

Tricyclic Antidepressant Overdose

Slide 1 Title Slide

Welcome to this month's internet CE module. In this module we will review the Poisoned Patient and Overdose Protocol by focusing on tricyclic antidepressant overdose.

This continuing education activity is approved by the University of Texas Southwestern Medical Center at Dallas, an organization approved by the Texas Department of Health (TDH) and accredited by the Continuing Education Board for Emergency Medical Services for 1.5 Continuing Education Hours.

Slide 2 Objectives

At the completion of this CE module, the paramedic will be able to

1. Understand the pharmacokinetics of tricyclic antidepressants.
2. Be familiar with some of the major physiological effects of the tricyclic antidepressants.
3. Be familiar with current pharmacologic therapies associated with the treatment of tricyclic antidepressant overdose.

Slide 3 Title Slide Introduction

"O, true apothecary thy drugs are quick."

Shakespeare; Romeo and Juliet, act V, scene 3, line 119

The precursor of the present day tricyclic antidepressant (TCA) was first discovered in the late nineteenth century. Due to the sedative-hypnotic effects it possessed, it was used to treat psychoses of every nature. By 1958, however, medical science found the "true calling" of the TCAs as they were employed in the treatment of endogenous depression. Later that year, it was reported that 83% of all patients using TCAs showed signs of improvement.¹ The next year, the first lethal overdoses were recorded.

Slide 4 Introduction

In 1990, the leading ingested substances directly causing fatalities were the TCAs.² In one study, over 50% of all overdose admissions to an adult intensive care unit (ICU) involved TCAs.³ A sad fact is that most people who die from TCA overdose never reach the hospital.⁴ Since TCAs are used to treat major depression, they are frequently available to the suicidal patient. However, TCAs are also prescribed as a pharmacological treatment for childhood bedwetting, and, therefore, accidental overdoses can occur.⁴

Slide 5 Introduction

The term tricyclics is derived from the three-ring chemical structure of the central portion of the molecule. Prior to 1980 there were seven drugs released for use in this country that were considered TCAs. Since that time, there have been several other drugs released that have four rings or structural modifications to the original three-ring configuration, and these drugs are called second generation antidepressants. The original seven are similar in their structure, pharmacology and toxicity and this essay will be limited to those true TCAs.

Slide 6 Title Slide Indications

The original TCA agents are still the drugs of choice for most patients with major depressive disorders.^{5,6}

Slide 7 Indications

A diagnosis of major depression is made when five or more of these symptoms persist for at least two weeks. The drug chosen for therapy will be determined by the side effects the clinician and patient wishes to avoid or produce.⁷ For instance, nortriptyline or desipramine is preferred in elderly patients who are vulnerable to orthostatic hypotension, whereas amitriptyline or doxepin may be appropriate in patients with depression who are sleepers.⁷

Imipramine has been used to control enuresis (bed-wetting) in children older than six years. It works by constriction of the internal sphincter of the bladder. However, at present it is used cautiously because of the potential for cardiac and other cardiovascular effects.

Slide 8 Title Slide Pathophysiology and Mechanism of Action

Slide 9 Mechanism of Action

Neurons, also nerve cells, are highly specialized cells that conduct messages in the form of nerve impulses. The impulses are transmitted away from the cell body along nerve fibers called axons. Since axons of one neuron are never in direct contact with the axons of another neuron, the nerve impulse must be able to jump from one neuron to another.

Slide 10 Mechanism of Action

When the impulse reaches the end of the axon, it causes the release of chemicals called neurotransmitters into the extracellular space, or synapse. The neurotransmitter diffuses across the space and binds to specific protein receptors that are densely clustered on the other side of the synapse. These neurotransmitters excite or inhibit other neurons or effector cells on target organ membranes with which the axon is in close contact. Simply put, the neurotransmitters allow neurons to carry on "conversations" with many other neurons or organs at the same time.

