

EDITORIAL

CLINICAL DRUG INTERACTIONS

A large number of patients receive multiple regimens of potent drugs, increasing the chances of drug-drug interactions or interaction of drugs with non-therapeutic agents. The end result may be a clinically important alteration of drug's action. Data on the magnitude of this problem in resource-poor countries are scarce, but in the West it has been estimated that approximately 3% of hospital admissions are related to drug interactions(1). This editorial covers key elements needed for the proper understanding of drug interactions. These are: (a) types of drug interactions, (b) mechanisms of drug interactions, (c) severity and clinical significance of drug interactions, (d) ways of avoiding or dealing with drug interactions and (e) sources of information on drug interactions.

Classification: Drug interactions can be classified as inconsequential, harmful, life-threatening/fatal or beneficial. An understanding of this classification is useful in making clinical decisions regarding drug interactions.

Mechanisms: Drug interactions can be classified into two broad categories(2): (i) Pharmacokinetic interactions are those which affect the absorption, distribution, and elimination of drugs with or without an effect on the pharmacological effect of the drug and; (ii) Pharmacodynamic interactions are those that involve alteration of the pharmacological response to a drug through a direct or indirect mechanism. The outcome of this type of interaction can be described by the following terms, depending on whether the drugs involved are active or inactive(3):

- Synergism is when both drugs are active and the response produced by interaction is greater than predicted;
- Potentiation is when one drug is active and the response is greater than predicted;
- Coalism is when neither drug is active but the response is greater than predicted;
- Additivity is when both drugs are active and the response is equal to that predicted;
- Inertism is when one or both drugs are inactive but the response is equal to that predicted;
- Antagonism is when one or both drugs are active, but the response is less than predicted;
- Idiosyncrasy is when the response is unexpected, based on the known pharmacology of the individual drugs.

Factors which may determine the type of interaction include(2):

- Drug-related factors such as physico-chemical properties, formulation and clinical pharmacology;
- Patient-related factors such as the underlying disease, other drugs/treatments (herbal products, homeopathic

remedies, etc), social habits (drinking, smoking), diet, genetics and sex of the patient

Clinical significance: Not all drug interactions are clinically relevant. "Clinical significance", a measure of the degree to which the underlying disease or condition of the patient is affected by the drug interaction(4), can be difficult to define. But one can use the following definitions of severity of the interaction as a rough guide(2):

- Minor: potential harm to patient is slight or unlikely.
- Moderate: potential harm possible and intervention/monitoring may be necessary.
- Major: outcome may be life threatening.

Two pharmacokinetic factors are important in making general statements on whether a drug-drug interaction is likely to be clinically relevant or not. These factors are (a) degree of binding to plasma/tissue proteins and (b) hepatic extraction ratio. In general, drug-drug interactions involving displacement from plasma protein binding sites are clinically important only for drugs which are normally highly (>95%) protein bound, have small volumes of distributions, have unusual kinetics (e.g. non-linear kinetics) and/or steep dose-response curves. This is especially true for drugs with a high hepatic extraction ratio. For such drugs, for example phenytoin which has a low hepatic extraction ratio and is highly bound to plasma proteins, interactions involving displacement from protein binding sites are not clinically important since there is a corresponding increase in clearance such that the unbound concentrations remain essentially unaltered.

Hepatic extraction ratio is also important in those interactions involving inhibition and induction of drug metabolism. Drugs with low (<0.2) hepatic extraction ratios are susceptible to large (and potentially clinically important) clearance changes from induction or inhibition following both parenteral and oral administration. An example is the induction of the metabolism of warfarin, a drug with a low hepatic extraction ratio, by rifampicin when the former is administered orally. For drugs with a high (>0.7) extraction ratio, potentially clinically important interactions involving induction or inhibition of metabolism will only occur following oral administration. Following parenteral administration of such drugs, no clinically relevant interaction occurs since clearance is dependent on hepatic blood flow, not on intrinsic enzyme activity. An example is alprenolol. Phenobarbitone treatment induces the metabolism of alprenolol following oral administration but not after intravenous administration of the latter.

There are several examples of clinically useful drug-drug interactions. For example, grape juice contains compounds which inhibit cytochrome P-450 (CYP) 3A4, the principal isoenzyme found mainly in the liver, but also

present in the gut wall. Cyclosporin is a substrate for this isoenzyme, and administration of cyclosporin together with grape juice has been used as a means of increasing systemic concentrations of cyclosporin. Another example is the use of ritonavir, a potent CYP3A4 inhibitor, to increase the concentrations (allowing for dose reduction) of selected antiretroviral drugs. Other clinically useful drug-drug interactions involve renal excretion, for example the use of probenecid with penicillin, and the alteration of urine pH in cases of poisoning with weakly acidic or basic compounds. An example of a useful drug-food interaction is the increase in oral bioavailability of some drugs following administration with food. For example, the bioavailability of halofantrine, a lipophilic compound, is increased when it is taken with a fatty meal.

There are some types of interactions which may be clinically important (undesirable) in some patients, but unimportant in others. For example, bacteriostatic agents such as tetracycline should not be used together with bactericidal agents such as penicillins in severe infections (e.g. meningitis) where a rapid bactericidal activity is required. However, this interaction appears to be unimportant in less severe infections.

Dealing with and avoiding drug interactions: Except in cases where an interaction is not clinically important or in a few instances where a drug interaction produces a clinically desirable outcome such as the use of ritonavir to enhance the blood concentrations of other antiretroviral drugs(5), most drug interactions should be avoided. Several strategies for doing this have been suggested(5):

- Unless absolutely necessary, avoid combining drugs with interaction potential.
- If possible, delay administration of one of the drugs.
- Avoid concurrent administration of drugs with overlapping adverse effect profiles.
- Use the smallest effective doses.

Sources of information: The key to understanding drug interactions is willingness/ability to read extensively. Those with the responsibility of teaching pharmacology and therapeutics to medical and pharmacy students must take

a lead in this area. Several excellent texts(7,8) are available, but one can also access published information on individual drugs or mechanisms, depending on one's area of interest. A few examples are given below(9-12). It is the only way to understand the true extent and clinical significance of drug interactions.

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