

## PHARMACOKINETICS, PHARMACODYNAMICS, AND DRUG DISPOSITION

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During the last decade, the application of pharmacokinetic and pharmacodynamic modeling techniques has become an increasingly important aspect of contemporary clinical psychopharmacology (1–5). These techniques have been applied during the process of development of new drug entities as well as for the improved understanding of the clinical actions of drugs that are already marketed. Techniques for the study of drug metabolism *in vitro* have advanced substantially during the last decade, and now are an integral component of preclinical drug development and the link to subsequent clinical studies of drug metabolism and disposition. Kinetic-dynamic modeling techniques have been combined with *in vitro* metabolism procedures and *in vitro–in vivo* mathematical scaling models to provide insight into the general problem of pharmacokinetic drug interactions in clinical psychopharmacology (6–9).

This chapter reviews some advances in pharmacokinetics, pharmacodynamics, and drug metabolism, along with methodologic applications to selected problems in clinical psychopharmacology.

### POPULATION PHARMACOKINETICS

#### Principles

Pharmacokinetic studies based on a traditional intensive-design model are usually conducted using carefully selected volunteer subjects, a controlled experimental design, and collection of multiple blood samples. After measurement of drug and metabolite concentrations in all samples, pharma-

cokinetic models are applied to determine parameters such as elimination half-life, volume of distribution, and clearance. During the new drug development process, a series of pharmacokinetic studies are conducted to determine the influence of major disease states or experimental conditions hypothesized to affect drug disposition. Such factors might include age, gender, body weight, ethnicity, hepatic and renal disease, coadministration of food, and various drug interactions. Classical pharmacokinetic studies can quantify the effects of anticipated influences on drug disposition under controlled circumstances, but cannot identify the unexpected factors affecting pharmacokinetics. A number of examples of altered drug pharmacokinetics became apparent in the patient care setting only in the postmarketing phase of extensive clinical use. Examples include the digoxin-quinidine interaction, altered drug metabolism due to cimetidine, and the ketoconazole-terfenadine interaction.

Population pharmacokinetic methodology has developed as an approach to detect and quantify unexpected influences on drug pharmacokinetics (10–18). Population pharmacokinetic studies, in contrast to classical or traditional pharmacokinetic studies, focus on the central tendency of a pharmacokinetic parameter across an entire population, and identify deviations from that central tendency in a subgroup of individual patients. One software program widely applied to population pharmacokinetic problems is the nonlinear mixed-effects model (NONMEM). Analysis of clinical data using a population approach allows pharmacokinetic parameters to be determined directly in patient populations of interest and allows evaluation of the influence of various patient characteristics on pharmacokinetics. Because the number of blood samples that need to be collected per subject is small, this approach is often suitable for patient groups unable to participate in traditional pharmacokinetic studies requiring multiple blood samples (e.g., neonates,

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children, critically ill patients, or individuals who are not able to provide informed consent) (19). In many cases the population approach has yielded pharmacokinetic parameter estimates similar to those delineated in classical pharmacokinetic studies of the same drug.

### Application: Methylphenidate Pharmacokinetics

The population approach is illustrated in a study of methylphenidate (MP) pharmacokinetics in children (20). This is a patient group for whom the multiple-sample pharmacokinetic study design may not be appropriate for ethical and practical reasons. Participating subjects were 273 children aged 5 to 18 years having a primary diagnosis of attention-deficit/hyperactivity disorder (ADHD). They had been receiving MP at a fixed dosage level for at least 4 weeks, and were under treatment for at least 3 months. The treating physician for each patient judged MP to be clinically effective.

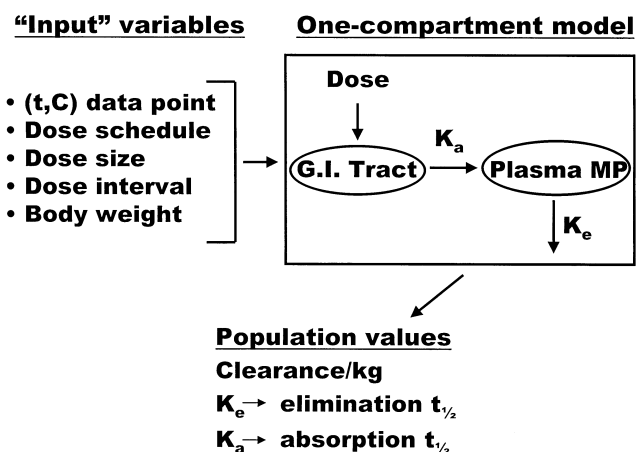
Children meeting the eligibility criteria had an initial screening visit, at which one parent or a legal guardian provided written informed consent, and the child provided assent. Demographic characteristics were recorded, including the dosage of MP, the usual times for individual doses, and the duration of treatment.

The second visit, which followed shortly, was a blood-sampling day. Each child, accompanied by parent or guardian, arrived at the investigator's office 30 to 60 minutes prior to blood sampling. The time and size of the last MP dose, and of any other medication received that day or during the prior 2 weeks, were recorded. A 5-mL whole blood sample was obtained by venipuncture. This sample was immediately centrifuged, and a 2-mL aliquot of plasma was removed for subsequent determination of MP concentrations by a liquid chromatography/mass spectroscopy/mass spectroscopy (LC/MS/MS) assay.

### Analysis of Data

The identified independent variables were age, sex, body weight, size of each dose, and time of sample relative to the most recent dose. Since only single samples were available for all but 16 of these children, the contribution of within-subject variance to overall variability in outcome could not be assessed. The pharmacokinetic model was a one-compartment model with first-order absorption and first-order elimination, under the assumption that all subjects were at steady state (Fig. 38.1).

The overall model was specifically modified for each of the 273 subjects to incorporate the individually applicable independent variables, as well as the dosage schedule (b.i.d. or t.i.d.). Individual values of continuous variables ( $t$  = time sample taken relative to the first dose;  $C$  = plasma MP concentration) were fitted to a single set of iterated



**FIGURE 38.1.** Population pharmacokinetic model for methylphenidate (MP). A series of data points, each consisting of the time ( $t$ ) after the first dose of the day and the plasma MP concentration ( $C$ ) at that time, was available from 273 subjects (one data point per subject). Each of these was linked to that subject's individual dose schedule, size of each dose, interval between doses, and body weight. These variables were entered into a one-compartment pharmacokinetic model with first-order absorption and first-order elimination, as shown. Using nonlinear regression, the process yielded "typical" population values of clearance per kilogram body weight, the elimination rate constant ( $K_e$ ), and the absorption rate constant ( $K_a$ ).

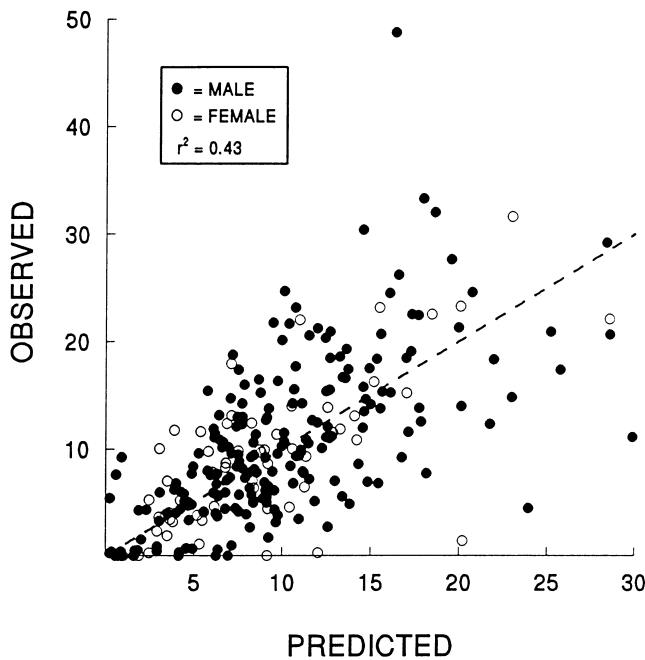
variables using unweighted nonlinear regression (Fig. 38.1). When the time between first and second doses, or between second and third doses, was not available, the mean value was assigned based on cases in which the data were available. For the b.i.d. dosage, the mean interval was 4.3 hours. For the t.i.d. dosage, the mean intervals were 4.1 and 3.7 hours, respectively. As is customary, clearance was assumed to be proportional to body weight.

### Results

The total daily dose of MP was significantly lower in subjects receiving MP b.i.d. ( $n = 109$ ) compared to subjects on a t.i.d. schedule ( $n = 164$ ); the mean total daily dosages in the two groups were 25 and 39.3 mg, respectively ( $p < .001$ ). Within each group, clinicians' choices of total daily dosages were influenced by body weight, as mean total daily dose increased significantly with higher body weights. However, the association of body weight with mean plasma concentration was not significant for the b.i.d. dosage group, and of only borderline significance ( $.05 < p < .1$ ) for the t.i.d. group. This finding is consistent with the underlying assumption that clearance is proportional to body weight.

