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EDITORIAL

Drug Interactions in Clinical Perspective

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Few topics in clinical medicine have attracted more attention during the past decade than undesirable interactions between pharmacotherapeutic agents administered concomitantly which decrease therapeutic effectiveness or result in drug toxicity. Many thousands of experimental studies in animals and humans, clinical observations, and epidemiologic studies have been reported. Hundreds of review articles on interactions between drugs have appeared, and more than a dozen books have been entirely devoted to the subject. These intensive efforts have greatly increased our understanding of the mechanisms and of the clinical consequences of drug interactions.

Most adverse interactions between drugs have now become predictable. Accordingly, untoward consequences of using several drugs simultaneously are generally preventable, primarily by appropriate dosage adjustments. The effectiveness and safety of drug therapy should have been correspondingly increased. Unfortunately, many physicians remain insufficiently familiar with clinically important interactions between commonly prescribed drugs. Some even remain unconvinced that drug interactions have any relevance to their therapeutic practices. This situation may be traced primarily to the utter lack of clinical perspective that characterizes much of what has been written about drug interactions.

The clinical problem presented by undesirable interactions between drugs has been vastly overestimated in some quarters and its applicability exaggerated beyound all reason. Tables have been published that list many thousands of "drug interactions". Should anyone who prescribes drugs to patients ever take such lists seriously, he would fall victim to the drug-interaction-anxiety-syndrome [1], or even be struck by instant therapeutic paralysis. A more probable outcome is a judgement by the practicing physician that such lists don't agree with his clinical experience and that the entire concept of drug interactions is an academic chimera or make-work scheme that practitioners of medicine can safely ignore. It is unlikely that this attitude can be overcome unless we focus the attention of physicians on those drug interactions which really do influence the efficacy or safety of human drug therapy.

What goes into the make-up of the uncritical, mammoth and therefore counterproductive drug interaction lists? They tend to be chock-full of misinformation and compiled without a trace of clinical perspective. Many interactions included are purely theoretical, although the number of theoretically conceivable drug interactions approaches that of all possible combinations of all drugs. Pathways of drug metabolism from absorption to elimination are limited and almost any drug could conceivably influence to some extent the pharmacokinetic fate of another. Innumerable drugs affect the function of such organs as the brain or heart, and thus can be considered to interact pharmacodynamically. This is particularly true when one considers that most drugs are not highly specific in their action, and both their main and side effects are taken into account. To list drug "interactions" on this basis is to belabour the obvious and is not clinically helpful. Do physicians really need to be told that phenobarbital and pentobarbital "interact" additively in their hypnotic effect?

Some drug interactions have been accepted as occurring clinically on evidence limited to in vitro studies. Such studies can suggest at times that two drugs might interact during therapeutic use. For example, considerable displacement from human albumin in vitro of a highly bound drug by another drug raises the suspicion that an interaction may occur when these drugs are administered together [2].

However, the occurrence of a clinically important interaction between such drugs depends on many additional factors, such as their apparent volume of distribution, therapeutic margin, daily dose, sequence of administration, elimination half-life and extent of cumulation during chronic therapy, and their propensity to interact pharmacokinetically by other mechanisms, or to interact pharmacodynamically [3–9]. Evaluation of all these factors requires studies in human beings.

Many commonly cited drug interactions have been observed only during animal experimentation. For two reasons extrapolation of such information to the clinical situation is apt to be misleading. First, there are profound differences between species in the metabolic fate of many drugs, particularly binding at inactive sites and biotransformation. Thus, pharmacokinetic interactions between drugs demonstrated in animal experiments may not occur in man. Second, many drug interactions have been demonstrated in experimental animals only when the drugs were administered in amounts incomparably greater on a dose per unit body weight basis than those used therapeutically. Such information is clinically meaningless unless confirmed in humans given therapeutic doses.

There are literally hundreds of examples of drug interactions demonstrated in animals that do not occur during clinical therapy, but one will suffice. A sound and careful study in dogs clearly showed that a daily dose of meprobamate 96 mg/kg for 12 days greatly shortened the half-life of warfarin [10]. In contrast, no evidence exists that a clinically important interaction occurs between these two drugs. Controlled clinical studies have demonstrated that even high therapeutic doses of meprobamate are without influence on the metabolic fate or the pharmacological action of warfarin in humans [11, 12]. Nevertheless, many drug interaction reviews continue erroneously to list meprobamate as an antagonist of warfarin. An enormous amount of this type of misconception is continually perpetuated.

The evidence for the occurrence of many other supposed drug interactions consists solely of speculative interpretation of a single untoward clinical event. Such reports do, of course, serve a useful purpose in calling attention to the possible occurrence of clinically important drug interactions [4]. However, no one who is familiar with the usual complexity of the clinical situation from which these reports originate would accept suspicion as proof that a drug interaction did in fact occur. Uncritical acceptance of anecdotal case reports has once again led to much constantly repeated misinformation.

