REVIEW ARTICLE

A CRITICAL EXAMINATION OF DRUG INTERACTIONS

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A drug interaction is the alteration of the effect of one drug by another drug or chemical. More generally, essential components of the normal diet (including carbohydrates, lipids, proteins, minerals and vitamins) may also alter drug effects, and drugs may also interact with both disease states and laboratory tests. However, only drug-drug interactions will be considered here.

Interactions may be desirable or undesirable. Desirable interactions are integral factors in the combination therapy of some diseases - e.g., in the treatment of hypertension, asthma, infections, and malignancy where, by using several drugs, one can increase therapeutic effects while reducing toxicity. Undesirable interactions come under the general heading of one of several causes of adverse drug reactions.

A critical examination of lists of adverse drug interactions indicates that many interactions are neither scientifically valid nor clinically important. The standards of proof required to assess the validity reported in the literature must be made more vigorous. We should concern ourselves more with the clinical significance of drug interactions rather than elaborate long lists which focus excessively on the mechanisms of unimportant interactions.

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A review of the data from the Boston Collaborative Drug Surveillance Program (1) which involves the prospective surveillance of hospitalized medical patients suggested that drug interactions are a relatively minor part of the overall problem of adverse drug reactions. However, books exist which list over 400 pages of drug interactions. The number of potential drug interactions is too large to be readily handled by the human brain or listed in easy-to-read tables. Most of the interactions reported have not been scientifically verified in both man and laboratory animals (2). Contradictions and misinformations of the data occur frequently in the drug literature, and so far, there has not yet been proposed a proper method to assess the validity of adverse drug interactions scientifically.

A CRITICAL EXAMINATION OF SELECTION INTERACTIONS

In this section some of the drug interactions, especially the pharmacokinetic type, will be critically examined. Interactions between commonly used drugs, or drugs often given in combination for the treatment of certain conditions, will obviously be more frequent than interactions between rarely used drugs. Most reported interactions involve drugs with low therapeutic indices (e.g., digoxin, phenytoin) or drugs for which the therapeutic endpoint is carefully monitored (e.g., oral anticoagulants, antihypertensives) (3).

A. Drug Absorption Interactions

Drug absorption interactions are not often considered to be of clinical importance and have received relatively little attention. Since the absorption of drugs from gastrointestinal tract is a complex process that depends on many physiological and physiochemical factors, other less complex mechanisms are often thought to be responsible for the interactions. For example, in the interaction between phenobarbital and griseofulvin, it was initially suggested

that phenobarbital enhanced the metabolism of griseofulvin by inducing liver enzymes. However, the data in a randomized crossover trial strongly suggested that concurrently administered phenobarbital actually reduced the absorption of griseofulvin (4).

In general, drugs are absorbed by the process of passive diffusion (5). The passive diffusion is a pH-dependent process, hence a weakly acidic drug would be absorbed across the gastrointestinal epithelium more rapidly at low intraluminal pH because most of the drug is present in the unionized state. The reverse is true for basic drugs. But these theoretical concepts are not necessarily important in practice. There are two other important factors that may limit the rate of absorption of drugs: the dissolution rate and gastric emptying time.

The dissolution rate, i.e., the rate at which the drug dissolves into solutions from tablets or capsules, is the important rate-limiting step of the process of absorption of drugs in solid dosage forms. According to the pH partition hypothesis, alkalinization would enhance the absorption of basic drugs from the stomach, but in fact sodium bicarbonate has been shown to decrease rather than increase the absorption of some basic drugs through its effects on decreasing solubility (6).

Drugs which alter gastrointestinal motility or the rate of gastric emptying can have significant effects on the absorption of other drugs. However, in fact this is not always the case. Propantheline, which decreases, and metoclopramide, which increases gastric motility, have been shown to accelerate and retard, respectively, the absorption of digoxin (7). This apparent paradox is best explained by slow dissolution and absorption of digoxin, since this interaction does not occur with liquid preparations of digoxin or with the tablet preparations that release drug quickly (8). Also, demonstrating the complex explanation of some interactions, rapidly moving dissolved

digoxin past its usual absorptive site in a short segment of the upper small bowel will decrease absorption.

