REVIEW

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Tricyclic antidepressant poisoning

ABSTRACT

Tricyclic antidepressant poisoning causes predictable electrocardiographic abnormalities and can be lethal. Cardiac arrhythmias, hypotension, seizures, and coma are common. Sodium bicarbonate is still considered the treatment of choice for severe toxicity, although a variety of supportive measures may be taken. Hypertonic saline appears to be a promising alternative.

KEY POINTS

A QRS interval longer than 100 ms appears to be a better predictor of serious complications than is an elevated serum tricyclic antidepressant level.

Cardiovascular toxicity is classically manifested as ventricular dysrhythmias, hypotension, heart block, bradyarrhythmias, or asystole.

Activated charcoal binds tricyclic antidepressants. Give 30 to 50 g orally or by nasogastric tube with or without a cathartic (sorbitol 0.5 g/kg or 30 g of magnesium sulfate).

Sodium bicarbonate is indicated if the QRS duration is more than 100 ms or the terminal right-axis deviation is more than 120°. The suggested dosage is 1 to 2 mEq/kg, repeated as needed.

Tricyclic antidepressants are used not only for depression but also for chronic pain syndromes, obsessive-compulsive disorder, panic and phobic disorders, eating disorders, migraine prophylaxis, and peripheral neuropathies.

AFTER A REPORTED OVERDOSE, a 54-year-old woman was brought to the emergency department. She had a history of suicidal ideation, having presented 2 years earlier threatening to slash her wrists. Emergency medical services personnel reported that the contents of a bottle of imipramine were unaccounted for.

On arrival, the patient was breathing spontaneously but was drowsy and noncommunicative. She moaned incoherently in response to painful stimuli. She was given 2 grams of naloxone without effect. A rapid blood sugar test indicated her blood glucose level was 127 mg/dL. Thiamine 100 mg was given. Blood was drawn for arterial blood gases (TABLE 1), a complete blood count, toxicologic screening, and levels of electrolytes, ethanol, acetaminophen, and salicylates. A urine sample was sent for toxicology screening. Oxygen was started via a nasal cannula.

Physical examination

The patient's skin was dry and flushed. Her sclerae were anicteric; her pupils were 6 mm and sluggishly reactive to light. She had no fixed motor abnormalities; she withdrew symmetrically from painful stimuli. Her extremities had no track marks, cyanosis, or edema. Her breath sounds were symmetric. Cardiac examination revealed no murmurs, gallops, or rubs. Her abdomen was soft with diminished bowel sounds. Her stool tested negative for occult blood.

Treatment

Recognizing the likelihood of tricyclic antidepressant (TCA) overdose, the physicians started specific therapy for it. Sodium bicarbonate 2 ampules (88 mEq) was given intravenously, plus another 44 mEq in an infusion of dextrose 5% and 0.45% saline. Although the patient was noncommunicative, she was breathing

spontaneously and was clinically able to protect her airway; for this reason, she was not intubated. Gastric lavage with saline retrieved no visible pill fragments. She was given 50 grams of activated charcoal via a 40-French orogastric tube.

An electrocardiogram revealed sinus tachycardia with a heart rate of 110 beats per minute, with a QRS duration of 114 ms (FIGURE 1). The sinus tachycardia was felt to be consistent with tricyclic antidepressant poisoning. The patient received two more 44-mEq boluses of sodium bicarbonate while in the emergency department and was admitted to a monitored bed.

The laboratory reported that the patient's initial tricyclic antidepressant level was 1,179 ng/mL (therapeutic range 200–300 ng/mL). Three days later, her imipramine level was 170 ng/mL and her desipramine level was 158 ng/mL, for a combined imipramine-desipramine level of 328 ng/mL. The patient was transferred for psychiatric referral on the third hospital day.

TABLE 1

The patient's blood gas values

TEST	ON ADMISSION*	30 MINUTES LATER†	NORMAL RANGE
pH	7.27	7.39	7.35–7.45
Pco_2, mm Hg	52	52	(34–46)
Pao_2, mm Hg	66	196	(85–95)

*While breathing room air
†While receiving oxygen via a nasal cannula

TRICYCLIC ANTIDEPRESSANT OVERDOSE: 120 DEATHS PER YEAR

How common is toxicity?