Slide 11 Mechanism of Action

The neuron conducting impulses toward the synapse is called the presynaptic neuron. The

neuron conducting impulses away from the synapse is called the postsynaptic neuron. The postsynaptic cell may be another neuron or an effector cell (a muscle cell or gland cell). The changes prompted by neurotransmitter-protein binding are extremely brief (a few milliseconds) because the neurotransmitter is either quickly destroyed by enzymes at the receptor sites or sucked back into the presynaptic axon. Reuptake of the neurotransmitter allows them to be recycled and therefore, the neuron has only to replace those that were destroyed by enzymes.

Slide 12 Mechanism of Action

The group of neurotransmitters that are most closely associated with emotional behavior are the biogenic amines. This broad group contains the subgroups catecholamines (dopamine, norepinephrine, and epinephrine) and indolamines (serotonin and histamine). TCAs act by preventing the reuptake of norepinephrine and serotonin by the presynaptic neuron. This results in an increased supply of these neurotransmitters in the synapse, which continues to stimulate the effector cells and organs. It is this constant stimulation that is believed to be responsible for the clinical improvement in depression.

Slide 13 Mechanism of Action

Unfortunately, this simplistic theory may not fully explain the actions of the TCAs in the treatment of depression. Administration of the TCAs causes a very rapid rise in the level of those neurotransmitters in the body. However, it may take several weeks before the effects of the drugs are seen. This suggests that depression may not be directly caused by the lack of those neurotransmitters, but instead by a secondary reaction that may take longer to correct.

Slide 14 Mechanism of Action

In addition to central effects, TCAs are also competitive antagonists of histamine H₁ and H₂ receptors.⁸ They also block muscarinic acetylcholine and alpha-one adrenergic receptors. It is not known which of these, if any, helps to exert its antidepressant effects. Even though the effects of the TCAs in the body is understood, their efficacy in the treatment of depression is still a mystery.

Slide 15 Title Slide Pharmacology

Slide 16 Pharmacology

TCAs are readily absorbed from the gastrointestinal tract and because they are lipophilic (drawn to lipids), are widely distributed and strongly bind to tissues. Most complications occur soon after ingestion. However, with particularly larger doses, absorption will be delayed because the anticholinergic effects of the drug will slow gastric emptying time. Nevertheless, as evidenced by serious clinical presentation within a few hours of ingestion, it is obvious that absorption proceeds at a fast enough rate to cause death.

Slide 17 Pharmacology

Once in the bloodstream, virtually all drugs are transported either attached to carrier proteins or unbound in solution. Drugs that are bound are unable to cross cell membranes and consequently, are unable to exert their biological effects. Only unbound or free drugs are able to exert their pharmacological effects.

Slide 18 Pharmacology

When TCAs enter the bloodstream, a large but variable portion binds to the plasma membranes.⁹ When unbound TCAs circulate, uptake occurs in a preferential fashion. Levels have been found to be roughly five times greater in myocardial cells, thirty times greater in liver cells, and forty times greater in brain tissue than in plasma.^{10,11}

Slide 19 Pharmacology

Of significant therapeutic importance is evidence to suggest that this binding is pH dependant. Increasing serum pH from 7.38 to 7.5 in an in-vitro study resulted in a 21% reduction in free TCA.¹² As serum pH increases, the drug becomes increasingly bound to plasma proteins and less available to the tissue.

Slide 20 Pharmacology

Metabolism of TCAs occurs primarily in the liver. Some compounds, including haloperidol, Antabuse, and morphine may prolong TCA toxicity by interfering with hydroxylation in the liver.⁹ Because of the lipophilic nature of the TCAs, these drugs have long half-lives. Mean half-lives range from ten to eighty-one hours, but is highly variable among patients.^{13,14}

Slide 21 Title Slide Clinical Presentation

Depending upon the amount of drug ingested and the time since ingestion, patients may present with no symptoms at all.

Slide 22 Clinical Presentation

The progression from being alert with mild symptoms to life-threatening toxic effects may be extremely rapid.¹⁵ With few exceptions, patients that have significant ingestions will exhibit signs and symptoms within the first few hours. Because complications may occur suddenly and without warning, all patients with suspected TCA overdose should be evaluated promptly.

