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Treating the Tricyclic Antidepressant Poisoning Victim

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Authors

Tobis, JM

Aronow, WS

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Tricyclic antidepressant drugs have become the modern physician's most common weapon against patient depression. Yet ironically, the overwhelming majority of tricyclic poisoning cases today are suicide attempts—by depressed patients who lose hope and turn these drugs into a final solution to their mental problems.

Another threatening aspect of tricyclics is their narrow range of safety. While a 75 mg dose of imipramine (Tofranil®) is standard for enuresis, a 200 mg overdose may cause death in the child who ingests it accidentally.

Because of the increased use of tricyclics, poisonings due to their abuse are also increasing. Today, for example, physicians issue over 18 million prescriptions for amitriptyline (Elavil®) yearly in the United States alone.

Because our understanding of the pathophysiology of tricyclics is incomplete, there still remains controversy as to the correct treatment for severe complications. However, much is known about the manifestations and clinical stages of tricyclic antidepressant poisoning, as well as the pitfalls encountered treating them. Clearly, in order to respond effectively in an emergency poisoning situation, physicians must be well-versed in the pharmacology, pathophysiology, clinical presentation, and the various modes of therapy available.

Increased CNS Adrenergic Tone

The diversity of actions of tricyclic antidepressant drugs is complex and fascinating. Their basic chemical structure is a central ring with two adjacent benzene rings. Substituting radicals on the central ring creates the various tricyclic compounds. Presently, physicians in the United States can prescribe six tricyclics: imipramine, amitriptyline, desipramine, nortriptyline, protriptyline and doxepin. All are tertiary amines except protriptyline, which is a secondary amine. When ingested, tertiary amines are metabolized by the liver to secondary amines. Both forms have antidepressant effects, as well as the potential to cause toxicity.

The primary route of excretion is renal. They are highly lipid soluble and protein-bound. The usual half-life is between 24 and 72 hours, but this can be extended

with overdosage. Blood levels may not be helpful because there is a wide (up to 10-fold) variability of plasma drug levels for patients taking the same therapeutic doses. However, 15–25 micrograms % is considered to be in the "safe" range. ECG changes can occur below these upper limits in some people. The lethal dose varies between 10 and 30 mg/kg. Peak therapeutic activity occurs approximately two to three weeks after commencing therapy.¹

In therapeutic doses, these agents cross the blood/brain barrier and exert their antidepressant effect by increasing CNS adrenergic tone.²

The tricyclic antidepressants also block the re-uptake of catecholamines at the neural-end organ interface. This leads to an exaggerated adrenergic tone and the

possibility of more severe tachycardia and hypertension. In addition, it lowers the ventricular fibrillation threshold.

Another common property of potent psychotherapeutic drugs including tricyclics, phenothiazines, and anti-Parkinsonian agents is their anticholinergic activity.³ This creates an imbalance in autonomic tone with various

side effects: sinus tachycardia, mydriasis, inhibited salivation, diminished sweating with resultant hyperpyrexia, depressed gastrointestinal motility, urinary retention, and mental changes such as agitation, hallucinations, seizures, and coma.⁴

Finally, these agents have a direct cellular depressant action. In fact, their local anesthetic properties are reported to be more potent than cocaine, causing myocardial contractility and cardiac output to fall with high doses.⁵ This action may also partly explain the cardiac conduction abnormalities seen in overdose victims.

Once ingested, the tricyclics are rapidly absorbed in the small intestine and distribute quickly to lipid stores. There is preferential binding of these drugs to heart muscle with concentrations up to five-fold greater than in skeletal muscle. They have a quinidine-like effect on the myocardium and can thus decrease coronary blood flow, heart rate, and myocardial contractility.¹ In addition, it should be noted that arrhythmias can still occur several

TREATING THE TRICYCLIC ANTIDEPRESSANT POISONING VICTIM

by Jonathan M. Tobis, M.D., Cardiology Division
University of California, Irvine Medical Center
Orange, California
and Wilbert S. Aronow, M.D., Chief, Cardiovascular Section
Veterans Administration Hospital, Long Beach, California

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Denver, Colorado

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Northwestern University Medical
School, Chicago, Illinois
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University Hospitals
Cleveland, Ohio
Harold B. Vogel, M.D.,
Chief
Division of Neurosurgery
Denver General Hospital
Denver, Colorado
Louis Weinstein, M.D., Ph.D.,
Professor
Infectious Diseases
Harvard Medical School
Boston, Massachusetts

days following the ingestion of large amounts of tricyclic antidepressants despite all clinical signs returning to normal.⁶

It is important to avoid the concurrent administration of drugs such as MAO inhibitors, atropine, alpha-methyl-dopa or sympathomimetic amines. In combination with tricyclics, these drugs can cause an atropine-like toxicity.

