Pharmacokinetic Factors Affecting Antidepressant Drug Clearance and Clinical Effect: Evaluation of Doxepin and Imipramine—New Data and Review

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The selection of a starting dose for an antidepressant, and subsequent clinical titration to an appropriate therapeutic dosage, should be based on pharmacokinetic and pharmacodynamic principles. In the past decade, therapeutic monitoring of antidepressant drugs and use of pharmacokinetic principles have been shown to be an improvement over the dose–response approach. Endogenous (e.g., genetic metabolic phenotype, hepatic blood flow, and protein binding) and exogenous factors (e.g., smoking, dietary habits, concurrent medications) are capable of influencing physiological and pharmacokinetic variables in patients, accounting for the marked interindividual differences in the clearance rates of cyclic antidepressants. Interpatient variability for steady-state concentrations in plasma (Cpss) >20-fold are observed at a fixed dose of imipramine (r² = 0.525, df = 346, t = 19.541, P < 0.0001) or doxepin (r² = 0.506, df = 128, t = 11.403, P < 0.0001). Analysis of doxepin in plasma vs estimated in oral clearance for 61 patients demonstrates a significant decline in oral clearance as a function of Cpss. At doses approaching the upper range recommended for the treatment of depression, Cpss appear to approach, in at least a few individuals, the maximum metabolic capacity of the patient (Vmax), leading to greater-than-expected increases in concentrations for a given dosage increment. Significant alterations in oral clearance are observed when medications are administered concomitantly. A greater-than-threefold difference in mean oral doxepin clearance rates is observed between two groups of patients receiving additional medications that are either inducers or inhibitors (P < 0.0001, df = 32, t = 6.687).

Pharmacokinetic principles defining and explaining the determinants of oral clearance can provide the clinician with a greater insight into the reasons for therapeutic failure and toxicity.

Antidepressants may be classified based on either structural or neurochemical profile. Structurally, they include monoamine oxidase inhibitors, tricyclic antidepressants (TCAs), and "second-generation" antidepressants. 5 Antidepressants, except for the monoamine oxidase inhibitors, can collectively be classified as the cyclic antidepressants. The efficacy of these cyclic antidepressants in the treatment of depression is well established. A review of 88 controlled studies on amitriptyline, desipramine, doxepin, imipramine, and protriptyline showed marked superiority of TCAs over placebo therapy in 57 (65%) of these trials (1). Generally, between 50% and 80% of patients treated with cyclic antidepressants recover, with the average efficacy reported to be 70% (2). Approximately 25% to 33% of empirically treated patients do not respond adequately to TCAs, necessitating a systematic approach designed to optimize benefit while reducing the risks of therapy.

The clinician must first decide whether drug therapy is appropriate on the basis of various environmental and psychosocial factors, as well as on the type of depression. Concomitant medical diseases and medications should also influence the treatment decision-making process. Figure 1 outlines a therapeutic flow chart for treatment of patients with depression. The selection of a starting dose, and subsequent clinical titration to an appropriate therapeutic dosage, should be based upon pharmacokinetic and pharmacodynamic principles. In the past decade, therapeutic moni-

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5 Nonstandard abbreviations: TCA, tricyclic antidepressant; TDM, therapeutic drug monitoring; DOX, doxepin; IMI, imipramine; DMI, desipramine; AMI, amitriptyline; NT, nortriptyline; NS, not (statistically) significant. Other (pharmacokinetic) abbreviations, more or less widely accepted, are found in Table 2, and abbreviations used in equations are explained in the text following.

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Fig. 1. Pharmacokinetic approach to the treatment of depression
This flow chart facilitates consideration of various pharmacokinetic variables that can confound evaluations of drug CP vs response. The process for TDM is described in the context of Cpss interpretation guidelines.
toring of antidepressant drugs and use of pharmacokinetic principles have been shown to be an improvement over the dose–response approach (3).

Numerous studies have illustrated the weak correlation between the administered dose of a cyclic antidepressant and the resulting concentrations in plasma, and the considerable interindividual variability (4). Endogenous (e.g., metabolic phenotype, hepatic blood flow, and protein binding) and exogenous factors (e.g., smoking, dietary habits, concurrent medications) are capable of influencing physiological and pharmacokinetic factors in patients, accounting for the marked differences in the clearance of cyclic antidepressants (5–9). As a result of the interaction of the above processes, it becomes apparent that the relationship between dose and the concentration in plasma (CP) can be quite dynamic and unpredictable, leading to extremely large interindividual differences in steady-state drug concentrations in plasma (Cpss). The application of pharmacokinetics to dosage selection can significantly increase the likelihood of a successful treatment outcome, because concentration vs response relationships for many of the TCAs have been documented (10).

Materials and Methods

This review of the literature on the pharmacokinetics of cyclic antidepressants is supplemented by original data obtained from the Texas Department of Mental Health and Mental Retardation Therapeutic Drug Monitoring (TDM) program. The results presented from the TDM program were obtained by compiling patient information from the established data base. The information analyzed was obtained prospectively from facilities throughout the state, with use of standardized procedures for plasma sample handling and data collection. All patients who had TDM ordered by their physicians are included in our data base. All patient data are coded, to protect confidentiality. The results of our initial analyses of the doxepin (DOX) and imipramine (IMI) TDM program in 212 patients are reported (see Table 1). The College of Pharmacy at The University of Texas, the Departments of Pharmacology and Psychiatry at the University of Texas Health Science Center, San Antonio, and The University of Texas Mental Sciences Institute provided data analyses and assay support. Clinical pharmacy and psychopharmacology consultation programs, co-sponsored by The University of Texas, are established at two state hospitals and one county facility affiliated with The University of Texas. Uniform procedures for TDM were developed and implemented in consultation with The University of Texas. Standardization procedures for venipuncture and sample handling include: plasma is sampled 10–12 h after a dose, but before the patient's next dose; samples are obtained after a minimum of one week at the same dose, ensuring steady-state determinations; venipuncture is performed in the facility's clinical laboratory, with use of a vacuum container system (Venoject KT200LH) proven not to contain interfering plasticizers in the rubber stopper; samples are rapidly centrifuged and the plasma is stored in Teflon-capped glass tubes; plasma is stored at room temperature but protected from light; and samples are shipped by mail and analyzed within two to three days of collection. The standard data-collection form, required to be completed before assay, contains the following information: patient demographics (age, gender, weight, race, smoking history); medical and psychiatric diagnoses based on the Diagnostic and Statistical Manual, 3rd edition, revised; complete medication history for at least the past week, including dosing history for the agent to be assayed and all concomitant medications; and the Clinical Global Impressions Rating Scale. Outpatient data, primarily from the one county facility, are included in the data set, but >80% of all concentrations are measured in inpatients, who are receiving their medications from the facility's nursing service. Data are stored in a microcomputer data base and are available for downloading.

The TCAs are analyzed by a validated "high-performance" thin-layer chromatographic method developed by The University of Texas Mental Sciences Institute (11). Sensitivities by this method are as low as 5 ng/mL (for desipramine). The standard curves used for routine analysis are linear from 5 to 200 ng/mL. Between-day coefficients of variation (CVs) are <6% from 25 ng/mL to 200 ng/mL. For in situ quantification of the developed chromatographic plates we used a Zeiss or a Shimadzu scanning densitometer. Measurements were made in the reflectance mode for ultraviolet absorption. A deuterium light source was used with a monochromator and set to the optimum wavelength for each TCA.

Figure 2 illustrates the mean of and standard deviation for Cpss of IMI plus desipramine (DMI) in 25 patients from whom two or more samples were obtained at the same dosage of IMI. These data illustrate the reproducibility of the assay under field-test conditions, because variability in the observed concentrations is the result of patient-specific variables (e.g., compliance, potential timing errors by nursing staff) as well as the variability inherent in the assay.

The data were analyzed with a Macintosh II® microcomputer with 68020 and 68881 processors, with use of StatView 512K plus®, and Microsoft Excel® spreadsheet. They were plotted by using MacDraw®, Cricket Graph®, and

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Fig. 2. Imipramine sampling/CP reliability: TDM/HMR TDM; sum IMI + DMI CP

The reproducibility of the TDM program for TCAs under actual field-test conditions is illustrated by the relatively small standard deviation of the mean for each pair or triplicate serial Cpss (at the same dosage of IMI) in 25 patients. The mean CV for these 25 patients is <12%.
SuperPaint®. Statistical analyses of data included: Pearson product moment correlation analysis for linear regression, polynomial regression, Student's unpaired two-tailed t-test for comparison of normally distributed variables, analysis of variance for evaluation of independent categorical variables, and natural log transformation of clearance data. The mean of two or more CPs at the same dose was used for data analysis, decreasing weighting artifacts. The following guidelines were used as the criteria for deleting data from the unedited data-base output before statistical analyses: (a) if one CP differed by more than 50% from the mean of two other concentrations at the same dose; (b) if for outpatient data two CPs at the same dose differed by more than 50% (presumed noncompliance); (c) if patients had unstable medical illnesses; (d) if toxicity secondary to overdose or medication error was documented; or (e) if one of two CPs at the same dose was not detectable (typically at the lower limits of the assay) but the other was quantified. The classification scheme used for drug interaction effects on clearance secondary to concomitant medications are summarized in the Drug Interactions section of this paper.