Slide 23 Clinical Presentation

Before we begin to look at the symptoms associated with TCA toxicity, let us first look at some of it's effects at therapeutic levels. Even at therapeutic doses, competing effects

interplay on the heart.¹⁶ Blockade of fast sodium channels results in altered repolarization and conduction. This altered conduction notably occurs at the His-ventricular portion of the atrioventricular (AV) node.¹⁷ The ECG changes can be seen within a few weeks of beginning therapy and may be manifested as tachycardia, increased PR interval, widened QRS interval, widened QT interval, and depressed T waves.¹⁸ The delay in conduction also predisposes the myocardium to reentrant arrhythmias, such as ventricular tachycardia. These ECG changes are of little clinical significance and all will disappear once the antidepressant therapy is discontinued.

Slide 24 Clinical Presentation

Orthostatic hypotension is a common side effect of TCA therapy and seems to be unrelated to the patient's age or duration of use. Orthostasis is caused predominantly by peripheral alpha-receptor blockade.¹⁸ Alpha-receptors are found primarily in the smooth muscle tissue of peripheral blood vessels. When stimulated, they result in contraction of those smooth muscle tissues with a resulting increase in blood pressure. When blocked from stimulation, the opposite effect occurs.

Slide 25 Cardiovascular Toxicity

Sinus tachycardia is the most common sign associated with TCA overdose. In one study, it was seen in 71 out of 100 consecutive overdoses in which only three conduction abnormalities and no mortality was observed.¹⁹ In a separate retrospective study, sinus tachycardia was present in only 20 of 113 fatalities who were alive at the time of hospital admission.²⁰ These two studies seem to suggest that the presence of sinus tachycardia is a poor indicator for the development of serious toxicity and death and this is evident by looking at the different mechanisms of each. Sinus tachycardia is primarily an anticholinergic effect, whereas conduction disturbances and arrhythmias are primarily related to the quinidine-like action of TCAs.^{20,21}

Slide 26 Cardiovascular Toxicity

Conduction delays are common in TCA overdose and arrhythmias can include premature atrial contractions, premature ventricular contractions, supraventricular tachycardia, junctional tachycardia, idioventricular rhythm, ventricular tachycardia, and ventricular fibrillation. Life-threatening arrhythmias occur in fewer than five percent of TCA overdose.²² When asystole occurs, it is usually preceded by sinus bradycardia and hypotension, however, it is important to note that cardiac arrest can occur with only non-specific ECG changes.^{23,24} Because of the conduction delays associated with TCA use, widening of the QRS may result in a sinus tachycardia that may be difficult to distinguish from ventricular tachycardia. Since ventricular tachycardia and fibrillation can be unusually difficult to control, any ventricular irritability should be viewed as significant in this setting.^{25,26}

Slide 27 Cardiovascular Toxicity

Hypotension is a very common sign found in TCA toxicity and may well be a precursor to cardiac arrest.^{4,27} It is found in approximately fifteen to twenty percent of patients.²² There are several factors that contribute to this hypotension, including vasodilation, central or peripheral alpha-receptor blockade, and cardiac depression.^{21,25,28} When hypotension is severe or accompanied by arrhythmias, overall mortality increases.²² Seizures and acidosis may help to contribute to this problem.

Slide 28 CNS Toxicity

Altered mental status occurs frequently, with clinical findings ranging from confusion, delirium and agitation, hallucinations, myoclonus, and seizures to drowsiness and coma following serious TCA overdose.^{19,20} Altered mental status may progress rapidly to coma and respiratory arrest. Most patients who become unconscious usually regain consciousness within the first twenty-four hours.¹⁶ Only those patients who develop hypoxic encephalopathy remain unconscious for longer periods of time.

Slide 29 CNS Toxicity

Generalized seizures have been associated with increased mortality and have been witnessed occurring immediately before cardiac arrest.^{24,29} Seizures have been reported in up to twenty-four percent of in-hospital patients.²² Level of consciousness is not a reliable indicator of the possibility of seizure activity. Patients may remain well oriented up until the time that the seizure begins. Seizures are usually brief and self-limiting.²² Seizures can increase the acidity of the blood by causing the patient to become hypoxic. This acidity helps to release the TCA from the blood proteins and make more of the drug available to membranes and reaction.

