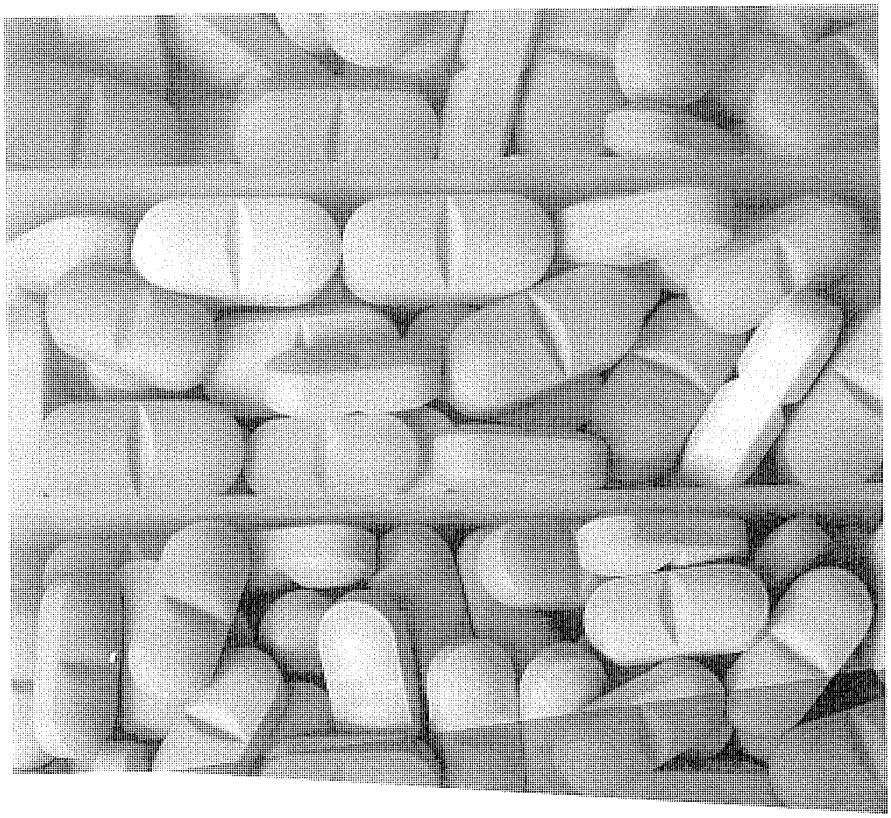

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Pharmacokinetic Drug Interaction Mechanisms and Clinical Characteristics

The administration of more than one drug is a frequent occurrence, and the probability of a drug interaction increases with the number of drugs a patient is taking. The same pharmacokinetic and pharmacodynamic principles that determine the behavior of drugs in the body can be applied to drug interactions. The absorption, distribution, or elimination of one drug can be altered by another. Additionally, the pharmacodynamics of an agent may be altered independently from changes in its pharmacokinetics. An understanding of these basic principles as they apply to drug interactions enhances the ability to predict possible outcomes resulting from the coadministration of two drugs known, or suspected, to interact. Likewise, knowledge of the various mechanisms of drug interactions is helpful in understanding how to avoid the adverse effects of drug interactions. This chapter reviews the basic information regarding common properties and mechanisms of drug-drug interactions.

THE TIME COURSE OF DRUG INTERACTIONS

The time course of drug interactions can vary dramatically; some interactions occur in a matter of seconds or minutes, while others develop over several weeks. When considering the time course of drug interactions, there are several time points that are of clinical interest:

- Time of onset of the interaction (when the interaction first becomes detectable).
- Time for maximal pharmacokinetic or pharmacodynamic effect of the interaction.
- Time that the patient experiences an adverse response to the interaction.
- Time required for the dissipation of the interaction.

For some drug interactions, clinical information is available on one or more of these time points, such as the time of onset, maximal pharmacokinetic or pharmacodynamic effect, and dissipation. Although the time that the patient will experience an adverse effect from an interaction is more difficult to predict, one often can estimate the time of maximal risk and take appropriate precautions.