Results

Pharmacokinetic Overview of the Antidepressants

Although there is still some disagreement about the relationship between CP and therapeutic efficacy, at least in selected populations, a therapeutic concentration range can be defined (12). Furthermore, it has been demonstrated that a greater proportion of patients can be successfully treated if their drug doses are adjusted on the basis of their CPs (13). Recently, the American Psychiatric Association Task Force on Laboratory Tests concluded that CP measurements of IMI, DMI, and nortriptyline (NT) are unequivocally clinically useful in certain situations; that these measurements are helpful in many situations; and that the usefulness of CP measurements is likely to increase (14). For amitriptyline (AMI), various studies have demonstrated a linear, curvilinear, or no relationship between CP and outcome (14–16). In the few studies that evaluated the relationship between CPs for DOX plus desmethyldoxepin, and clinical response, a tentative linear therapeutic relationship is reported (17, 18). For the newer antidepressants—amoxapine, fluoxetine, maprotiline, and trazodone—there are insufficient data as yet to show whether or not there is a meaningful relationship between CPs and therapeutic outcome.

Consistent with reports in the literature, our TDM data for DOX and IMI have shown large variability for CPs on a standard dose of a given drug. Table 1 lists relevant demographic and descriptive information for all patients included in the IMI and DOX TDM data base. Figures 3 and 4 demonstrate the large interpatient variability on standard doses of DOX and IMI, respectively. These data include all patients examined, and do not control for drug interactions. A large proportion of patients have CPs that are known to be associated with either a poor therapeutic outcome or an increased incidence of side effects/toxicity. The modest correlation coefficients suggest that the dosage alone is a poor predictor of CP.

To decrease the potential confusion resulting from the widely varying conventions used for abbreviations and symbols in pharmacokinetics, standardized nomenclature has been proposed. Table 2 lists widely accepted terms used to characterize pharmacokinetic models of cyclic antidepressants (19).

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<th>Table 2. Commonly Used Pharmacokinetic Abbreviations</th>
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A review of pharmacokinetic parameters, with illustrations of their clinical application and significance, suggests that cyclic antidepressants have many similarities. The following discussions of absorption, first-pass effect, distribution, and hepatic clearance highlights the relevant similarities and differences between antidepressants.

Absorption

**Physicochemical:** Cyclic antidepressants are basic lipophilic amines whose absorption is believed to take place in the alkaline environment of the small intestine. There is little or no absorption across biological membranes at the acidic pH of the stomach, owing to ionization of the drug. Absorption has been shown to be almost complete for all cyclic antidepressants except maprotiline (20), as assessed from analytical recovery and measurement of all urinary metabolites.

**Absorption rate:** Absorption of TCAs such as IMI is relatively rapid, with the peak CP (Cp_max) within 2 to 8 h after a single oral dose (21, 22) or after multiple doses (23). The newer antidepressants show a greater diversity in their absorption characteristics than do the TCAs. For instance, maprotiline’s absorption is slow, with Cp_max occurring 8 h or more after a dose (24). Being a relatively strong base with a reported pKₐ of 10.5 (in water), maprotiline is almost completely protonated at physiological pH and therefore penetrates lipophilic barriers relatively slowly. Protriptyline also has a slower absorption profile, with a time to peak concentration (T_max) averaging 8.5 h, with range of 6 to 12 h (25).

**Bioavailability factor (F).** This is the fraction of the orally administered dose that reaches the systemic circulation. After absorption from the gastrointestinal tract, drugs must pass through the liver, along with the entire blood supply draining the upper gastrointestinal tract, where some of the drug is lost by metabolism before reaching the systemic (general) circulation. This is known as the “first-pass” effect. This first-pass metabolism or extraction accounts for most of the dose of TCA that is “lost” (26). This large first-pass effect accounts for the low systemic bioavailability (F = 0.2 to 0.7) of the TCAs, in spite of their complete absorption. Table 3 summarizes pharmacokinetic parameters for cyclic antidepressant agents, including the range of bioavailabilities reported for each drug. Protriptyline and maprotiline demonstrate higher bioavailability (F = 75%-90%), with an estimated metabolism on first pass through the liver of only 10% to 25% of the oral dose. On the other extreme, DOX seems to be least bioavailable, with F between 13% and 45% (27).

F can be described both in terms of the extraction ratio (E), the proportion of the blood flowing through the liver that is cleared of the drug, and in terms of the ratio of the area under the CP vs time curve (AUC) for oral and parenteral administration as illustrated by the following equation:

\[ F = 1 - E = \frac{AUC_{po}}{AUC_{iv}} \]  

(1)

The determinants of hepatic clearance also influence a drug’s bioavailability. A more scientific approach to drug dosage adjustment results from an understanding of these pharmacokinetic parameters. In general, drugs with E > 0.6 will have a low F, and vice versa. These high-hepatic extraction drugs have a large intrinsic hepatic clearance (CLint). CLint, defined in equation 2, is a measure of the maximal ability of the hepatocyte to irreversibly remove the drug from plasma without limitations from flow or protein binding:

\[ CL_{int} = \frac{V_{max}}{K_{m}} \]  

(2)

Vmax and Km are the maximum rate of metabolism and the Michaelis substrate-affinity constant for the enzyme, respectively.

Elimination of drugs from the body is usually described in terms of clearance (CL), which is defined as the volume of plasma cleared of drug per unit time. Because renal excretion of drug is negligible for TCAs, total CL is equal to hepatic CL (CLH). The determinants of CLH can be described as follows:

\[ CL_{H} = (Q \cdot f_{u} \cdot CL_{int}) + (f_{o} \cdot CL_{int}) = Q \cdot E \]  

(3)

Equation 3 indicates that the systemic CL of a drug that is eliminated solely by metabolism in the liver is a function of hepatic blood flow, Q, the fraction of the drug that is unbound in plasma, f_u, and the intrinsic ability of the liver to metabolize the drug. For drugs with a low E and hence a low CLint—e.g., barbiturates and anticonvulsants—Q is much greater than CLint, and it follows that equation 3 reduces to:

\[ CL_{H} = CL_{int} \]  

(4)

For these drugs, CLint is the principal determinant of systemic CL. It is not surprising, then, that certain diseases or concomitant drugs that inhibit or induce enzymes in the liver will affect the systemic CL of low-E drugs.

Alternatively, for drugs that have CLint values that significantly exceed hepatic blood flow—e.g., beta blockers, lidocaine, and protriptyline—clearance shows a strong dependence on Q. This can be demonstrated by considering an opposite limiting case for equation 3, where CLint is much greater than Q. Equation 3 can thus be approximated by:

\[ CL_{H} = Q \]  

(5)

Figure 5 illustrates the possible effect on the oral CL of TCAs of a concomitant disease, that alters hepatic blood flow and function. This case of a 57-year-old woman receiving IMI and who had moderate to severe congestive heart failure, subsequently digitalized with return of near-normal cardiac output, demonstrates an increase in her oral clearance rate from 0.5 L/min to 0.9 L/min.

In general, the systemic CL of drugs that show hepatic-blood-flow dependent elimination is affected by factors such as cardiac and hepatic diseases or concomitant medications that affect the cardiovascular system. The systemic CL of
these drugs depends less on factors that affect drug-metabolizing enzymes in the liver. However, the magnitude of the first-pass effect will be affected by the enzyme-metabolizing activity of the liver, even for drugs that show flow-dependent elimination. Therefore, a decrease in the drug’s F would result from the co-administration of an enzyme-inducing agent, resulting in a measured increase in oral CL (see Drug Interactions section).

Although cyclic antidepressants in general have intermediate E values, there are certain exceptions. Maprotiline and protriptyline both have an F between 0.75 and 0.90, hence they will have a low E (0.10–0.25). Theoretically, these drugs should be more susceptible to changes in systemic CL, owing to enzyme induction or inhibition, and less likely to demonstrate CL changes caused by hepatic blood-flow alterations. Most cyclic antidepressants such as AMI have E values ranging between 0.4 and 0.70, indicating that both hepatic blood flow and first-pass effects will contribute to CL variability.

Food. Unlike IMI (28), where food seems to have no effect on F, Cemax, and Tmax, trazadone’s absorption is delayed by food, with a decrease in the Cemax. However, no effect on the AUC is observed (unpublished data, Mead Johnson).