Although the incidence may decline now that safer antidepressants are available, in recent years, tricyclic antidepressant (TCA) toxicity has been the cause of 120 deaths per year among approximately 19,000 cases of overdose.[1]

TCA toxicity is a long-standing problem. In the 1980s, TCAs were the fourth most common cause of overdose seen in emergency departments in the United States,[1] and accounted for 37% of all poison-related admissions to intensive care units.[2] In 1992, they were responsible for more than 25% of drug-related deaths reported to poison centers.[3] In 1995, 168 antidepressant-related deaths were reported to the American Association of Poison Control Centers database, making antidepressant toxicity the most prevalent cause of fatalities due to drug ingestion that year.[4] In 1997, 154 deaths were attributed to antidepressant overdose—second only to the rate due to narcotics overdose, by drug class.

The frequency of overdose is not unexpected, since TCAs are used to treat depressed patients who may become suicidal. In addition, many patients take them for other indications, including chronic pain syndromes, obsessive-compulsive disorder, panic and phobic disorders, eating disorders, migraine headache prophylaxis, and peripheral neuropathies. The primary care provider will therefore continue to see TCA toxicity even though newer and safer antidepressants are available.

Is TCA toxicity always the result of intentional overdose?

No. Many mechanisms have been proposed to explain how TCA toxicity can develop while taking therapeutic doses. Patients may be taking medications such as antihistamines and antipsychotic medications that have similar pharmacologic actions. Some patients metabolize TCAs slowly or are taking drugs with the potential to inhibit metabolism of TCAs. Patients with an underlying seizure disorder or cardiac disease may develop TCA toxicity at therapeutic doses.

TCAs cause more deaths than any other class of prescribed drugs

What are the chemical properties of TCAs?

TCAs all consist of a three-ring aromatic nucleus with an aliphatic amino propyl side chain; the structure of the side chain differs among the various agents.

The "tertiary" TCAs such as amitriptyline and imipramine (also called tertiary amines) undergo demethylation in the liver, yielding pharmacologically active metabolites called secondary amines: amitriptyline is metabolized to nortriptyline and imipramine is metabolized to desipramine. Laboratory measurements of imipramine and amitriptyline

