clinically important adverse drug interactions

nervous system, endocrine system and infusion therapy

edited by

J. C. PETRIE

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Preface to Volume 2

The aim of this three-volume series is to provide authoritative guidelines, based on clinical pharmacological principles, of the clinically important adverse drug interactions associated with the principal drug groups used in clinical practice. Volume I considers cardiovascular and respiratory disease therapy. This volume deals with nervous system, endocrine system and infusion therapy.

Each set of authors has been invited to highlight the relevant clinical pharmacological information about each drug group and to deal with the drugs within the group used in clinical practice. This includes mode of action, pharmacokinetic properties, adverse reactions and drug-host-disease interactions. Pharmacokinetic and pharmacodynamic drug-drug adverse interactions are then discussed against this background of clinical pharmacological information and appropriate emphasis given to clinically important adverse drug-drug interactions.

The series aims to counter the proliferation of published reports of poorly evaluated interactions and to give a realistic clinical perspective to the published collations of drug-drug interactions. Many of the available texts provide long lists and tables of terse statements, which necessarily are often based upon anecdotal and poorly validated reports of clinically observed events, or in vitro studies, or when non-therapeutic doses of drugs are used in patients. In addition, reports of acute, single-dose studies in healthy volunteers and catalogues of potential, theoretical interactions do not provide the information that doctors and pharmacists need regarding adverse drug-drug interactions.

Many physicians and pharmacists have become confused and disillusioned by the uncritical tabulations of interactions and, unable to memorise the lists and unimpressed by many of the alleged interactions, have turned away from the problems. Unfortunately, because the clinically important information has not been clearly separated from the flood of theoretical information, the health of patients is thereby put at risk.

The specialist authors in this volume, taken with the other two volumes in the series, address these problems in a critical manner. The interested reader should consult carefully the indexes of the respective volumes as the perspectives of the different specialists must vary in their emphasis because of their greater clinical

experience of the 'other' drug group involved in the respective drug-drug interactions.

The subject of drug interactions is fascinating and difficult. We hope that this series will help clinicians, pharmacists, pharmacologists and others to understand, control and even prevent unnecessary drug-induced morbidity and disease.

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Methods of study of drug interactions

Ronald B. Stewart and Leighton E. Cluff

1. HISTORICAL BACKGROUND

Drug interactions result when the effect of one drug is modified by the prior or concurrent administration of another drug. The resultant effect may be an enhanced or diminished activity of the drugs and may be desirable or undesirable.

Within the past several years increasing numbers of drug interactions have been reported. As this process continues methods are needed to identify possible interactions, and determine their clinical significance.

Many drugs are given to people without a clear understanding of possible untoward consequences, and this has led to increasingly frequent and serious adverse effects as a result of chemical or pharmacological interactions. The ease of rationalizing expected therapeutic benefit from prescribing many drugs contrasts with the unpredictability of deleterious effects. The problem of drug interaction is further compounded by the use of over-the-counter remedies.

Drug interactions may result in diminution of a pharmacologic effect rather than an injurious effect. For instance, failure of tetracycline therapy may result from concurrent treatment of peptic ulcer disease with aluminium hydroxide, or a patient's hypertension which was previously well controlled by guanethidine may become uncontrolled as a result of therapy with a new tricyclic antidepressant drug.

There are many examples depicting the difficulty and lag time that often occurs before identifying relationships between a single drug and an undesirable side-effect. The possibility that an adverse effect may be attributable to concurrent administration of two drugs makes the problem even more difficult.

The response of patients to a drug varies depending on factors such as dosage, absorption, volume of distribution and protein binding. In addition, a drug may have a multiplicity of biologic as well as placebo effects.

Drug–drug interactions may occur in many different ways. The combined effect of two or more drugs may be additive, synergistic, or antagonistic. The mechanisms by which these effects are produced are numerous and include such phenomena as modification of absorption, distribution, transport across cell membranes, protein binding, receptor site sensitivity, metabolism and renal clearance. Interactions between drugs can take place prior to administration as a result of direct chemical or physical interaction, as for example, intravenous admixtures. These interactions may produce visible signs of incompatibility such as precipitates, turbidity, or colour changes. However, inactivation of the drugs may occur with no overt indication.

Drug interactions and adverse effects may not result when a drug combination is administered to the 'average patient', but may occur in patients with renal and liver disease. Some patients are genetically predisposed to drug adverse effects.

Medication practices of patients and prescribing patterns of physicians create the settings where drug interactions occur. Investigation of drug interactions in such settings, involving sick patients using a variety of prescription and non-prescription drugs is essential. The physician is not likely to administer together drugs known or suspected to interact adversely, and is less likely to administer several test drugs simultaneously to sick patients. It is with this background that the approaches used up to now and proposed in this chapter have been developed.