The drug may also interact with specific ions or other drugs in the gut to produce a non-absorbable complex, for example, tetracycline and iron salts or aluminum, calcium, or magnesium containing antacids (9). Some drugs have ion exchange properties. For example, cholestyramine is an anionic exchange resin with a strong affinity for acidic molecules. As a result, cholestyramine can interfere with the intestinal absorption of phenylbutazone and warfarin (10).

The complex mechanisms of drug absorption interactions discussed above make prediction of drug absorption interactions difficult. However, based on the facts of the interaction, physicians and patients may frequently avoid these interactions through modification of medication schedules.

When dealing with drug absorption interactions, it is important to differentiate between interactions which alter the rate of drug absorption and those which alter the extent or the total amount of drug absorbed, since the consequences are different (11,12). A change in the rate of absorption of a long-acting drug such as warfarin would probably have little or no effect, whereas a change in the total amount absorbed may result in serious undesired outcomes. In contrast, if the rate of absorption of a drug with a short biological half-life such as procainamide is reduced, therapeutic plasma concentrations may never be reached. When a rapid effect is required, e.g., with analgesics and hypnotics, the rate of absorption must be fast enough for the drug to exert its desired effect.

B. Displacement From Plasma Protein Binding

This is one of the most popular mechanisms implicated in drug interactions in the literature. Many protein-bound drugs have been claimed to displace, or be displaced by, other protein-bound drugs. The resulting rise in the concentration of free or unbound drug is then usually said to cause transient potentiation of the drug's effects.

These phenomena definitely exist, since many acidic drugs are highly bound to plasma albumin and may displace one another depending on their relative plasma concentrations and particular binding characteristics (13). Although many basic drugs are also highly protein-bound, protein binding displacement interactions for them have not been documented. This could be explained by the fact that most basic drugs have a large volume of distribution and relatively small amounts of drug are present in the plasma.

It is often postulated that if,for example, a drug is 99% bound in the plasma, displacement of only 1% of the protein-bound drug will double the free concentration. This would apply only in the unlikely event that both bound and free forms were wholly confined to the intravascular compartment. What will actually happen is that the liberated drug will distribute into other compartments, thus dissipating the rise in the concentration of free drug.

The displacement interactions which are likely to be of clinical significance are those involving highly bound drugs which have a small apparent volume of distribution. Drugs present in the plasma in high concentration would tend to displace those in low concentrations (13). For drugs with large volumes of distribution, where only a small fraction of the drug is present in the plasma, redistributional interactions involving plasma proteins could have only trivial direct effects on the concentration of free drug.

Some of the clinically important interactions ascribed to this displacement mechanism are the warfarin interactions, in particular those with phenylbutazone (14,15), chloral hydrate (16), and clofibrate (17). Others include the precipitation of kernicterus by sulfonamides displacing bilirubin in neonates (18) and the precipitation of hypoglycemia when sulfaphenazole is added to tolbutamide (19,20).

One should always exclude or allow other pharmacokinetic interactions in dealing with the displacement interactions. A fall in the concentration of total plasma drug, or a rise in free drug, could stem from processes other than displacement from plasma protiens. The very presence of a distributional drug interaction makes it necessary, but at the same time difficult, to evaluate any other pharmacokinetic effects that might be occurring simultaneously. The most important factors to exclude are other types of redistributional effects (e.g., at the tissue level) and interactions at the pharmacokinetic levels of absorption, metabolism, and excretion (12).

The phenomenon of displacement interaction is temporary, unless clearance of the drug is also altered (4). Subsequent to the displacement, free drug would be more available for metabolism and urinary excretion. Thus, the concentration of total and free drug in the plasma will decrease progressively until a new steady-state is reached. Even without dosage adjustment, the free drug concentration and intensity of effect would eventually be the same as before the addition of displacing drug. However, total plasma concentration of the drug will be lower. Thus, this process eventually corrects itself, but may result in serious effects before it can do so, especially with drugs having a low margin of safety such an anticoagulants. When clearance of the drug is also decreased, progressive accumulation might occur as a consequence of protein binding displacement if dosage is not reduced.