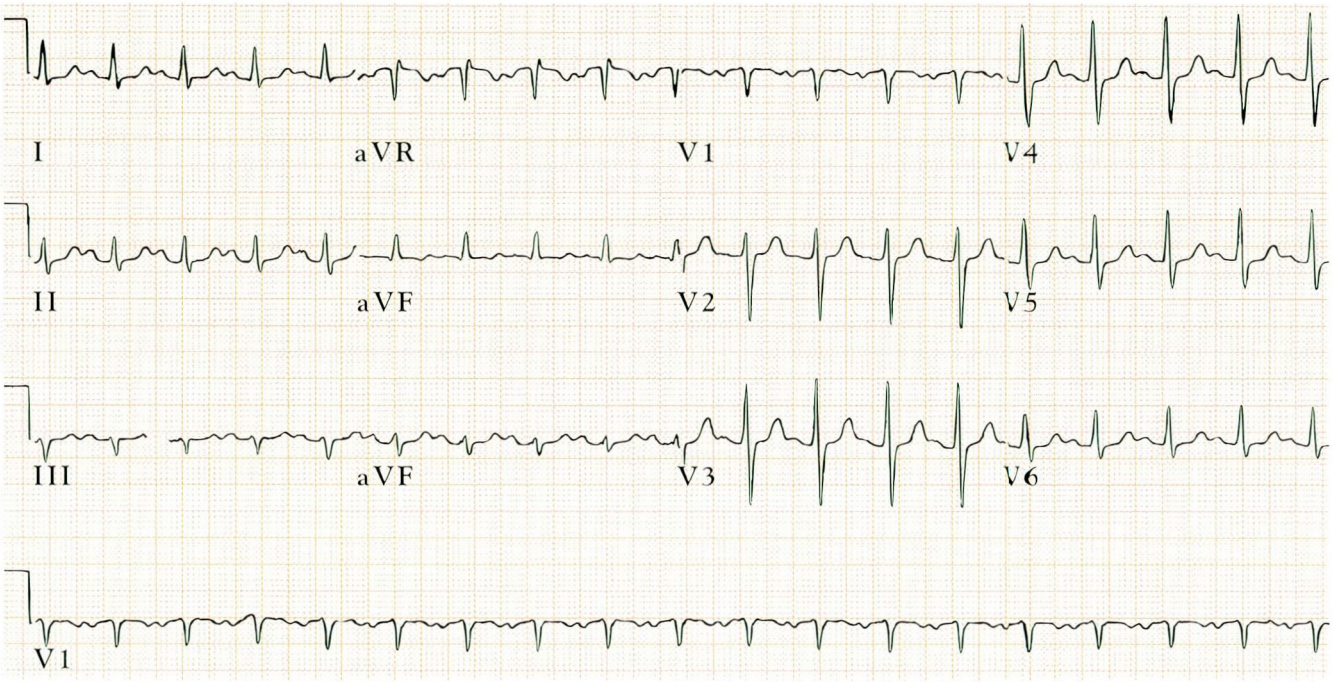

FIGURE 1. The patient's electrocardiogram, demonstrating sinus tachycardia and a QRS duration of 114 ms.

The rate of TCA elimination varies widely from patient to patient

levels reflect both the tertiary amine and its active metabolite.

Most other TCAs such as doxepin have minor alterations of the basic three-ring structure. Doxepin is a tertiary amine and is metabolized to desmethyl doxepin.

Other cyclic antidepressants exist, two of which have the same potential for causing seizures and cardiovascular toxicity as do the TCAs: amoxapine, a tricyclic dibenzoxipine compound first marketed in the United States in 1980, and maprotiline, the first tetracyclic antidepressant (TABLE 2).[5]

What are the pharmacokinetics of TCAs?

TCAs are rapidly absorbed from the gastrointestinal tract, reaching peak serum concentrations 2 to 8 hours after a therapeutic dose. Their elimination is almost entirely due to hepatic metabolism, and the rate of elimination varies from patient to patient. They are partially secreted into the bile, reabsorbed, and excreted by the kidneys. The half-life of TCAs ranges from 25 to 81 hours,[6] but may be longer in overdose.

Therapeutic doses are generally in the range of 1 to 5 mg/kg per day. In most overdose cases involving life-threatening symptoms or death the patient took more than 10 mg/kg: most of those who died ingested more than 1,000 mg. However, life-threatening symptoms and deaths have occurred with the ingestion of as little as 500 mg.

Of note: serum antidepressant levels may rise after death as TCAs are released from tissue, so serum levels may not accurately reflect risk to the patient or adequacy of resuscitation while alive.

How does volume of distribution affect therapy?

TCAs have a large volume of distribution (10–20 L/kg), and in some tissues such as the heart tissue levels are 10 to 100 times blood levels.[7] Moreover, they are highly (up to 95%) protein-bound, representing pharmacologically inactive drug.

Since only 1% to 2% of the total body store of TCAs is found in blood, TCAs are extremely difficult to remove. Hemoperfusion, hemodialysis, and forced diuresis are unproductive.

How do TCAs induce toxicity?

TCAs have at least four major properties that induce toxicity; these are discussed in order of lethality.

TCAs block the fast sodium channel in heart muscle cells, slowing the speed of ventricular conduction. This effect is manifested most commonly by a prolonged QRS interval, corresponding to phase 0 depolarization. Sodium channel blockade is often referred to as a membrane-stabilizing or local anesthetic effect.

Impaired sodium entry into myocardial tissue leads to decreased contractility. Bradycardia with widening of the QRS complex indicates profound sodium channel blockade. In fact, the most potent sodium channel blocker, desipramine, also causes the highest mortality.

This effect is similar to that of the type Ia antiarrhythmic drugs, such as quinidine, procainamide, and disopyramide. In TCA poisoning, therefore, the practitioner should avoid the use of these agents for any reason.

TCAs have anticholinergic effects, including dry mouth and axillae, sinus tachycardia, flushing, dilated pupils, intestinal ileus, urinary retention, and hyperthermia. Central anticholinergic effects include agitation, hallucinations, confusion, sedation, coma, and seizures.

TCAs have alpha-1 antiadrenergic actions, inhibiting the amine pump and thereby blocking the reuptake of norepinephrine and serotonin, allowing these neurotransmitters to accumulate at central nervous system sites. This is also how TCAs exert their therapeutic effect. Patients may present with tachycardia and hypertension initially, and with hypotension later. Optimal treatment of hypotension in TCA overdose is based on this action.

