THE NORTHERN HOSPITAL

TRICYCLIC ANTIDEPRESSANT OVERDOSE

"Phoenicopterus ruber, the Greater Flamingo", hand coloured lithograph, Edward Lear, The Birds of Europe, Vol. 4 (1832-37) John Gould.

"It is not the shape of either the body or its parts, which gives rise to the habits of animals and their mode of life, but it is, on the contrary, the habits, mode of life, and all the other influences of the environment, which have in course of time built up the shape of the body and of the parts of animals"

Jean-Baptiste Lamarck, Philopsophe Zoologique, 1809.

Edward Lear's beautiful 19th Century lithograph of the Flamingo demonstrates the three most strikingly recognizable characteristics of this creature. Firstly its pink coloration, which is due to its diet of brine shrimp, which contain a carotenoid necessary to create pink feathers, (flamingos are not naturally pink, they are naturally white) and secondly its odd behavior of standing on one leg, possibly in an effort to conserve heat. The third characteristic is its beak, unique to the bird world. It is designed to work upside down! It works as a filter feeder in its natural environment of hypersaline lakes. By inverting its head into the briny waters it feeds on various crustaceans. Its smaller upper jaw being hinged via a ball and socket joint, in contrast to all other birds, (whose upper jaws are larger than their lower jaws and fixed) acts functionally as a lower jaw when it feeds with its head upside down in the water as shown by the sitting bird.

The great paleontologist Stephen Jay Gould used the beak of the flamingo as an example of an early controversy of the pre-Darwinian age concerning theories of evolution. Contrary to popular belief Darwin did not "invent" the theory of evolution. The idea that species could "transmute" into different ones had been extensively discussed before. Darwin's great contribution to science was to determine just how this was done, by natural selection. Before Darwin a "chicken and egg" debate raged between "structuralists" such as Etienne Geoffroy St Hilarie and "functionalists" such as Jean-Baptiste Lamarck. The structuralists held that an animal's anatomy altered, (according to some mystical laws of form) and that following this alteration a new way of life then ensued. According the functionalists a new way of life preceded any anatomical adaptations that would in due course make this new way of life more efficient. In other words the flamingo's beak according to the structuralists developed its inverted arrangement first, and then to its surprise it found that this was perfectly suited to filter-feeding in briny waters, which it then sought out. The functionalists on the other hand would explain the flamingo's beak in terms of its initial attempts at feeding in the briny waters of its environment and the appropriate anatomical adjustments followed as a consequence of this behavior. Time would of course prove that the functionalist Lamarck was correct and Gould points out that it is for this major contribution in our understanding of how evolution works he should be remembered. However when evolution is taught in our schools Lamarck is held up as a figure of ridicule. How can this be?

The reason is that his functionalist theory has largely been forgotten in the grander scheme of things and instead he is remembered today as the exponent of a false theory on just exactly how the functional anatomical changes occurred in animals faced with a new behavior or environment. He claimed that characteristics that were acquired during the life of an animal could then be passed onto its off spring. As an example giraffes that constantly stretched their necks to reach the tops of tall trees, would consequently have off spring with longer necks. This is held up in traditional teaching of evolution as one of the more silly ideas that Darwin had to fight against. Darwin's great break through of

course was his discovery that anatomical change was bought about by natural selection of pre-existing genetic variants in a population of animals subjected to a changing environment. Nonetheless Darwin's theory of natural selection did to an extent stand on the shoulders of a number of predecessors, including Thomas Malthus, Charles Lyell and not least of all Lamarck, whose functionalist theory that anatomical alteration came secondary to its alteration in habit or environment. As Gould points out, Lamarck was entirely correct in what he had said on evolution, but for the wrong reasons, he just did not understand the exact mechanism by which it occurred. It took Darwin's additional insight of natural selection to complete the theory of evolution which has subsequently improved our understanding immeasurably about the natural world we inhabit.