Slide 30 CNS Toxicity

Myoclonic jerking may precede or mimic seizure activity.²⁵ Myoclonus is a relatively benign muscle contraction of the extremities that can be mistaken for prolonged seizure activity. One of the distinguishing factors about myoclonus is that the patient rarely loses consciousness.

Slide 31 Title Slide General Management

Every patient who has ingested a significant amount of TCAs should be evaluated in the emergency room, even if they are asymptomatic when encountered. In addition, every patient who presents with signs or symptoms of toxicity should be evaluated regardless of how small a dosage they claim to have taken. Only after careful monitoring in the emergency room and the absence of clinical signs or symptoms for a period of six hours can the patient be assumed to be safe.³⁰

Slide 32 General Management

As with every case, the ABC's are checked first. The airway should be established and

intubation is indicated in the event of respiratory depression or a threat to the airway exists. The patient should receive oxygen, intravenous access with two large bore catheters, pulse oximetry, capnography, and continuous cardiac monitoring.

Slide 33 General Management

As soon as possible, gastric emptying will need to occur. This is usually performed in the hospital by insertion of a large bore orogastric tube and lavage of the stomach until clear of pill fragments and stomach contents. Syrup of ipecac is contraindicated since rapid deterioration in the patient's mental status may occur and this would place the patient in increased danger of tracheal aspiration. In addition, ipecac therapy may delay the administration of activated charcoal.

Slide 34 General Management

Activated charcoal is a substance obtained by combustion of organic materials and treated (activated) to increase its surface area. Charcoal is an inert substance that is not absorbed from the GI tract and binds most substances, preventing them from being absorbed. Although the binding of substances is reversible, little if any toxin is released once it is bound to charcoal. Activated charcoal significantly absorbs TCA.³¹

Slide 35 General Management

If the patient is alert with stable vital signs and no apparent risk of sedation, administer charcoal by mouth in the standard dose of 1 gram of charcoal per kilogram of body weight. Charcoal should not be administered to patients with altered mental status or in any patient who cannot protect their airway for whatever reason. Keep the patient in a semi-sitting position with the head of the stretcher at about a 30 degree angle and monitor for airway compromise and potential vomiting.

Slide 36 Management of CNS Toxicity

Coma and altered mental status are frequent complications. Coma usually resolves within twenty-four hours.¹⁶ Endotracheal intubation will be needed to protect the airway until resolution is complete. In the event that the coma has not reversed itself within that time frame, other etiologies must be investigated including hypoxic encephalopathy, head trauma, or ingestion of other toxins.

Slide 37 Management of CNS Toxicity

Although seizures are usually brief and self-limiting, their appearance has been associated with increased mortality and have been noted immediately before cardiac arrest.^{24,29} The acidosis that results from frequent or prolonged seizure activity helps to unbind the TCA from the plasma proteins and then makes them available for binding to the cell membranes and increases the toxic effects. Aggressive treatment is therefore, of paramount importance.

Slide 38 Management of CNS Toxicity

Diazepam should be considered the first-line drug to halt seizure activity. For the adult patient, protocol allows you give diazepam in 2.5 increments slow IV push until the seizure stops or 10 milligrams have been given. Any additional doses must be authorized by BioTel. Diazepam's anticonvulsant effects last for only about twenty minutes as the TCA redistributes; thus multiple doses may be necessary to control the activity. Prophylactic use of diazepam for seizure control has remained controversial.

Slide 39 Management of CNS Toxicity

For the pediatric patient, standing orders do not allow the IV administration of diazepam. Instead, you may give 0.5 mg per kg rectally under standing orders, to a maximum dose of 10 mg. Any additional or an alternative dosing route must first be cleared with BioTel.