TCAs cause competitive antagonistic binding of histamine.[8]

Do other antidepressants cause similar toxicity?

Bupropion (a unicyclic antidepressant), trazodone, and the selective serotonin reuptake inhibitors (SSRIs) fluoxetine, sertraline, paroxetine, and fluvoxamine have a markedly different toxicity profile and are not linked toxicologically to the TCAs. TCAs are considerably more lethal than the SSRIs.[9]

What are the typical causes of death in TCA overdose?

TABLE 2

Cyclic antidepressants available in the United States

GENERIC NAME	PROPRIETARY NAME
Tricyclics	
Tertiary amines	
Amitriptyline	Elavil
Amoxapine	Asendin
Clomipramine	Anafranil
Doxepin	Sinequan
Imipramine	Tofranil
Trimipramine	Trimipramine
Secondary amines	
Desipramine	Norpramin
Nortriptyline	Pamelor
Protriptyline	Vivactil
Tetracyclics	
Maprotiline	Ludiomil
Mirtazapine	Remeron
Other older antidepressants	
Nefazodone	Serzone
Venlafaxine	Effexor

Note: All of the cyclic antidepressants have been reported to induce seizures and tachycardia in overdose

The therapeutic range for TCA levels is 200 to 300 ng/mL

The most feared complications are cardiac and central nervous system disorders. These generally occur within 4 to 6 hours of arrival at the hospital and seldom if ever occur more than 24 hours after presentation. Patients who have ingested an overdose of TCAs can deteriorate catastrophically even if they present with trivial or no signs of poisoning, generally within 1 hour of presentation.

Cardiovascular toxicity is classically manifested as ventricular dysrhythmias, hypotension, heart block, bradyarrhythmias, or asystole. Hypotension in TCA overdose may be a result of decreased contractility, blockade of norepinephrine reuptake, and reduced myocardial catecholamine levels. Alpha-adrenergic blockade, negative inotropy, decreased cardiac output, and catecholamine depletion may all be synergistic in lowering blood pressure.[10]

TABLE 3

Complications of tricyclic antidepressant overdose

Aspiration pneumonia
Anoxic encephalopathy
Hyperthermia
Rhabdomyolysis
Acute renal failure
Pulmonary edema
Seizures (usually brief)
Hypercapnia
Respiratory arrest
Arrhythmias

Early central nervous system effects include confusion, delirium, and hallucinations. Later, any of the following may occur: clonus, choreoathetosis, hyperactive reflexes, myoclonic jerks, extensor plantar response, seizures, or coma.

Respiratory depression may precede either cardiac or central nervous system events. TABLE 3 enumerates some complications of TCA overdose.

Suspect concomitant ingestions in any TCA overdose

DIAGNOSING AND ASSESSING TRICYCLIC OVERDOSE

Why test for other substances in intentional TCA overdose?

In up to 70% of cases of intentional overdose, patients also ingest other drugs or alcohol. Our patient's serum ethanol level was 248 mg/dL, which undoubtedly contributed to her depressed level of consciousness. (Serum ethanol levels greater than 100 mg/dL may indicate intoxication.) Her urine toxicology screen was positive for benzodiazepines. No acetaminophen or salicylate could be detected in her serum.

No single screening test can detect all the possible drugs a patient may have taken. Therefore, it is important to test for substances with which the presentation is consistent. Benzodiazepines and cocaine are frequently coingested, and it is reasonable to obtain qualitative urine toxicologic screening for them in most cases of intentional overdose of any substance. In addition, acetaminophen use is ubiquitous and an antidote for it is available; therefore, many believe in checking for acetaminophen in all potentially serious cases of ingestion.

Are serum TCA levels of value in acute overdose management?