Distribution

Cyclic antidepressants are very soluble in fat and so are extensively distributed in tissue, resulting in large volumes of distribution (V), up to 63 L/kg, with great intersubject variability (see Table 3). Like TCAs, most of the newer cyclic compounds behave as lipophic bases, with concentrations in tissue exceeding that in plasma in animal studies, e.g., maprotiline (29), amoxapine (30), trazadone (31), and bupropion (32). Therefore, hemodialysis or hemoperfusion may not be successful in removing these drugs after an overdose. The animal data of Bickel et al. (33) showed that the highest concentrations of IMI were found in the lung, kidney, brain, small intestine, liver, skeletal muscle, and skin; the lowest concentrations were in plasma and adipose tissue. These experimental data imply that adipose tissue may not be the site of sequestration of antidepressants and suggests that significant decreases in clearance may not be observed in obese patients. A weak relationship ($r^2 = 0.251$, df = 61, $t = 4.49$, $P < 0.0001$) between weight and DOX CL is observed: DOX oral CL = 0.069 weight (kg) – 1.914. One patient with morbid obesity had a DOX CL rate twice that of any other patient. For IMI no significant relationship is observed between these two parameters ($r^2 = 0.055$, df = 139, $t = 0.0642$, NS).

Metabolism/Excretion

Cyclic antidepressants are metabolized almost entirely by the liver. Of the administered dose, <5% is excreted unchanged in the urine (34). The major metabolic pathways are oxidation and conjugation; N-oxidation and dealkylation are minor pathways. Side-chain N-demethylation and hydroxylation in the ring structures are the most important routes of metabolism. Hydroxy metabolites are then conjugated before being eliminated in urine and bile. There is very little evidence of metabolism in the gut wall; however, some evidence exists for biliary excretion and reabsorption, i.e., enterohepatic circulation (35).

Of the tricyclics, IMI is the most extensively studied. Figure 6 illustrates the metabolism of IMI via hepatic demethylation (yielding DMI) and hydroxylation (2-hydroxy-IMI and 2-hydroxy-DMI). DMI can be further demethylated to the primary amine, didesmethyliimipramine. Bio-transformation of the other tricyclics are analogous to that of IMI, with few variations. Table 4 lists the active metabolites of TCAs, and the metabolite to parent drug concentrations at steady state.

Occasionally, oxidative metabolism can alter the pharmacological profile of the metabolite or significantly alter pharmacokinetic properties, accounting for adverse effects not associated with the parent compound. As an example, hydroxylation primarily accounts for amoxapine metabolism, producing 7-hydroxyamoxapine and 8-hydroxyamoxapine. The 7-hydroxy compound, although present in plasma in extremely low concentrations (1–5 ng/mL), has neuroleptic effects comparable in potency to those of haloperidol (36). The 8-hydroxy metabolite, which exceeds the CFs of the parent compound at steady state, owing to its longer elimination half-life, accounts for most of the antidepressant activity (37). Trazadone’s metabolism, in addition to hydroxylation, includes N-oxidation to an active metabolite, m-chlorophenylpiperazine. This metabolite, in contrast to trazadone, is a direct serotonergic agonist, acting mainly at the

![Fig. 5. CP IMI, DMI, sum vs dose: case CF](image-url)

This 57-year-old woman was titrated up to 200 mg of IMI per day and experienced exacerbation of her underlying congestive heart failure (CHF). On this dose, her Cpes of IMI plus DMI was 445 ng/mL with an estimated oral CL of 0.5 L/min. Subsequently, after the reduction of dosage to 150 mg/day and the successful treatment of her congestive heart failure with digoxin, her Cpes was 222 ng/mL with an estimated CL of 0.9 L/min. Normalization of cardiac function with subsequent increases in liver blood flow probably account for the large increase in oral CL.

![Fig. 6. Metabolic pathway of IMI](image-url)

Imipramine is metabolized to DMI, an active metabolite. The 2-hydroxy metabolites are also considered to be active. Elimination from the body follows glucuronidation of the hydroxy metabolites, leading to renal and fecal excretion. Less than 5 to 10% of active drug or metabolites are renally excreted.
Demethylation routinely may when with the clinical correlation measured. Always have might chronic time blockade postsynaptic active (protiline). For TDM, do all active metabolites of an administered drug need to be quantified? Most cyclic antidepressants have metabolites that are pharmcologically active and that penetrate the brain. Therefore, routine TDM assays will always measure the demethylated metabolites of TCAs, e.g., the sum IMI and DMI are reported when an IMI CP is measured. Attempts have been made to assess the relationship between clinical effect and concentrations of hydroxy metabolite. However, limited data are available, because clinical studies of the administration of hydroxy metabolites in patients are lacking. Different antidepressants have different ratios of hydroxy metabolite to parent drug (see Table 4). In one study, measurement of the concentration of 2-hydroxy DMI alone did not provide as useful a correlation with response as did assay of DMI (40). The combination of the parent and its hydroxy metabolite did not improve the correlation over that seen with DMI alone. Failure to observe a relationship might be due to the relatively low (~0.4) ratio of 2-hydroxy DMI to DMI after dosing with either IMI or DMI. Only slight improvement in the correlation between response and CP of AMI plus NT was shown when 10-hydroxy NT was included (41), even though NT has a 10-hydroxy metabolite/parent ratio of approximately 1.4. The 10-hydroxy AMI and the 2-hydroxy IMI metabolites may be of lesser clinical importance than 10-hydroxy NT, owing to lower CP relative to their parent compounds (42). The role of the hydroxy metabolites in adverse effects or efficacy is as yet unclear, and there is little justification for routinely assaying them (43).

If metabolic conversion is constant for most patients over the dosage range used, then the measured concentrations of the tertiary- and (or) secondary-amine TCAs should be proportionately representative of the hydroxy metabolites' CPs. Although this appears to be true, the large interindividual variability observed in the ratio of parent to metabolite suggests that a few patients may have atypical metabolic patterns (e.g., they may be slow hydroxylators), leading to potentially clinically significant differences in how TDM results should be interpreted (see Nonlinear Kinetics and Pharmacogenetics sections).

Data generated from our TDM program for doxepin and IMI support a linear kinetic model based on the population relationship between the administered dose and the CP (see Figures 3 and 4). However, the correlations for dose vs observed concentration are modest, indicating that CPs cannot be predicted from dosage alone. Intertreatment variability for CPs >20-fold is observed at a fixed dose of IMI \( (r^2 = 0.525, df = 346, t = 19.541, P < 0.0001) \) or DOX \( (r^2 = 0.506, df = 128, t = 11.403, P < 0.0001) \). Additionally, the strong correlation \( (r^2 = 0.848, df = 32, t = 13.56, P < 0.0001) \) found between DOX and desmethylxopen CPs in 34 patients with no known interacting drugs over a wide concentration range suggests that demethylation does not reflect saturation. In contrast, the ratio of DOX to desmethylxopen CPs in all patients in the data base varies widely over the dosage range of 25 to 300 mg/day \( (r^2 = 0.024, df = 73, t = 2.01, P = 0.13) \). The linear regression-derived equation for this ratio of CPs = -0.002 dose + 1.491, demonstrates a slope-zero relationship with extremely high interindividual variability. Concomitant medications, concurrent illness, age, and endogenous characteristics such as V and CLint account for much of the variability observed in the above relationships. The section on Drug Interactions explores how controlling for category of concomitant medication can improve correlations between dose and CPs.

**Interpretation of Antidepressant CPs**

Within the dosage range recommended by the manufacturers, cyclic antidepressants have been described as pharmacokinetically linear—i.e., the amount of drug absorbed or eliminated over time is directly proportional to the amount available for these processes (5). This proportional relationship between dose and CP means that changes in drug doses will produce changes in CPs that bear a constant (linear) relationship to the dosage changes. It is the premise upon which all dosage predictions and titrations are based. The pharmacokinetic behavior of these drugs can be described by the following formula:

\[
C_{Pav} = \frac{(F \cdot \text{dose})}{(CL \cdot \tau)}
\]

(6)

Clearance is the product of the rate of elimination (\( k \)) and V. In normal situations, the only term in the equation that changes with an increase or decrease in dose is \( C_{Pav} \) (the average steady-state plasma concentration). Tau (\( \tau \)) is the dosing interval. Thus, with all other terms being constant (a), the equation can be rearranged as:

\[
C_{Pav} = \frac{(\text{dose})}{(a)}
\]

(7)

Therefore, from equations 6 and 7 a proportionality can be set up equating a target CP with an estimated dosage to achieve this concentration: new dose = present dose (target CP/present CP), e.g., double the dosage to double the CP. The elimination rate is therefore assumed to be constant for all concentrations of drug and is related to half-life \( (t_{1/2}) \) by equation 8:

\[
k = \frac{0.693}{t_{1/2}}
\]

(8)

For antidepressant drugs, \( k \) is almost entirely controlled
by hepatic metabolism. The t<sub>1/2</sub>, a clinically useful pharmacokinetic parameter, is used to characterize the rate of accumulation and decline of drug in the body. The time required to attain C<sub>peaks</sub> from chronically administered doses of medication depends on k and can be estimated as 4 to 5 × t<sub>1/2</sub>. CPs, except of cases of toxicity, should be obtained at steady state, to ensure accurate interpretation and safe application to dosage adjustment.