Estimates of the time course of drug interactions in specific patients are just that—estimates. Even though the time course for an interaction may be relatively consistent in a group of similar patients, some patients, for unknown reasons, will develop the interaction much more quickly or slowly than others.

Importance of Considering Time Course

Estimating the time course of a drug interaction in a given patient can help the clinician minimize the likelihood of an adverse effect from the interaction and reduce the costs of monitoring for the interaction.

Patient Monitoring. Knowledge of the time course allows the clinician to select the most appropriate times to monitor the interaction. For example, assume a patient receiving warfarin (eg, *Coumadin*) is started on a drug that gradually increases the hypoprothrombinemic response over several weeks. It probably would be sufficient to obtain prothrombin times no more often than every 4 or 5 days to prevent excessive hypoprothrombinemia. On the other hand, if a drug rapidly increases the hypoprothrombinemic response to warfarin, the prothrombin time should be monitored more frequently.

Assessing Clinical Importance. Knowledge of the time course of an interaction may allow the clinician to estimate the clinical importance of an interaction in a given

patient. For example, nonsteroidal anti-inflammatory drugs (NSAIDs) are known to gradually reduce the effect of a variety of antihypertensive drugs over a period of 1 to 2 weeks.[1] Thus, the short-term administration of an NSAID to treat dysmenorrhea or headache is unlikely to adversely affect blood pressure control in a clinically important way. Similarly, use of the enzyme inducer rifampin (eg, *Rifadin*) for 2 days (eg, prophylaxis of bacterial meningitis) is unlikely to stimulate the metabolism of other drugs sufficiently to reduce the desired therapeutic effect. This is because enzyme induction is a gradual process that generally takes several days to a week or more to maximally reduce the effect of a drug.

Discovering New Interactions. When performing clinical research, it is important to study a drug interaction over a sufficient time period to minimize the likelihood of false-negative conclusions. For example, in early studies, tricyclic antidepressants (TCAs) were not observed to alter the antihypertensive response of guanethidine (*Ismelin*). The drug interaction was not detected because these studies were performed over a period of hours. When the period of study was extended, the interaction was found to take 1 or 2 days to develop, and the TCAs were noted to substantially inhibit the antihypertensive response to guanethidine.[2]

Determinants of Time Course

Numerous factors can affect the time course of drug interactions, and it often is necessary to consider several when estimating the time course of a given interaction in a particular patient.

Half-Lives of Drugs Involved. The half-life of the *precipitant drug* (ie, drug that causes the altered action of the other drug) can be an important consideration because the half-life dictates the time course of the precipitant drug's accumulation to steady state. If it takes a long period of time for the precipitant drug to reach a plateau level, the interaction may be delayed. For example, when phenobarbital therapy is started, it generally takes approximately 1 week to reach steady-state serum phenobarbital concentrations. Thus, the maximal interactive effects of phenobarbital would not be expected during the first few days of therapy. Similarly, the discontinuation of phenobarbital tends to result in a gradual dissipation of its interactions at least in part because the serum concentrations of phenobarbital gradually decline over approximately 1 week.

The half-life of the *object drug* (ie, drug whose action is altered by the interaction) is also an important determinant. As an example, consider what happens when cimetidine (eg, *Tagamet*) is added to the chronic therapy of a patient receiving either theophylline (eg, *Theolair*) or warfarin. Since theophylline has a relatively short half-life, patients receiving theophylline will usually manifest the new increased steady-state serum theophylline concentrations a few days after starting cimetidine.[3] On the other hand, when cimetidine is added to the therapy of a patient stabilized on warfarin, serum warfarin concentrations will increase over 1 week or more.[4] When estimating how long it will take for an object drug to reach a new plateau level in these situations, remember it is the *new* half-life that has been prolonged (or reduced) by the precipitant drug that must be considered. Thus, it typically takes more time (or less time) for the new steady-state serum concentrations to be achieved than might be expected from an average half-life value in the population at large.

