Therapeutic Drug Monitoring of Tricyclic Antidepressants

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The traditional dose–response method of medication adjustment depends on several assumptions that are not met in the case of tricyclic antidepressants (TCAs), which makes therapeutic drug monitoring (TDM) particularly useful with these drugs. TDM can facilitate treatment by providing objective guidelines for dose adjustment. It provides a means of assessing compliance, ensuring an effective concentration, and avoiding toxicity. The latter is an often-overlooked benefit of therapeutic monitoring of TCAs and yet is just as important as improving response. The cardiac and central nervous system toxicity of TCAs is concentration-dependent and potentially life-threatening. Such toxicity will predictably occur in up to 5% of patients on standard antidepressant doses of TCAs when TDM is not used to rationally adjust the dose. Without TDM, such toxicity is difficult to detect early. A cost/benefit analysis supports the cost effectiveness of TDM as a standard part of TCA chemotherapy when doses in the 100–300 ng/day range are used.

Therapeutic drug monitoring (TDM)⁴ of tricyclic antidepressants (TCAs) enhances the physician’s ability to use these agents more rationally, increasing both their safety and efficacy. Patients have substantial interindividual differences in the metabolism and elimination of TCAs. Therefore, widely different drug concentrations may be measured in different patients on the same dose of the same drug, leading to markedly different outcomes, ranging from no response to improvement to iatrogenic toxicity.

For TDM to be useful, the drug concentration in plasma must correlate with the patient’s clinical outcome better than the standard approach of dosage titration based on clinical response. Effective TDM allows the patient to receive a therapeutic dose more quickly. The search for consistent relationships between TCA in plasma and clinical response has been a continuing subject of research for over a decade. However, TDM cannot be expected to be a panacea. The drug concentration is a principal determinant of clinical response, but not the only one. There also exist interindividual differences in tissue sensitivity that contribute to wide variations in response. Still, TDM of selected drugs is an important advance in psychiatric care. In essence, it represents a refinement of the dose–response approach typically used in prescribing medications.

Unlike other medical tests such as a screening electrocardiogram or chest roentgenograms, TDM of a medication with a well-defined concentration/response relationship always provides useful information. The test is directed to something that should be there. If the concentration of the drug is not measurable, it suggests noncompliance or very rapid metabolism—either of which may cause nonresponse. If the drug is measurable, then the question is whether the concentration is appropriate, subtherapeutic, or toxic.

Reasons for Therapeutic Drug Monitoring

In psychiatry as in other areas of medicine, there are five reasons why drug concentrations should be monitored:

1. To check compliance. This is an important issue with regard to both initial and maintenance treatment response, especially in depressed patients, whose lack of concentration and motivation may lead to inadvertent and sporadic noncompliance.

2. To maximize clinical response. Since well-defined concentration/response relationships exist for some antidepressant medications, knowing drug concentrations in plasma helps the physician to adjust drug dosage more rationally, to optimize the therapeutic effect.

3. To avoid toxicity. Because a relationship has also been demonstrated between the concentration in plasma and toxicity for certain antidepressant agents, the risk of inadvertent drug toxicity owing to slow metabolism can be minimized by rationally adjusting drug dosage. Also, when other drugs are co-prescribed that induce or inhibit metabolism of TCAs (e.g., anticonvulsants, neuroleptics), a previously effective TCA dose can quickly be rendered ineffective or toxic. Generally, a check of the TCA concentration after a change in other therapy can ward off problems.

4. To minimize cost. First, noncompliance or inappropriately low concentrations will delay the onset of clinical response, and thus will prolong the stay for hospitalized patients and the time for remission in outpatients. Second, supratherapeutic concentrations also may delay response or cause toxicity and thus prolong the hospitalization and complicate care. The cost-effectiveness of plasma monitoring is readily seen if a hospital stay is shortened by even one day or increased societal productivity is realized by a patient’s earlier return to work. The cost-effectiveness is even more appreciable if cardiotoxicity or delirium can be avoided by rationally adjusting the dose in a patient with slow metabolism.

5. To aid in avoiding medical-legal problems. This is particularly important in this era of malpractice suits. For example, a physician may observe a good response, with no apparent toxic effects, only when the patient is on unusually high doses. Monitoring drug concentrations can provide objective evidence to substantiate the need for and safety of unusual doses in certain patients.