Age was significantly correlated with body weight ( $r^2 = 0.54$ ,  $p < .001$ ) and with height ( $r^2 = 0.77$ ). Height and body weight also were significantly correlated ( $r^2 = 0.77$ ).

An acceptable estimate of absorption rate constant could be derived only for the b.i.d. dosing data. The iterated pa-

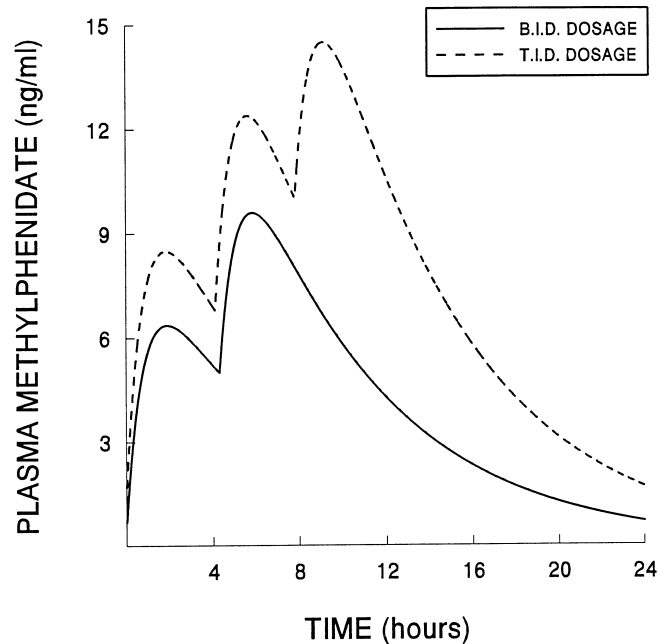


**FIGURE 38.2.** Overall relation of observed and predicted plasma methylphenidate concentrations (ng/ml). The  $r$ -square value of 0.43 indicates that the model accounts for 43% of the overall variance in plasma concentrations. (From Shader RI, Harmatz JS, Oesterheld JR, et al. Population pharmacokinetics of methylphenidate in children with attention-deficit hyperactivity disorder. *J Clin Pharmacol* 1999;39:775–785, with permission.)

parameter estimate was 1.192/h, corresponding to an absorption half-life of 34.9 minutes. This estimate was then fixed, and the entire data set analyzed to determine clearance per kilogram of body weight, and the first-order elimination rate constant. The iterated estimates were 0.154/h for elimination rate constant, corresponding to an elimination half-life of 4.5 hours (relative standard error: 23%). For clearance, the estimate was 90.7 mL/min/kg (relative standard error: 9%). The overall  $r$ -square was 0.43 (Fig. 38.2). There were no evident differences in pharmacokinetics attributable to gender. Figure 38.3 shows predicted plasma MP concentration curves for b.i.d. and t.i.d. dosage schedules, based on the population estimates.

### Implications

Pharmacokinetically based approaches to the treatment of ADHD with MP are not clearly established (21–25). In the present study of prescribing patterns in particular clinical practices, the mean prescribed per dose amount for the whole study population was 0.335 mg/kg per dose (range = 0.044–0.568), and 36% of the children received between 0.25 and 0.35 mg/kg per dose. The mean total daily dose was 0.98 mg/kg/day for the entire sample, and increased significantly in association with larger body weight.



**FIGURE 38.3.** Predicted plasma methylphenidate concentration curves for b.i.d. and t.i.d. dosage schedules, based on parameter estimates from the population analysis, together with mean values of input variables (body weight, size of doses, intervals between doses). (From Shader RI, Harmatz JS, Oesterheld JR, et al. Population pharmacokinetics of methylphenidate in children with attention-deficit hyperactivity disorder. *J Clin Pharmacol* 1999;39:775–785, with permission.)

This may reflect the clinicians' considering body weight in their choice of total daily dosage, or it may be that the dose was titrated according to response, which in turn was influenced by associations among concentration, clearance, and weight.

The pharmacokinetic model explained 43% of the variability in plasma MP concentrations during typical naturalistic therapy. The model fit equally well for both genders. Assuming that clearance is proportional to body weight in the context of intercorrelated age and weight allows age, weight, and daily dosage to be used to predict plasma concentrations of MP during clinical use in children. These findings support the value of prescribing MP on a weight-adjusted basis.

Our typical population value of elimination half-life was 4.5 hours, with a confidence interval of 3.1 to 8.1 hours. This estimate somewhat exceeds the usual range of half-life values reported in single-dose kinetic studies of MP (25, 26). This could reflect the relatively small number of plasma samples from the terminal phase of the plasma concentration curve, upon which reliable estimates of beta are dependent. MP kinetics may also have a previously unrecognized dose-dependent component, in which estimated values of half-life are larger at steady state than following a single dose.

The single-sample approach described in this study allows relatively noninvasive assessment of pharmacokinetic parameters in a group of children and adolescents under naturalistic circumstances of usual clinical use, when blood sampling is not otherwise clinically indicated. This approach in general can be applied to other special populations such as neonates, the elderly, or individuals with serious medical disease.

## KINETIC-DYNAMIC MODELING

### Principles

Pharmacokinetics is the discipline that applies mathematical models to describe and predict the time course of drug concentrations in body fluids, whereas pharmacodynamics refers to the time course and intensity of drug effects on the organism, whether human or experimental animal (Fig. 38.4). Both have evolved as the techniques for measuring drug concentrations, and drug effects have become more accurate and sensitive. Evolving in parallel is kinetic-dynamic modeling, in which the variable of time is incorporated into the relationship of effect to concentration (Fig. 38.4) (27–32). A concentration-effect relationship is, in principle, the most clinically relevant, because it potentially validates the clinical rationale for measuring drug concentrations in serum or plasma.

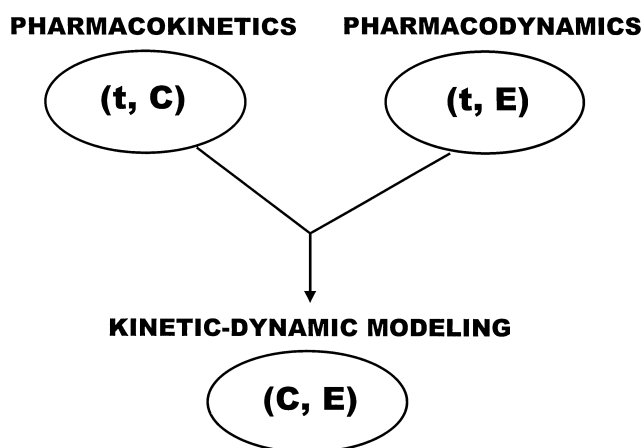
A kinetic-dynamic study in clinical psychopharmacology typically involves medication administration (usually under placebo-controlled, double-blind laboratory conditions) followed by quantitation of both drug concentration and clinical effect at multiple times after dosing. Measures of effect

necessarily depend on the type of drug under study. For sedative-anxiolytic drugs such as benzodiazepines, effects of interest may include subjective or observer ratings of sedation and mood; semiobjective measures of psychomotor performance, reaction time, or memory; or objective effect measures such as the EEG or saccadic eye movement velocity. The various measures differ substantially in their relevance to the principal therapeutic actions of the drug, the stability of the measure in terms of response to placebo or changes caused by practice or adaptation, the objective or subjective nature of the quantitative assessment, and the comparability of results across different investigators and different laboratories (Table 38.1). The extent to which the various pharmacodynamic measures provide unique information, as opposed to being overlapping or redundant, is not clearly established.

Pharmacokinetic and pharmacodynamic relationships initially are evaluated separately, and the relationship of effect versus concentration at corresponding times is examined graphically and mathematically. Effect measures are usually expressed as change scores: the net effect ( $E$ ) at post-dosage time  $t$  is calculated as the absolute effect at this time ( $E_t$ ) minus the predose baseline value ( $E_o$ ), that is,  $E = E_t - E_o$ . Several mathematical relationships between effect and concentration ( $E$  versus  $C$ ), often termed “link” models, are of theoretical and practical importance (5,32). The “sigmoid  $E_{\max}$ ” model, incorporates a value of  $E_{\max}$ , the maximum pharmacodynamic effect, and  $EC_{50}$  is the “50% effective concentration,” the concentration that is associated with half of the maximum effect (Fig. 38.5). The exponent  $A$  reflects the “steepness” of the concentration-response relationship in its ascending portion. The biological importance of  $A$  is not established.

A concentration-effect relationship that is consistent with the sigmoid  $E_{\max}$  model may be of mechanistic importance, because drug-receptor interactions often fit the same model. The  $E_{\max}$  and  $EC_{50}$  values allow inferences about questions such as the relative potency or efficacy of drugs producing the same clinical effect, individual differences in drug sensitivity, the mechanism of action of pharmacologic potentiators or antagonists, and the possible clinical role of new medications.