Quantitative serum levels are not generally available on a "stat" basis, and do not typically guide emergency treatment. Qualitative screening tests exist for detecting TCAs in the urine (Biosite Diagnostics) and serum (DuPont), and take approximately 15 minutes to perform.[11]

Serum TCA levels greater than 1,000 ng/mL have been associated with QRS durations longer than 100 ms, but studies have shown serum levels to be unreliable for predicting complications. Convulsions, conduction disturbances, and dysrhythmias have occurred with TCA levels as low as 571 ng/mL. On the other hand, other patients with levels as high as 3,660 ng/mL have not had seizures or cardiovascular evidence of poisoning.[12] Serum TCA levels also do not adequately predict toxicity based on the level of orthostatic hypotension or QRS interval prolongation. The therapeutic range for TCA levels is 200 to 300 ng/mL.[13]

Structurally similar drugs may cross-react and give false-positive results on qualitative screening tests for TCAs. These include diphenhydramine, cyclobenzaprine, cyproheptadine, carbamazepine, and phenothiazines. Not surprisingly, some of these substances share certain toxicities with TCAs.

Quicker ways to diagnose TCA toxicity have been sought, including risk stratification by electrocardiography.

Can the electrocardiogram be used for risk stratification?

Yes. A variety of electrocardiographic findings are useful in cases of TCA overdose.

The QRS duration is often prolonged (ie, > 100 ms). In 80% to 90% of cases, the QRS duration has already reached a maximum by the time the patient comes to the emergency department, and in the remaining 10% to 20% of cases it reaches a maximum within a mean of 3 hours of presentation.[14]

The QRS duration is commonly used to assess likelihood of toxicity. In one report,[12] no patient whose QRS duration was less than 100 ms (0.10 seconds) developed seizures or ventricular dysrhythmias, but those with a QRS duration longer than 100 ms had a 34% incidence of seizures and a 14% incidence of ventricular dysrhythmias. Ventricular dysrhythmias were seen only in patients whose QRS duration was more than 160 ms. Those with a QRS duration of 100 to 160 ms had a moderate risk of seizures but a negligible risk of ventricular arrhythmias. QRS duration appeared to be a better predictor of toxicity than were TCA levels. Patients with a QRS duration less than 100 ms rarely have a seizure or dysrhythmia. When the QRS duration was more than 160 ms, the incidence of seizure was 50%.[12]

The QRS duration may be hard to measure accurately, however. One study[15] found that, in 20% of cases, three experienced toxicologists disagreed as to whether the maximal QRS duration was longer or shorter than 100 ms. This problem can be reduced by increasing the paper speed from 25 to 50 mm/second.

TCAs are difficult to remove: hemodialysis is ineffective

Other conduction abnormalities may include prolonged PR, QRS, and QT intervals (eg, a corrected QTc ≥ 418 ms), and right bundle branch block. High-degree AV blocks are unusual. These abnormalities normalize within a median time of 30 hours in 50% to 60% of patients who present with a QRS interval of more than 100 ms.[16]

Axis deviation. The most specific electrocardiographic sign of TCA toxicity is a distortion of the terminal 40-ms vector of the QRS complex in the frontal plane (T40-ms axis). A terminal QRS axis of between 130° and 270° appears to be a sensitive and specific indicator of toxicity.[17] It is postulated that the distal conduction system of the right side of the heart is most susceptible to TCAs.

The diagnosis may be made most easily by looking for an R wave in aVR, with an S wave in lead 1. This finding resolves with recovery (FIGURE 2). An R/S ratio of 1:4 and an R wave of 3 mm or more in aVR may predict subsequent seizures and arrhythmias.[18]

Wolfe et al[19] confirmed that the mean T40-ms axis was significantly higher in a group of patients with TCA overdose group than a group that had overdosed on other drugs (179° vs 86° mean). In that study, 8 of 48 patients with TCA overdose did not have a T40-ms axis of 120° to 270°. Nonetheless, only half of patients with a T40-ms axis greater than 140° will develop an event such as seizure or dysrhythmia. The T40-ms axis is generally maximal at time of presentation or at most 3 hours after arrival and frequently does not normalize during hospitalization.

Dysrhythmias and other abnormalities associated with TCA overdose include:

- Sinus tachycardia
- Other supraventricular dysrhythmias (AV junctional tachycardias, atrial fibrillation and flutter)
- ST-T wave changes
- Ventricular dysrhythmias: premature ventricular contractions, idioventricular dysrhythmias, ventricular tachycardia including torsades de pointes, ventricular fibrillation
- Asystole.

Duration of abnormalities. In one report,[14] electrocardiographic abnormalities persisted significantly longer in patients who developed seizures or dysrhythmias. They may persist long after the danger from clinical toxicity has passed.