Therapeutic monitoring of TCAs is a cost-effective tool when used as a standard component of the inpatient treatment of major depressive disorder (MDD). As a conservative current estimate, savings of more than $350 per patient can be realized by the routine use of TDM. This estimate is based on the following considerations:

Increased efficacy. Only 40–50% of patients with MDD respond to TCAs during the first three weeks of treatment when dosage titration based on clinical response is used, as compared with a 70–75% response rate when TDM is used.
Thus, about 250 of every 1000 patients treated have at least a delayed response, owing to the failure to utilize TDM. If 250 of these patients had their hospital stays extended by an average of five days because of delayed or suboptimal response, the cost would be approximately $271,250 ($217 per hospital day × 250 inpatients × 5 days).

Increased safety. TCAs have serious and potentially fatal effects on the heart (i.e., delayed intracardiac conduction and rhythm disturbances) and on the brain (i.e., delirium and seizures). These effects are concentration-dependent. The risk of such toxicity is significantly increased when concentrations exceed 450–500 µg/L. While the incidence and consequences of cardiac toxicity have not been well defined, these factors have been defined for brain toxicity resulting from high concentrations of TCAs, as we outline below. Thus, the savings realized by avoiding brain toxicity can be estimated.

Sixty of every 1000 inpatients treated with TCAs without the benefit of TDM will develop drug-induced delirium. The costs occasioned by this toxicity include an average seven-day extension to the hospital stay ($217 per hospital day × 7 days × 60 patients = $91,140); 83% of these patients will have a CAT scan ($17,380); 67% will have an electrocardiogram ($8,965); half will have a neurologic consultation ($4,050); and 100% will have additional routine laboratory tests such as a complete metabolic and electrolyte evaluation ($4,380). Thus, the cost of such toxicity is conservatively estimated at $125,915. Therapeutic monitoring of TCAs substantially decreases, if not eliminates, the risk of such toxicity.

The cost of therapeutic monitoring of TCAs varies substantially from laboratory to laboratory, but an average current figure would be $35 per assay. Thus, the cost of using therapeutic monitoring of TCAs as a standard part of treatment is $35,000 per 1000 patients. The savings realized by using TDM as a standard part of treatment is $397,165 if only the hospital expenses associated with reduced efficacy ($271,250) and brain toxicity ($125,915) are included. Thus, the net savings per patient realized by using TDM would be over $350 ($397,165 − $35,000 divided by 1000).

In the next sections, we present data to support the improvement in efficacy and safety of TCA pharmacotherapy expected to result from the use of TDM.

Therapeutic Drug Monitoring vs the Dose–Response Approach

Second to lithium, TCAs have been found to have the most clinically dependable drug-concentration/clinical-response relationship in psychiatric practice. Various pharmacokinetic and pharmacodynamic characteristics of a drug, summarized in Table 1, determine whether plasma monitoring is likely to be useful. The elementary principle of TDM is that the concentration of the drug at some site in the body determines the pharmacodynamics of the drug. With antidepressant drugs, this site is presumably the brain. An implicit but testable assumption is that the concentration in the peripheral sample (plasma) reflects the concentration at the effector site (brain). With TCAs, there is a linear relationship between concentrations of drug in the blood and concentrations of drug in the brain under steady-state conditions (1). Thus, TDM provides an index of the concentration of the medicine in the brain of the patient.

Until therapeutic monitoring of TCAs became available, the standard way of determining the appropriate dosage of these agents was based on the dose–response titration approach. In this approach, patients with major depressive disorder were typically treated with a conservatively small starting dose of TCA. If the response was judged to be inadequate after three to four weeks, the dosage was increased until an optimal response occurred, whereupon the dosage was maintained, or until side effects occurred, in which case the dosage was reduced (Figure 1). Using this approach, a good response can be expected in only 40% to 60% of patients after three or four weeks of treatment (2). Unfortunately, a substantial number of the remaining 40% to 60% of patients are not actually drug nonresponders; rather, they do not respond because of incorrect dosage. Moreover, this approach puts approximately 5% of patients at unnecessary risk of serious TCA toxicity.

The dose–response titration method is commonly used in medicine. To work well, this approach requires: (a) a standard starting dose, (b) a short time between starting the drug and assessing response, (c) an objectively measured response, (d) a linear relationship between increased dosage and improvement, and (e) readily identifiable and easily measured adverse effects that are related to excessive drug concentrations rather than being highly variable or idiosyncratic.