C. Drug Interactions At the Cell Transport Level

Many poorly lipid soluble drugs utilize active membrane transport systems to reach the site of action. Adrenergic neurone blocking drugs are concentrated over a thousand-fold from plasma into the adrenergic nerve ending by the "active amine pump" (21). Therefore, one drug may interfere with the uptake and transport of another to intracellular sites of action. A well-known and important interaction illustrating the point occurs between guanethidine and antidepressants. Certain other drugs share this antagonistic effect --e.g., phenothiazines and certain sympathomimetic amines, all of which prevent uptake of guanethidine to its site of action (22,23).

Starr and Petrie (24) examined interactions of adrenergic-neurone blocking drugs in outpatients. Theoretical potential interactions were noted in 22 out of 64 patients, but actual loss of hypotensive effect was seen in only 3 patients (14% of those at risk). For individual drugs the figures were more impressive--one out of six patients on tricyclic antidepressants, and 2 out of 4 patients on ephedrine had clinically detectable antagonism. However, these figures may be underestimated because of the retrospective nature of the study.

This analysis teaches us several things. First, it is drugs with powerful, dose-related effects that are predominantly involved in important interactions. Second, it cannot be assumed that interactions will necessarily occur in all patients receiving a given combination of drugs having a potential interaction in man. Third, if an interaction is not looked for it will not be found. Conversely, if the patient's response is monitored, then the interaction will be detected, in this case, as a lack of effect. Some response will be made by the physicians. Either the antihypertensive drug will be changed, or the interacting drug will be stopped until something is

found which works without causing an interaction. Careful clinical follow-up and knowledge of drug interactions will suffice to detect and react to a drug interaction of this sort.

D. Drug Interactions At the Receptor Site or On the Same Physiological System

Drugs with appropriate chemical structures can bind to the same receptor and modify response. Some interacting drugs are actually pharmacologic antagonists, i.e., drugs which have a high affinity for the receptor, elicit no effect themselves, but prevent other pharmacologically active drugs from reaching receptor sites.

There are also drugs whose mechanisms of action are not precisely known or which may not act through the same receptor mechanisms, but which produce the same pharmacological effects by acting on the same physiological systems at different sites. Combinations of drugs acting at the same site or influencing the same physiological system may either decrease or increase responses. Anticoagulant-aspirin interactions are partially of this type. Affecting hemostasis in the same direction can cause serious interactions, regardless of the mechanisms involved.

Drug interactions involving additive, synergistic or antagonistic effects of drugs acting on the same receptors or physiological systems are probably the most obvious, but have not received enough attention. According to the data from the Boston Study (1) the greatest problem of pharmacodynamic interactions appear to be caused by drugs acting on the central nervous system. This is obviously due to the fact that the adverse effects produced are easy to recognize.

In contrast to pharmacokinetic interactions, extrapolation of interactions demonstrated with one compound to other closely related drugs may be relevant, even though confirmation in man is lacking. However, a single drug may have more than one pharmacological action

or interact with more than one receptor. For example, phenothiazines have been shown to have dopaminergic-blocking, alpha-adrenergic blocking, and antihistaminic properties (25). Therefore, it would be difficult to ascertain the clinical significance of drug interactions in terms of receptor mechanisms in this case.

Some well-known pharmacological properties may, in fact, not account for the mechanisms of drug interactions. Imipramine has been shown to antagonize the hypotensive effect of clonidine, an α-receptor agonist (26). The possible mechanism of interaction is thought to be due to the fact that tricyclic compounds are weak α-receptor antagonists.

Receptor interactions are predictable with drugs having well-defined mechanisms of action, and should be avoidable with knowledge of the mechanisms of drug action. Reports of such interactions reflect the ignorance of the prescriber and confirm the known pharmacological effects of the drugs.