Four Clinical Stages

The various symptoms exhibited by tricyclic antidepressant overdose victims can be subdivided into different stages which correlate to the severity of the ingestion. Although these stages are useful to describe the manifestations of tricyclic antidepressant excess and estimate prognosis, they are only a guideline and there are overlaps between the divisions. Also be aware that these symptoms may be progressive over time and may recur. As we'll see, close attention to your patient's developing condition through these stages becomes an essential component of successful therapy.

STAGE I

Stage I characterizes victims with predominant anticholinergic side-effects. Your patient may be alert but disoriented, agitated, drowsy or obtunded. The pupils will be dilated and the mouth dry. An ECG usually shows sinus tachycardia with a normal or right axis; the QRS is normal in width. Whether these patients progress to further stages depends on the amount of drug ingested and the time elapsed since the overdose.

STAGE II

Stage II is noted for more severe CNS depression manifested by seizures or coma. There is excess adrenergic activity secondary to the inhibition of catecholamine re-uptake with a subsequent supraventricular tachycardia. Hypertension may be present. The anticholinergic effects still persist with dilated pupils, depressed secretions, inhibited GI motility, and urinary retention.

STAGE III

Deep coma and persisting seizures mark the third stage of tricyclic antidepressant poisoning. Cardiotoxicity and the threat of death present themselves. The patient's QT interval may increase following QRS widening. Supraventricular or ventricular tachycardia may occur and possibly degenerate to ventricular fibrillation. You'll often notice a severe right axis deviation consistent with left posterior hemiblock.

The etiology of severe cardiotoxicity is not completely understood and there are probably multiple factors.⁷ Continuing anticholinergic activity and the excess catecholamines combine to form an increasing imbalance in autonomic tone. The authors demonstrated experimentally a marked lowering of the ventricular fibrillation threshold with amitriptyline.⁸ This effect can be reversed with either physostigmine or propranolol, thus implicating the autonomic imbalance as the etiologic factor. It is important at any rate, to be aware that the overdose victim's vulnerability to ventricular tachycardia and death is great in this stage of toxicity.

STAGE IV

If catecholamines become blocked from neuronal re-uptake, they eventually are cleared. At this point, rela-

tive adrenergic depression manifested by hypotension and bradycardia is evidenced. Your patient may experience a high degree A-V block, severe bradycardia, or cardiac arrest. Conduction abnormalities and heart block may be due to direct effects of tricyclic antidepressants on the myocardium.

TABLE I

Clinical Presentations

| | |
|------------|--|
| Stage I: | Anticholinergic signs: mydriasis, confusion, dry mouth, decreased GI motility, urinary retention, sinus tachycardia. |
| Stage II: | Excess adrenergic effects: supraventricular tachycardia, hypertension, progression of CNS effects to hallucinations, seizures, coma. |
| Stage III: | Marked cardiotoxicity: broad QRS, severe RAD, ventricular tachycardia, ventricular fibrillation. |
| Stage IV: | Catecholamine depletion, cellular depression: hypotension, severe bradycardia, high degree heart block. |

Immediate Response

Victims of tricyclic antidepressant poisoning should have their cardiac status observed immediately with both a continuous cardiac monitor and frequent ECGs. In addition, administer oxygen and respiratory support as indicated from arterial blood gas determinations and clinical status.

You'll also do well to restrict fluid intake, since the degeneration of cardiac capability can lead to pulmonary edema and congestive heart failure. However, in certain stages of tricyclic antidepressant overdose, hypotension occurs. Therefore, be prepared to use a Swan-Ganz catheter during fluid administration.

Patients who present with symptoms of Stage I should receive Ipecac, if alert, or have gastric lavage performed. These maneuvers should be followed by a cathartic such as magnesium sulfate, 15 g for adults and 250 mg/kg in children. Also, give 30 g (10-15g in children) of activated charcoal following gastric emptying. Do not delay the above therapy since the history may be unreliable, and the patient's symptoms may progress rapidly.