Ten years ago an uncontrolled observation on a single patientled to the suggestion that chloral hydrate inhibited the hypoprothrombinaemic action of coumarin anticoagulants [13]. It was postulated that the inhibition might be due to induction by chloral hydrate of coumarin-metabolizing enzymes, even though chloral hydrate had not been shown to have enzyme-inducing ability. No further reports of clinically important inhibition of coumarin action by chloral hydrate have ever appeared. In a prospective study on interactions of warfarin with other drugs in 500 patients we were unable to find a single patient in whom chloral hydrate inhibited the hypoprothrombinaemic action of warfarin [4, 14]. Rather, warfarin action was significantly potentiated in 54% of the evaluable patients. Controlled clinical and laboratory studies have shown that the temporary potentiation is due to partial displacement of warfarin from albumin by trichloroacetic acid, a major metabolite of chloral hydrate [2, 15–17]. Thus, the dose of warfarin may have to be decreased temporarily upon initiation of chloral hydrate therapy [5, 16, 18]. However, most drug interaction reviews and tabulations still maintain that chloral hydrate antagonizes the action of oral anticoagulants.

In the United States the concomitant use of monoamine oxidase inhibitors and tricyclic antidepressants has been pronounced contraindicated by the drug regulatory agency. A few inconclusive case reports in the 1960s had suggested that these drugs could interact to produce excitement, delirium, hyperpyrexia, tremors, convulsions, coma and death. The mechanism of the supposed interaction has never been explained, nor has its occurrence been convincingly established. On the contrary, careful clinical observation of large numbers of patients has detected no untoward consequences of concomitant administration of members of these two classes of drugs, and their combined use appears therapeutically useful in certain depressed patients [19–23]. If monoamine oxidase inhibitors and tricyclic antidepressants ever interact dangerously, they to so only in very rare patients who are unusual in some unknown way. At this stage of knowledge a caution about the combined use of these drugs would be more appropriate in terms of its apparent benefit to risk ratio than its flat interdiction.

Drug interactions can be fully accepted as occurring during treatment only on the basis of convincing clinical evidence. Ideally this should consist of appropriately controlled epidemiological or experimental studies. The methodology for such studies has been well defined [4, 6, 15, 18, 24]. Controlled studies in an appropriate number of patients or normal subjects, which demonstrate that two drugs do not interact in a clinically important fashion, should

relegate extrapolations from animal experiments and clinical anecdotes to speedy oblivion.

Perhaps the most important distinction for the practicing physician is between clinical importance and statistical significance. For example, in an appropriately designed study on normal fasting volunteers it would be quite feasible to show that some drug causes a statistically significant 10% decrease in the completeness of absorption of another, when they are given together by mouth [25]. It is unlikely that an effect of this magnitude would ever be of any concern to a clinician. In the case of chronically administered drugs even manifold changes in their rate of absorption caused by other drugs are unlikely to be clinically important.

Adverse drug interactions are important for the clinician only when they influence the effectiveness or safety of drug therapy. Whether an interaction falls into this category does not depend only on the intensity of the interaction. Equally important are the slope of the dose-response curve and the therapeutic ratio of the interacting drugs. The steeper the former and the smaller the latter, the more likely is it that an interaction will influence the therapeutic outcome. For drugs such as cardiac glycosides, antiarrhythmics and anticoagulants a relatively minor decrease or increase in the intensity of their action can lead to therapeutic failure or to important toxicity. These and similar drugs are likely to be involved in clinically important adverse interactions. Other drugs have a very wide therapeutic range and the intensity of their action could be doubled or halved by a drug interaction without any important impact on effectiveness or safety. We must also remember that drug interactions constitute only one of the many factors that contribute to the wide variability in human responses to drugs [26]. If the maximal influence of a drug interaction on the dose-effect relationship of one or both drugs is but a small fraction of the overall individual variation in this relationship, it is unlikely to be of much clinical importance.

Once clinical pharmacologists direct the concern of physicians to clinically important drug interactions that occur during human drug therapy, they will regain credibility and the entire problem will shrink to manageable proportions. A number of useful publications that approach the drug interaction problem with this clinical perspective are available [3, 27–32].

Not many drug interactions are potentially disabling or life-threatening, and they rarely involve drugs other than oral anticoagulants, cardiac glycosides, antiarrhythmics, sympathomimetic amines, antihypertensives, anticonvulsants, oral hypoglycaemics or cytotoxic drugs. Their common manifestations are haemorrhages, cardiac arrhythmias, severe hypertension or hypotension, convulsive seizures or hypoglycaemia. These are the interactions of which any prescriber of drugs can and must always be aware. They are the events whose possible occurrence clinical pharmacologists should effectively call to the attention of prescribing physicians.

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