The sigmoid  $E_{\max}$  model does not necessarily apply to all concentration-effect data (32). When experimental data are not consistent with the model, the corresponding misapplication of the sigmoid  $E_{\max}$  relationship can lead to misleading conclusions about  $E_{\max}$  and  $EC_{50}$ . Some data sets are consistent with less complex models, such as exponential or linear equations (Fig. 38.5); in these cases, the concepts of  $E_{\max}$  and  $EC_{50}$  are not applicable. Kinetic-dynamic modeling is further complicated when drug concentrations measured in serum or plasma do not reflect the concentration at the site of action, which is sometimes termed the “effect site.” This is illustrated by the data described below.



**FIGURE 38.4.** Schematic relation between pharmacokinetics, pharmacodynamics, and kinetic-dynamic modeling, based on the status of the variables of time ( $t$ ), concentration ( $C$ ), and effect ( $E$ ). Note that kinetic-dynamic modeling incorporates both pharmacokinetics and pharmacodynamics, with time subsumed into the relation of concentration and effect.



**TABLE 38.1. PHARMACODYNAMIC ENDPOINTS APPLICABLE TO STUDIES OF GABA-BENZODIAZEPINE AGONISTS**

| Classification<br>(with Examples)                                | Relation to Primary<br>Therapeutic Action     | Effect of<br>Placebo | Effect of<br>Adaptation/Practice | Need for "Blind"<br>Conditions | Approach to<br>Quantitation                            |
|------------------------------------------------------------------|-----------------------------------------------|----------------------|----------------------------------|--------------------------------|--------------------------------------------------------|
| Subjective<br>Global clinical ratings;<br>targeted rating scales | Close                                         | Yes                  | Yes                              | Yes                            | Transformation of<br>ratings into numbers              |
| Semi-objective<br>Psychomotor function<br>tests; memory tests    | May be linked to<br>adverse effect<br>profile | Yes                  | Yes                              | Yes                            | Test outcomes are<br>quantitative                      |
| Objective<br>Electroencephalography                              | Not established                               | No                   | No                               | No                             | Fully objective<br>computer-determined<br>quantitation |

GABA,  $\gamma$ -aminobutyric acid.

### Application: Kinetics And Dynamics Of Intravenous Lorazepam

In this study the benzodiazepine derivative lorazepam was administered intravenously according to a complex bolus-infusion scheme (33). On the morning of the study day, a rapid intravenous dose of lorazepam, 2 mg, was administered into an antecubital vein, coincident with the start of a zero-order infusion at a rate of 2  $\mu\text{g/kg/h}$ . The infusion continued for 4 hours and then was terminated. Venous blood samples were drawn from the arm contralateral to the site of the infusion prior to drug administration and at multiple time points during 24 hours after the start of lorazepam infusion. Samples were centrifuged, and the plasma separated and frozen until the time of assay. The

EEG was used as the principal pharmacodynamic outcome measure (Table 38.1). The EEG was recorded prior to lorazepam administration, and at times corresponding to blood samples. EEG data were digitized over the power spectrum from 4 to 30 cycles per second (Hz), and analyzed by fast Fourier transform to determine amplitude in the total spectrum (4 to 30 Hz) and in the beta (12 to 30 Hz) frequency range (33–35). Concentrations of lorazepam in plasma samples were determined by gas-chromatography with electron-capture detection.

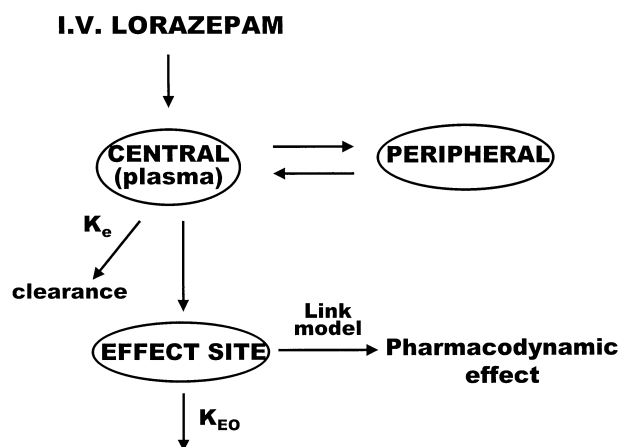
### Analysis of Data

The relative EEG beta amplitudes (beta divided by total, expressed as percent) in the predose recordings were used as the baseline. All values after lorazepam administration were expressed as the increment or decrement over the mean predose baseline value, with values averaged across eight recording sites. The EEG change values were subsequently used as pharmacodynamic effect ( $E$ ) measures in kinetic-dynamic modeling procedures described below. For pharmacokinetic modeling, the relation of plasma lorazepam concentration ( $C$ ) to time ( $t$ ) was assumed to be consistent with a two-compartment model (Figs. 38.6 and 38.7).

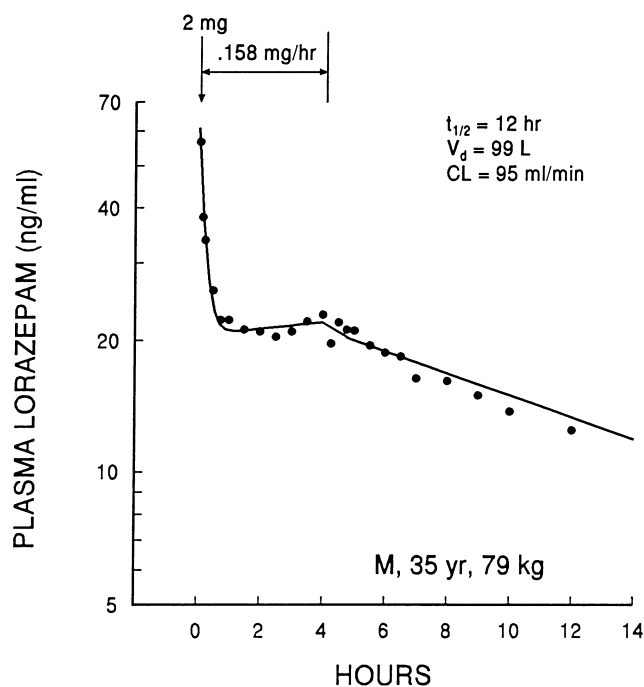
Examination of plots of pharmacodynamic EEG effect versus plasma lorazepam concentration ( $E$  vs.  $C$ ) indicated counterclockwise hysteresis (see below), suggesting a delay in equilibration of lorazepam between plasma and the site of pharmacodynamic action in brain. This equilibration effect has been described in previous clinical and experimental studies of lorazepam (34,36–39). Accordingly the relationship was modified to incorporate a distinct "effect site," at which the hypothetical lorazepam concentration is  $C_E$  (Fig. 38.6). The apparent rate constant for drug disappearance from the effect compartment is  $k_{EO}$ ; this rate constant determines the apparent half-life of drug equilibration between

$$\begin{aligned}
 &\textbf{Sigmoid } E_{\max} \\
 &E = \frac{E_{\max} \cdot C^A}{C^A + EC_{50}^A} \\
 &\textbf{Exponential} \\
 &E = m \cdot C^A \\
 &\textbf{Linear} \\
 &E = m \cdot C
 \end{aligned}$$

**FIGURE 38.5.** Three mathematical relationships between concentration ( $C$ ) and change in pharmacodynamic effect ( $E$ ) that are commonly applied in kinetic-dynamic modeling procedures. For the sigmoid  $E_{\max}$  model,  $E_{\max}$  is maximum pharmacodynamic effect,  $EC_{50}$  is the concentration producing a value of  $E$  equal to 50% of  $E_{\max}$ , and  $A$  is an exponent. For the exponential and linear models,  $m$  is a slope factor.



**FIGURE 38.6.** Schematic representation of the kinetic-dynamic model for the lorazepam study. Intravenous lorazepam was assumed to have kinetic behavior consistent with a two-compartment model: reversible distribution to a peripheral compartment, and first-order elimination (clearance) from the central compartment (rate constant:  $K_e$ ). Lorazepam in plasma was postulated to equilibrate with a hypothetical effect site, from which the exit rate constant is  $K_{EO}$ . Finally, effect-site concentrations were presumed to be the principal determinant of pharmacodynamic effect, via a kinetic-dynamic link model as shown in Fig. 38.5.



**FIGURE 38.7.** Plasma lorazepam concentrations (solid circles) together with the pharmacokinetic function determined by nonlinear regression (solid line), in a representative volunteer subject. Shown are the derived pharmacokinetic variables of elimination half-life ( $t_{1/2}$ ), volume of distribution ( $V_d$ ), and clearance (CL).

plasma and effect site. Under these assumptions, the relation of  $E$  to  $C_E$  was postulated to be consistent with a sigmoid  $E_{\max}$  model (Fig. 38.5).