The complex clinical effects of interactions between drugs, however, requires a multidirectional approach to their investigation. Drug interactions can be studied initially in patients, laboratory animals or in vitro models. Suspicions arising from clinical observations can lead to laboratory investigation or this process may occur in the reverse order.

Much work has been done on drug interactions. Hundreds of studies have been conducted in human subjects to evaluate suspected drug interactions. Many proposed interactions have been confirmed but most have been shown either not to occur or to be of little clinical significance. The American Pharmaceutical Association conducted a project over a 6-year period to evaluate more than 100 drug interactions reported in the medical literature. This resulted in an authoratative text entitled 'Evaluations of Drug Interactions' which serves as a guide to physicians and pharmacists (American Pharmaceutical Association 1976). The series of which this volume is a part also attempts to provide a comprehensive analysis of clinically important adverse drug interactions (Petrie and Cluff, 1980).

The clinical problem of drug interactions can be expected to increase in the future. The availability of newer more potent therapeutic agents will result in an ever increasing flurry of reported interactions. For instance, cimetidine, with its

profound effect on gastric acid secretions and its ability to interfere with microsomal enzyme systems responsible for drug metabolism can be expected to alter the performance of hundreds of therapeutic agents (Longstreth, 1976; Klotz and Reimann, 1980). Specialization in medical practice will also make it more difficult for drug prescribers to be knowledgeable concerning medication prescribed by other physicians for their patients. Rapid advances in drug analysis will increase our knowledge about the effect that one drug can have on another. These and many other factors will make the study of drug interactions a more important area for clinicians in the years ahead.

Unfortunately one can never control all clinical variables. Perhaps the best that can be accomplished at the present time is to develop approaches with an awareness of the existing variables. This chapter will identify problems in investigating drug interactions, review methods that have been employed to study interactions and suggest approaches to the problem.

2. FACTORS TO BE CONSIDERED IN THE INVESTIGATION OF DRUG INTERACTIONS

2.1. Introduction

Investigation of drug interactions requires that careful consideration be given to three major determinants. These are: the peculiar properties of each drug; the physical and psychological status of the patient and, the total number of drugs to which the patient is exposed. Goodman (1964) has described numerous factors entering into the study of drug efficacy, and many of these factors are equally applicable to the study of drug interactions. Response to drug therapy is a complex phenomenon and is influenced by the drug taken, the patient receiving it and the physician prescribing it (Table 1.1). Several of these factors will be discussed as examples although all bear careful consideration when studying drug interactions.

2.2. Drug determinants

A drug's physical and chemical properties can influence it's potential to interact with other drugs. Whether a drug is absorbed depends on properties such as water solubility, partition coefficient, dissociation constant and molecular weight. Binding properties of a drug to tissue and plasma proteins can influence factors such as distribution, rate of passage through membranes and the magnitude of pharmacological effect. Knowledge of these physical and chemical properties may enable one to suspect and predict potential interactions. For example, information concerning the pK_a of a drug will allow one to predict whether a concurrently admin-

TABLE 1.1

The problem of drug efficacy

A. *Drug factors:*	
Doses employed	Tolerance
Multiple effects	Side-effects
Absorption	Toxicity
Distribution	Idiosyncrasy, hypersensitivity
Metabolic fate	Margin of safety
Excretion	Precautions
Duration of effect	Contraindications
Route, duration of administration	Pharmaceutical properties
Habituation	Chemical properties
Addiction liability	Drug interactions
B. *Patient factors:*	
Sex, age	Contraindications, precautions
Body size and weight	Toxicity
Pregnacy	Margin of safety
Pharmacogenetic factors	Concomitant therapy
Biochemical status	Personality factors
Nutritional status	Attitude toward disease, drugs, doctors
Drug metabolism	Halo and milieu influences
Disease (vast multiplicity of factors)	Cost
Idiosyncrasy, hypersensitivity	
C. *Physician factors:*	
Training	Attitude toward drug therapy
Diagnostic skill	Attitude toward patient
Therapeutic skill	Attitude toward disease
Experience with drugs	Halo and milieu influences
Concomitant therapy	
Factors affecting drug efficacy[a]	

[a] From Goodman (1964).

istered agent such as sodium bicarbonate can alter the pH of the urine to a degree necessary to significantly affect elimination of another drug.

A thorough understanding of a drug's mechanism of action can suggest the occurrence of interactions between drugs, but the number of different drugs available makes it almost inconceivable for a physician to possess this understanding completely.