Unfortunately, none of these points holds true for TCAs. First, a truly standard starting dose is not feasible because of substantial interindividual differences in metabolism (3). Second, the time between starting the drug and achieving antidepressant response is on the order of weeks. Third, response measures are far less objective than measuring, for example, the blood-pressure response to an antihypertensive drug or changes in clotting time in response to an anticoagulant. Fourth, there is evidence that increasing the dose does not necessarily increase response (3). Finally, the side effects that most physicians use as a guide for titrating dosage are not related to excessive concentration or to the

<table>
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<tr>
<th>Table 1. General Features That Make Monitoring Plasma Drug Levels Useful</th>
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<td>• Well-defined concentration/response relationships with regard to:</td>
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<td>• Beneficial effects</td>
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<td>• Nuisance effects</td>
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<td>• Toxic effects</td>
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<td>• Small therapeutic index—i.e., the concentration of drug producing toxic symptoms is near the concentration producing a therapeutic response</td>
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<td>• Large individual variability in the dose/plasma-concentration relationship; some patients may be at a toxic concentration while that of others is subtherapeutic</td>
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<td>• Long delay in onset of action</td>
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<td>• Detection of early toxicity clinically difficult</td>
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Fig. 1. Schematic diagram of dosage determination by clinical response
much more serious CNS or cardiotoxic effects of these drugs but instead to peripheral anticholinergic effects (4). In fact, these side effects may occur at concentrations well below those that are clinically therapeutic.

Clinical Overview of Tricyclic Antidepressants

To understand and effectively utilize therapeutic monitoring of TCAs in the treatment of patients with major depressive disorders, the physician needs to be familiar with the improvements in the diagnosis and selection of patients for treatment with TCAs and with the clinical pharmacology of TCAs.

The early literature on the antidepressant actions of TCAs showed that there is a high degree of variability in antidepressant response among patients (2). This variability is caused by two factors. First, major depressive disorder is a clinical syndrome of unknown pathophysiology. Hence, patients with the same apparent diagnosis may actually have pathophysiologically different illnesses and thus not be responsive to the same therapy. The best way to minimize this cause of response variability is to improve diagnostic acumen. The second cause of variability is the numerous pharmacological effects of TCAs. Fortunately, these effects predominate at different concentrations. By monitoring TCA concentrations, the physician can rationally adjust the dose to maximize the desired effect.

Improvement in the diagnosis of major mood disorders is reflected in the development of better criteria over the last two decades for the selection of patients for clinical trials evaluating TCAs in the treatment of depression. In early studies, any potential subject who complained of low mood was treated for depression (2). However, low mood is neither the sine qua non nor necessarily the most important symptom of major depression. Low mood can occur in the absence of a psychiatric illness and in a number of psychiatric conditions other than major depression (e.g., obsessional disorder, anxiety disorders, antisocial personality disorder, hysteric, and schizophrenia), as well as in various medical illnesses.

A diagnosis of major depressive disorder requires not only mood complaints but also vegetative signs and symptoms, such as changes in appetite, sleep, weight, libido, and concentration/attention, as well as feelings of guilt, suicidal ideation, and loss of interest in usual activities. The presence of this complex of signs and symptoms—the depressive syndrome—is a better predictor of antidepressant drug response than is reliance on the single symptom of dysphoria (2).

In terms of clinical pharmacology, TCAs can be divided into two broad groups: tertiary amines and secondary amines. Tertiary amines include imipramine (DMI), amitriptyline (AMI), trimipramine, and doxepin; secondary amines include desipramine (DMI), nortriptyline (NT), and protriptyline. This distinction is clinically important because tertiary amine TCAs, as a rule, are more potent than secondary amine TCAs in causing sedation, anticholinergic effects, cardiotoxicity, orthostatic hypotension, weight gain, and cognitive impairment.

Also, the secondary amine TCAs are demethylated metabolites of the tertiary amines. Thus, a patient who receives a tertiary amine drug, such as IMI, achieves concentrations in plasma of both this compound and its primary demethylated metabolite, DMI, and its hydroxylated metabolites, 2-hydroxymipramine and 2-hydroxydemethylimipramine. As a result, the clinician must consider both the actions of the parent drug and its metabolites as factors in determining outcome.

