TRICYCLIC ANTIDEPRESSANT POISONING

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Objectives

1. Understand the pathophysiology of tricyclic antidepressant (TCA) poisoning
2. Become familiar with the clinical presentation of patients poisoned by TCAs
3. Know what decontamination methods are most effective in a given patient
4. Understand the treatment of TCA ingestions with specific emphasis on alkalinization therapy
5. Become familiar with the monitoring parameters for patients being treated for TCA poisoning.

I. TRICYCLIC ANTIDEPRESSANTS

Incidence and Severity

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coma</td>
<td>35%</td>
</tr>
<tr>
<td>Conduction blockade</td>
<td>21%</td>
</tr>
<tr>
<td>Supraventricular or ventricular dysrhythmias</td>
<td>6.2%</td>
</tr>
<tr>
<td>Hypotension</td>
<td>14%</td>
</tr>
<tr>
<td>Seizures</td>
<td>8.4%</td>
</tr>
<tr>
<td>Mortality</td>
<td>2.2%</td>
</tr>
</tbody>
</table>

Available Forms

<table>
<thead>
<tr>
<th>Tertiary Amines (tricyclic antidepressants)</th>
<th>Trade Names</th>
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</thead>
<tbody>
<tr>
<td>Amitriptyline</td>
<td>Elavil™</td>
</tr>
<tr>
<td>Doxepin</td>
<td>Sinequan™</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Tofranil™</td>
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<tr>
<td>Trimipramine</td>
<td>Surmontil™</td>
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<tr>
<td>Amoxapine</td>
<td>Asendin™</td>
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<tr>
<td>Maprotiline</td>
<td>Ludiomil™</td>
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<tr>
<td>Clomipramine</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary Amines (tricyclic antidepressants)</th>
<th>Trade Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nortriptyline (metabolite of amitriptyline)</td>
<td>Pamelor™</td>
</tr>
<tr>
<td>Protriptyline</td>
<td>Vivactil™</td>
</tr>
<tr>
<td>Desipramine (metabolite of imipramine)</td>
<td>Norpramine™</td>
</tr>
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Pharmacology
Four main mechanisms of action that account for therapeutic and toxic effects:
1.) Potentiate the actions of biogenic amines in the CNS by inhibition of their reuptake at nerve terminals.
2.) Anticholinergic effects through the competitive antagonism of muscarinic acetylcholine receptors.
3.) Antagonism of alpha1-adrenergic receptors, possibly leading to severe hypotension.
   • Due to its selective alpha1-adrenergic receptors agonistic activity, norepinephrine is the preferred agent to reverse TCA-induced hypotension.
4.) Quinidine-like type 1A antiarrhythmic effect (membrane stabilizing effect) leading to either suppressed or precipitated dysrhythmias and altered myocardial conduction. This activity occurs due to the membrane-stabilizing effect from blockade of inward/fast sodium channels, resulting in altered repolarization and conduction. This effect occurs distal to the AV node, producing a depression of the His-Purkinje conduction system and a direct negative inotropic effect.
   • Intravenous sodium bicarbonate is the preferred pharmacologic treatment of choice to reverse TCA-induced cardiac conduction defects and arrhythmias caused by the blockade of inward/fast sodium channels by tricyclic antidepressants.

Estimate of Acute Toxicity

• **Adults:** Ingestions of 10-20 mg/kg of most TCAs constitutes a moderate to serious exposure. Ingestions > 35 mg/kg are likely to be fatal without treatment.

• **Pediatrics:** Doses > 3.5 mg/kg /day are associated with EKG changes. A normal dose of imipramine for treatment of enuresis is 1.5 mg/kg/day. As there is limited toxicity data in children, patients ingesting > 1.5 mg/kg should be referred into the ED.