Few drugs have precise and narrow ranges of action. Salicylates, for example, produce many different effects (Woodbury, 1971) including (1) local irritant

effects on mucosa; (2) changes in the EEG; (3) direct stimulation of respiration; (4) increased volume of bile; (5) reduced plasma-prothrombin levels; (6) increased urinary excretion of urates; (7) decreased aggregation of thrombocytes; (8) negative nitrogen balance in large doses; (9) alteration of acid-base balance; (10) uncoupling of oxidative phosphorylation with inhibitory action on many ATP-dependent reactions. Any drug having effects similar or opposite to these actions may interact with salicylates producing additive or antagonistic effects.

The effect of one drug may be altered leading to an adverse reaction not because of drug–drug interaction but because of drug–host–drug influences. Thiazide diuretics, for example, when used in conjunction with digitalis in the management of congestive heart failure may produce a hypokalaemia which can increase the toxic effects of cardiac glycosides. Similarly, paralysis of skeletal muscle may result from the same potassium-depleting mechanisms especially in patients receiving a neuromuscular blocking agent.

Many drugs are metabolized by hepatic microsomal enzymes which change the lipid-soluble active compound into a more polar metabolite. In this form the drug is more readily eliminated by renal clearance mechanisms. Many drugs have an ability to increase the amount of enzyme substance (enzyme induction) and thereby induce not only their own metabolism but also the metabolism of a variety of other drugs. A change in the rate of a drug's metabolism may produce clinically significant effects on the patient. Modifying the biological half-life of a drug by the administration of other drugs complicates therapy and can result in serious consequences to the patient such as those observed when barbiturates are co-prescribed with warfarin.

Drugs given for dissimilar therapeutic purposes may have similar pharmacological effects causing adverse reactions. Use of Combid® for nausea, Hist-span® for a cold, Benadryl® for leg cramps. Tofranil® for depression, Donnatal® and Librax® for dyspepsia in middle aged women produced additive anticholinergic activity. Routine use of all six of these seemingly unrelated drugs provides six different chemicals with anticholinergic activity and may result in significantly decreased intestinal motility and other adverse effects.

Manufacturers of drug products may occasionally change the ingredients in a product without changing the trade name. For instance, the ingredients for Nervine®, a popular non-prescription sleep aid, were changed from bromides to methapyrilene with no changes in the name of the product. Similarly, Liquiprin®, a popular liquid analgesic used in paediatric therapy was changed from salicylamide to acetaminophen although the trade name was not altered (Anon, 1976). These changes may go unrecognized by the patient or physician and may have major therapeutic implications.

While most physicians recognize the variations that exist among drugs and patients, they may not consider that a more subtle difference exists between 'identical' drugs produced by different manufacturers. Inequivalence of drug products

must be considered as a variable when investigating interactions between drugs. Results of interaction studies may vary because of this difference in drug products. Epidemiological investigations identifying an interaction at one institution using brand A, therefore, may not be duplicated in another institution employing brand B.

Glazko et al. (1968) studied the absorption characteristics of four different chloramphenicol preparations. Subjects were given a single 500 mg oral dose of chloramphenicol, and one product produced plasma levels which were nearly twice as great as a product by a different manufacturer. These observations emphasize the need for caution when assuming that absorption is the same for different products containing identical amounts of drug.

Variations in the biological availability of digoxin from four manufacturers was documented by Lindenbaum et al. (1971). In this cross-over study, identical doses of digoxin from different manufacturers were administered to patients. Significant differences in serum digoxin levels were achieved, with one product producing peak serum levels 7-fold greater than those obtained with another product. Significant variations were also observed between different lots of the same manufacturer's product. Dilantin® manufactured by Parke Davis Co., is a slow release formulation of phenytoin that can be administered on a once daily dosing schedule while another available product produces different blood levels and cannot be used for single daily dosing.

The problem of bioinequivalence of drug products has been gaining more attention in recent years. In 1981, 49 of the states in the U.S. had adopted laws allowing or mandating pharmacists to select generic products (Anon, 1981) rather than the drug brand prescribed by a physician. In the United States the Food and Drug Administration has required drug companies to demonstrate bioequivalence of their products.

The importance of bioequivalence on drug interactions was observed in a study concerning the effect of propantheline on the absorption of digoxin. Propantheline significantly increased the amount of digoxin absorbed from a slow-dissolving brand of digoxin while it exerted only a minimal increase with a fast dissolving brand of digoxin (Manninen, 1973).

Since the intensity of pharmacological response elicited by many drugs is probably directly related to the concentration or activity of the drug in the immediate vicinity of the receptor site in the body, it would follow that interactions would also depend on the concentrations of the drug at that site. In view of this it is likely that similar variations could be found among many other products and this should be considered when evaluating possible drug interactions.

2.3. Host determinants

Every individual will have a peculiar set of characteristics which may alter the