TRICYCLIC ANTIDEPRESSENT OVERDOSE

Pharmacokinetics

- TCAs block the presynaptic reuptake of biogenic amines (serotonin and norepinephrine).
- Absorbed rapidly from GI tract in the alkaline small intestine
- Anticholinergic effects of TCAs may impair gastric emptying and delay peak serum levels up to 12 hours after ingestion
- Extremely lipophilic, resulting in a large volume of distribution
- Tissue levels of TCAs far exceed those found in plasma; levels are 40 times greater in the brain and 5 times greater in the myocardium

Mode of toxicity

- TCAs produce a wide variety of toxic effects; the most severe toxicity occurs in the cardiovascular system, the peripheral nervous system (PNS), and the central nervous system (CNS).
- Cardiovascular toxicity results from direct myocardial depression, cardiac conduction disturbances, effects on peripheral vasomotor tone, and changes in the autonomic nervous system.

TCAs bind to and inhibit the cardiac fast sodium channel, thereby slowing depolarization in His-Purkinje and ventricular myocytes . This results in slowed cardiac conduction (eg, prolonged QRS on the ECG), impaired cardiac contractility (via impaired cellular calcium entry), and possible ventricular dysrhythmias (caused by nonuniform sodium channel blockade).

- TCAs inhibit alpha1-adrenergic receptors, resulting in peripheral vasodilation and orthostatic hypotension. These effects mediate, in part, refractory hypotension observed with severe TCA poisoning.
- TCAs produce tachycardia from competitive blockade at muscarinic acetylcholine receptors.
- TCAs block norepinephrine reuptake in the CNS and PNS (autonomic ganglia). Initially, this may result in hypertension and tachycardia. However, with prolonged blockade of reuptake, norepinephrine is depleted from the presynaptic nerve terminal (most norepinephrine released is from a recycled neurotransmitter), which results in refractory hypotension and bradycardia.
- Neurologic toxicity results from CNS blockade of muscarinic acetylcholine, H1-histamine, and GABA receptors; inhibition of norepinephrine, serotonin, and dopamine reuptake; and blockade of neuronal fast sodium channels.

- Muscarinic acetylcholine receptor blockade, causing a variety of anticholinergic effects that characterize the early stages of intoxication

Features

- Anticholinergic effects: sinus tachycardia, dry mucous membranes, dilated pupils, urinary retention, ileus, altered mental status (agitation, confusion, lethargy),
- Cardiac effects: Hypertension (early and transient, should not be treated), tachycardia, and hypotension, Arrhythmias (including VT and VF).ECG changes (prolonged QRS, QT and PR intervals)
- Central nervous system effects: coma, seizure, increased tone and hyperreflexia may be present with extensor plantar reflexes, In deep coma all reflexes (including brain-stem reflexes) may be abolished.
- Pulmonary effects: Hypoventilation resulting from CNS depression

Management

- **ABCs**
    a. Anticipate airway compromise resulting from possible rapid deterioration of neurologic and cardiovascular functions
    b. Secure the airway if gastric lavage and/or charcoal administration are to be performed in a patient with a decreasing level of consciousness

•Activated Charcoal (50g PO/NG) if presenting within 1 hour of ingestion of more than 5mg/kg, only if airway is protected

•**Sodium bicarbonate:**

Alkalization and sodium loading has been shown to be effective in the treatment of TCA-induced conduction disturbances, ventricular arrhythmias, and hypotension
Sodium bicarbonate attenuates TCA cardiotoxicity via several mechanisms:

1. Alkalinization of blood to a pH of 7.45-7.55 appears to uncouple TCA from myocardial sodium channels
2. Sodium increases extracellular sodium concentration and, thus, improves the gradient across the channel (to overcome the competitive fast sodium channel blockade produced by TCA).

•Give sodium bicarbonate at dose of 50ml of 8.4% if:
-metabolic acidosis
-QRS duration >120 msec
-Arrthymias
-Hypotension resistant to fluid resuscitation
Can give further doses depending on clinical response to achieve an arterial pH 7.5-7.55

- Bicarbonate administration produces CO2, which crosses cell membranes more rapidly than bicarbonate, potentially worsening intracellular acidosis.
- Caution with: pulmonary oedema (may worsen), pregnancy,renal disease

- Effects include: alkaosis, hypernatraemia, hypokalaemia, hypocalcaemia (increased binding of calcium to serum proteins), decreased fibrillation threshold, will form precipitate with Ca salts and potentially clog IV lines

- Ventricular arrhythmia refractory to sodium bicarbonate may require treatment with lignocaine, magnesium sulfate but suggest seek advice from UK NPIS
- Patients with hypotension refractory to fluid resuscitation and sodium bicarbonate may require vasopressor support
    - Direct acting alpha-agonists (eg, norepinephrine,) are indicated when significant hypotension persists despite adequate volume replacement (as monitored by central venous pressure or pulmonary capillary wedge pressure)
    - Dopamine may not be as effective because its action is mediated by the release of endogenous catecholamines that may be depleted during TCA toxicity. Use of dopamine or dobutamine alone may result in unopposed beta-adrenergic activity resulting from TCA-induced alpha blockade and, therefore, may worsen hypotension

•Consider 10mg IV glucagons for severe hypotension and myocardial depression
Glucagon has dose-dependent positive inotropic and chronotropic qualities. It increases myocardial intracellular calcium concentration by stimulating adenyl cyclase, thus enhancing myocardial contractility. This action is thought to occur at nonadrenergic receptors. Glucagon has rarely been used in the treatment of severe tricyclic poisoning but theoretically it is a valuable vasoactive agent as its actions are independent of the adrenoreceptors which are affected in tricyclic excess.

- Seizures can be controlled with benzodiazepines. Phenytoin is best avoided as it also blocks sodium channels and may increase the risk of cardiac arrhythmias
- Diazepam can be used for the extreme agitation or delirium that occasionally are observed because of the anticholinergic effects of TCAs
- Forced diuresis, haemodialysis and haemoperfusion are not beneficial due to the large volume of distribution of TCAs.