Concentrations in Plasma: Relation to Dosage Schedule and Sampling Time

Standardization of sampling times and interpretation of CPs of cyclic antidepressants in relation to dosage schedule is a requirement for TDM. There have been few studies investigating the stability of C<sub>peaks</sub> of cyclic antidepressants during the 24-h dosing interval. Kragh-Sorensen et al. (45) examined the effect of a single dose of NT on steady-state concentrations and found little change in CP during the subsequent 8 h. Additionally, studies with NT or AMI have both yielded comparable CP (post-distribution phase) in volunteers receiving the drug on either a “three times daily” or “at bedtime” dosage schedule. Overall, the mean CPs were stable (within 20%) during the sampling period and similar on the two schedules (44, 45). Studies with IMI and DMI also showed similar results, with relatively stable CPs on both dosage schedules. No significant differences have been found between dosage schedules and the therapeutic effectiveness or severity of side effects of TCAs (9). The observed differences of up to 20% to 30% in the C<sub>peaks</sub> on different dosage schedules that have been reported might not be significant with regard to TDM, especially if the assay’s CV is ≥10%.

Although uniformly spaced doses throughout the day are comparable to at bedtime only, patients on other, special dosage regimens can show significant differences in C<sub>peaks</sub> measured at the same daily dosage. Figure 7 illustrates the increased variability present in C<sub>peaks</sub> in a patient in our TDM program receiving IMI four times daily (8 a.m., noon, 4 p.m., and 8 p.m.) vs at bedtime only. Note that the 100-mg bedtime dose of IMI produces values for C<sub>peaks</sub> exceeding those obtained with 30 mg four times daily.

Binding by Protein

Protein binding is another important factor in the determination of the concentration of the active drug—free fraction or f<sub>a</sub>—available at the receptor site. For most drugs, only a small portion of the total amount in the body is freely diffusible in the aqueous portions of the circulation and the extravascular tissue. It is generally believed that it is this freely diffusible drug that is in equilibrium with the receptor site and relates to the onset, magnitude, and duration of the pharmacological and toxicological effects.

Reversible drug binding can be represented as follows:

\[ D_F + S \rightleftharpoons D_B \]  

(9)

where D<sub>F</sub> is free drug. S is a free binding site, and D<sub>B</sub> is bound drug. This leads to the relationship of D<sub>B</sub> to D<sub>F</sub> as follows:

\[ D_B = (S_F) (D_F)/K + D_F \]  

(10)

where S<sub>F</sub> is the total concentration of binding sites (capacity) and K is the equilibrium dissociation constant (inverse affinity).

In plasma, drugs are usually bound to blood constituents, particularly to plasma proteins. Acidic and neutral lipophilic compounds tend to bind to albumin; basic compounds such as cyclic antidepressants and certain neutral compounds bind to α<sub>1</sub>-acid glycoprotein, lipids, and cholesterol. Changes in the concentration of binding substances can influence V, C<sub>peaks</sub>, t<sub>1/2</sub>, IMI, and DMI. Thus increases in them can decrease hepatic metabolism or renal excretion, because only the unbound fraction of the drug is available to the metabolic or excretory sites.

Protein binding of cyclic antidepressants is highly variable, ranging between 68% and 98%. Binding to albumin, α<sub>1</sub>-acid glycoprotein, plasma lipids, and erythrocytes (46) occurs with a range of affinities as well as capacities. According to one study (47), a physiological concentration (0.67 g/L) of isolated α<sub>1</sub>-acid glycoprotein in water bound 69% of the IMI with high affinity. Piafaky and Borgia (48) reported a negative correlation between the free fraction of IMI and the concentration of α<sub>1</sub>-acid glycoprotein, but no correlation between the IMI f<sub>a</sub> and albumin concentration in plasma. These data suggest that α<sub>1</sub>-acid glycoprotein may play an important role in determining the degree of binding in plasma. In one study, the use of ultrafiltration techniques yielded an f<sub>a</sub> of IMI of 7.9% (48), whereas in another the mean f<sub>a</sub> was only 4.2% (49). These large interindividual differences in free fraction might result in correspondingly large differences in the total CP vs clinical effect relationship for a specific patient. However, differences in methodologies used to determine D<sub>F</sub> can explain part of the observed variability between studies. The degree of binding of cyclic antidepressant might also change over the course of therapy, with one study reporting a decreased free fraction secondary to increased α<sub>1</sub>-acid glycoprotein concentrations (50). Being one of the “acute-phase reactants,” α<sub>1</sub>-acid glycoprotein concentrations in plasma are known to increase in short- and long-term inflammation, malignancy, “stress,” and in various hematological conditions, possibly resulting in a decrease in f<sub>a</sub>. Alternatively, α<sub>1</sub>-acid glycoprotein will tend to decrease in hepatic disease, nephrotic syndrome, pregnancy, malnutrition, and with the use of oral contraceptives, resulting in a higher f<sub>a</sub> (48). A change in lipoprotein can also affect binding of antidepressants, as exemplified by increased binding of IMI in patients with hyperlipoproteinemia (51).

When a drug in plasma is displaced by another drug, the f<sub>a</sub> can increase, which increases V. Because C<sub>peaks</sub> is propor-
tional to CL (see equation 6), it follows that a change in binding might affect relative concentrations of total and free drug. For a medication with a low E, an increase in $f_a$ increases the CL of a drug, resulting in a decrease in $C_p_{av}$. However, $D_P$ remains unchanged, because the displacer drug increases $f_a$. Therefore, no change in maintenance dosing would be needed, even though $C_p_{av}$ might change.

For drugs with a large E, $C_p$s would not be altered by the addition of a displacer or decrease in binding-protein concentration (assuming an intravenous route of administration), because $C_{L\text{q}2}$ is limited primarily by Q (see equations 3, 4, and 5). However, changes in binding of orally administered drugs with moderate to large E by a displacer—e.g., cyclic antidepressants—can result in changes in $C_p_{av}$ and $f_a$ that resemble low-E drugs. One of the reasons for this difference between intravenous and oral routes of administration is a decreased E, owing to greater first-pass metabolism of the orally administered drug. First-pass metabolism is influenced by changes in $f_a$ despite the high E (i.e., E-dependent systemic CL).

However, the large V of the TCAs decreases the total potential change in measured $C_p$s secondary to binding-site changes. To illustrate the relative unimportance of drug interactions for cyclic antidepressants, which are secondary to changes in $f_a$ caused by drug displacement, consider this worst-case scenario: $f_a$ in plasma = 10%, V = 40 L (an underestimate), and a plasma displacer capable of causing $f_a$ to approach 100%. Re-equilibration of drug into the large reservoir of tissue occurs rapidly, resulting in a marked reduction of CP so that $D_P$ is only 5% to 10% greater than the concentration at baseline (52). Only immediately after a displacer is given would there be a significant risk for increased adverse effects. Table 5 summarizes the effects of protein-binding/drug-displacement interactions for orally administered medications with various pharmacokinetic properties. Therefore, depending on a drug's pharmacokinetic properties, TDM results might not accurately reflect the concentration of pharmaco logically active medication. Additionally, IMI protein-binding studies have shown up to a fourfold interindividual variability in free fraction (49, 53–55). Therefore, the differences in $f_a$ between patients might be of sufficient magnitude to reduce the robustness of $C_p$s vs response relationships in these few individuals with $D_P$ at the extremes of the distribution for the population.

TDM of TCAs for most patients should not require adjustment of the therapeutic range if binding proteins are known to be decreased or if a displacer drug is added (see Table 5).

It is unclear whether or not measurement of free-drug concentration would help improve the quality of TDM. Although many studies have investigated the relationship between CPs of antidepressants and efficacy, only a few studies have examined the relationship between $D_P$ and clinical response, because the methodologies are limited. Equilibrium dialysis is cumbersome, and ultrafiltration techniques may result in loss of drug secondary to binding to the filtration devices (27). In addition, the concentrations of free antidepressants (3–20 ng/mL) are typically below the usual detection limits for most assays. Free AMI concentration did not seem helpful in explaining the relationship between CPs and clinical response in one study (41). However, in another study, free NT concentrations >10 ng/mL tended to correlate with poorer response in patients treated for three weeks, whose $C_p$s were between 50 and 150 ng/mL (42).

Prospective Dosing

There are significant differences in cyclic antidepressant CPs among patients who are receiving the same dose of a given drug. Monitoring of CP partly resolves this problem, but traditional TDM approaches require that sampling be obtained at steady state. A desirable goal might be to try and individualize drug-dosage regimens at the onset of treatment. This idea was first implemented by Alexander son and colleagues (56–59) in studies performed on healthy volunteers. Results for DMI and NT showed an excellent correlation between drug clearance after a single oral dosage and that obtained after repeated medication.

