Kinetics of Drug–Drug Interactions

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Since many drug–drug pharmacokinetic interactions are dependent on the concentrations of the interacting species, the degree of interaction should be a graded phenomenon varying with drug and/or metabolite concentration and thus drug administration and time. Hence one should be able to develop predictive kinetic models for such interactions. A change in drug plasma levels when a compound is administered as a single dose together with another drug can arise from a change in drug clearance, displacement from binding sites, a change in elimination rates, or a combination of any or all of these possibilities. The interaction of phenobarbital and the sparingly soluble oral antifungal agent, griseofulvin, is one example. Analysis shows that there is no change in elimination half-life of griseofulvin but that phenobarbital reduces the extent of griseofulvin absorption rather than enhances its elimination. Sulfaphenazole inhibits the metabolism and markedly prolongs tolbutamide plasma levels. An anticipated sudden drop in the excretion rate of the tolbutamide metabolites at maximum sulfonamide plasma levels is associated with an almost complete block of tolbutamide oxidation. The inhibitor constant \(K_i\) for this interaction has been calculated, allowing one to predict tolbutamide and metabolite levels when the inhibitor is administered. Drug–drug interaction resulting from protein displacement has been hypothesized by a number of authors. However, the potentiation of the anticoagulant warfarin in patients receiving phenylbutazone is more complicated than has been envisioned previously. While displacement occurs, data suggest that phenylbutazone primarily acts through selective inhibition to alter the isomeric composition and potency of the racemic warfarin administered. The warfarin–phenylbutazone interaction study stresses the importance of measuring metabolites as well as intact drug.

KEY WORDS: drug-drug interactions; plasma protein displacement; griseofulvin–phenobarbital interaction; tolbutamide–sulfaphenazole interaction; Michaelis-Menten kinetics; inhibitor constants; tolbutamide metabolites; warfarin–phenylbutazone interaction.

Open any current medical journal and one is reminded that the co-administration of two or more drugs can either cause deleterious effects or...
lead to ineffective therapy. Those concerned with drug therapy are increasingly aware of this phenomenon but are confronted with the problem that a patient may be taking three, four, and, on occasions, even more drugs simultaneously. The computer will aid in the storage and retrieval of such information and act as a useful early warning signal, but prudent multiple drug therapy, if deemed necessary, can only be achieved with a better understanding of the nature and quantitative aspects of drug interactions.

A drug interaction might broadly be defined as any reaction between one drug and another substance within or out of the body. In this review, the definition is restricted to events occurring within living systems with major emphasis on the alteration by one drug on the rate and extent of absorption, distribution, metabolism, and excretion of another. Prescott (1) has called these "pharmacokinetic interactions" to distinguish them from the numerous interactions between drugs at their sites of action (2). This distinction is somewhat arbitrary, as any or all possibilities can occur in vivo. The interaction may be direct, such as the competitive inhibition of drug metabolism and the displacement of a drug from binding sites, or it may be indirect. One example of the latter is the decreased renal clearance of amines and increased renal clearance of acids, whose renal clearance is sensitive to urinary pH, produced when the urine is rendered alkaline using either the carbonic anhydrase inhibitor, acetazolamide, or sodium bicarbonate. Another example is the prolongation of the elimination half-life of lidocaine by dl-propranolol. The elimination of lidocaine, primarily by hepatic metabolism, is hepatic blood flow limited, which propranolol diminishes (3).

Many review articles (4-7) and books (8, 9) cover the whole array of drug interactions. While useful, many, however, are little more than topographical maps with little weighting as to the quantitative significance of any sites of interaction.

Our knowledge of the pharmacokinetics of drugs in animals and man has increased substantially over the past few decades (10). Models have been developed which accurately describe the concentration profile of drugs in various biological fluids following drug administration. Considerable success has also been gained in relating the kinetics of a graded pharmacological response to a drug with its pharmacokinetics (11, 12). Since many drug-drug pharmacokinetic interactions are dependent on the concentrations of the interacting species, the degree of interaction should also be a graded phenomenon varying with drug (and metabolite) concentrations and therefore drug administration and time. Hence one should be able to develop predictive kinetic models for such drug interactions. Although awareness of this fact exists, there have been relatively few systematic attempts to establish these models. The careful studies on the kinetics of the interaction between salicylate and acetaminophen (13) and between acetaminophen and sali-