Pharmacokinetics

A.) Absorption
   • Rapid and complete absorption with therapeutic doses, but the anticholinergic effects of TCAs may decrease GI motility causing absorption to be slow and erratic.
   • TCAs may remain in the gut for more than 12 hours after an overdose, making treatment with multiple-dose activated charcoal a required intervention.
   • Peak concentration occurs within 2 to 8 hours. (highly variable)

B.) Distribution
   • TCAs are highly lipid soluble resulting in a very large volume of distribution of 10 to 50 L/ kg.
   • Highly protein bound (85% to 90%)  
   • Measures to enhanced TCA elimination such as hemodialysis and hemoperfusion are ineffective, due to the large volume of distribution and high protein binding.

C.) Elimination
   1. Extensive first pass metabolism with glucuronide conjugation occurring in the final step.
      • After hepatic metabolism, a small fraction of the TCA enters an enterohepatic cycle with less than 5% of the ingested dose excreted in the bile. Another 5% to 10% is excreted in the gastric juices.
      • Metabolites may have pharmacological activity equal to the parent drug (e.g., desipramine is a metabolite of imipramine)
   2. Following an overdose, renal excretion accounts for 3% to 4% of the ingested dose.
   3. Elimination half-life ranges from 16 to 81 hours depending on the compound involved.
**Overdose and Toxicity**

Patients presenting with a suspected TCA overdosed may exhibit no symptomatology or minor complications. *Although the patients may appear well initially, they can rapidly and without warning develop life-threatening complications* (hypotension, seizures, cardiac arrest)!! When in-hospital deterioration occurs, it is almost always within the first few hours after arrival and frequently within the first 60 minutes.

A.) **Cardiovascular effects:**

1. **Hypotension** is the most frequent serious cardiovascular effect that occurs secondary to:
   a. Vasodilation form alpha$_1$-adrenergic receptor blockade.
   b. Direct quinidine-like myocardial depression
   c. Depletion of presynaptic norepinephrine stores
      • Hypotension has been strongly correlated to the subsequent development of life-threatening-ventricular arrhythmias.

2. **Sinus tachycardia** lasting hours to days results from the anticholinergic toxicity.
   • Supraventricular tachycardia (SVT) may occur secondary to anticholinergic toxicity.
   • By itself, sinus tachycardia or SVT is usually not a serious complication in the setting of a TCA overdose.

3. **Conduction delays**
   a. Widening of the QRS complex may result in unusual ECG patterns, and sinus tachycardia may be difficult to distinguish from ventricular tachycardia.
   b. Other ECG conduction abnormalities include prolonged PR and QTc interval, right axis shift, and high degree atrioventricular block.

4. **Arrhythmias** include premature ventricular or atrial contractions, ventricular tachycardia, ventricular fibrillation, slow idioventricular rhythm, electromechanical dissociation, and asystole. When asystole occurs, hypotension and bradycardia usually precede it.

**NOTE:** Metabolic acidosis may contribute to cardiotoxicity by further depressing the fast sodium channels.

B.) **CNS effects:**

1. **Altered Mental Status**
   a. Delirium, agitation, and hallucinations may occur secondary to anticholinergic toxicity.
   b. Patient may have a level of consciousness ranging from mild sedation to coma.

2. **Myoclonus and choreoathetosis** are relatively benign muscle contractions that are sometimes mistaken for prolonged seizures.

3. **Seizures**
   a. Prior mental status does not predict the occurrence of seizures
   b. Usually brief and self-limited.
   c. Prolonged seizures do occur, and resulting acidosis and hypoxia may potentiate cardiotoxicity.
   d. Amoxapine and maprotiline appear to have a relatively greater seizure potential.
C.) **Anticholinergic effects:** Peripheral autonomic nervous system complications are common and by themselves do not cause significant morbidity. Centrally mediated anticholinergic effects are a more serious complication (see CNS effects) requiring close monitoring and supportive care. The presence or absence of anticholinergic symptoms does not predict more serious complications.