If the patient shows CNS depression typical of Stage II, intubate at the first clinical or laboratory signs of respiratory compromise. Intubation prevents aspiration and is mandatory prior to lavage in an obtunded individual. Treat coma or seizures with physostigmine 1-2 mg IV. This drug is an anticholinesterase which reverses the central anticholinergic effects of the tricyclic antidepressants. Unlike neostigmine and pyridostigmine, it can readily cross the blood/brain barrier. Administer physostigmine slowly since rapid administration can cause seizures. There is usually a 5-15 minute lag time until there is enough acetylcholine build-up to compete with the anticholinergic effects of the tricyclic. The effect of physostigmine is short-lived and may need to be repeated every 30 minutes.

Some authors recommend against the use of physostigmine because of its potential for causing seizures with rapid administration. We feel, however, that the danger of prolonged coma outweighs the risk, since patients may develop aspiration pneumonia and nerve palsies secondary to prolonged immobilization. Recurrent seizures respond acutely to diazepam 5–10 mg IV as needed. In addition, there are few results as dramatic in acute primary care as watching someone “wake up” from tricyclic antidepressant coma after physostigmine therapy.^{9,10}

Coping With Cardiotoxicity

During Stage III, when cardiotoxicity manifests and the ventricular fibrillation threshold is low, physostigmine can also be employed to maintain the heart rate below 130 beats/minute.¹¹ If the QRS interval becomes greater than 0.11 seconds, physostigmine is also indicated. Success with lidocaine and practolol for treatment of ventricular tachycardia secondary to tricyclic antidepressants has also been demonstrated.¹² However, should your patient’s heart rate drop below 100 beats/minute, physostigmine or beta blockers could present the threat of bradycardia. For the same reason, digitalis is generally felt to be contraindicated, especially in the face of QRS lengthening. Should severe bradycardia develop with physostigmine, it can be counteracted with atropine 0.5–1.0 mg IV.

Several researchers report successful treatment with sodium bicarbonate in tricyclic associated arrhythmias.¹³ Brown *et al.* have shown that tricyclic antidepressants are significantly protein bound at a higher pH.¹⁴ Since only the unbound drug can interact with the myocardium, raising the pH induces more protein binding and, therefore, less drug is available. We suggest maintaining the pH at 7.4 with sodium bicarbonate in all seriously overdosed tricyclic victims. The dose is 1 mEq/kg in an IV bolus.

Propranolol should be reserved for those patients in which there are ventricular arrhythmias unresponsive to bicarbonate. You can administer it to children in a dose of 0.25 mg IV and to adults at 0.5 to 1.0 mg IV and repeat as needed every 5 minutes to a maximum of three doses. Contraindications include heart block, congestive heart failure, asthma, and a lengthening QRS.

During Stage IV when hypotension and bradycardia manifest, management of the patient takes on critical dimensions. Nearly any corrective action you take could threaten a possible negative reaction. Conductive abnormalities and heart block may respond temporarily to cardiac pacing, and you can hope that sodium bicarbonate will reverse some of the toxic effects of this stage. Hypotension can be treated with fluids, but a delicate balance must be maintained to prevent pulmonary edema and heart failure. Vasopressors such as dopamine can also be helpful, but beta stimulation can often cause further arrhythmias. The use of isoproterenol is a last resort—its efficacy has never been proven in this setting. If fluids or vasopressors are to be used, place a Swan-Ganz catheter to fully monitor cardiac status. There are no reports of effective forced diuresis, peritoneal dialysis or hemodialysis in this setting probably because of strong tissue and protein binding. Hemoperfusion, however, may deserve further study.

TABLE II

Treatment of TCA Overdose

- 1) Prevent absorption; Ipecac, gastric lavage, MgSO₄, charcoal.
- 2) Arterial blood gases: Treat acidosis with NaHCO₃.
- 3) Mental changes, (hallucinations, seizure, coma) respond to physostigmine 1–2 mg IV prn, q30–60 minutes.
- 4) ICU monitoring with continuous ECG observation.
- 5) Treat supraventricular tachycardia 130/min or QRS .11 sec with physostigmine 1–2 mg IV.
- 6) Severe hypotension, bradycardia may respond to NaHCO₃ or pacemaker.