Can we predict early on who is at risk of complications?

In one review[20] of 165 patients presenting with TCA overdose, no patient developed a major complication without having an arrhythmia, coma, seizure, conduction defects, or significant alteration in mental status in the emergency department. Sinus tachycardia alone did not predict complications. In 18 fatal cases of TCA overdose,[21] the initial signs most commonly found in the emergency department included coma, tachycardia, hypotension, respiratory depression, and seizures. QRS prolongation was present initially in only 5 (28%).

In one case,[22] a 38-year-old woman was stable for 6 hours in the emergency department but died within 3 hours of admission to a psychiatric service. Her only signs of poisoning in the emergency department were slurring of speech and an initial tachycardia of 125 beats per minute.

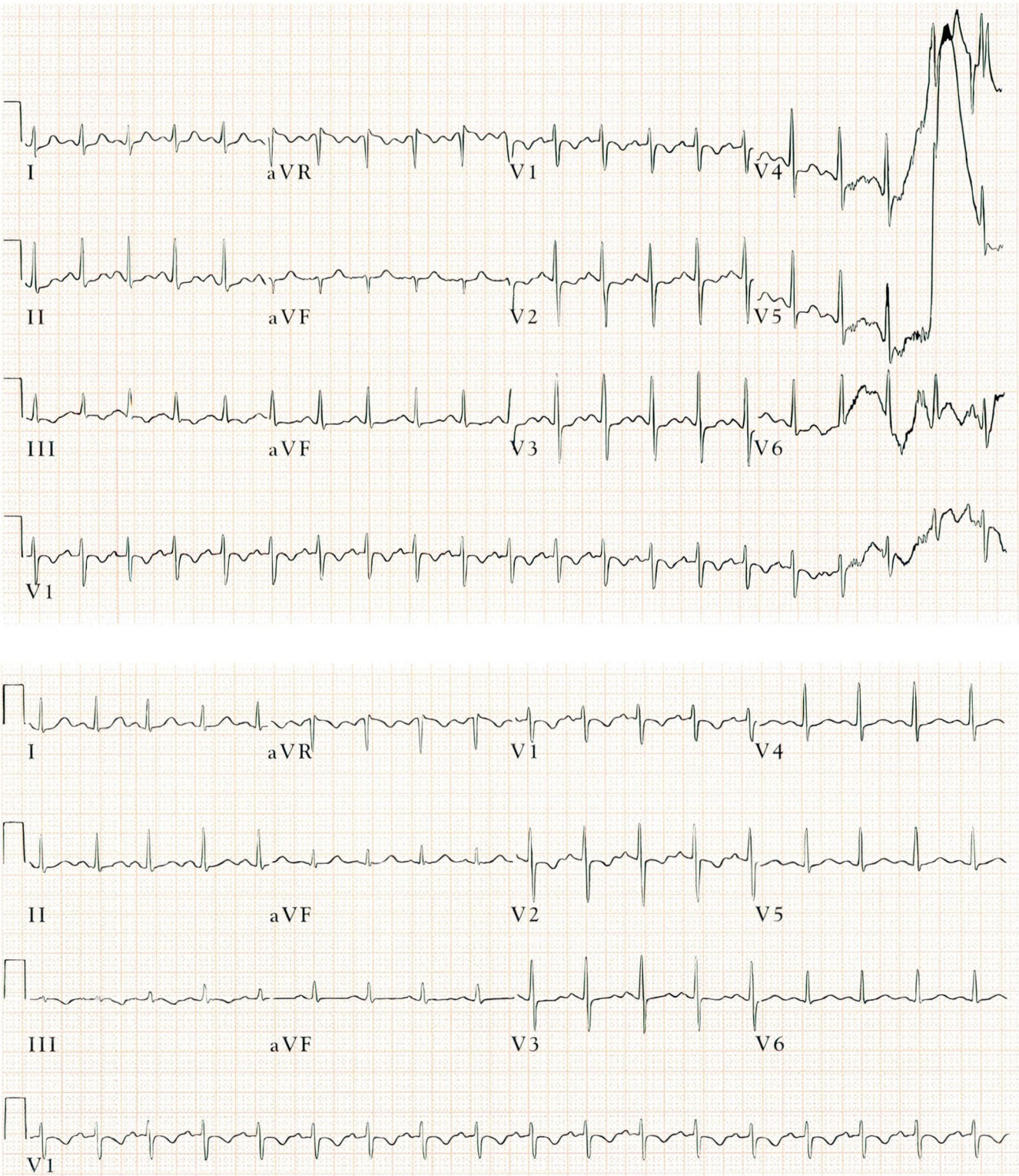

FIGURE 2. Serial electrocardiograms from a different patient, a 43-year-old woman who had also taken an overdose of a tricyclic antidepressant. **Top,** the tracing on presentation in the emergency department shows deep S waves in lead 1 and R waves in lead aVR. These findings, representing a rightward shift of the terminal 40 ms of the QRS complex, had resolved by the time the second tracing was obtained 4 hours later (**bottom**).

In another review[23] of 92 patients presenting with TCA overdose, the level of consciousness in the emergency department was the best predictor of serious complications, including seizures, hypotension, hemodynamically significant arrhythmias, or death. A Glasgow coma score of less than 8 was a more sensitive predictor of serious complications in this report than was the QRS interval.

TREATING OVERDOSE

What are the suggested criteria for admission?

The following, if present in the emergency department, mandate admission:

- A QRS interval of more than 100 ms (Note: in one series this alone did not predict serious complications.[20])
- An abnormal T40-ms axis on presentation
- Altered mental status
- Significant anticholinergic symptoms
- Seizures
- Vital sign abnormalities
- Conduction defects other than isolated QTc prolongation
- Depressed respiration
- CNS depression.

Patients with no signs or symptoms for 6 hours after ingestion or those whose most serious evidence of toxicity is sinus tachycardia may be medically cleared. Psychiatric consultation may then be accomplished as with any other intentional overdose.

What is optimal emergency treatment?