<table>
<thead>
<tr>
<th>Peripheral Anticholinergic Effects</th>
<th>Central Anticholinergic Effects</th>
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<tbody>
<tr>
<td>Sinus tachycardia</td>
<td>Delirium (&quot;mad as a hatter&quot;)</td>
</tr>
<tr>
<td>Reduced secretions (&quot;dry as a bone&quot;)</td>
<td>Anxiety</td>
</tr>
<tr>
<td>• dry mouth</td>
<td>Disorientation</td>
</tr>
<tr>
<td>• dry skin</td>
<td>Hallucinations</td>
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<tr>
<td>(axillary regions are the most reliable sites for this assessment)</td>
<td>Confusion</td>
</tr>
<tr>
<td></td>
<td>Paranoia</td>
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<tr>
<td></td>
<td>Incoherent speech</td>
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<td></td>
<td>Impaired recent memory</td>
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<tr>
<td></td>
<td>Purposeless movements</td>
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<tr>
<td></td>
<td>Obtundation, Coma</td>
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<tr>
<td></td>
<td>Seizure</td>
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<tr>
<td>Flushed skin (&quot;red as a beet&quot;)</td>
<td></td>
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<tr>
<td>Fever (&quot;hot as a Hades&quot;)</td>
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<tr>
<td>Dilated pupils</td>
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<tr>
<td>Blurred vision (&quot;blind as a bat&quot;)</td>
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<tr>
<td>Urinary retention</td>
<td></td>
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<tr>
<td>Decreased bowel motility</td>
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**NOTE:** Pupils may not be dilated in TCA overdose patients as the alpha1-adrenergic blockade caused by TCAs can counteract this effect to produce normal-sized pupils.

D.) **Metabolic Acidosis**
- TCA poisoning alone is not a primary cause of metabolic acidosis.
- Metabolic acidosis appears in TCA-poisoned patients secondary to other abnormalities such as TCA-induced seizures and/or tissue hypoxia secondary to TCA-induced cardiovascular instability.

D.) **Respiratory effects:** Patients presenting with serious or potentially serious TCA toxicity generally require intubation to establish an airway and provide ventilation due to the risk of respiratory depression and hypoxia. Risk of aspiration in patients with depressed sensorium also requires protection of the airway.

E.) **Hyperthermia:** Significant CNS toxicity particularly seizures (may or may not be a manifestation of anticholinergic toxicity) places the patient at risk for developing hyperthermia. Uncontrolled hyperthermia is a cause of significant patient morbidity and mortality.

**Decontamination and Initial Patient Prep**

1. Check ABCs, correct acidosis, check vitals
2. **ESTABLISH IV ACCESS IMMEDIATELY (one or two large-bore catheters).** This is done in order to allow for the rapid administration of drugs and fluids if needed.
3. **Fluid resuscitation in the hypotensive patient** (10-20 ml/kg IV bolus of normal saline followed by maintenance of 2-5 ml/kg/hour).
4. Endotracheal intubation should be done in patients who present with decreased level of consciousness and/or respiratory status. Protection of airway should be established with a cuffed endotracheal tube before decontamination begins.
5. Place patient on a heart monitor and get a stat 12-lead ECG.
5. **Naloxone (1-2 mg IV bolus)** should be given to patients with altered mental status in order to rule out potential opiate intoxication.

6. Check blood glucose via fingerstick method using portable glucose measuring device in order to rule-out hypoglycemia. May also empirically give 50 ml D50W to help rule out hypoglycemia.

7. **FLUMAZENIL** (ROMAZICON™), a relatively new benzodiazepine receptor antagonist, **is contraindicated in the setting of a suspected TCA overdose** due to the risk of "unmasking" underlying seizure activity.

6. Obtain blood for ABGs, electrolytes, glucose, BUN, creatinine, and tox screens.

7. Gastric lavage should be performed with a large bore orogastric tube (36 - 42 Fr) in the following patients:
   - comatose
   - presenting within 1-2 hours of ingestion
   - presenting with an unknown time of ingestion

8. Activated charcoal (AC) should be administered (50 gm PO or NG).

9. If bowel sounds are present, then one-half the original dose may be given every 2 to 4 hours for **one or two more doses** to adsorb the ingested TCA that may be undergoing delayed GI absorption.