Drug Dosage. The dosage of the object drug can influence the time course of an interaction. For example, if a patient is receiving a large dose of an object drug and the serum concentration of that drug is at the upper end of the therapeutic range, it may take only a short time for the serum concentration to rise into the toxic range following administration of another drug that inhibits the elimination of the object drug. Conversely, when a patient is receiving a low dose of the same object drug or when this patient has a serum concentration that is in the low therapeutic or subtherapeutic range, it will take more time for the serum concentration to rise to the

toxic range (if it gets there at all) following the administration of a drug that inhibits its elimination.

In general, larger doses of a precipitant drug would result in a somewhat more rapid onset of the interaction since the serum concentration necessary to produce the interaction may be achieved more rapidly. Similarly, it may take longer for the interaction to dissipate after discontinuation of large doses of the precipitant drug because it may take longer for the serum concentration of the precipitant drug to drop below the threshold level required for the interaction.

Routes of Administration. Routes of administration that rapidly achieve therapeutic serum concentrations of interacting drugs will tend to result in more rapid development of drug interactions. For example, in a patient receiving a CNS depressant, the IV administration of an additional CNS depressant is likely to more rapidly affect the patient than if the second agent is given orally.

Drug Metabolites. If it is the metabolite rather than the parent form of the precipitant drug that is involved in the interaction, it may take longer than expected for the interaction to occur. For example, there is some evidence that a metabolite of erythromycin (eg, *E-Mycin*), rather than erythromycin itself, is responsible for the inhibition of theophylline metabolism in patients taking the combination.[5] It would be expected that adding an inhibitor of hepatic metabolism such as erythromycin to theophylline therapy would significantly increase serum theophylline concentrations within 2 or 3 days of starting the erythromycin. However, in most patients, increases in serum theophylline caused by erythromycin are delayed by at least 5 days. This may reflect the time required for the erythromycin metabolite to be produced and to accumulate in the serum until there is a sufficient concentration to inhibit the hepatic metabolism of theophylline.

The metabolites of object drugs also may affect the time course of drug interactions, particularly if active metabolites are involved. For example, cimetidine inhibits the hepatic metabolism of diazepam (eg, *Valium*) and its active metabolite, desmethyldiazepam.[6] Thus, in estimating the lag time before the maximal effects of the interaction are seen, consider not only the half-life of diazepam, but also its active metabolite. Accordingly, the dissipation of this interaction following discontinuation of cimetidine is dependent upon the half-life of both the parent drug and active metabolite.

Dose-Dependent Pharmacokinetics. Consider dose-dependent pharmacokinetics when estimating the time course of drug interactions. When the elimination of an object drug is dose dependent, the addition of a drug that reduces its elimination can increase the serum concentrations of the object drug into the zero order range. As a consequence, the increased half-life of the object drug can result in serum concentrations that increase over a longer time period than would be expected on the basis of its "normal" half-life. For example, isoniazid (INH; *Nydrazid*) inhibits the hepatic metabolism of phenytoin (eg, *Dilantin*), a drug that displays dose-dependent pharmacokinetics.[7] When INH is added to phenytoin therapy, the serum phenytoin concentration can be increased into the range where its half-life is prolonged, and the serum phenytoin concentrations can increase steadily over a period of several weeks.

Effect of Drug Interaction Mechanisms on Time Course

Knowledge of the mechanism for a given drug interaction is useful in estimating the likely time course, but it is important to realize that the mechanism must be considered in concert with the other determinants discussed above.

GI Absorption Interactions. When a precipitant drug binds with or otherwise inhibits the GI absorption of an object drug, the serum concentration of the object drug usually will *begin* to decrease within hours of concurrent use of the 2 drugs. This situation is like lowering the dose of the object drug. However, the rate of decline of the serum concentration of the object drug depends upon its half-life.

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