To understand other factors that can influence TCA concentrations in plasma, it is necessary to understand the absorption, distribution, metabolism, and elimination of these drugs. TCAs are pharmacologically complex (5). Usually taken orally, they are absorbed from the small bowel, enter the portal blood, pass through the liver (which extracts as much as 70% to 90% of the drug from the portal blood into hepatocytes), and then enter the systemic circulation for distribution to peripheral compartments. The drug extracted into hepatocytes collects in the gall bladder and is emptied into the small bowel. It is then recirculated back into the portal blood stream via reabsorption from the small bowel. The absorbed drug eventually enters the systemic circulation and ultimately affects neurotransmission.

The ability of TCAs to inhibit neuronal amine re-uptake pumps for norepinephrine and serotonin is believed to be the mechanism of action underlying their antidepressant efficacy, and it occurs at therapeutic antidepressant concentrations. They also bind to and block a number of receptors in the brain and periphery. Their blockade of muscarinic cholinergic receptors results in atropine-like effects such as dry mouth, constipation, and urinary retention, and this blockade occurs at subtherapeutic concentrations. TCA blockade of alpha adrenergic receptors can produce orthostatic hypotension. The sedative effects of TCAs are thought to be related to their blockade of central serotonin and histamine receptors. As the drug concentration in plasma increases to supratherapeutic concentrations, TCAs act as local anesthetics. They inhibit membrane ATPase and directly stabilize excitable membranes. This effect accounts for the cardiotoxicity observed in patients who develop high drug concentrations in plasma as a result of either genetically determined slow metabolism or intentional drug over-
doe. These multiple actions underlie the usefulness of TDM of TCA because concentrations in plasma are an index of concentrations in tissue, which determine these different pharmacological effects (1).

Clinical Applications of Therapeutic Monitoring of TCAs

As the dosage (i.e., concentration) of any drug increases, the degree of beneficial response it will produce also increases until some maximum point (or plateau) is reached. Above a certain dosage (or concentration in plasma), toxic effects will also begin to be seen. The upper threshold, then, is the concentration above which the risk of toxicity outweighs the chance of any further beneficial response. The upper (or toxic) threshold divided by the lower (or therapeutic) threshold is the therapeutic index of the drug (Figure 2).

Some drugs (e.g., lithium) have a very narrow range between efficacy and toxicity. Hence, TDM of lithium is helpful in improving the safe and effective use of the drug. Other psychotropic drugs have a wide therapeutic range. In these cases, TDM does not offer a significant advantage over a clinical observation of response. An example is diazepam: its acute toxic effects are relatively minor, easily recognized, and occur at much higher concentrations than those needed for efficacy.

TCAs are more like lithium than diazepam in regard to their therapeutic index. The therapeutic antidepressant plasma concentration range for most TCAs that have been studied is approximately 100 to 300 µg/L, while toxic effects routinely occur when the plasma concentration exceeds 500 µg/L. Although this approximately fivefold therapeutic index may appear reasonably safe, the wide variability in elimination rates among patients means that some patients will develop toxic concentrations even though they are receiving standard doses. Hence, TDM is a useful means of rationally guiding TCA dosage adjustments to achieve the concentrations at which the drugs are most efficacious while at the same time avoiding potentially serious adverse effects.

Studies of TCA concentrations in plasma have been ongoing for over a decade. Four TCAs have been studied enough for there to be a consensus on their therapeutic concentration ranges (6): NT, AMI, IMI, and DMI (Table 2).

The best-studied TCA is NT, for which the effective range in terms of antidepressant response appears to be between 50 and 150 µg/L. NT has repeatedly been observed to have an upper limit of effective concentration in plasma that is below its toxic concentration. In this case, a patient could have a concentration too high to have a beneficial effect, but a physician who does not utilize TDM would be tempted to continue increasing the dose because of the apparent absence of toxicity.

The second best-studied TCA is IMI. The lower limit for the concentration of this drug in plasma seems to be a combined value for IMI and the active metabolite, DMI, of about 150 µg/L; combined values exceeding 300 µg/L offer no clear advantage in terms of the risk/benefit ratio. This result seems to hold true in studies both of depressed children and adults. This point was well demonstrated in a recently completed study of 38 children with major affective disorder (4, 7). In this study, an 80% response rate was observed after three weeks of drug treatment if the plasma concentration of IMI plus DMI was between 125 and 250 µg/L (7). In contrast, no patient remitted whose total plasma drug concentration was outside this range. Patients with values >250 µg/L did no better than those with values below 125 µg/L. Plasma monitoring was useful not only from an antidepressant-response standpoint but also from a safety standpoint. Prolongation of intracardiac conduction was routinely found in children whose drug concentrations in plasma exceeded 250 µg/L, but was not found in those with values <250 µg/L (4). A comparison of patients before and during drug administration showed that those whose values exceeded 250 µg/L had greater increases in diastolic blood pressure and standing and supine heart rate than those whose values were less (4). Thus, above an apparent upper (i.e., toxic) threshold of approximately 250 µg/L, there was prolongation of intracardiac conduction, elevation in diastolic blood pressure, and increase in heart rate—with no apparent increase in antidepressant efficacy in children.