The possibility of predicting individual dosage regimens from pharmacokinetic data obtained after the administration of a single test dose has been demonstrated. Several assumptions must be valid if this method is to be useful: (a) the drug fits a linear, non-dose-dependent kinetic model; (b) there are no time-dependent kinetic changes (e.g., enzyme induction); (c) absorption is rapid and complete; (d) the sample is obtained in the post-distributive elimination phase (beta-phase) of the CP vs time profile; and (e) the therapeutic range is established. Most of these assumptions are valid for cyclic antidepressants that fit a linear kinetic model in the general population. Figure 8 depicts the $C_p$s in a patient who had received four different dosages of IMI. The linear correlation between IMI + DMI $C_p$s vs dose is excellent ($r^2 = 0.96$, $P < 0.05$). Recently, however, there have been case reports and studies observing nonlinearity in the kinetics of DMI, IMI, NT, DOX, and clomipramine (see Nonlinear Kinetics below).

One method used to make a prospective dosage prediction is to calculate an abbreviated area under the curve (AUC) from several timed blood samples obtained during the drug's beta-elimination phase:

$$AUC_{\text{abbreviated}} = \frac{C_{\text{extrapolated}}}{k} \quad (11)$$

Where $AUC_{\text{abbreviated}}$ is determined by estimating the terminal elimination phase (beta) and extrapolating the line to time zero. $C_{\text{extrapolated}}$ is the concentration at time zero, where the extrapolated line for beta-phase CP vs time crosses the ordinate.
The C\textsubscript{SS} resulting from repeated administration of this test dose can be predicted with the following equation:

$$\text{C}_{\text{SS}} \text{ test dose} = \frac{\text{AUC}_{\text{abbreviated}}}{\text{time}}$$ \hspace{1cm} (12)

The maintenance dose required to achieve a desired C\textsubscript{SS} can be estimated with the equation

$$\text{dose} = \left(\frac{\text{C}_{\text{SS}}}{\text{C}_{\text{SS}} \text{ test dose}}\right) \times \text{test dose} \hspace{1cm} (13)$$

Although this method yields reliable predictions of steady-state concentrations for the secondary-amine TCAs, NT and DMI hydrochloride (56–58), it is relatively tedious, requiring several blood samples to determine the slope of the beta-phase.

A more promising approach—the single-dose single-point method—was suggested by Cooper et al. (59), who found that the concentration of lithium in serum 24 h after an initial test dose of it correlated in a highly linear manner with C\textsubscript{SS}. The above method has since been applied to IMI (60, 61), DMI (45, 47, 48), AMI (62, 63), and NT (10, 63–67). All of these investigators reported high correlations between post-dose test CP (obtained between 12 to 72 h after the test dose, depending upon the study) and those achieved at steady state. In some of these studies, a nomogram was constructed to allow the dosage to be adjusted from the test level (67).

The first prospective studies of TCA dosage prediction were not done until 1980. When the abbreviated AUC method was used to predict the C\textsubscript{SS} of DMI, a strong linear correlation ($r = 0.97; P < 0.001$) was found (61). Similarly, Dawling et al. (64) used this abbreviated AUC method to predict steady-state NT CPs, but did not find as good a correlation ($r = 0.71; P < 0.002$).

As an illustration of the application of the single-dose, single-point technique, in a prospective study using the 24-h CP of DMI (concentration measured 24 h after administration of a single dose of the drug) to predict its C\textsubscript{SS}, Potter et al. (61) found a moderately strong relationship ($r^2 = 0.84; P < 0.01$) between predicted and observed levels. These studies (65, 66, 69) also demonstrated that it is possible to predict C\textsubscript{SS} for NT from a single blood sample taken 24, 48, or 72 h after a single oral test dose with comparable correlation strength to those previously reported in the area-under-the-curve method. In addition, the estimation of a therapeutic dose using this single-point technique is reported to be superior to the method in which the $t_{1/2}$ in plasma is calculated (69).

Any single-point method for predicting C\textsubscript{SS} will be limited by the accuracy with which the method measures low concentrations. Studies by Dawling et al. (64) indicated that, for TCAs, greater predictive power is achieved from single-test CP measured at 72 h than at 24 h. In addition, predictions will be influenced by the stability of clearance over time—e.g., by extraneous factors that transiently influence concentration, such as alcohol consumption within 24–48 h of the procedure. There might also be significant departures from predicted values, if the relationship between dose and C\textsubscript{SS} over the usual concentration range used for depression is not linear (dose-dependent kinetics).

**Nonlinear Kinetics**

TCAs C\textsubscript{SS} have been used to guide dose adjustment, and recently 24-h CPs have been advocated for predicting therapeutic doses. Both these methods of dose adjustment assume linear drug kinetics. Over the past few years, however, there have been numerous reports that suggest nonlinearity in antidepressant pharmacokinetics. In some patients a dose increase results in a disproportionately high increase in the C\textsubscript{SS}. In 1979, Amsterdam et al. (5) reported a 14-fold increase in plasma DMI when the dose was tripled. A retrospective review of the records of all patients who had TCA C\textsubscript{SS} determined while on two different dosages revealed apparent nonlinear kinetics with DMI, but not with AMI (70). The investigators attributed this lack of observed nonlinearity in AMI kinetics to differences in metabolic pathways. There is evidence that N-demethylation and C-hydroxylation of a drug are independent pathways; for example, N-demethylation of diphenylamine does not correlate with metabolism of debrisoquine, a drug commonly used to assess hydroxylator status. Diminished metabolism of debrisoquine is associated with impaired 2-hydroxylation of DMI (71). Moreover, the TCAs share the same hydroxylation pathway as illustrated by the inhibition of AMI hydroxylation by NT. Demethylation may be the rate-limiting step in the metabolism of a tertiary tricyclic TCA such as AMI, in contrast to hydroxylation being rate limiting for secondary amines.

This dose-dependent phenomenon has been reported by others: one case was an elderly patient, whose three sisters also have a metabolic defect (72), and another was a 44-year-old patient who was subsequently determined to be a slow debrisoquine hydroxylator; these demonstrate the phenotypic variables (71). The first prospective study on the nonlinear kinetics of DMI and 2-hydroxy DMI was done by Cooke et al. (73). They demonstrated that in six patients who completed 21 days of fixed-dosage treatment, 150 mg per day, and who were then placed on 250–300 mg per day for an additional week, a disproportionate increase in normalized DMI and 2-hydroxy DMI concentrations was found. In another prospective study, 11 of 42 patients demonstrated linear DMI kinetics with ratios of C\textsubscript{SS} to low vs high doses of 1.02 or less (74). In a third of the sample (14/42), concentrations increased by 50% more than expected, and in four of the 42 patients, concentrations increased twice as much as would be predicted by a linear relationship. These patients had low initial concentrations, with low estimated $K_m$ (Michaelis–Menten rate constant), suggesting rapid drug clearance at low dosage (74). Nonlinear kinetics have also been reported with IMI (75–77), NT (78), DOX (79), and AMI (80). Brosen et al. (77), in a prospective study, found that there was an increasing DMI/IMI C\textsubscript{SS} ratio with increasing IMI dose and age. There was also a highly significant correlation between 2-hydroxy DMI/IMI C\textsubscript{SS}
and 2-hydroxy DMI/DMI Cps ratios, which suggests that the hydroxylation metabolic step had become saturated. In our analyses of the Cps of various TCAs, we have found individual cases of nonlinearity for DOX, IMI, and DMI. An illustrative case is depicted in Figure 9 for IMI. Additionally, a plot of DOX Cps vs ln DOX oral CL for 61 patients (Figure 10) demonstrates a significant decline in oral CL as function of Cps. Therefore, at doses that approach the upper range used in clinical practice, Cps appear to approach—in at least a few individuals—the maximum metabolic capacity of the patient (V \text{max}), leading to greater than expected increases in concentrations for a given increase in dosage.

Decreased hepatic biotransformation of TCAs to the hydroxy metabolite at higher Cps seems to be frequently observed but not widely appreciated by clinicians. Interestingly, other multicyclic compounds that are hydroxylated by the cytochrome P-450 system, such as phenytoin, are well documented to demonstrate nonlinear Michaelis–Menten model kinetics (81).

Drug Interactions

Drug interactions further confound the clinician’s ability to predict CP based on dose, and they complicate the dose–response relationship observed with antidepressant therapy. Such interactions can alter a given cyclic antidepressant’s pharmacokinetic and pharmacodynamic profile. Pharmacokinetic interactions can occur at many different levels: gastrointestinal absorption, metabolic degradation, renal clearance, and changes in distribution caused by protein-binding displacement. Changes in these variables may alter the concentrations of the drug in the plasma and (or) at the site of action, modulating both intensity and duration of effect. The pharmacodynamic interaction of two concomitantly administered agents at the same receptor site can enhance or diminish therapeutic effects. The sum of these interactions will determine whether a drug will antagonize or potentiate the effects of another.