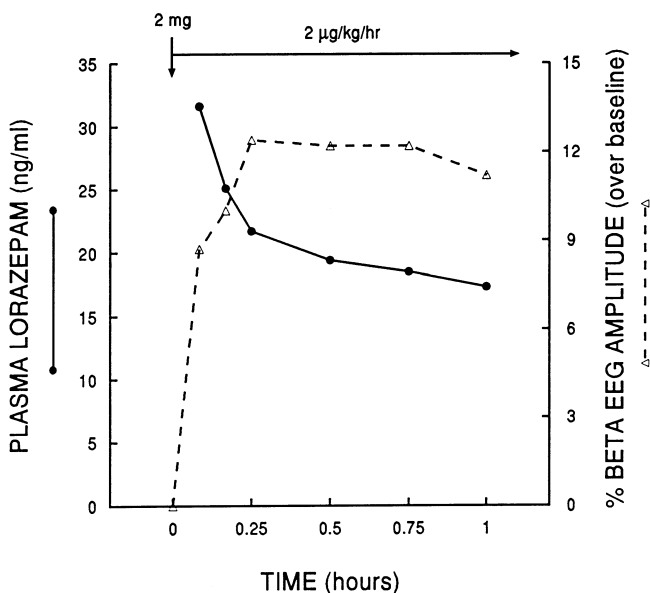
## Results

Kinetic variables for lorazepam were similar to those reported in previous single-dose studies of lorazepam pharmacokinetics (34,40–45). Overall mean values were volume of distribution, 1.7 L/kg; elimination half-life, 14 hours; clearance, 1.44 mL/min/kg. The bolus-infusion scheme rapidly produced mean plasma lorazepam concentrations in the range of 18 to 19 ng/mL, values close to the mean predicted value of 24 ng/mL.

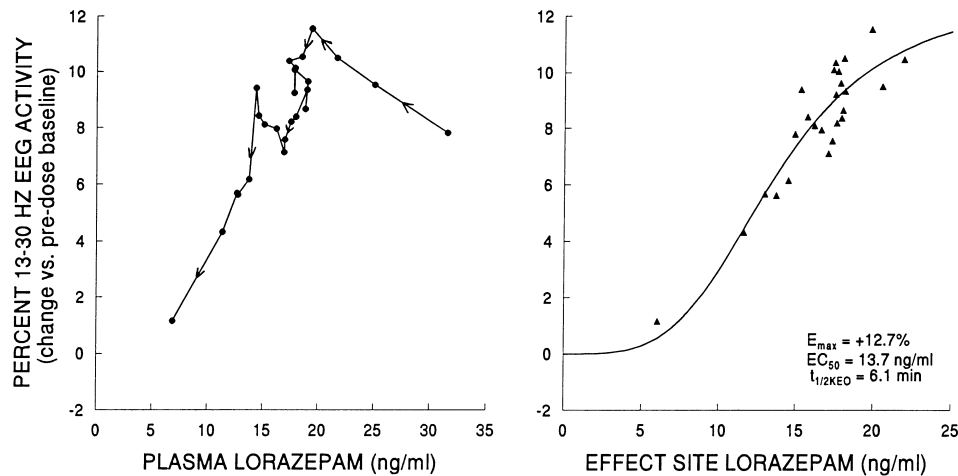
Lorazepam infusion produced significant increases in EEG beta amplitude throughout the 24-hour duration of the study. The maximum change over baseline was measured at 0.25 to 0.75 hours after the initiation of lorazepam dosage, whereas the maximum plasma concentration was measured immediately after the loading dose (Fig. 38.8). The effect-site model eliminated the hysteresis, with a mean equilibration half-life of 8.8 minutes (Fig. 38.9).

## Implications

Maximum EEG effects of lorazepam were significantly delayed following the initial intravenous bolus dose. Previous single-dose pharmacodynamic studies of lorazepam, using the EEG or other methods for quantitation of benzodiaze-



**FIGURE 38.8.** Mean values of plasma lorazepam concentration, and of EEG beta amplitude, during the first hour of the study. Note that pharmacodynamic EEG effects are delayed following the peak value of lorazepam in plasma.



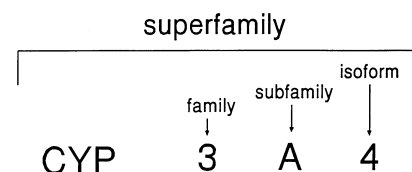
**FIGURE 38.9.** Left: Mean values of plasma lorazepam concentration versus pharmacodynamic EEG effect at corresponding times, with arrows indicating the direction of increasing time. As indicated in Fig. 38.8, the maximum EEG effect is delayed, and does not correspond in time to the maximum plasma concentration. Right: The scheme shown in Fig. 38.6 was applied to the data points, with the link model being the sigmoid  $E_{max}$  relationship shown in Fig. 38.5. The data points (closed triangles) are the hypothetical effect site concentrations and pharmacodynamic effect values at corresponding times. The solid line is the link model function determined by nonlinear regression, yielding the indicated values of  $E_{max}$  and  $EC_{50}$ . The overall mean equilibration half-life was 8.8 minutes.

pine effect, consistently demonstrate a delay in attainment of maximum drug effect compared to attainment of peak concentrations in plasma (34,36,37). After rapid intravenous dosage, for example, maximum effects may be delayed for an average of 30 minutes after dosage. Experimental studies of the time-course of whole-brain concentrations of lorazepam, or of the degree of benzodiazepine receptor occupancy, indicate that the delay is attributable to the slow physical entry of lorazepam into brain tissue, probably because of the relatively low lipid solubility of lorazepam (34, 38,39). The delay was mathematically consistent with a kinetic-dynamic model incorporating a hypothetical “effect site” distinct from the central compartment. The half-life for equilibration between plasma and the effect compartment was approximately 9 minutes. This matches clinical experience indicating that intravenous lorazepam cannot easily be used in situations requiring minute-to-minute titration of sedative or amnestic effects (40). Nonetheless, intravenous lorazepam can be used for the treatment of status epilepticus, although its onset of action may be somewhat slower than that of intravenous diazepam (46,47).

### CYTOCHROMES P-450 IN PSYCHOPHARMACOLOGY: THE IMPORTANCE OF P-450-3A ISOFORMS

The cytochrome P-450 (CYP) superfamily of drug metabolizing enzymes is now established as being of primary impor-

tance for the metabolism and clearance of most drugs used in psychopharmacology and in other areas of clinical therapeutics (6–9,48–55) (Fig. 38.10). For the CYP isoforms most relevant to human drug metabolism, each has its own distinct pattern of relative abundance, anatomic location, mechanism of regulation, substrate specificity, and susceptibility to inhibition and induction by other drugs or foreign chemicals (Table 38.2). The expression and *in vivo* function of at least two CYP isoforms (CYP2D6 and CYP2C19) are regulated by a genetic polymorphism, such that some members of a population fail to express “normal” levels of enzyme or expresses poorly functional protein (56–62). Individuals identified as “CYP2D6 poor metabolizers,” as an example, have very low clearance of drugs that are major substrates for biotransformation by CYP2D6 (such as desipramine, nortriptyline, venlafaxine, tramadol, and dextromethorphan). Such individuals are at risk for developing high and potentially toxic plasma concentrations of these



**FIGURE 38.10.** Nomenclature system for the cytochrome P-450 (CYP) superfamily of enzymes. Following the CYP designation, the number-letter-number sequence indicates the family, subfamily, and specific isoform.

**TABLE 38.2. OVERVIEW OF HUMAN CYTOCHROMES P-450**

| CYP Isoform | Relative Hepatic Abundance | Genetic Polymorphism | Representative Substrates                                      |
|-------------|----------------------------|----------------------|----------------------------------------------------------------|
| 1A2         | 13%                        | ?                    | Caffeine, theophylline, tacrine                                |
| 2B6         | <1%                        | —                    | Bupropion, propofol                                            |
| 2C9         | 15%                        | +                    | S-warfarin, phenytoin, tolbutamide, NSAIDs                     |
| 2C19        | 4%                         | +                    | S-mephenytoin, omeprazole (partial contributor to many others) |
| 2D6         | 2%                         | +                    | Some psychotropic and cardiac drugs                            |
| 2E1         | 7%                         | —                    | Chlorzoxazone, some inhaled anesthetics                        |
| 3A4/5       | 29% <sup>a</sup>           | —                    | Many (see also Table 38.3)                                     |

CYP, cytochrome P-450; NSAID, nonsteroidal antiinflammatory drug.

<sup>a</sup>Also present in gastrointestinal tract mucosa.

substrate drugs despite dosages in the usual therapeutic range.