   **NOTE:** Some clinicians advocate activated charcoal be given every two hours to bind enterohepatically excreted drug. Although repeat doses of activated charcoal may enhance the removal of the TCA from the vascular space, the large volume of distribution results in only minute quantities of the total ingested dose extracted from the blood, making this intervention clinically insignificant. Furthermore, the risk of charcoal ileus and bowel obstruction with multiple-dose activated charcoal therapy makes this form of treatment less appealing.

10. **USE OF IPECAC IS CONTRAINDICATED DUE TO THE POTENTIAL FOR RAPID LOSS OF CONSCIOUSNESS AND SEIZURES.**

**Diagnosis**

TCA intoxication should be suspected in any patient with lethargy, coma, or seizures accompanied by QRS interval prolongation or an increase in the amplitude of the RaVR wave. An RaVR wave ≥ 3 mm or a QRS interval > 100 msec in the limb leads suggest severe poisoning.

1. **Serum TCA concentrations** are not routinely used to guide management due to the slow turnaround time (hours to days) and potentially misleading results. Although serious complications generally occur with total TCA concentrations > 1000 ng/ml, problems have occurred with lower TCA concentrations. Conversely, despite serum concentrations > 1000 ng/ml, patients may not develop serious complications.

2. **ECG**

   **Continuous heart monitor and repeat 12-lead EKGS.**

   a. Although controversial, a **wide QRS complex** (> 100-120 msec) should be used to identify patients who may be at higher risk for developing serious complications. A QRS > 160 msec is strongly suggestive of an impending life-threatening arrhythmia or seizure. **A narrow QRS complex by itself should not rule out the possibility of serious complications developing.**

   b. 12-lead EKGS should be repeated every 2 to 3 hours as needed. Remember that serious complications usually occur within the first 12 hours.

   c. **Terminal 40 msec of QRS complex:**
• A negative final deflection in lead I and a positive final deflection in lead R indicate a rightward shift of the terminal 40 msec frontal plane QRS vector. Its appearance in patients with an unknown overdose strongly suggests a TCA ingestion.

• $R_{avR}$ and $R/S_{avR}$ reflect rightward shift of the terminal QRS axis in patients with TCA toxicity. An increase in $R_{avR} \geq 3$ mm may be predictive of impending arrhythmia or seizure but further study is required to determine whether these ECG changes can be effectively used in the assessment of the TCA poisoned patient.
The following figure depicts a normal and an abnormal aVR tracing from a 12-lead ECG.


**NOTE:** The next page of this handout provides an example of an ECG from a patient with an imipramine overdose. The final 40 msec of the QRS complex in lead I is in the negative direction, and in lead AVR it is in the positive direction (see arrows). Also note that the calculated QRS interval is characteristically widened to 180 msec and that the $R_{AVR}$ is 5 mm.
ECG from the same patient 40 hours later:

Wide QRS interval of approximately 200 msec

Positive Detection in the R-wave (5 mm) of the aVR lead

Negative Detection in Lead I

UNCORRECTED

ECG:
NONSPECIFIC INTERVENTRICULAR CONDUCTION BLOCK (130+ MS DURATION)
UNDETERMINED REGULAR RHYTHMN
ABNORMAL ECG

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Treatment

A.) **Sodium bicarbonate** (IV bolus dosing combined with alkalinization using continuous intravenous infusion) is the first-line treatment for TCA-induced conduction defects (QRS > 100 msec), arrhythmias, and hypotension.

**Mechanisms of action:**
- Sodium-dependent effect manifested by increasing the sodium gradient across the poisoned fast sodium channels. This is likely the primary mechanism by which sodium bicarbonate reverses membrane stabilization.
- pH dependent effect manifested by the production of an increased fraction of the more freely diffusible unionized drug that can be liberated from the fast sodium channel.
- TCAs are weak bases, therefore an increase in extracellular pH may enhance protein binding thereby preventing the free drug acting at the tissue-receptor sites. This theory has fallen out of favor in recent years.

