antidiabetic agents	Increased requirements for insulin and oral hypoglycaemic agents may occur
Antihypertensives	Reduced efficacy of guanethidine, cyclopenthiazide, and methyldopa possibly due to contraceptive-induced Na and fluid retention
Pethidine (meperidine)	Possible increased analgesia and CNS depression due to inhibition of metabolism of pethidine
Phenothiazines and drugs causing breast enlargement	Phenothiazines, reserpine, imipramine, chlordiazepoxide and chlorprothixene increase prolactin secretion resulting in mammary hypertrophy and galactorrhoea: this effect is potentiated (at the breast) by oestrogen and progesterone combinations
Troleandomycin	Pruitus and jaundice followed combined use of OCs and this antibiotic. Both components have been reported separately to cause jaundice.

Immunosuppressants

Reports of interactions involving immunosuppressant agents have largely centred on cyclosporin (ciclosporin). Such reports include a cyclosporin-methyltestosterone interaction in a kidney graft patient that resulted in severe cyclosporin toxicity. A cyclosporin-erythromycin interaction in a similar transplant patient resulted in a four to five-fold increase in blood cyclosporin concentrations. Also, seriously, five case reports from Jones **et al.** (1986) related to an interaction between cyclosporin and sulphadimidine that resulted in inadequate immunosuppression in orthoptic cardiac transplantation.

The latest interaction reported is between cyclosporin and the calcium channel-blocking agent, diltiazem; the interaction resulted in greatly increased cyclosporin blood concentrations due to interference by diltiazem in cyclosporin clearance. (Grino **et al.**, 1986; Pochet and Pirson), 1986).

It is clear from such reports that cyclosporin is metabolised extensively by hepatic enzyme systems and that drugs which inhibit the P-450 enzyme system will reduce cyclosporin clearance and that drugs which induce liver enzymes will enhance cyclosporin clearance and reduce its immunosuppressant activity (Table 4).

(Cont. on page 35)

Table 4 Drug interactions involving cyclosporin

Corticosteroids Erythromycin Ketoconazole Methyltestosterone	increased cyclosporin serum levels resulting in enhanced graft acceptance, or nephrotoxicity*
Phenytoin Rifampicin Sulphadimidine Trimethoprim	reduced cyclosporin levels and endanger the transplant**

*Less well substantiated reports with: cimetidine, danazol, diltiazem, cotrimoxazole, thiazides and oral contraceptives.

**Less well substantiated reports with: carbamezepine, isoniazid, and phenobarbitone

Aminoglycosides (Gentamicin, Tobramycin) Amphotericin Melphalan Sulphonamides/ Co-trimoxazole Trimethoprim	enhanced/additive nephrotoxicity*

*less well substantiated reports with acyclovir, some cephalosporins, etoposide, frusemide, indomethacin, mannitol and ranitidine.

Interactant	Sequelae
Cyclophosphamide	increased/additive hepatotoxicity; possible leucopenia
Diuretics (K retaining)	possible hyperkalaemia
K supplements	possible hyperkalaemia
Etoposide	increased toxicity and antineoplastic effects
Frusemide	increased/additive hepatotoxicity
Minoxidil	increased/excessive hirsuitism
Oral contraceptives	incerased/additive hepatotoxicity
Phenytoin	increased phenytoin levels due to decreased hepatic metabolism
Prednisolone	increased prednisolone levels due to decreased hepatic metabolism
Propranolol	antagonism of immunosuppressive effect (animal studies)
Ranitidine	increased/additive hepatotoxicity
Vaccines	reduced efficacy of vaccine prophylaxis
Verapamil	increased immunosuppression

(Cont. from page 33)

Conclusion

It must be apparent from this brief account of clinically important drug interactions and the examples that have been cited that most of the drugs involved are those on which patients are carefully stabilised for long periods. Past experience has shown that it is these drug-stabilised patients who are at special risk from any interaction that will influence the potency or availability of their medication. This is especially so for the elderly patient who is at a substantially greater risk than the younger patient of experiencing adverse reactions to medication.

It must be clearly understood, however, that drug interactions **per se** are no threat to the patient; most of the adverse events that they cause are capable of speedy reversal. Their real threat is the practitioners' ignorance either through lack of knowledge of the interaction, or through lack of adequate observation of the patient and the proper interpretation of new events. It is under such circumstances that interactions become dangerous.

REFERENCES

Except for specific points, statements in the text have not been referenced to source largely because of the number that would have been involved. Much of the text has been abstracted from Griffin, D'Arcy and Speirs 'Manual of Adverse Drug Interactions' (1988) and this volume is a fruitful source of more detail and literature references on the whole topic of drug interactions.

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