Although there still is some controversy about the lower threshold for antidepressant response in relationship to combined values for AMI and its NT metabolite, AMI is one of the best-studied TCAs in terms of an upper threshold with regard to avoiding potentially serious adverse side effects. Decreased efficacy is associated with concentrations of AMI plus NT in plasma below about 100–150 µg/L (3, 6). If the concentration is between a lower limit of 100–150 µg/L and an upper limit of approximately 250–300 µg/L, there is an increased chance of an optimum response without an appreciable risk of adverse effects. At concentrations in plasma around 350 µg/L, asymptomatic AMI-induced electroencephalographic changes begin to occur (8). At concentrations in excess of 450 µg/L, there is an increased risk of AMI-induced delirium (9). Overdose data indicate that coma, seizures, and the need for supportive respiration routinely occur when concentrations exceed 1000 µg/L (10). Information on DMI continues to accumulate. At present, its optimum range appears to be 125–300 µg/L.

| Table 2. Pharmacological and Pharmacokinetic Characteristics of Four Antidepressant Drugs |
|-----------------------------------------------|------------------|------------------|------------------|------------------|
| | Tertiary amines | | | |
| | Tertiary variation in | Individual | Half-life, h | Dosage | Apparent optimal |
| | | metabolism | Mean | Range | range, | plasma drug ranges, |
| | | | | | mg/day | µg/L |
| | | | | | | |
| | Amtriptyline (Elavil, | 10-fold | 16 | 10-25 | 50-300 | 150-300 |
| | Endep) | | | | | |
| | Imipramine (Janimine, | 30-fold | 28 | 18-34 | 50-300 | 150-300 |
| | SK Framine, Tofranil) | | | | | |
| | Secondary amines | | | | | |
| | Nortriptyline (Aventyl, | 30-fold | 36 | 16-56 | 30-100 | 50-150 |
| | Pamelor) | | | | | |
| | Desipramine (Norpramin, | 10-fold | 21 | 12-30 | 50-300 | 125-300 |
| | Pertorfrane) | | | | | |

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Although beneficial antidepressant effect and serious adverse effects are related to drug concentrations in plasma of depressed pediatric patients, this does not often hold true for more common "nuisance" side effects from TCAs. This is an important point, because physicians often titrate TCA dosage based on patients' responses to questions about side effects such as dry mouth, drowsiness, dizziness, lethargy, sleep problems, nausea, constipation, fainting spells, palpitations, chest pains, stomachaches, and perspiration. When a structured scale was used to rate the presence and severity of these side effects of TCAs in these children before and during drug administration, no relationship was found between drug concentrations in plasma and side effects (4). The failure to find such a relationship suggests that basing dosage titration on the patient's own account of these side effects will not be a reliable means of achieving therapeutic drug concentrations. The results of these studies in depressed pediatric patients show how TDM can offer a significant improvement over the standard method of determining dosage by clinical response.

In contrast to nuisance side effects, the occurrence of CNS toxicity (Table 3) is strongly related to TCA concentrations in plasma. There have been several independent studies where CNS toxicity (i.e., TCA-induced delirium) have been reported in patients. Cumulatively, they comprise nearly 1000 patients, from children to the elderly. In these studies, the incidence of CNS toxicity ranged from 1.5% to 13%, and in most of these studies was between 4.0% and 8.0% in patients taking standard clinical doses of TCAs (Table 4).