E. Metabolic Drug Interactions

Hundreds of drugs have been shown experimentally to stimulate either their own metabolism, that of other drugs, or both (3). These drugs include analgesics, oral hypoglycemic agents, CNS depressants, anticonvulsants, and anti-inflammatory agents. More recently it has been shown that rifampicin enhanced the metabolism of quinidine (27) and of corticosteroids (28). In general, the ability of a drug to induce the metabolism of other drugs in the liver depends on its concentration, and its duration of exposure to liver tissues. Drug metabolizing enzymes generally differ from enzymes involved in intermediary metabolism because they lack substrate specificity explaining nonspecific nature of enzyme induction.

A drug may also be capable of inhibiting the metabolism of other drugs. Such inhibition may lead to exaggerated and prolonged pharmaco-

logical effects increasing the risk of toxicity. Examples of drugs that can inhibit hepatic metabolism are disulfiram, phenylbutazone, metronidazole, oral contraceptives, griseofulvin, dextropropoxyphene, allopurinol, sulphonamides, isoniazid and cimetidine (3,10,29,30). Some interactions may arise through inhibition of non-microsomal enzymes. The classical example is monoamine oxidase inhibition.

This is a case where enzyme inhibition is itself a desired property. Inhibitors of monoamine oxidase have been used as antidepressants in psychopharmacotherapy and as antihypertensive agents. However, the interactions between monoamine oxidase inhibitors (MAOI) and other drugs or foodstuffs and beverages are widely appreciated. Administration of adrenergic drugs (e.g., phenylpropanolamine in cold medications) to patients taking MAOI may cause severe hypertension (31).

A drug may also alter the metabolism of other drugs by altering hepatic blood flow (32). This mechanism is important for those drugs which are mainly and rapidly removed from the plasma by liver. Propranolol is a good example. The beta-blocking effect of propranolol decreases cardiac output. This in turn decreases hepatic blood flow and affects the drug's clearance, and also decrease the metabolic clearance of other concurrently administered drugs (e.g., lidocine, morphine, nitroglycerin) with a high hepatic extraction ratio (11). For drugs which do not have a high hepatic first pass clearance, metabolic drug interactions mainly alter the duration of action and steady-state blood concentrations of the drugs.

There are some differences in the time course of changes due to inhibition and to induction (33). Enzyme inhibition occurs rapidly since it requires only the presence of the interacting drug. Induction of drug metabolizing enzymes, on the other hand, may require 2-3 weeks to achieve its maximal effect since it involves new enzyme synthesis.

Metabolic drug interactions, like other pharmacokinetic interactions, are not easily predicted by animal studies. Whether a drug is an enzyme inducer in man cannot always be predicted in laboratory animals. Tolbutamide has been shown to be a potent inducer of oxidative drug metabolizing enzymes in rats and dogs, but it has little or no enzyme-inducing effect in man (34). The concept of metabolic inhibitors can lead one to overlook other interactions which may be even more important clinically. MAOI's have been shown to interact with drugs which are not themselves metabolized by this enzyme (35).

F. Drug Interactions At the Level of Urinary Excretion

Urinary excretion of several drugs may be changed by alteration of pH or electrolyte concentrations. Interactions of this type may be unwanted or may be desired, particularly to enhance the elimination of a toxic substance. Diuretics are the drugs which most often alter urinary pH and electrolyte concentrations. Such changes may not only produce major alterations in renal clearance of other drugs, but also alter their pharmacodynamic actions; e.g., diuretics enhance the toxic effects of digitalis by producing hypokalemia.

The renal clearance of drugs may be modified by urinary pH changes only with weak organic bases having pKa values of 7.5 - 10 and weak organic acids having pKa values of 3.0 to 7.5 (33). The clearance of weak organic acids is higher in alkaline than in acid urine, and vice versa with organic bases. The clearances of strong acids and bases are not affected by changes in pH, since they are almost completely ionized over the physiological range of urine pH.

Another major drug interaction involving the kidney is the effect of one drug on the renal tubular secretion and subsequent excretion of another drug. In general, tubular transport mechanisms exist separately for organic acids and organic bases. Organic acids will be able to

compete with other organic acids for tubular excretion. The same goes for organic bases. However, this concept may not be readily extrapolated, since organic bases have also been shown to increase urinary acid excretion (36).