***A QRS interval of > 0.1 sec and/or an R_{avr} wave ≥ 3 mm may be predictive of impending seizure or arrhythmia. If this is present, the patient alkalinization should be considered. (See discussion above on monitoring the terminal 40 msec of QRS wave.)***

**Indications for Sodium Bicarbonate**

1) QRS interval > 0.1 sec and/or R_{avr} ≥ 3 mm.
2) TCA induced arrhythmias or hypotension
3) Acidosis

**NaHCO3 Dosing for Conduction Defects, Acidosis and Hypotension in the TCA-Poisoned Patient**

1. Administer sodium bicarbonate.

   **Dose:** 1-2 mEq/kg bolus, rebolus prn to maintain a desired arterial pH of 7.5.

   - Sodium bicarbonate infusion is usually required to maintain a desired pH of 7.45-7.55. Dose: 100-150 mEq NaHCO3 per liter in D5W 1/2 NS at 150-200 cc/hr (rates should be adjusted per patient).

2. **Therapeutic End-Points of NaHCO3 Therapy:**
   - Maintain alkalinization (arterial pH ~ 7.5)
   - Resolution of conduction abnormalities, hypotension, and/or acidosis.
   - Although sodium bicarbonate induced alkalinization likely helps prevent life-threatening ventricular arrhythmias from occurring, there have been no well designed human studies performed demonstrating such a preventative effect.

3. **Hyperventilation** has been used to rapidly raise pH, but at least in animal studies, sodium bicarbonate has been shown to be more effective.
• Metabolic acidosis makes the patient more susceptible to arrhythmia. Given that hyperventilation is more effective at rapidly raising the systemic pH, it should be strongly considered to rapidly correct metabolic acidosis in the TCA poisoned patient.

**NOTE:** Recent studies suggest that the infusion of a hypertonic saline solution in the setting of TCA intoxication may reverse the effect of TCAs on the fast sodium channels, thereby preventing or treating TCA induced complications.

**NaHCO₃ Dosing for Ventricular Arrhythmias**

1. Sodium bicarbonate IV bolus dosing is the most effective first-line treatment.
   - **1-2 mEq/kg IV bolus; repeat as per ACLS guidelines.**

   **NOTE:** *Bolus dosing of sodium bicarbonate* is required as a first-line antiarrhythmic agent even if the patient is already on continuous IV maintenance fluids which contain sodium bicarbonate.

2. Lidocaine followed by bretyllium can be used per ACLS guidelines for refractory arrhythmias unresponsive to sodium bicarbonate therapy. Lidocaine can be used simultaneously with sodium bicarbonate to treat TCA-induced arrhythmias but sodium bicarbonate must be considered a first-line agent in the ACLS guidelines when managing TCA-induced arrhythmias.

3. In the hemodynamically unstable patient, the above measures along with direct-current counter shock should be attempted. ACLS guidelines should be followed in all patients.

**DO NOT USE TYPE 1A ANTIARRHYTHMIC AGENTS (PROCAINAMIDE, QUINIDINE, DISOPYRAMIDE) IN PATIENTS SUFFERING FROM TCA POISONING**

• TCA-induced cardiotoxicity is caused by its membrane stabilizing effect, therefore, type 1A antiarrhythmic agents such as procainamide may likely exacerbate TCA-induced cardiotoxicity if administered to the TCA poisoned patient.

B.) Seizures

1. Diazepam is the first choice.
   - **Dose:** Adult - 5-10 mg (no faster than 5 mg/min); may repeat every 15 minutes up to 30 mg
     Child - 0.25-0.4 mg/kg/dose up to 10 mg maximum total dose.

   **Second Line Agents:**
   2. Phenobarbital loading dose: 10-20 mg/kg (rate < 50 mg/min); monitor for respiratory depression and hypotension.
   - Animal studies would seem to indicate that phenobarbital may be more efficacious than phenytoin for treatment of TCA induced seizures.