Various factors may explain the variability in the risk of developing TCA-induced CNS toxicity reported in these studies. First, these studies examined different populations. One dealt exclusively with children (16); another concentrated on the elderly (15); most examined a general adult population (9). Second, definitions of CNS toxicity varied somewhat between studies. Some investigators specifically reported only patients with frank delirium (9, 14). Others included a broader sample of patients who experienced more subtle symptomatology (15). Nevertheless, these figures demonstrate that a significant proportion (on average, 6%) of a general psychiatric population treated with standard doses of TCAs experience CNS toxicity. Interestingly, the overall incidence of 6% is in the range of 4.0 to 7.0% of individuals who, on standard doses of TCAs, will achieve values above 450 µg/L (17). Thus, the proportion of patients who develop excessively high TCA concentrations in their plasma is virtually identical to the proportion who develop CNS toxicity. Although interesting, this comparison does not by itself support a cause/effect relationship between high TCA in plasma and CNS toxicity.

Examination of several studies reporting values for TCA in plasma of patients who are experiencing symptoms of CNS toxicity does support a causal relationship. In these studies, the relationship of CNS toxicity to supratherapeutic TCA concentrations in plasma is striking. In three controlled studies with AMI, IMI, and DMI, 450 µg/L was used as a threshold (Table 5). A summary of these studies yields 27 patients with values >450 µg/L, and 98 with values <450 µg/L. Of the 27 patients, 18 (67%) had CNS toxicity attributable to the TCA. Only one of the 98 patients with values <450 µg/L experienced such toxicity.

Other studies have examined a lower threshold of 300 µg/L and also find significant results (Table 6). In this case, 33% of the patients with total TCA >300 µg/L developed symptoms of CNS toxicity, while only 3% of those with lower values developed toxicity. In these reports, the number of patients with TCA values >450 µg/L was not given, but the trend towards increased risk of CNS toxicity with higher TCA concentrations is clear. Thus, of the 367 patients studied in these six reports, the vast majority of the 41 who had CNS toxicity also had plasma TCA values well above the therapeutic range. Without TCA therapeutic monitor-
ing, a small but significant proportion of patients who were receiving standard doses of TCAs will develop such drug concentrations in their plasma.

Variability of TCA Plasma Concentrations

Significant differences in TCA concentrations in plasma occur among patients who are receiving the same dose of the same TCA (Table 2). A 10- to 30-fold difference in TCA concentration in plasma is routinely found between the fastest and slowest metabolizers who are receiving the same dose of a given drug. Such variability is primarily determined genetically (19). Physical illnesses—especially cardiac, liver, and renal disease—and advanced age can further accentuate such variability. This variability is clinically important. For example, of 350 patients treated with standard doses of amitriptyline, half were outside the apparent optimum plasma drug range, about 30% were below, and the rest were above this range (10).

Although the drug concentration in plasma that a patient will achieve on a given dose of a TCA is primarily determined by genetics, many other variables can also affect the steady-state value achieved on a given dose. For example, there is a strong relationship between advancing age and drug concentration in plasma (20). If the total TCA (AMI + NT) concentration in plasma is plotted as a function of age, there is no relationship between age and concentration for patients under 40. But for those older than 40 years, there is, for AMI, a linear direct relationship between age and total TCA in plasma. In fact, patients older than 60 y develop approximately twice the plasma concentration per milligram of AMI administered as do patients under 40. This observation provides a rationale for the common clinical practice of initiating TCA therapy in the elderly at approximately half the standard dose used for younger individuals. However, there is still large interindividual variability in TCA elimination rates (and hence concentration in plasma) in the geriatric population. Consequently, some elderly patients will develop concentrations approximating those of younger patients who are slow metabolizers. Others will develop concentrations in plasma that exceed the average for patients under 40 by more than twofold.

Metabolism of the hydroxylated forms of TCAs is also age-dependent. Recent studies suggest that, in younger patients, concentrations of 10-hydroxyamitryptiline are equal to or up to twice those of the parent drug. In the elderly, however, this ratio is increased to three- to fourfold (21). The mechanism of this age-related increase in TCA in plasma is not well understood but may be related to declines in liver mass, hepatic blood flow, and hepatic enzymatic content and activity, as well as age-related changes in renal function affecting the elimination of the hydroxylated metabolites.

Regardless of the reason, the relationship between age and the drug concentration in plasma provides the clinician with a rationale for modifying the starting dose for elderly patients as a general rule. More important, it underscores the advantages of TDM of TCA to rationally guide individual dosage adjustment.

Alcohol can significantly impair the ability of the liver to extract the drug from portal blood, so that acute alcohol ingestion before taking the TCA can increase the amount of TCA absorbed by a factor of two to three (22). The first-pass metabolism of TCAs is also an important consideration in patients with various medical conditions. For example, cirrhosis of the liver causes significant portocaval shunting. As a result, blood bypasses the liver, leading to high drug concentrations in plasma and hence higher concentrations of the drug in the tissues. Thus, such patients are put at risk for increased adverse side effects of drugs.