### The CYP3A Isoforms

The overall importance of the CYP3A subfamily of drug-metabolizing enzymes, particularly in the field of psychopharmacology, has become increasingly evident over the last decade (6–9,63–69) (Table 38.3). The CYP3A isoforms are the most abundant of the CYPs, accounting on average for approximately 29% of identified cytochrome P-450 in liver (70) (Table 38.2). Within the CYP3A subfamily, CYP3A4 is the most important in the adult human, in terms of drug-metabolizing activity as well as quantitative dominance. CYP3A5, another CYP3A isoform, is also detected

in varying amounts in some human livers and in esophagus, but quantities of CYP3A5 are less than quantities of CYP3A4. It is not established to what extent hepatic CYP3A5 is of clinical significance for drug-metabolizing activity. CYP3A7 is principally a fetal-specific isoform. The location and sequence of the genetic element responsible for CYP3A4 expression have been identified, as well as a regulatory segment located on the 5' flanking region corresponding to the CYP3A gene.

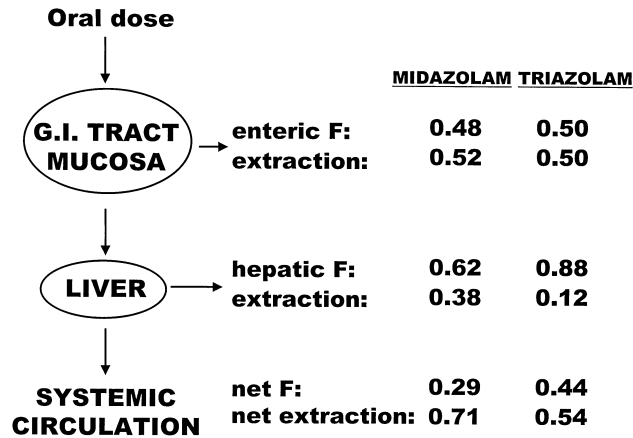
CYP3A4 typically functions as a high-capacity, low-affinity enzyme. Its high substrate capacity is a consequence of both the relatively high value of maximum reaction velocity ( $V_{\max}$ , expressed in nanomoles of product produced per unit time per milligram of protein) in a Michaelis-Menten relationship, as well as the high quantitative abundance of the protein in hepatic tissue. The low-affinity characteristic is reflected in the high  $K_m$  value (substrate concentration corresponding to 50% of  $V_{\max}$ ) in a Michaelis-Menten relationship. One consequence is that CYP3A-mediated metabolism usually is not "saturable" at substrate concentrations within the therapeutic range, because this range is likely to be far below the reaction  $K_m$ . Furthermore, in situations in which CYP3A is one of several cytochromes contributing to metabolism [e.g., amitriptyline *N*-demethylation (71), citalopram *N*-demethylation (72), or zolpidem hydroxylation (73)], the relative importance of CYP3A will increase at higher substrate concentrations. However, this is not invariably true. Nefazodone is a CYP3A substrate, but  $K_m$  values for production of the various metabolites are relatively low (74), and kinetics are nonlinear (75). Midazolam has a low  $K_m$  for the principal pathway (76,77), and there is evidence of nonlinear kinetics at higher concentrations in humans (78).

Significant quantities of CYP3A exist in gastrointestinal (GI) tract mucosa (65,69,79). The quantitative expression/

**TABLE 38.3. PSYCHOTROPIC DRUG SUBSTRATES FOR HUMAN CYP3A**

| Contribution of CYP3A to Net Clearance |                   |               |
|----------------------------------------|-------------------|---------------|
| Complete or Nearly Complete            | Partial           | Small         |
| Midazolam                              | Diazepam          | Fluoxetine    |
| Triazolam                              | Desmethyldiazepam | Sertraline    |
| Alprazolam                             | Flunitrazepam     | Nortriptyline |
| Bromazepam                             | Clonazepam        |               |
| Nefazodone                             | Zolpidem          |               |
| Trazodone                              | Citalopram        |               |
| Reboxetine                             | Haloperidol       |               |
| Buspirone                              | Clozapine         |               |
| Gepirone                               | Olanzapine        |               |
| Adinazolam                             | Mirtazapine       |               |
| Quetiapine                             | Amitriptyline     |               |
| Sildenafil                             | Imipramine        |               |





**FIGURE 38.11.** Relative contributions of CYP3A enzymes present in gastrointestinal (GI) tract mucosa, and in the liver, to net bioavailability ( $F$ ) of orally administered midazolam and triazolam. Both of these compounds have net  $F$  values of less than 50% (29% for midazolam, 44% for triazolam). Both compounds undergo approximately 50% extraction during passage through the G.I. tract mucosa. However midazolam undergoes another 38% extraction across the liver, compared to only 12% for triazolam.

activity of GI tract CYP3A is not correlated with its expression/activity in liver, even though the expressed protein is identical at the two sites. For a number of moderate or high-clearance CYP3A substrates (e.g., midazolam and triazolam), GI tract metabolism contributes importantly to pre-systemic extraction (first-pass metabolism) after oral dosage (79–81); incomplete oral bioavailability therefore results from a combination of GI tract and hepatic presystemic extraction (Fig. 38.11). For low-clearance CYP3A substrates having oral bioavailability in the range of 80% to 90% or greater (e.g., alprazolam), the contribution of the GI tract is apparently small.

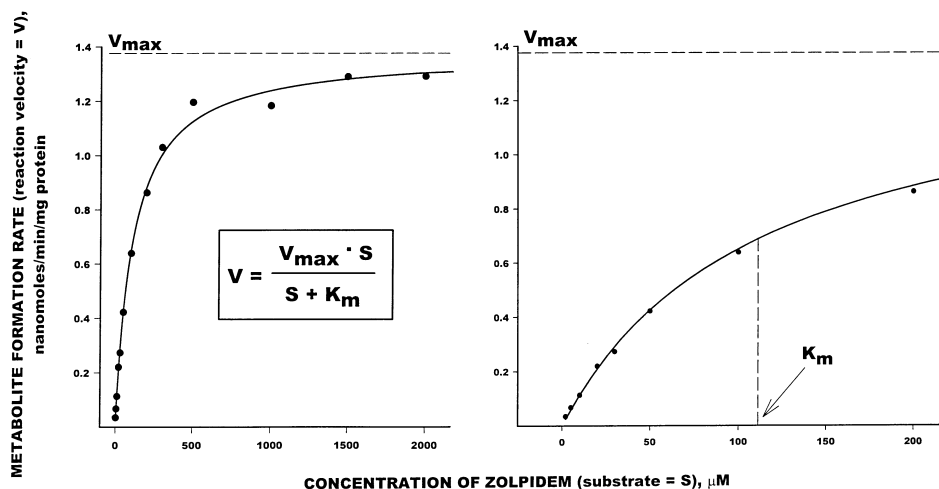
Inhibition and induction by other drugs or chemicals may modify CYP3A activity both *in vitro* and *in vivo* (Table 38.4). Identification of these compounds is of clear clinical importance, because it may allow anticipating of drug interactions that may be either potentially hazardous or of therapeutic benefit (6–9,65,69,79–85). Inhibiting drugs may also be used for investigating the relative contribution of CYP3A to net clearance, or for distinguishing the contribution of hepatic and GI tract CYP3A to overall presystemic extraction (81). Among the most potent CYP3A inhibitors are the azole antifungal agents (ketoconazole, itraconazole, fluconazole), the antidepressants nefazodone and fluvoxamine, and the calcium channel antagonists verapamil and diltiazem. These compounds produce “reversible” inhibition, by a competitive, noncompetitive, or mixed mechanism. Other potent inhibitors, such as the macrolide antimicrobials erythromycin and clarithromycin produce “mechanism-based” inhibition via a metabolic intermediate that complexes with and inactivates the CYP3A enzyme (86, 87). The HIV protease inhibitor ritonavir and the nonnu-

**TABLE 38.4. REPRESENTATIVE DRUGS HAVING CLINICALLY IMPORTANT EFFECTS ON THE HUMAN CYP ENZYMES**

| Drug                                                  | Inhibition of:   | Induction of: |
|-------------------------------------------------------|------------------|---------------|
| <b>Azole antifungals</b>                              |                  |               |
| Ketoconazole                                          | CYP3A            |               |
| Itraconazole                                          | CYP3A            |               |
| Fluconazole                                           | CYP3A, 2C9       |               |
| Terbinafine                                           | CYP2D6           |               |
| <b>Antidepressants</b>                                |                  |               |
| Fluoxetine                                            | CYP2D6           |               |
| Paroxetine                                            | CYP2D6           |               |
| Fluvoxamine                                           | CYP1A2, 2C19, 3A |               |
| Nefazodone                                            | CYP3A            |               |
| St. John's wort                                       |                  | CYP3A         |
| <b>Antipsychotics</b>                                 |                  |               |
| Perphenazine                                          | CYP2D6           |               |
| <b>Anticonvulsants</b>                                |                  |               |
| Carbamazepine                                         |                  | CYP3A         |
| <b>Antithrombotics</b>                                |                  |               |
| Ticlopidine                                           | CYP2D6, 2C19     |               |
| <b>Anti-infectives</b>                                |                  |               |
| Erythromycin                                          | CYP3A            |               |
| Clarithromycin                                        | CYP3A            |               |
| Ciprofloxacin                                         | CYP1A2           |               |
| Rifampin                                              |                  | CYP3A         |
| <b>Viral protease inhibitors</b>                      |                  |               |
| Ritonavir                                             | CYP3A            | CYP3A         |
| <b>Nonnucleoside reverse transcriptase inhibitors</b> |                  |               |
| Delavirdine                                           | CYP3A            |               |
| Nevirapine                                            |                  | CYP3A         |
| <b>Cardiovascular agents</b>                          |                  |               |
| Quinidine                                             | CYP2D6           |               |
| Diltiazem                                             | CYP3A            |               |
| Verapamil                                             | CYP3A            |               |
| <b>Antiulcer agents</b>                               |                  |               |
| Cimetidine                                            | CYP3A            |               |
| Omeprazole                                            | CYP2C19          |               |

cleoside reverse transcriptase inhibitor delavirdine also are potent CYP3A inhibitors (88–91). A component of grapefruit juice inhibits CYP3A in the GI tract (92). Inducers of CYP3A include carbamazepine, rifampin, phenobarbital, nevirapine, dexamethasone, St. John's wort, and possibly venlafaxine. Ritonavir is an inducer as well as an inhibitor, yielding a net effect on CYP3A metabolism that is difficult to predict (88–91,93–95).