Drug interactions based on changes in gastrointestinal absorption are not well documented for TCAs. Gastrointestinal motility, transit time, and physicochemical interactions such as adsorption or solubility changes are not documented in the literature, suggesting that they are not clinically significant. Differences between two generic or branded drug’s formulations can lead to significant intra-individual alterations in the F and absorption rate (82).

A drug that affects the glomerular excretion or tubular reabsorption of another medication that is renally eliminated can alter the rate of CL of the latter. For cyclic antidepressants renal clearance of unchanged drugs is negligible. However, after a single dose of IMI, up to 8% is excreted as the metabolite 2-hydroxy DMI. Therefore, a potential exists for accumulation of active metabolites in patients with changes in renal function secondary to disease or a concomitantly administered drug.

Medications affecting the metabolic enzyme systems can interact with cyclic antidepressants on both the pharmacokinetic and the pharmacodynamic levels. For instance, monoamine oxidase inhibitors, when combined with TCAs, potentiate their pharmacological action, leading to increases in adverse effects and therapeutic efficacy in refractory depressed patients. Agents that either stimulate or inhibit the nonspecific cytochrome P-450 mixed-function oxidase system in the hepatocyte may cause metabolic drug interactions. Additionally, based on equations 1–5, alterations in plasma protein binding and hepatic blood flow may alter the drug’s CL. The magnitude of this change in CL depends on the characteristics of the antidepressant (high vs low E).

Table 6 lists medications and a few of the physiological phenomena that can affect the clearance of cyclic antide-
pressants. Enzyme-inducing agents increase the activity or concentration of the oxidative enzymes in the P-450 system, leading to an increase in metabolism and a corresponding decrease in the concentration in plasma, potentially exacerbating the illness. Alternatively, drug toxicity can result when the inducing agent is discontinued without a concomitant dosage decrease for the metabolically induced drug. Hepatic CL can be increased, depending on the individual drug's pharmacokinetics characterized by changes in E and (or) Q.

Interactions that most significantly increase CLH of cyclic antidepressants involve direct stimulation of the oxidative system by another drug or chemical, e.g., phenobarbital, carbamazepine, rifampin, phenytoin, and compounds ingested as a result of cigarette smoking. The pattern of microsomal isoenzymal induction differs between compounds such as phenobarbital and polycyclic hydrocarbons. The interval before onset of induction varies, ranging from within two days (for, e.g., rifampin) to a week (for, e.g., phenobarbital). Maximal enzyme induction for these drugs can take two or more weeks, leading to a lag period for maximal change in CL of cyclic antidepressants (83, 84). The magnitude of this drug interaction effect is illustrated in Figure 11. The patient, while at steady state on IMI, 150 mg/day, and alprazolam had a combined Cpes of IMI plus DMI of 465 ng/mL. After being placed on IMI, 200 mg/day, carbamazepine was initiated and maintained for two weeks before the next CP. Despite the 33% increase in dosage, the Cpes decreased by 23% to 360 ng/mL. Changes in clearance of up to 10-fold have been observed in patients receiving psychotropic medications while on and off of carbamazepine (85).

Cigarette smoking induces the microsomal enzyme system, including the aryl hydrocarbon hydroxylase enzyme complex, and increases the oral CL of a variety of psychotropic medications (86–89). The time to onset of enzyme induction and to peak effect are not clear for smoking, but may resemble the same pattern as that for polycyclic hydrocarbon compounds. Smoking and other drug interactions can introduce significant variability into pharmacokinetic data if not adequately controlled. To illustrate, Figure 3 depicts the dose vs Cpes for DOX plus desmethylloxepin in all patients analyzed from the TDM data base. The moderate coefficient of correlation reported, $r^2 = 0.506$, is typical of published values. If one analyzes a subset of the population who either did not receive concomitantly interacting drugs or received only clearance-inhibiting agents, the correlation coefficients are modestly increased: $r^2 = 0.596, (df = 58, t = 9.172, P < 0.0001)$ and $r^2 = 0.601 (df = 52, t = 8.769, P < 0.0001)$, respectively. However, if the subpopulation of patients not receiving drugs and who are not smokers is evaluated, the correlation is considerably better: $r^2 = 0.734, (df = 31, t = 9.108, P < 0.0001)$.

In our TDM data base, smoking history is coded for usage pattern (packs per day). In prior studies, we have attempted to evaluate for the differences in oral CL of psychotropics by excluding occasional smokers (<one pack per day). Unfortunately, this information was not reliably provided to us by the individuals completing the TDM form for DOX. Despite this limitation, a positive ($n = 10$) vs negative ($n = 10$) smoking history significantly changed CL rates for oral DOX: 2.50 (SD 1.09) L/min vs 1.51 (SD 0.78), with $P < 0.05$, $df = 18$, and $t = 2.341$, in the patient subgroup on CL-inhibiting drugs.

Metabolism can be inhibited by either competitive or noncompetitive interactions with the mixed-function oxidase system. In competitive inhibition, the drug acts as an alternative substrate for the enzyme, reducing binding of the cyclic antidepressant. In contrast, substrate binding remains unchanged in the case of noncompetitive inhibition; however, the enzyme is inactivated. Inhibitors that act through an enzyme system common to the metabolism of numerous drugs, e.g., microsomal cytochrome P-450, will affect a large number of medications from a variety of chemical classes. Interacting substances that either bind to the metabolic enzyme or are toxic to the enzyme system manifest changes in CL of TCAs within 24 to 48 h after an effective concentration of the inhibitor is present (e.g., ethanol, cimetidine). However, the time to maximal inhibition will be slower when the interacting drug acts by decreasing the bioavailability of the metabolic enzyme (90).

Among the enzyme inhibitors, cimetidine has been shown to increase the F of IMI from 40.2% to 75.3%, and decrease its systemic CL from 15.1 to 9.0 mL/min per kilogram body weight. This large decrease in CL is due to cimetidine’s ability to decrease Q in addition to its inhibition of microsomal enzymes (91). Cimetidine decreases both the systemic and oral CL of low-extraction drugs to the same extent. Oral CL (which accounts for F) of drugs showing high hepatic extraction tends to decrease 30% to 50% after cimetidine administration, whereas systemic CL decreases by only 15% to 30%. TCA and cimetidine interaction with DOX (92) and AMI (93) has also been reported. Studies of NT are still controversial (94, 95); however, its major active metabolite, 2-hydroxy NT, was increased in patients to whom cimetidine was co-administered (95).

Another highly significant drug interaction occurs during the co-administration of TCAs and antipsychotic agents, leading to a mutually competitive inhibition of metabolism (96–98). Twice as high a mean Cpes of DMI was found in patients who were concurrently taking antipsychotics than in those who were not taking these agents (99). Another case report documented a greater than twofold decrease in Cpes of NT when perphenazine was discontinued. While on perphenazine, this case documented Cpes of NT well above the usual therapeutic range (100).
Other agents that are likely to increase TCA Cpses significantly are chloramphenicol and disulfiram. In contrast to cimetidine or antipsychotics, disulfiram inhibits a number of enzymes, including alcohol dehydrogenase, dopamine beta-hydroxylase, xanthine oxidase, and the cytochrome P-450 system. Chloramphenicol inhibits cytochrome P-450 in a noncompetitive manner and may also impair enzyme synthesis. Another antibiotic, erythromycin, binds to the P-450 enzyme system, diminishing its activity. The erythromycin-TCA interaction is illustrated in Figure 12, where a 33% dosage increase of imipramine, from 75 mg/day to 100 mg/day, resulted in a 151% increase in the combined Cpses. The latency of the full interaction effect is demonstrated by the increase in Cpses from the first week to the second week that the patient was receiving erythromycin. Interestingly, this patient’s Cpses might not have reached the therapeutic range without the drug interaction.

In addition to significant drug interactions being reported in the literature for individuals, our TDM data for DOX illustrate a significant effect on mean oral CL as a function of drug-interaction status for the population (analysis of variance: \( P < 0.0007 \), df = 3, \( F = 6.38 \)). Figure 13 depicts the mean oral CL for patients with known interactions, categorized on the basis of the data in Table 6. Doxepin oral CL in the group on no interacting drugs, 2.91 L/min, is significantly less than the oral CL rate in the group on enzyme inducers, 7.09 L/min (\( P < 0.02 \), df = 35, \( t = -2.631 \)), and greater than the CL rate in the group on CL inhibitors, 1.93 L/min (\( P = 0.09 \), df = 61, \( t = 1.711 \)). A greater than threefold difference in mean oral CL rates is observed between inducers and inhibitors (\( P < 0.0001 \), df = 32, \( t = 6.687 \)). The mixed category denotes patients on combinations of agents that both inhibit or increase TCA clearance. The reader will recall from equation 1 that a threefold change in oral CL translates directly to the change in dose needed to maintain the same Cpses. Therefore, a patient who was switched from carbamazepine to erythromycin, for instance, might require up to a threefold dose decrease to keep the Cpses constant. These data do not address possible changes in hydroxylated metabolite concentrations, which might obscure the clinical effects resulting from these drug interactions.