Drugs which may interact by competing with tubular active transport systems include sulphonamides, thiazides, salicylates, probenecid, methotrexate, penicillins and phenylbutazone. These drugs are all organic acids; thus, they may also displace each other from plasma protein-binding sites. This makes it difficult to assess drug interactions solely by examining urinary excretion.

However, it can be assumed that this type of interaction is generally important when the kidney is mainly responsible for disposition of active metabolites of the drug to a significant extent (e.g., $\geq$20% or so). When a drug is excreted by extrarenal as well as renal pathways, a decrease in renal excretion may be compensated for by an increase in extrarenal excretion.

GUIDELINES FOR COPING WITH THE PROBLEM OF DRUG-DRUG INTERACTIONS

The mechanisms of drug-drug interactions are highly complex and may involve several simultaneous phenomena. It is also difficult to distinguish a drug interaction from all the others that alter response to therapy. The evidence is still lacking to support the validity of many of the adverse interactions reported in the literature. Pharmacokinetic interactions shown with one drug combination may not necessarily occur with other combinations involving closely related drugs (11).

There are two crucial points to keep in mind for dealing with the problem of drug interactions. First, only the more clinically significant interactions should be of concern. Second, virtually all

known adverse interactions are avoidable if the drugs are administered properly and the mechanisms of interactions are known. Knowledge of drug interactions enables a physician to prevent or minimize drug toxicity without losing the ability to simultaneously administer drugs with beneficial therapeutic effect.

SUGGESTIONS FOR PHYSICIANS

1. Take a drug history so that you know what the patient is getting from other prescribers and what OTC medications he takes as well as the drugs you prescribe for him.

2. Prescribe as few drugs as are needed to achieve a desired effect. Avoid unnecessary combinations.

3. Know the effects (both wanted and unwanted) of all the patient's drugs. The spectrum of drug interactions will often be contained within these effects. Know the slope of dose-response curves for each drug; i.e., is the drug one for which the dose doesn't matter much, or is it a drug whose dosage has to be finely tuned? It is the drug of the latter sort that will be troublesome.

4. Observe and monitor the patient for drug effects, particularly after any alteration in regimen (e.g., starting or stopping a drug). Some interactions may take weeks to appear, e.g., metabolic effects depending on drug induction. Other may appear promptly.

5. Consider drug interactions as possible cause of any unexplained change in the patient's course.

6. The prescriber should be particularly aware of the more predictable clinical drug interactions where modification of the pharmacological activity can be serious or lead to ineffective therapy, e.g., those interactions involving antihypertensive drugs, anticoagulants, anticonvulsants, oral hypoglycemic agents, cardiac glycosides,

antidepressants and cytotoxics.

7. If clinical responses are unexpected, measurement of blood levels may help to explain pharmacokinetic interactions. Consult the literature or someone who has an interest in drug interactions. But, the most appropriate response is to alter the dose of the drug until the desired effect is obtained; and if this fails, change the drug to one that theoretically will not interact.

SUGGESTIONS FOR A CLINICAL SCIENTIST FACED WITH SORTING OUT A POSSIBLE DRUG INTERACTION

1. Document all disease states and all drugs being taken, including OTC medications and alcohol.

2. Search the literature on related drugs for possible mechanisms of interactions and epidemiological studies of the clinical importance of these interactions.

3. Perform the necessary animal and then human experiments to elucidate mechanisms and determine the severity of adverse interactions.

4. The investigator's goal should include confirming or denying the importance of a drug interaction and providing guidelines for prescribers for avoiding the unwanted effects of drug interactions.

CONCLUSION

A critical examination of lists of the published drug interactions indicates that many interactions are neither scientifically valid nor clinically important. The standards of proof required to assess the validity of interactions reported in the literature must be made more vigorous. We should concern ourselves more with the clinical significance of drug interactions rather than elaborate long lists and focus

excessively on the mechanisms of unimportant interactions. Only if the clinical significance of an interaction is established should its mechanisms be investigated. For convenience, interactions can be divided into direct and indirect types. Direct interactions involve drugs having similar actions and should be predictable based on their cumulative effects. Indirect interactions involve drugs having dissimilar actions and cannot be automatically predicted. However, both types of interactions can lead to an unexpected amount of the expected effect.

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