Variability among individuals in CYP3A activity is substantial, even when relatively homogeneous groups of healthy subjects are studied. A consistent finding in population studies of CYP3A activity is that distributions are unimodal, without evidence of genetic polymorphic regulation (96,97). However, several studies of CYP3A substrates have demonstrated a small number of individuals with unusually low clearance (96,98). The explanation for these observations is unclear, but the genomic determinants of such individual variations in clinical CYP3A activity have become



**FIGURE 38.12.** Example of an *in vitro* metabolism study using human liver microsomes (73). The substrate in this study was zolpidem, of which varying concentrations were incubated with liver microsomes and appropriate reaction cofactors. At each concentration of zolpidem, the rate of formation ( $V$ ) of the principal metabolite of zolpidem (termed the M-3 metabolite) was determined. The relation between substrate concentration ( $S$ ) and reaction velocity ( $V$ ) was analyzed by nonlinear regression to determine the maximum reaction velocity ( $V_{max}$ ) and the substrate concentration ( $K_m$ ) producing a reaction velocity of 50% of  $V_{max}$ . **Left:** A substrate concentration range up to 2,000  $\mu\text{M}$ . **Right:** The lower range of concentrations shown on an expanded scale.

an active research topic. A number of genetic variants or single nucleotide polymorphisms in either the promoter or coding regions of the human CYP3A4 gene have recently been described (99–105). One of the promoter region polymorphisms, designated as CYP3A4\*1B, is more prevalent in the African-American as opposed to the Caucasian populations. However, there is no evidence to indicate that any of the identified CYP3A4 variants accounts for individual variation in clearance of CYP3A substrates.

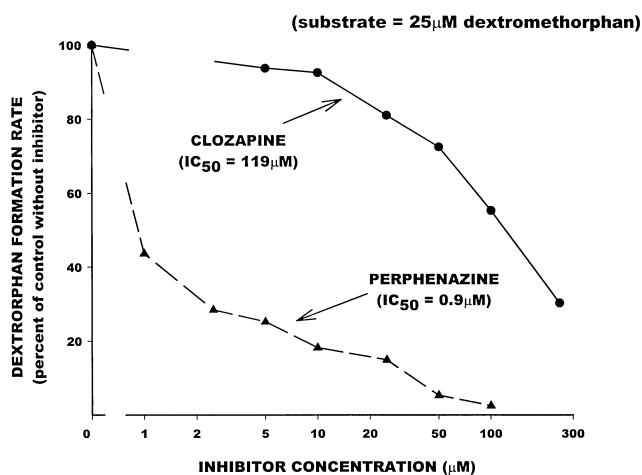
### In Vitro Models of Drug Metabolism

*In vitro* systems now are extensively utilized to provide presumptive answers to fundamental clinical questions regarding drug metabolism and drug interactions, and to guide the planning of clinical pharmacokinetic studies (6–9,48–55, 71–74,82–84). If drug X is biotransformed in humans to metabolite Y, two core questions occur: (a) What CYP isoform or isoforms mediate the biotransformation of X to Y? (b) What CYP isoforms do X or Y themselves either induce or inhibit?

Human liver microsomes generally are an important component of currently utilized *in vitro* systems. These preparations contain the various human CYPs in proportion to their abundance in human liver *in vivo*. If biotransformation of a specific substrate to its initial metabolite or metabolites can be replicated in microsomal preparations (Fig. 38.12), inhibition of that reaction by a relatively specific chemical inhibitor can be used as evidence supporting the contribution of the corresponding cytochrome. Chemical

inhibitors can also be used in clinical studies, but the *in vitro* model has the advantages of lower cost, more rapid implementation, no risk of human drug exposure, the availability of a greater number of potential chemical inhibitors for research purposes, and the possibility of determining both the quantitative and qualitative contributions of specific cytochromes. Antibodies with relatively specific inhibitory activity against individual human cytochromes can also be used to support or confirm data from *in vitro* chemical inhibition studies (106,107). *In vitro* approaches have been strengthened with the availability of microsomes containing pure human cytochromes as expressed by cDNA-transfected human lymphoblastoid cells (108–110). These heterologously expressed pure cytochromes further support definitive identification of cytochromes mediating a specific reaction *in vivo*.

The quantitative inhibitory potency of a series of drugs and their metabolites against specific index reactions can also be determined using human liver microsomes *in vitro* (6,7). The first of two general approaches uses fixed concentrations of the index substrate co-incubated with varying concentrations of the inhibitor in question. The relation of decrement in metabolite formation rate to inhibitor concentration is used to estimate a 50% inhibitory concentration ( $IC_{50}$ ). This procedure is expeditious and relatively inexpensive, and the numbers can be used to compare the potency of a series of inhibitors (Fig. 38.13).  $IC_{50}$  values themselves are not dependent on knowledge of the specific biochemical mechanism of inhibition. However,  $IC_{50}$  values depend on substrate concentration when inhibition is competitive, and



**FIGURE 38.13.** Example of an *in vitro* study of inhibition of CYP2D6 by two antipsychotic agents, perphenazine and clozapine. A fixed concentration of the substrate dextromethorphan was incubated with liver microsomes, appropriate cofactors, and varying concentrations of perphenazine or clozapine. Rates of formation of dextromethorphan (mediated by CYP2D6) with inhibitor present were expressed as a ratio versus the control velocity with no inhibitor. The relation of the velocity ratio to inhibitor concentration can be used to calculate a 50% inhibitory concentration ( $IC_{50}$ ). The results indicate that perphenazine ( $IC_{50} = 0.9 \mu M$ ) is likely to be a clinically important inhibitor of CYP2D6, whereas clozapine ( $IC_{50} = 119 \mu M$ ) is a weak inhibitor.

can be applied to *in vitro*–*in vivo* scaling only when the mechanism of inhibition is noncompetitive (111,112). Inhibitory potency can also be estimated by determining the inhibition constant ( $K_i$ ), a number that reflects inhibitory activity in reciprocal fashion. Estimation of  $K_i$  requires the study of multiple substrate concentrations and multiple inhibitor concentrations and therefore involves more work, time, and expense. The numerical value of  $K_i$  depends on the specific biochemical mechanism of inhibition, which may be unknown. Nonetheless, the inhibitor  $K_i$  is independent of substrate concentration and can be used under some defined circumstances for quantitative *in vitro*–*in vivo* scaling of drug interactions. In general,  $K_i$  is always less than or equal to  $IC_{50}$ ;  $K_i$  will be essentially equal to  $IC_{50}$  if inhibition is noncompetitive, or if inhibition is competitive and the substrate concentration is far below the reaction  $K_m$ . Both  $K_i$  and  $IC_{50}$  should provide similar or identical rank-order estimates of relative inhibitory potency for a series of inhibitors of a specific reaction. When the inhibition is purely competitive,  $K_i$  values for a specific inhibitor should theoretically be identical across different substrates metabolized by that particular CYP. However, this principle is not supported by experimental data, probably because of *in vitro* experimental artifacts, and because actual biochemical mechanisms of inhibition are not purely competitive. Therefore, absolute values of  $K_i$  or  $IC_{50}$  cannot be assumed to cross different substrates for the same cytochrome, al-

though the relative rank order of inhibitory potency should be maintained.