Concomitant medications also affect concentrations of TCAs in plasma. For example, neuroleptic drugs inhibit TCA metabolism (23). Starting a standard dose of neuroleptic drug can induce a 50% to 100% increase in TCA in plasma, owing to such inhibition. Conversely, discontinuation of a neuroleptic can cause a decline in TCA in plasma because of the loss of neuroleptic-induced enzyme inhibition. Cimetidine, widely used in the treatment of ulcers, has an identical effect, through a combination of decreased gastric motility and liver enzyme inhibition (24). Barbiturates and related drugs induce hepatic enzyme systems, increasing TCA metabolism and therefore decreasing the concentration that will be achieved on a given dose. Patients taking standard doses of barbiturates will develop TCA concentrations in plasma that are 50%–100% below the concentration they would otherwise achieve. Conversely, if the barbiturate is discontinued in a patient who is taking both a barbiturate and a TCA and was previously at a steady-state condition, there will be an increase in TCA in plasma owing to the loss of the enzyme-inducing effects of the barbiturate. In essence, stopping the barbiturate without adjusting the dose of the TCA is equivalent to doubling the dose of the TCA.

Dosage Adjustment by Steady-State and Single-Dose TCA Concentrations in Plasma

These data on the relationship between TCA in plasma and clinical response are based on steady-state or stable TCA concentrations in plasma. Most medications, including TCAs, are metabolized in direct proportion to the amount of drug accumulated in the body; i.e., they follow first-order pharmacokinetics. Consequently, there is a generally linear or proportional relationship, over a reasonable range, between TCA in plasma and the amount of drug administered, with the possible exception of some elderly or medically ill patients (25, 26). This proportional relationship between dose and concentration means that patients with a concentration of 100 µg/L while taking 50 mg/day will attain approximately twice this concentration when the dose is doubled. Once the relationship between dose and steady-state concentration in plasma is known for a given patient, the clinician can make changes in dosage to achieve proportional changes in the drug concentration in plasma. Using this proportionality between dose and concentration within an individual, the clinician can also use repeated TDM to assess compliance. A change in dose that does not produce a concomitant and proportional change in drug values is presumptive evidence that the patient is not complying. Or there might be a bioavailability problem resulting from changing brands of the drug.

Medications that adhere to first-order kinetics also clear or decrease in the plasma compartment by 50% according to the specific drug's biological half-life. With a concentration of 100 µg/L in plasma, it will take one half-life to reach 50 µg/L and then another to reach 25 µg/L. The concepts of half-life and first-order kinetics are extremely helpful in TDM. A standard principle is that it should take approximately five half-lives to attain steady-state. NT has a half-life of approximately 36 h (Table 2); therefore, it will take approximately 180 h (seven to eight days) to attain steady-state. It is important to point out the wide range of NT's half-life. A rapid metabolizer will require only three days to
attain steady-state; a slow metabolizer will require 11 or 12 days. This wide range underscores the potential advantages of utilizing single-dose prediction to hasten rational dosage adjustment, thus speeding the attainment of therapeutic concentrations and shortening the lag time before antidepressant effects begin to appear. This approach is based on the fact that the same first-order pharmacokinetic factors that eventually determine the final steady-state TCA concentrations in plasma are active after the first dose. Several studies have demonstrated excellent correlation between values for several TCAs (e.g., NT) sampled 24, 36, and 48 h after a single dose and the final steady-state concentration in plasma achieved on the same dose (27–29). In the most common prediction test, plasma is sampled 24 h after a single dose and, on the basis of that result, an individualized dosage regimen is suggested that will maximize the chances that the eventual steady-state concentration will be within the therapeutic range. Single-dose prediction testing could represent a significant advance over conventional treatment. It may lead to decreased lengths of stay for hospitalized patients, an important consideration with the present emphasis on medical cost containment.

TDM of TCAs has emerged as a clinically useful and cost-effective tool in the medical management of depression. TDM permits physicians to rationally adjust the dosage of TCAs for which effective concentrations have been well characterized. TDM of these medications can improve clinical response and avoid drug toxicity, thereby helping the physician to provide safe and efficacious treatment in a cost-effective manner.

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References