For cyclic antidepressants with well-documented therapeutic Cpses ranges, TDM might be an extremely effective intervention to reduce the potential for toxicity or loss of therapeutic effectiveness, when concomitant medications are added to or deleted from a patient’s drug regimen. In instances where the interacting drug to be added or deleted possesses psychotropic activity—e.g., antipsychotics, alprazolam, and carbamazepine—changes in therapeutic response cannot be solely attributed to the alteration of the drug regimen. Oftentimes, the changes observed in Cpses of the antidepressant might be the important factor accounting for the change in a patient’s clinical response and (or) side-effect profile.

Cyclic antidepressant interactions with alcohol are also highly significant. Acute ethanol administration inhibits oxidation indirectly through its metabolite, acetaldehyde, which depletes NADPH. At very high concentrations, ethanol can also be a direct competitive inhibitor of the cytochrome P-450 component of the microsomal system. Ethanol inhibits Phase II biotransformation (i.e., conjugation) by inhibiting UDP glucuronic acid synthesis in addition to Phase I, oxidative processes. Dorian et al. (101) reported that \( D_\theta \) values for AMI were dramatically increased during the drug-absorption phase in patients who had recently ingested alcohol, resulting in a free AUC increase of 48% \( \pm \) 13% over an 8-h period. These kinetic changes were accompanied by an impairment in mental functioning. Conversely, chronic ethanol exposure results in enzyme induction if hepatic cirrhosis has not occurred. Ciraulo et al. (102) compared the pharmacokinetics of IMI with clinical response in depressed alcoholic and nonalcoholic patients. Lower Cpses and higher CL rates were found in the alcoholic group. These lower Cpses were associated with less improvement, as assessed by the Hamilton Depression Rating Scale.

Concomitantly administered drugs and (or) alcohol can alter synthesis or elimination of endogenous or exogenous binding compounds, e.g., \( \alpha \)-glycoprotein and cholesterol, leading to changes in V and tissue concentrations (52). This in turn may result in a decrease, increase, or no change in the cyclic antidepressant’s CL, depending upon V, E, Q, and CLint (see Table 5). If binding compound concentrations are significantly altered, then \( D_\theta \) might differ sufficiently from the normative population of patients used to define CP vs response relationships that TDM data might be difficult to interpret.

Fig. 12. CP IMI + DMI vs dose and erythromycin Rx: case DS

A 33% dosage increase of IMI, from 75 to 100 mg/day, resulted in a 151% increase in the combined Cpses of IMI plus DMI in a 23-year-old woman. Erythromycin was then started for a presumed streptococcal throat infection. The combined Cpses—on erythromycin and IMI, 100 mg/day—was 215 ng/mL at one week vs 241 ng/mL two weeks later (denoted by arrows).

Fig. 13. Doxepin clearance vs drug interactions

All patients on DOX with available data for concomitant medications were classified into different categories of drug interactions based on criteria in Table 6. Changes in mean oral CL secondary to drug interactions are sufficiently large to suggest that clinically significant alterations in Cpses are likely if a patient has an interacting drug added to or removed from the regimen while receiving TCAs.
Pharmacogenetics of the Metabolism of Antidepressants

Several distinct genetic polymorphisms of metabolism for antidepressants have been described, characterized by a deficiency of a specific enzyme of the cytochrome P-450 system in the liver. About 5% to 10% of the population displays an inherited deficiency in oxidative hydroxylation as determined by the debrisoquine test. An analysis of debrisoquine and its hydroxylated metabolite concentrations in urine are converted to a ratio, which characterizes a patient's enzyme phenotype. Cyclic antidepressants such as AMI, DMI, and NT have been shown to be under the same genetic control. In a group of volunteers given a single oral dose of AMI and subjected to the debrisoquine test, poor metabolizers of debrisoquine were found to have higher levels of AMI and NT (103). Highly significant correlations between the debrisoquine ratio and the CP of NT (but not AMI) are reported. Amitriptyline's main metabolic pathway is N-demethylation, which is genetically independent of the debrisoquine-hydroxylator phenotyping. Similar correlations have also been demonstrated with DMI (104). One clinical implication of this genetic hydroxylation deficiency that has been suggested (14) is an altered risk for toxicity. Enzyme saturation could occur at lower DMI concentrations in slow hydroxylators, resulting in greater ratios of parent to hydroxy CP (21). Saturability of the hydroxylator system also explains why some drugs reliably interfere with the metabolism of TCAs. Thioridazine and other phenothiazines, which are competitive inhibitors of hydroxylation (105), have been shown to significantly increase DMI CP (106).

Studies comparing identical and fraternal twins, with or without concurrent medications, further support the genetic basis of TCA metabolism. Identical twins given oral NT achieved similar Cps, in contrast to fraternal twins, who demonstrated significantly greater interindividual variability when concomitant medications were strictly excluded from both groups. The intra-pair similarity in Cps was not observed in identical twins simultaneously treated with drugs containing barbiturates (6).

There are inter-ethnic differences in drug metabolism. Non-depressed Asian volunteers had higher CP 24 h after a single dose of clo mipramine than did their native British counterparts (107). After a single dose of desipramine, Asians also tended to exhibit slower metabolism, with more anticholinergic side effects reported, than did their white counterparts (108). In a study comparing the pharmacokinetics of Anglo and Hispanic volunteers after a single dose of NT (109), no significant differences in the various parameters (k, V, AUC, CL, and Cmax) were found between the two ethnic groups. This is in contrast to other studies in which significant differences have been found between Asian and white groups in the CL of DMI (110).

Analyses of the data obtained through our TDM program for inter-ethnic differences in oral CL have revealed no statistically significant differences among blacks, whites, and Hispanics for IMI (analysis of variance, df = 3, F = 1.77, P = 0.15). Results for the comparisons of IMI oral CL in Hispanic (n = 32) vs white (n = 97) and Hispanic vs black (n = 8) were suggestive of potential differences: 3.06 (SD 2.70) L/min vs 2.42 (SD 1.96) L/min (P = 0.15, df = 127, t = 1.457) and 3.06 (SD 2.70) L/min vs 1.73 (SD 1.36) L/min (P = 0.19, df = 88, t = 1.337), respectively. Unfortunately, information on racial background was not available for 26% of the patients in the TDM data base, decreasing the power of our observations. Also, an inadequate number of patients had their racial background documented in the DOX data base, precluding analysis.

Pharmacokinetics in the Elderly

The effects of age on drug biotransformation and excretion can be of clinical significance for drugs with a low therapeutic index. Clearance of drugs via the cytochrome P-450 system may be reduced with advancing age, secondary to decreased metabolic capacity of the liver enzyme system and (or) decreased hepatic blood flow, leading to possibly increased side effects and toxicity. Decreases in glomerular filtration rate with age can also explain the observed increases in unconjugated hydroxy TCA metabolite CPs in the elderly. During chronic therapy with DMI, elderly patients were noted to have greater concentrations of 2-hydroxy DMI than did younger patients. There was no statistical difference in DMI CP (111). In another study, DMI CP were reported not to increase with age, suggesting that there were no age-related decreases in oral hydroxylation of the parent compound (112). However, changes in V and oral CL were not completely evaluated.

Cyclic antidepressants, having a large E, will demonstrate a decreased CL, leading to increased Cps from age-related reductions in hepatic blood flow. In contrast to Cutler and Kitanaka (111, 112), other studies evaluating the disposition of these agents in the elderly suggest that Cps of AMI, DMI, IMI, and NT are increased during chronic therapy (23, 113). After single oral doses, both NT and AMI were found to demonstrate decreased oral CL in the elderly compared to young controls (49, 114). In a study comparing IMI disposition in elderly vs young volunteers receiving either intravenous or oral IMI in single doses, the t½ was found to be markedly prolonged both in elderly males (28.6 vs 16.5 h) and females (30.2 vs 17.8 h) (115). These increases in t½ were due to decreased CL, no change in V being observed. T½max was shorter in older women than in younger women, but not different for men. Maximum Cps were greater in the elderly of both sexes (males: 40.2 vs 19.5 ng/mL; females: 44.7 vs 10.4 ng/mL). No difference in absolute F was found between the elderly and young of either sex. This study (115) also evaluated DMI pharmacokinetic parameters but did not find any differences in older vs younger women for t½ or oral CL. Elderly males demonstrated a significantly longer t½ for DMI than did younger men. The rate of metabolism of IMI by demethylation appears to be more sensitive to the effects of age than DMI, for which the major metabolic pathway is hydroxylation (115).