Limitations and drawbacks of *in vitro* systems should be recognized. *In vitro* studies generally utilize substrate concentrations that are one or more orders of magnitude higher than those encountered clinically, even if extensive partitioning of lipophilic drugs from plasma into liver tissue is accounted for. If mathematical models and parameter estimates are valid, the outcome of studies of higher concentrations can be extrapolated down to clinically relevant substrate concentrations. However, a clinically important “high-affinity” metabolic reaction (i.e., one with a low  $K_m$  value) could be missed if low substrate concentrations cannot be accurately measured due to limitations of assay sensitivity. The specificity of chemical inhibitor probes is of concern for *in vitro* and *in vivo* studies, because all inhibitors ultimately become nonspecific at higher concentrations. Finally, data from cDNA-expressed human cytochromes can be misinterpreted unless they are considered in the correct context. Pure cytochrome studies can yield quantitative data on the activity of one or more particular cytochromes as a mediator of a specific reaction. However, this information cannot be extrapolated to an estimate of the relative activity of different cytochromes, either *in vivo* or in liver microsomes *in vitro*, without a parallel estimate of the relative quantitative abundance of the cytochromes in question. That is, the importance of a specific cytochrome depends on both activity and abundance.

## DRUG INTERACTIONS IN PSYCHOPHARMACOLOGY

During the last two decades the general problem of pharmacokinetic drug interactions has received increased attention. New classes of medications introduced into clinical practice over this period include the selective serotonin reuptake inhibitor (SSRI) and related mixed mechanism antidepressants, the azole antifungal agents, newer macrolide antimicrobial agents, and the highly active antiretroviral therapies (HAARTs) used against HIV infection and AIDS (Table 38.4). These and other classes of medications have had a major beneficial impact on the therapy on some serious and life-threatening illnesses, but many of the drugs have the secondary pharmacologic property of inducing or inhibiting the human CYP enzymes, thereby raising concerns about pharmacokinetic drug interactions during multiple drug therapy.

One major objective of the drug development process is to generate data on drug interactions, so that treating physicians have the information necessary for safe clinical therapy involving multiple medications. However, the number of possible drug interactions is very large, and time and resources available for implementation of controlled clinical pharmacokinetic studies are inevitably limited.

Some needed studies will therefore be postponed until after a new drug is marketed, and some studies may be bypassed altogether. As discussed above, *in vitro* data are becoming increasingly important as a resource for identifying probable, possible, or unlikely drug interactions, and thereby encouraging rational planning and allocation of resources to more definitive clinical studies.

### Pharmacokinetic Versus Pharmacodynamic Drug Interactions

A pharmacokinetic interaction implies that the drug producing the interaction (the “perpetrator”) causes a change in the metabolic clearance of the drug being affected by the interaction (the “victim”), in turn either decreasing or increasing concentrations of the victim drug in plasma and presumably also at the site of action. This change may or may not alter the clinical activity of the victim drug. One pharmacokinetic interaction variant involves modification by the perpetrator of the victim drug’s access to its pharmacologic receptor site, without changing the systemic clearance or plasma levels of the victim. A familiar example is the antagonism of benzodiazepine agonist activity by flumazenil; a less familiar example is benzodiazepine receptor antagonism by ketoconazole (113).

A pharmacodynamic interaction involves either inhibition or enhancement of the clinical effects of the victim drug as a result of similar or identical end-organ actions. Examples are the increase or decrease of the sedative-hypnotic actions of benzodiazepines due to coadministration of ethanol or caffeine, respectively.

### Mechanisms of Inhibition Versus Induction of Metabolism

Drug interactions due to inhibition as opposed to induction of CYP-mediated metabolism involve mechanistically different processes. Chemical inhibition is an immediate phenomenon that becomes evident as soon as the inhibitor comes in contact with the enzyme, and is in principle reversible when the inhibitor is no longer present [an exception is “mechanism-based” inhibition (86)]. The magnitude of inhibition depends on the inhibitor concentration at the site of the enzyme in relation to the intrinsic potency of the inhibitor. *In vitro* systems can be used to develop quantitative estimates of inhibitory potency, such as the inhibition constant ( $K_i$ ) or the 50% inhibitory concentration ( $IC_{50}$ ) (Fig. 38.13). However, application of  $K_i$  or  $IC_{50}$  values from *in vitro* systems to quantitative predictions of drug interactions *in vivo* is not straightforward, and requires knowledge of the effective concentration of inhibitor that is available to the enzyme. A generally applicable scheme for relating total or unbound plasma concentrations of inhibitor to effective enzyme-available concentration has not been estab-

lished. In any case, the theoretical assumption that unbound plasma concentrations are equal to enzyme-available intrahepatic concentrations is incorrect in reality, and may yield underestimates of observed *in vivo* drug interactions by as much as an order of magnitude or more (8,83,85).

Induction of CYP-mediated metabolism requires prior exposure to a chemical inducer, which signals the synthetic mechanisms to upregulate the production of one or more CYP isoforms (114–118). This process takes time, and the increase in CYP activity is of slow onset following initiation of exposure to the inducer, and slowly reverts to baseline after the inducer is removed. Increased CYP expression/activity due to chemical induction therefore reflects prior but not necessarily current exposure to the inducer. The extent of CYP induction probably depends on the dosage (concentration) of the inducer and on the duration of exposure. Induction, unlike inhibition, is not easily studied *in vitro*, because induction requires intact cellular protein synthesis mechanisms as are available in cell culture models.

Inducers and inhibitors of CYP3A can be expected to influence both hepatic and gastrointestinal CYP3A, although not necessarily to the same extent. Very strong inhibitors (such as ketoconazole) or very strong inducers (such as rifampin) will produce substantial changes in both hepatic and gastrointestinal CYP3A. A uniquely complex situation arises for ritonavir, which is both an inhibitor and inducer of CYP3A. Interactions of ritonavir with CYP3A substrate drugs will be time dependent. Initial exposure will produce CYP3A inhibition, but as the duration of exposure proceeds, CYP3A induction may offset the inhibitory effects of acute exposure. The net outcome typically is unpredictable and variable across individuals (93–95).

### Perspectives on the Clinical Importance of Drug Interactions

Based on the prevalence of polypharmacy in clinical practice, noninteractions of drugs are far more common than interactions. Coadministration of two drugs usually produces no detectable pharmacokinetic or pharmacodynamic interaction, and the pharmacokinetic disposition and clinical activity of each drug proceed independently of each other. A less common outcome of drug coadministration is a kinetic interaction that could be detected in controlled laboratory circumstances, but that is not clinically important in usual therapeutic circumstances because (a) the interaction, whether or not statistically significant, is not large enough to produce a clinically important change in dynamics of the victim drug; (b) the therapeutic index of the victim drug is large enough so that even a substantial change in plasma levels will not alter therapeutic effects or toxicity; or (c) kinetics and response to the victim drug are so variable that changes in plasma levels due to the drug interaction are far less important than inherent variability. Even less common are clinically important interactions that require



modification in dosage of the perpetrator, the victim, or both. Finally, the most unusual consequence of a drug interaction is a hazardous and contraindicated combination, as in the case of ketoconazole and terfenadine. These situations are rare, but unfortunately receive excessive attention in the public media.

Many secondary sources and compendia are available as summary guides to the extensive literature on drug interactions, but these sources do not necessarily assist clinicians in deciding which interactions should generate serious concern in the course of drug therapy. A useful general guideline is that drug interactions are more likely to be important when (a) the perpetrator drug is a powerful inducer or inhibitor, and produces a very large change in the kinetics and plasma levels of the victim drug; or (b) the therapeutic index of the victim is narrow. Case (a) is exemplified by powerful inducers or inhibitors of CYP3A (ketoconazole, ritonavir, rifampin) coadministered with CYP3A substrates, or powerful inhibitors of CYP2D6 (quinidine, fluoxetine, paroxetine) coadministered with CYP2D6 substrates. Case (b) is exemplified by victim drugs such as phenytoin, warfarin, and digoxin, for which small changes in plasma levels could have important clinical consequences.

### Application of Kinetic-Dynamic Methods to Study Drug Interactions

Drug interaction study protocols often incorporate pharmacodynamic endpoints to allow estimating the clinical consequences of drug interactions along with the usual pharmacokinetic outcome measures. The level of complexity of an integrated kinetic-dynamic study depends on the nature of the pharmacodynamic actions of the drug under study as well as the type of pharmacodynamic outcome measures that are required. A number of methodologic principles and dilemmas are illustrated by kinetic-dynamic design options for drug interaction studies involving sedative-hypnotic and anxiolytic drugs acting on the  $\gamma$ -aminobutyric acid (GABA)-benzodiazepine receptor system.