Slide 40 Management of Conduction Disturbances and Arrhythmias

The presence of cardiac abnormalities must not be treated lightly and aggressive therapy should be instituted at once. Life-threatening arrhythmias, such as asystole, ventricular tachycardia, and ventricular fibrillation do not have the same prognosis in TCA poisoning as they do in myocardial infarction. A case of full recovery with five hours of external cardiac massage following TCA poisoning has been reported.³² This suggests that a previously healthy myocardium can withstand a significant TCA insult.

Slide 41 Management of Conduction Disturbances and Arrhythmias

Alkalinization is the first line treatment for TCA-induced conduction defects, arrhythmias, and hypotension, either by the administration of intravenous sodium bicarbonate or hyperventilation, if the patient is being artificially ventilated. The optimal pH for the reversal of cardiovascular toxicity symptoms is not known, however, a slight alkalosis has been suggested.^{33,34} Over-alkalinization has its risks and should be avoided.

Slide 42 Management of Conduction Disturbances and Arrhythmias

Although the exact mechanism by which alkalinization of the blood reverses cardiovascular toxicity is not known, it is believed to be a result of the binding of the TCA to the plasma proteins. As serum pH increases, the drug becomes increasingly bound to plasma proteins and less available to the tissue. Alkalinization of the plasma also alkalinizes the urine and this was once thought to ionize the TCA which would then prevent its reabsorption across the renal tubules. This would then enhance elimination of the TCA via the urine in a process known as alkaline diuresis. This, unfortunately, is not the case and alkaline diuresis does not significantly enhance elimination.

Slide 43 Management of Conduction Disturbances and Arrhythmias

Biotel may authorize the administration of sodium bicarbonate in 1 mEq/kg doses IV push

for arrhythmias, especially tachyarrhythmias. Prophylactic administration of bicarbonate is a controversial issue. The potential benefits should be weighed against the possibility of overalkalinization. Its effectiveness in an asymptomatic patient with normal pH values still remains to be investigated.

Slide 44 Management of Conduction Disturbances and Arrhythmias

Since AV conduction disturbances in TCA overdoses are largely distal to the AV node, attempts to improve conduction through the node with atropine sulfate have been ineffective.³⁶ In severe conduction disturbances, temporary pacemaker insertion and overdrive may be the only solution.

Slide 45 Management of Conduction Disturbances and Arrhythmias

Ventricular ectopy or ventricular tachyarrhythmias that are refractory to alkalinization should be treated with lidocaine. Lidocaine does not significantly depress conduction or contractility and has been shown to be quite effective. Standing order allows you to administer a bolus of 1.0 mg per kilogram of lidocaine, no faster than 50 mg per minute. Following the bolus, BioTel may then order a maintenance infusion of 1-4 mg/min and a second bolus if the first was not successful.

Slide 46 Management of Conduction Disturbances and Arrhythmias

Hypotension usually responds well to alkalinization, saline infusion and/or the Trendelenberg position. Occasionally, though, pressor agents will have to be used. Agents with direct alpha-adrenergic effects are preferred. For patients with a systolic blood pressure between 70 and 90 mmHg, BioTel may authorize the administration of dopamine at a rate of 2-10 mcg/kg/minute. Dopamine relies on the release of stored norepinephrine from the presynaptic vesicles, and, since TCAs prevent the reuptake of norepinephrine, dopamine may have a diminished effect.

Slide 47 Management of Conduction Disturbances and Arrhythmias

For patients in profound shock with a systolic blood pressure less than 70 mmHg, BioTel may permit the administration of Levophed. Levophed is administered by IV drip at 8-12 mcg/minute. Norepinephrine (Levophed) appears to be more effective and is generally preferred.

Slide 48 Summary

Tricyclic antidepressants represent a significant improvement in the quality of life for persons suffering from endogenous depression. However, they are a very powerful class of drugs and their potential for misuse is high. TCA overdose is a serious attempt at suicide and quick intervention is necessary to prevent a successful attempt. Being familiar with the TCAs and the current medical research surrounding their use and misuse may help to guide your actions on that inevitable day that you encounter a potentially lethal

overdose.

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