Start supportive care in any case of suspected TCA ingestion; this should include cardiac monitoring and an intravenous line. Catheterize the bladder if the patient has urinary retention, hypotension, or depressed level of consciousness. Insert a nasogastric tube if bowel sounds are absent.

Specific therapies include the following:

Gastrointestinal decontamination. Activated charcoal binds TCAs. Give 30 to 50 g orally or by nasogastric tube with or without a cathartic (sorbitol 0.5 g/kg or 30 g of magnesium sulfate).

Gastric lavage is most effective if done within the first few hours after ingestion. It has never been shown to be superior to charcoal alone, and the recovery of ingested drug is poor—only an average of 110 mg of ingested TCA in one report.[24] However, some argue that since TCAs have anticholinergic effects and therefore delay gastric emptying, performing lavage may still be effective to prevent drug absorption later after ingestion than with other substances that do not delay gastric emptying.[5] In one large study of 472 poisonings in which the time of ingestion could be ascertained, the mean time from ingestion to arrival in the emergency department was 3.3 hours.[25]

Inducing vomiting with syrup of ipecac poses the risk of aspiration in patients with obtundation, potential seizures, and depressed level of consciousness, probably outweighing any benefits. In addition, ipecac has a prolonged duration of emetic effect, which can delay the administration of activated charcoal.[26]

Alkalinization of serum. Sodium bicarbonate is indicated if the QRS duration is more than 100 ms or the terminal right-axis deviation is more than 120°. The suggested dosage is 1 to 2 mEq/kg, repeated as needed. Add 3 ampules of sodium bicarbonate to 1 L of dextrose 5% or 2 ampules to 1 L of dextrose 5%/0.45% saline and infuse at 2 to 3 cc/kg/hour. The target serum pH is 7.45–7.55. Replace potassium as needed. The intent is not to alkalinize the urine, as for salicylate ingestion, unless rhabdomyolysis is present.

Activated charcoal binds TCAs: give 30–50 g by mouth or NG tube

Proposed mechanisms of action of bicarbonate include:

- Increasing the serum sodium concentration (At least one animal experiment indicates this may be the most important benefit of sodium bicarbonate therapy.[27])
- Lowering the serum potassium concentration; hypokalemia may protect against quinidine toxicity
- Decreasing the serum TCA concentration by dilution, and possibly by decreasing the unbound fraction of TCAs
- Increasing the blood pH, as acidosis has been shown to decrease the rate of phase 0 depolarization of isolated atrial muscle
- Expanding intravascular volume.