Biotransformation of the benzodiazepine triazolam is dependent on the activity of human CYP3A isoforms (119). Metabolism is strongly inhibited *in vitro* and *in vivo* by CYP3A inhibitors such as ketoconazole, itraconazole, ritonavir, and nefazodone (95,119–122). Some, but not all, of the macrolide antimicrobial agents also are CYP3A inhibitors via “mechanism-based” inhibition, in which the parent compound binds to the metabolically active site on the CYP3A enzyme, yielding a metabolic intermediate that inactivates the enzyme (86,87). We tested the inhibitory potency of four macrolide antimicrobial agents [troleandomycin (TAO), erythromycin, clarithromycin, azithromycin] versus triazolam hydroxylation using human liver microsomes *in vitro* (123). Appropriate mean  $IC_{50}$  values were TAO, 3.6  $\mu$ M; erythromycin, 30  $\mu$ M; and clarithromycin, 28  $\mu$ M. These values indicate that all three

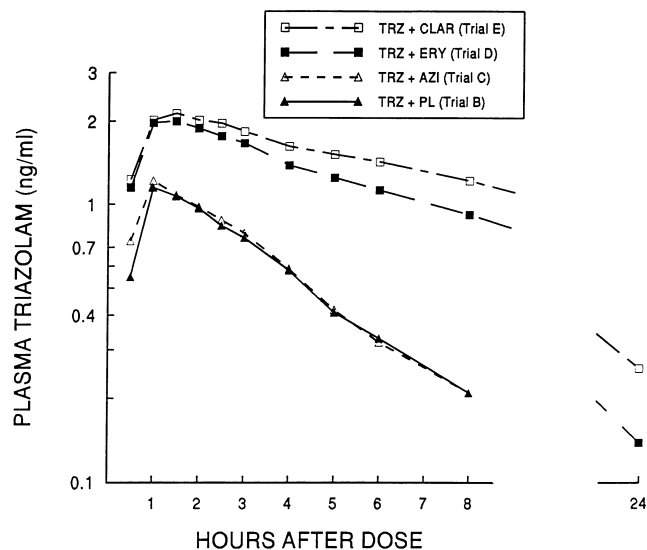
compounds produce substantial *in vitro* inhibition of triazolam hydroxylation and have the potential to produce a significant interaction with triazolam *in vivo*. However, azithromycin was a very weak inhibitor of triazolam *in vitro* ( $IC_{50} > 250 \mu$ M), and is anticipated to produce no significant interaction *in vivo*.

In a clinical pharmacokinetic-pharmacodynamic study (123), a series of healthy volunteers were exposed to the following treatment conditions:

- Triazolam placebo plus macrolide placebo
- Triazolam (0.125 mg) plus macrolide placebo
- Triazolam (0.125 mg) plus azithromycin
- Triazolam (0.125 mg) plus erythromycin
- Triazolam (0.125 mg) plus clarithromycin

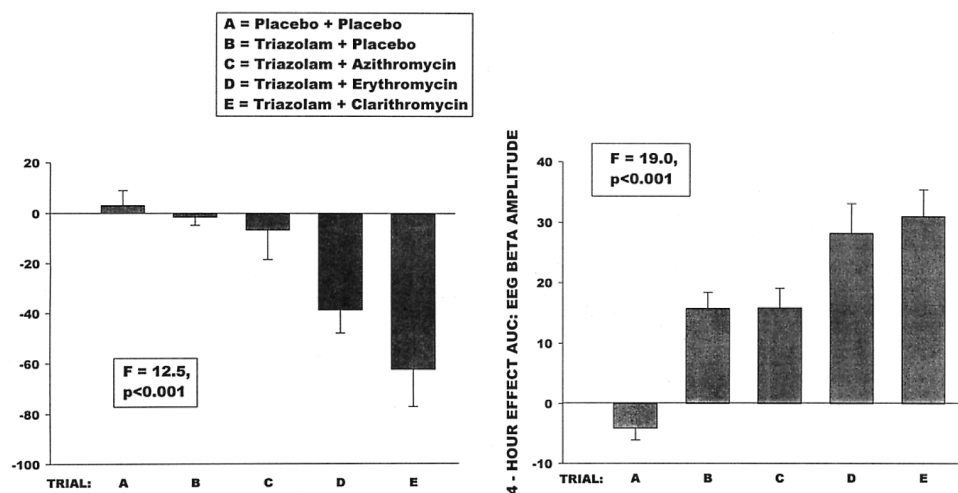
Dosage schedules of the coadministered macrolides were chosen to be consistent with usual dosage recommendations. The five trials were randomized in sequence, and the treatment conditions were double-blind.

Following each dose of triazolam (or placebo to match triazolam), multiple venous blood samples were drawn over a period of 24 hours, and multiple pharmacodynamic testing procedures were performed. Triazolam plasma concentrations were determined by gas chromatography with electron capture detection (Fig. 38.14).



**FIGURE 38.14.** Mean plasma triazolam concentrations following single 0.125-mg doses of triazolam during trials B, C, D, and E. Note that coadministration of triazolam with azithromycin (AZI, trial C) produced plasma levels nearly identical to triazolam administered with placebo (PL, trial B). However, coadministration with erythromycin (ERY, trial D) or clarithromycin (CLAR, trial E) produced a large increase in plasma triazolam concentrations. (Adapted in part from Greenblatt DJ, von Moltke LL, Harmatz JS, et al. Inhibition of triazolam clearance by macrolide antimicrobial agents: *in vitro* correlates and dynamic consequences. Clin Pharmacol Ther 1998;64:278–285, with permission.)





**FIGURE 38.15.** Mean ( $\pm$  standard error, SE) 4-hour pharmacodynamic effect areas for the digit-symbol substitution test (DSST) score (left), and for the EEG beta amplitude (right), during the five trials. Note that decrements in DSST score, and increases in EEG beta amplitude, were very similar between trials B and C, whereas effects were significantly enhanced during trials D and E.

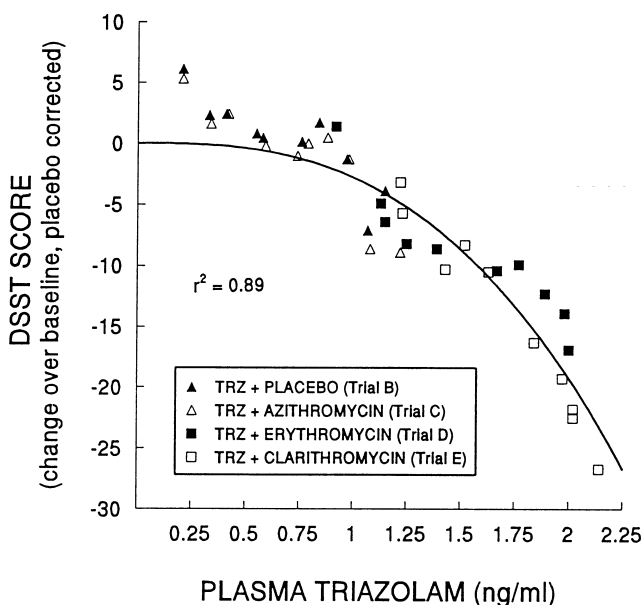
Mean clearance of triazolam during trials B and C was nearly identical (413 and 416 mL/min, respectively); that is, coadministration of azithromycin had no effect on the pharmacokinetics of triazolam (Fig. 38.14). However, triazolam clearance was significantly reduced to 146 mL/min by erythromycin (trial D), and to 95 mL/min by clarithromycin (trial E) (Fig. 38.14). Thus the *in vivo* kinetic results are highly consistent with the *in vitro* data.

The pharmacodynamic data indicated that the benzodiazepine agonist effects of triazolam plus placebo (trial B), and of triazolam plus azithromycin (trial C) were similar to each other, and greater than the effects of placebo plus placebo (trial A). However, coadministration of triazolam with erythromycin (trial D) or with clarithromycin (trial E) augmented the pharmacodynamic effects of triazolam when compared to trials B or C. The outcome was similar whether based on subjective measures, a semi-objective measure (the Digit-Symbol Substitution Test, DSST), or the fully objective measure (the EEG) (Fig. 38.15). Kinetic-dynamic modeling indicated that the increase in benzodiazepine agonist effects of triazolam caused by coadministration of erythromycin or clarithromycin was fully consistent with the increase in triazolam plasma concentrations (Fig. 38.16).

## COMMENT

Pharmacokinetic drug interactions in clinical psychopharmacology are assuming increasing importance as polypharmacy becomes more common, and more drugs with enzyme-inducing or -inhibiting properties are introduced into clinical practice. Contemporary approaches to the basic and clinical investigation of drug interactions and their pharmacodynamic consequences are illustrated in this chapter. It is evident that technologic and conceptual advances in phar-

macokinetics, pharmacodynamics, and drug metabolism may be usefully applied to the evaluation of drug interactions. An ideal approach would incorporate the collaborative participation of individuals representing expertise in molecular pharmacology, cytochrome biochemistry, *in vitro* metabolism, clinical pharmacokinetics-pharmacodynamics, and clinical therapeutics.



**FIGURE 38.16.** Relation of mean plasma triazolam concentrations to mean changes over baseline in DSST score at the corresponding times. The solid line represents the kinetic-dynamic model relationship based on an exponential function as shown in Fig. 38.5. (From Greenblatt DJ, von Moltke LL, Harmatz JS, et al. Inhibition of triazolam clearance by macrolide antimicrobial agents: *in vitro* correlates and dynamic consequences. Clin Pharmacol Ther 1998;64:278–285, with permission.)

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