Case Report: Comatose and Seizures

A 22 year-old woman ingested 1000 mg of amitriptyline. Upon arrival to the emergency room on Tuesday at 3 p.m., she was comatose and having repeated seizures. An initial electrocardiogram (lead II) on admission, shows supraventricular tachycardia with aberrant ventricular conduction (Figure 1). At 6 p.m. that same day the rhythm strip shows a continuation after 6 mg physostigmine IV (Figure 2). Shortly thereafter, she developed a ventricular tachycardia without a palpable blood pressure. As a result of additional physostigmine, she converted to normal sinus rhythm with an incomplete bundle branch block. Her vital signs stabilized. A rhythm strip from Wednesday at 10 a.m. (Figure 3) shows further changes brought about by physostigmine: a dramatically narrowed QRS and a controlled heart rate below 120 beats/minute. To achieve this improvement, a total of 22 mg of physostigmine was administered over the first 24 hour period.

Six days following admission, she remained in sinus rhythm but had frequent premature atrial contractions (Figure 4). A day later, she showed signs of cardiotoxicity with an ECG pattern of incomplete A-V dissociation due to a non-paroxysmal A-V junctional tachycardia (Figure 5). She was immediately given 2 mg of physostigmine IV with the restoration of normal sinus rhythm in 20 minutes (Figure 6).

This case report emphasizes the need for close and careful monitoring of these patients. Because of the sometimes overwhelming competitive blockade caused by tricyclics, large amounts of physostigmine may be required. In addition, be aware that it takes 15–20 minutes after administration before you’ll see an effect. Finally, note that for days following tricyclic antidepressant overdose, patients may demonstrate numerous potentially life-threatening cardiac arrhythmias and require appropriate and rapid therapy.

In the emergency department, a diagnosis of tricyclic antidepressant poisoning should be suspected in any mentally depressed person with dilated pupils and tachycardia. Remember that the pharmacologic properties of the tricyclics relate directly to the physiologic signs and symptoms. Patients tend to pass through several stages of severity progressively approaching death. This requires physicians to respond with a correct combination of appropriate therapies, ranging from physostigmine, sodium bicarbonate and beta-blockers, to possible cardiac pacing and vasopressors.

Finally, any discussion of tricyclic antidepressant poisoning must contain a caveat to physicians prescribing these drugs—especially since some 70% of these prescriptions are written by primary care physicians.² It should be noted that most poisonings due to tricyclic antidepressant overdose occur during a two to three week latent period prior to the onset of therapeutic effectiveness. Prescribing physicians would be well-advised to exercise extreme caution in dispensing these drugs to

Figure 1



Figure 2

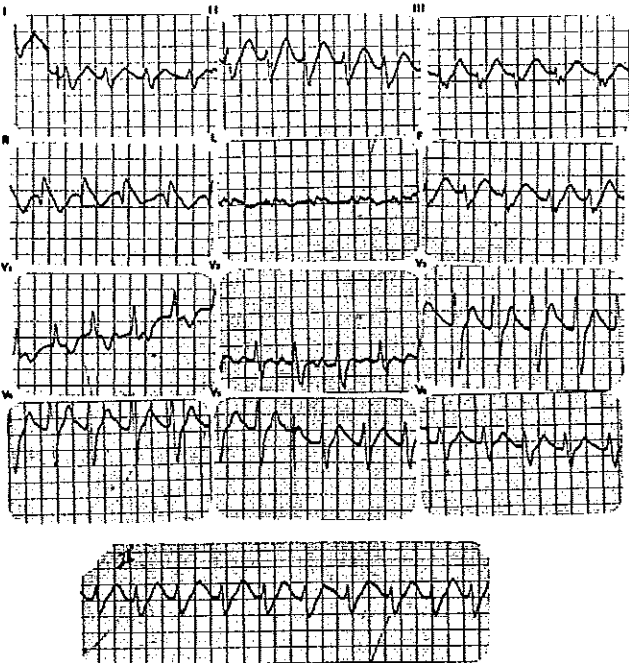


Figure 3



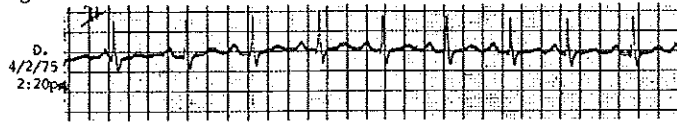
Figure 4



Figure 5



Figure 6



¹JAMA 235: 1474-1476, 1976. Reproduced with permission from the Journal of the American Medical Association.

a patient who may have suicidal tendencies. When in doubt, simply prescribe a less-than-lethal quantity—usually fewer than ten doses. Further, it is wise to issue a warning to patients that antidepressant effects may be delayed. In any case, psychiatric consultation is an advisable adjunct for depressive patients taking tricyclic antidepressant drugs.

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