

tricyclic antidepressant overdose

management

prevention of absorption:

- (i) gastric lavage:
 - Although gastric lavage has long been advocated in the initial management of most drug intoxications, there is little evidence to support its use.
 - the American Academy of Clinical Toxicology recommends that gastric lavage be considered only if it can be done within 1 hour after a potentially fatal ingestion.
- (ii) activated charcoal
 - an inert, nonspecific adsorbent that irreversibly binds most drugs and toxins and has a time-dependent effect on drug absorption.
 - In volunteer subjects, a single dose of activated charcoal decreases absorption by an average of 69% and 34% when administered within 30 and 60 minutes after drug ingestion, respectively.
 - Despite its proven ability to prevent drug absorption, randomized clinical trials have failed to show that a single dose of activated charcoal improves patient outcome. It should be considered in patients who present within 1 hour of overdose

enhancement of elimination:

- (i) multiple dose charcoal:
 - multiple-dose charcoal is not recommended for patients with TCA intoxication as studies examining TCA clearance in volunteer subjects have yielded inconclusive and often conflicting results, and no studies have examined this therapy in poisoned patients
- (ii) haemodialysis and haemoperfusion:
 - Hemodialysis and charcoal hemoperfusion would be expected to be ineffective in removing TCAs and their active metabolites, because avid tissue and plasma protein binding leaves only a small fraction of free drug available for diffusion or adsorption. It is not recommended.

sodium bicarbonate

- Several controlled trials in animals and case reports and case series in humans have demonstrated that administration of sodium bicarbonate is often effective in shortening the QRS interval, terminating ventricular dysrhythmias, and increasing blood pressure after TCA overdose
- Three potential mechanisms for these beneficial effects have been proposed.
 - (i) alkalinization of the serum increases protein binding of TCAs, thereby reducing the concentration of free drug.
 - (ii) by causing drug ionization, alkalinization may reduce the affinity of TCAs for the myocardial sodium channel receptor.
 - (iii) an increase in the serum sodium concentration may overcome sodium channel blockade. (This final mechanism may explain why hypertonic saline has been reported to reverse cardiac toxicity in some animal studies and in case reports in humans).
- Based on this information, it is currently recommended that patients with evidence of cardiac toxicity (i.e., QRS or QT prolongation, ventricular dysrhythmias, heart block, hypotension) receive sodium bicarbonate with the goal of achieving and maintaining an arterial pH of 7.50 to 7.55.

Dysrhythmias

- Ventricular tachycardia and fibrillation accompanying TCA overdose are often refractory to drug therapy, and treatment should focus on the administration of sodium bicarbonate and the correction of acidemia, hypoxemia, and electrolyte abnormalities.
- Antiarrhythmic drugs categorized as class IA (procainamide), IC (flecainide, propafenone), and III (amiodarone, bretylium, ibutilide, sotalol) are not only ineffective but should be avoided because they, like the TCAs, can prolong depolarization.
- Case series have described the successful use of both lidocaine and phenytoin in patients with cardiotoxicity refractory to sodium bicarbonate therapy, and case reports have suggested that magnesium sulfate and hypertonic saline may be effective in cases of refractory ventricular dysrhythmias.

Hypotension

- Because TCA-induced hypotension may result from vasodilation, impaired cardiac contractility, or both, right heart catheterization is often useful in determining the predominant cause and the most appropriate therapy.
- Vasodilation resulting from a 1-adrenergic blockade causes a drop in systemic vascular resistance (SVR) and is most effectively treated with volume resuscitation followed, if necessary, by the use of one or more vasopressors.
- On the other hand, impaired myocardial contractility leads to a fall in cardiac output and a compensatory rise in SVR and responds best to dobutamine and afterload reduction.
- Sodium bicarbonate administration is often effective in improving hypotension, regardless of the underlying mechanism.

Respiratory failure

- CNS depression or seizures may lead to decreased respiratory drive, hypoventilation, and inability to protect the airway, and patients with severe intoxication often require intubation and mechanical ventilation.
- In nonintubated patients, serial arterial blood gas measurements must be obtained to evaluate for respiratory (and metabolic) acidosis, and frequent clinical assessment of airway protective reflexes is required.

Seizures

- Successful control of seizures has been reported with benzodiazepines, phenytoin, and phenobarbital.
- Propofol has been effective in patients with refractory status epilepticus.

treatment of specific complications

clinical manifestations

Cardiovascular System	Central Nervous System	Miscellaneous
Sinus tachycardia	Central nervous system depression	Mydriasis
Prolonged QRS and QT intervals	Seizures	Ileus
Heart block	Respiratory depression	Urinary retention
Ventricular tachycardia/fibrillation		Fever
Hypotension/shock		Flushing

- Anticholinergic toxidrome:**
 - Patients typically present with symptoms and signs of an anticholinergic toxidrome ("Blind as a bat, Red as a beet, Hot as a hare, Dry as a bone, Mad as a hatter.") which may include mydriasis, ileus, urinary retention, fever, flushing, sinus tachycardia, CNS depression that ranges from lethargy to coma, and seizures.
- Alpha-1 blockade:**
 - Blockade of α 1-adrenergic receptors causes vasodilation that can lead to hypotension.
- Sodium channel blockade:**
 - TCAs also cause direct cardiac toxicity by blocking sodium channels in the His-Purkinje system and ventricular myocardium. This effect slows depolarization of the action potential. Consequences can be prolongation of the QRS and QT intervals and development of heart block or ventricular dysrhythmias or both.
 - Inhibition of the sodium current also may lead to decreases in myocardial contractility, stroke volume, and cardiac output.

diagnosis & evaluation

- General:**
 - The diagnosis of TCA overdose should be strongly suspected in any patient who presents with an anticholinergic toxidrome, especially if the electrocardiogram (ECG) demonstrates characteristic changes
- ECG changes:**
 - several ECG findings have been shown to accurately identify patients at risk for development of seizures and ventricular dysrhythmias.
 - The most commonly cited predictor is a limb-lead QRS duration greater than 0.10 second, although marked right axis deviation and R-wave amplitude greater than 3 mm in lead aVR have been reported to have a higher sensitivity and specificity for serious toxicity.
 - These ECG findings are especially useful because they usually are evident at the time of presentation and almost always precede the onset of serious symptoms and signs.
- Arterial blood gases:**
 - Arterial blood gas measurements are also essential in patients with TCA poisoning, both to assess the degree of respiratory depression and to determine arterial pH.
 - Acidemia reduces TCA-protein binding, thereby increasing the concentration of the free drug and the risk of serious toxicity.
 - Therefore, it is very important to maintain arterial pH within the normal range by administering sodium bicarbonate, adjusting mechanical ventilation, or both.

clinical course & monitoring

- Patients with TCA overdose can become critically ill very rapidly, even when initial symptoms or signs are minimal. However, patients who develop major signs of toxicity (coma, seizures, respiratory depression, hypotension, ventricular dysrhythmias) almost invariably do so within 6 hours after presentation
- The maximum QRS duration also typically occurs within the first 6 hours and usually returns to normal within 12 to 18 hours.
- Patients rarely develop seizures or ventricular dysrhythmias after the QRS interval has returned to less than 0.10 second.
- Based on this information, patients should be admitted to an ICU if they have major signs of toxicity or QRS prolongation or if they have been monitored for less than 6 hours in the emergency department.