3. Phenytoin use for TCA-induced seizures is not recommended.
4. Refractory seizures may require pentobarbital or general anesthesia.
5. Physostigmine may be of use in refractory seizures. However, because of its potential to cause severe complications in TCA ingestions, its use is not recommended without consultation with a toxicologist.
C.) Hypotension

1. Trendelenburg position, IV fluids, and sodium bicarbonate.
2. **Norepinephrine** is the drug of first choice as it is a potent selective alpha-adrenergic receptor agonist. TCAs are selective alpha-adrenergic blockers. *(requires IV placement of central line)*
   
   **Dose:** 0.1-0.2 mcg/kg/min initially and then titrate to effect.
3. **Dobutamine** may be used if the hypotension is due to a loss of inotropy where the cardiac output is low and the pulmonary artery wedge pressure is > 18 mm Hg.
   
   **Dose:** 2.5 mcg/kg/min initially titrated up to 15 mcg/kg/min
3. **Dopamine** use in managing the TCA poisoned patient is falling out of favor. Dopamine needs to be converted to norepinephrine for in order to achieve positive alpha-adrenergic stimulation in vivo. Overdoses involving TCAs as well as cocaine and amphetamines cause catecholamine depletion making dopamine less effective when managing hypotension in these cases.

**NOTE:** If hypotension does not initially respond to initial treatment, invasive hemodynamic monitoring should be considered. Agents with selective vasoconstrictive or inotropic properties may then be tailored to the individual patient.

D.) Enhanced elimination

- Forced diuresis and hemodialysis are not effective in removing TCAs.
- Hemoperfusion has been used in the past for critical cases with limited success.

E.) Physostigmine:

The morbid sequelae of TCA overdoses (ventricular arrhythmias, hypotension, respiratory depression) are generally unrelated to acetylcholine blockade. It is still unclear as to whether the seizure activity observed with TCA intoxication is also related to anticholinergic toxicity.

**Mechanism of Action:**

1. Reversible inhibitor of acetylcholinesterase that rapidly reverses both central and peripheral effects of anticholinergic toxicity.
2. Tertiary ammonium compound that is non-ionized, lipophilic, and easily crosses the blood-brain barrier.

**Clinical Applications:**

1. Effectively reverses coma, severe myoclonic and choreoathetoid activity, delirium, and hallucinations caused by excessive anticholinergic activity.
2. Even though physostigmine may effectively reverse supraventricular tachycardia (SVT) and sinus tachycardia (ST), most cases involving SVT or ST are not of hemodynamic significance and do not require any therapy.
3. In the past, physostigmine had been recommended as an antidote for every complication of TCA toxicity. However, physostigmine has no consistent effect on ventricular dysrhythmias and does not treat hypotension. Although controversial, it is in the setting of TCA induced toxicity where the use of physostigmine has been stated to cause seizures, worsen hypotension, and induce bradycardia and asystole, and it may be associated with increased mortality. Prominent toxicology references including Poisindex™, Ellenhorn and Barceloux's Medical Toxicology (Elsevier), and Goldfrank's Toxicologic Emergencies (Appleton & Lange) strongly caution the use of physostigmine, especially in the setting of TCA toxicity. Physostigmine is NOT recommended in the setting of TCA toxicity except to treat life-threatening symptoms that are unresponsive to other therapies.
Monitoring

A.) Check vitals frequently.
B.) Patients should be placed on continuous cardiac monitor for a minimum of 6 hours. If symptoms develop, monitoring should continue until the patient is asymptomatic and arrhythmia-free for 24 hours.
   • A 12-lead EKG should be repeated at 2-3 hours or as needed per patient.
C.) ABGs should be repeated every 2-4 hours for patients undergoing alkalinization. The goal is to maintain arterial pH at 7.45-7.55. Monitoring of urine pH plays no role in management.
D.) Check bowel sounds to govern use of repeat dose activated charcoal.
E.) If respiratory complications develop, obtain chest radiograph and repeat within the next 24 hours.
F.) Fluid and electrolyte status should be checked frequently.
G.) TCA levels are not useful in the initial management of TCA poisoning. They may, however, be of benefit if the diagnosis is unclear. Serum and urine drug screens may be useful if coingestants are suspected.

Suggested Reading