Hyperventilation to induce alkalosis may be a reasonable alternative, especially in

patients with renal failure, pulmonary edema, or cerebral edema. However, it induces a potentially dangerous alkalosis, especially in combination with sodium bicarbonate, with possible ionized hypocalcemia and impaired tissue oxygen delivery. In one animal study, hyperventilation did not shorten the QRS duration. Sodium loading and bicarbonate therapy may be more effective.

Correcting arrhythmias. Sodium bicarbonate is the therapy of choice. Lidocaine may be given for ventricular arrhythmias. Avoid class Ia agents (quinidine, procainamide, disopyramide), Ic agents (flecainide, encainide), beta-blockers, calcium channel blockers, and class III antiarrhythmic agents.

Treating hypotension. Hypotension should be treated aggressively. Metabolic acidosis will slow intraventricular conduction and predispose to life-threatening arrhythmias.

Dopamine may be ineffective because presynaptic norepinephrine stores are depleted by TCA poisoning, so any indirect pressor that acts by triggering the release of endogenous norepinephrine would not be indicated.

Treat hypotension aggressively in TCA overdose

Alpha agonists that act directly on postsynaptic receptors (norepinephrine, levarterenol) are posited to be more effective than dopamine, which requires presynaptic norepinephrine for its indirect pressor activity.[28] Therefore, norepinephrine is the pressor of choice if volume replacement alone does not raise the blood pressure.

Refractory hypotension has been treated successfully with glucagon, which has inotropic and chronotropic qualities.[29] Treat with fluids (0.9% NaCl in 10 mL/kg boluses, up to 30 mL/kg), and sodium bicarbonate. Hyperventilation as discussed above may be a consideration.

Treating seizures. Benzodiazepines are the drugs of choice for terminating seizures, which typically are brief in TCA overdose. The GABA-A antagonists diazepam (0.1 mg/kg) and lorazepam (0.04 mg/kg) are the initial drugs of choice. If further seizure control is needed, barbiturates (phenobarbital 15 mg/kg) or propofol may be needed. An adequate airway must be assured.

Some caveats. Flumazenil can precipitate seizures in TCA overdose or with mixed overdose involving benzodiazepines.[30–32] Physostigmine is no longer indicated in the management of TCA overdose. It causes its own toxicity, and it is now recognized that patients do not succumb to the anticholinergic effects of TCAs. Profound and fatal alkalemia can result from bicarbonate infusions combined with hyperventilation.[33]

Other intensive interventions. If advanced life-support measures, fluid replacement, vasopressor therapy, and other measures to decontaminate and enhance elimination of the agent fail, femoral-femoral extracorporeal circulation may help.[34] Some patients have survived even after prolonged resuscitation, including periods of asystole for over 90 minutes.

What newer therapies show promise?

Sodium bicarbonate is still the treatment of choice in reversing severe TCA toxicity; the following are experimental.

Neutralizing antibodies. Antibodies against imipramine and nortriptyline have been used in studies in animals. However, to neutralize an ingested dose of TCA with an equimolar dose of Fab fragments requires an excessive amount of protein to be injected.[35,36] For example, a 28 mg/kg dose of desipramine in a 70-kg man might require 330 g of antibody.[37] In addition, each antibody is drug-specific, so that a different one would be needed for each specific antidepressant.

Hypertonic saline. In one animal study of tricyclic toxicity induced by intravenous nortriptyline, hypertonic saline (7.5% NaCl) at 10 mL/kg (15 mEq/kg) was more effective at narrowing a widened QRS complex and raising blood pressure than either hyperventilation or 3 mEq/kg of sodium bicarbonate. The investigators concluded than sodium loading may be the most important factor in reversing TCA toxicity.[38]

When can patients be safely discharged home?

A patient can be sent home after 24 hours with a low risk of seizures or dysrhythmias if:

- He or she has improved clinically
- His or her altered mental status has resolved

- Hypotension has normalized, and
- The abnormal electrocardiographic intervals have improved.

What about psychiatric referral?

Patients who are suicidal require psychiatric evaluation. All patients who have been stabilized medically should be assessed by a psychiatrist before discharge to ensure that they are safe from themselves. Medical clearance entails 12 hours without symptoms. By definition, this includes a normal electrocardiogram, normal mental status, and resolution of all antimuscarinic symptoms.

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