Similarly, our TDM data for DOX support an age-related effect on oral CL Cps. Figure 14 demonstrates a weak but significant decline in oral CL vs age: r² = 0.164 (df = 58, t = 3.340, P < 0.002). Note that a large number of our patients on DOX are elderly, whereas the population on IMI is, on the average, much younger. Significant differences in the oral CL of DOX are observed when the population is divided into two groups by age, >55 (n = 40) vs ≤55 years (n = 23): 3.89 (SD 3.41) vs 2.04 (SD 1.35) L/min (P <0.003, df = 61, t = 3.06), respectively. Thus, a lower dose of cyclic antidepressants would be needed to achieve a targeted steady-state concentration in plasma of the elderly than of the younger population. Further data collection and analyses are needed to elucidate the relationships among aging, possible saturable metabolism, and increased adverse effects.
Pharmacokinetics in the Pediatric Patient

There are only a few published pharmacokinetic studies in children with regard to cyclic antidepressants. In general, the child has an increased hepatic surface area and body weight relative to the adult. Children also have proportionately more lean body mass than do adults, so that less drug might distribute into fatty tissue (116). In late infancy and childhood, many drugs are eliminated via hepatic metabolism at greater rates than in adults. Similar to adults, wide interindividual variation in elimination are observed. In pre-adolescent children the \( t_{1/2} \) of IMI is 6 to 15 h, requiring two or more divided daily doses to minimize differences in peak vs trough CP. A higher Cpe ratio of DMI to IMI was also noted in children relative to adults (117).

Cyclic antidepressants are less highly protein bound in children than in adults. Imipramine binding in cord and adult plasma have been found to average 74% and 86%, respectively, or a 26% \( f_l \) in the neonate vs 14% \( f_l \) in the adult. The binding values for seven- to 10-year-old children are intermediate between those found in the neonate and adults (118). These factors help to explain why a lower CP is sufficient for a therapeutic response in children, e.g., a proposed therapeutic range of 125–250 ng/mL for IMI.

Methodological Approaches for Kinetic Studies

Traditional definitive pharmacokinetic studies designed to evaluate drug interactions require intensive venipuncture, with use of a carefully controlled approach to standardize all aspects of the methodology. Typical data analysis requires a two-step approach: determine the kinetic parameters in each patient and then calculate the population mean and standard deviation. In contrast, population parameter estimation, using the program NONMEM (Nonlinear mixed-effects modeling), allows for a one-step analysis of data, combining all subjects' data into a single regression incorporating relevant physiological variables (age, weight, smoking, drug interactions). In the NONMEM program an extended least-squares approach is used to estimate a maximum-likelihood function. This method provides estimates of kinetic parameters by modeling fixed and random effects. Identification of potential sources of interindividual and intra-individual (residual) variability can result in an extremely sophisticated stepwise approach to kinetic model building (119). The population-parameter estimation method allows for increased flexibility in data-collection procedures, usually facilitating a more naturalistic study design.

Moreover, retrospectively collected data can be analyzed in this fashion, so long as detailed dosing histories relative to CP are documented along with relevant physiological variables. A third method of data analysis, the "naive pooled data method," can be used if a sufficiently large number of patients is available. The retrospective TDM information presented in this paper uses this third approach (120).

To illustrate the utility of the population-parameter estimation approach, we undertook a prospective controlled trial in collaboration with a multicenter consortium from the University of Missouri Kansas City and the University of Tennessee (sponsored by The Upjohn Company). The study evaluated the pharmacokinetic interaction between alprazolam and IMI in patients with major depressive disorder. The interaction was evaluated by a traditional multiple-dose study design with intensive sampling at steady state during dosing with IMI alone and with concomitant administration of alprazolam (121). The study was designed to permit assessment of the clinical significance of the interaction through side-effect and behavioral evaluations. Population pharmacokinetic analysis, for comparison with the traditional method, was based on additional CPs obtained before and after addition of alprazolam (122).

The AUC for IMI treatment alone was determined by intensive interval sampling on study day seven (prior to alprazolam). Multiple blood samples were obtained in 10 patients at 0.0 h (before the morning dose), and 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, and 12.0 h after the morning dose of IMI. Alprazolam, 1 mg/day, was then added to the subjects' treatment and the dose was increased by 1 mg/day every three to four days up to a maintenance dose of 4 mg/day. A repeat AUC was then obtained. An additional 19 subjects (total = 29) also had CP measured at flexibly scheduled times as outpatients for the population-parameter estimation component of the study. Nine CPs were obtained, on the average, from each of the 29 patients for population-parameter estimation. In contrast to the AUC study, these CPs were obtained periodically (but not strictly controlled for time of day or specific study day) while off and then on various doses of alprazolam, up to 4 mg/day. Careful record keeping by patients for dosing history was required.

When alprazolam was co-administered with IMI, statistically significant increases in IMI CP were observed at most sampling times. In the 10 traditionally studied patients, the following CPs were found: pre-alprazolam treatment, \( IMI = 43.9 \) and \( DMI = 72.2 \) ng/mL and on 4 mg/day alprazolam, \( IMI = 57.6 \) and \( DMI = 86.7 \) ng/mL. These higher IMI concentrations resulted in a 31% increase in the mean \( CP_{av} \), a 21% increase in \( CP_{max} \), and a 36% increase in \( CP_{min} \). Mean IMI CL decreased by 20.8% during therapy with alprazolam. No statistically significant differences in \( k \) or \( V \) were observed.

The results from the traditional AUC method agreed well with the \( CP_{av} \) population pharmacokinetic estimation of parameters (121, 122). Oral IMI CL from the population-parameter analysis was estimated to be 1.5 (SD 0.14) L/h per kilogram body weight vs the traditional oral CL of 1.49 (SD 0.36). Volume of distribution, estimated from the population analysis, was 21.6 L/kg vs 18.7 L/kg by the traditional kinetic approach. Using the alprazolam \( CP_{av} \) of 44 ng/mL from the AUC data, the population-parameter-estimated kinetic model yielded a predicted IMI CL of 1.3 L/h per kilogram, in excellent agreement with the traditional study's result of 1.19 L/h per kilogram while on concomitant alprazolam. The NONMEM estimated regression model,
Fig. 15. Imipramine + desipramine CP vs facility: effect of consult service

The mean Cpes of IMI plus DMI are significantly greater at San Antonio State Hospital (SASH), the University of Texas Mental Sciences Institute (UTMSI), and Austin State Hospital (ASH), where clinical pharmacy and psychopharmacology consultation services are available, than at all other facilities. The mean Cpes at each of these three consult facilities are above the minimum effective range suggested for response (>180 ng/mL), as opposed to possibly subtherapeutic mean Cpes observed at other facilities

where Cpe_av alprazolam is inversely proportional to the change in CL of IMI, predicted that a decrease in oral IMI CL of 21.1% should have been observed in the traditional AUC study. Clearly, this is an extremely good prediction via a- via the AUC-derived decrease in oral CL of 20.8% (121, 122).

Summary

TDM for cyclic antidepressants is an important advance towards the goal of optimizing the treatment of depression. Significant inter- and intra-individual variability in pharmacokinetic parameters is observed, owing to exogenous and endogenous factors. Drug interactions, smoking, concurrent disease states, physiological processes such as aging and renal function, and demographics all can affect the kinetic profile of cyclic antidepressants. Changes in oral CL caused by these variables translate directly to changes in a patient’s drug concentration in plasma. If, as is the case for many TCAs, a therapeutic range can be defined, then TDM can significantly improve the likelihood of good response in individuals. Pharmacokinetic principles defining and explaining the determinants of oral CL can give the clinician greater insight into the reasons for therapeutic failure and for toxicity. New cyclic antidepressants, for the most part, resemble the older TCAs in their pharmacokinetics. Therefore, much of the reported research with the TCAs can be (cautiously) applied to many of the newer cyclic compounds.

Clinical impact studies evaluating the pharmaco-economics of TDM are needed. The data analyzed to date for our TDM program for patients in The Texas Department of Mental Health and Mental Retardation facilities suggest clinical benefit. Figure 15 illustrates the mean Cpes for IMI plus DMI, by facility. The mean Cpes are significantly greater in those three facilities where clinical pharmacy and psychopharmacology consultation services are available. The mean Cpes for these three facilities are within the usual range suggested for optimal response. In contrast, the mean Cpes at all the other facilities combined is below the usual therapeutic range. Therefore, the availability of analytical capabilities is not sufficient per se to appreciably alter drug use unless a monitoring program is also established to interpret the CPs and standardize the process by which these concentrations are measured.

Areas of research requiring additional study include the role of free-drug concentration monitoring, the importance of the hydroxylated metabolites, pharmacodynamic modeling with use of time-dependent multivariate methods, and pharaco-economic impact studies evaluating the potential differences in cost of care among the various dosing methods: empirical dose titration vs TDM vs single-test-dose vs Bayesian dose forecasting. NONMEM analysis of patients’ data can result in the development of superior models to predict an individual’s CL. Bayesian dose forecasting utilizes population-parameter-estimated parameters to develop a physiological model incorporating intra-individual and interindividual sources of variability into its dosage recommendations (123, 124).

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