In the field of medical toxicology debate raged in past times about how exactly it was that the administration of sodium bicarbonate worked for the life- threatening arrhythmias that could develop in response to overdose with the tricyclic anti-depressants. The older view of alterations in protein binding now seems somewhat Lamarckian, the treatment is still correct, however not for the traditional protein binding reasons so stated. The modern "Darwinian" understanding of the importance of the sodium content of sodium bicarbonate has led to a vastly improved understanding of the toxicological world we now inhabit. It is now appreciated that it is in fact the sodium loading that overcomes the sodium channel blockade that provides the beneficial effects seen in tricyclic antidepressant overdose. By now knowing the correct mechanism by which sodium bicarbonate is beneficial we can apply this knowledge to any agent that has significant toxic effect via the blockade of sodium channels, and hence we have immeasurably improved our knowledge of the management of drugs with class one anti-arrhythmic action.

TRICYCLIC ANTIDEPRESSANT OVERDOSE

Introduction

The Tricyclic Antidepressants (TCAs) are comprised of three aromatic rings, (hence the name).

The major toxicity in overdose relates to the CNS and the CVS.

Intubation, hyperventilation and sodium bicarbonate are the mainstays of treatment in severe toxicity.

Preparations

Tricyclic Antidepressants currently available in Australia include:

- Amitriptyline
- Clomipramine
- Desipramine
- Dothiepin
- Doxepin
- Imipramine
- Nortriptyline
- Trimipramine

Pharmacokinetics

Absorption

- TCAs are rapidly absorbed orally.
- Peak levels are reached within 2 hours.

Distribution

- TCAs are highly bound to plasma and tissue proteins and hence have large volumes of distribution, (5-20 L/kg).

Metabolism and excretion

- TCAs undergo hepatic metabolism.
- There is some entero-hepatic circulation.

Pathophysiology

TCAs are non-selective agents, which primarily act by:

- Inhibition of the amine reuptake pump in neurons within the CNS, especially of noradrenaline and serotonin. This is thought to be the basis of their therapeutic activity.

- Muscarinic (M1) receptor blockade, leading to anti-cholinergic effects.
- Peripheral post-synaptic alpha$_1$-adrenergic receptor blockers.

Toxicological effects of the tricyclic drugs therefore include:

1. Myocardium:

   Conduction disturbance:

   Blockade of **fast sodium channels** (*a class 1a affect*) in **cardiac tissue.**

   This may lead to:

   - Severe cardiac conduction abnormalities.
   - Prolongation of the QT interval with consequent development of torsade de pointes.
   - Arrest rhythms, VT, VF and asystole.

   Myocardial depression:

   - There is also a direct myocardial depressant effect unrelated to conduction abnormalities.

2. Anticholinergic effects, which may lead to:

   A peripheral anticholinergic syndrome:

   - **Sinus tachycardia**, (common), blurred vision, urinary retention, gut ileus, reduced salivation and reduced sweating. The reduced sweating can lead to hyperthermia.

   A central anticholinergic syndrome:

   - Including drowsiness, confusion, hallucinations (visual), purposeless movements and myoclonic jerks. In more serious overdoses seizures and coma may occur.

3. Anti-alpha$_1$-adrenergic effects:

   - This may result in vasodilatation and hypotension.

4. Serotonin syndrome**:**

   - When used in combination with SSRI drugs.

Risk Assessment

The onset of severe toxicity usually occurs within 2 hours of ingestion.

Ingestion of > 10mg/kg is potentially life threatening.

Seizures and myoclonus are more common with dothiepin.

Dose related risk assessment:

Dose	Clinical Effects
< 5mg/kg	Minimal symptoms.
5-10mg/kg	Drowsiness Mild anti-cholinergic effects Major toxicity not expected.
> 10mg/kg	Potential for major effects to occur within 2-4 hours of ingestion, (coma, hypotension, seizures and arrhythmias). Anti-cholinergic effects likely, which may be masked by coma.
> 30mg/kg	Severe toxicity with pH dependent cardiotoxicity and coma expected to last > 24 hours

Effects are more severe in children at lower ingestion dosages.

Clinical Features

Severe toxicity is characterized by **rapid deterioration** in conscious state within 1-2 hours of ingestion.

The predominant toxic effects will relate to the CNS and the CVS.

1. Neurological:

   These usually precede CVS signs.

   - **The commonest presentation is drowsiness or coma**.

Loss of consciousness may occur very rapidly.

- Confusion, (anticholinergic effects)
- Hallucinations may occur, (anticholinergic effects)
- Purposeless/ choreoathetosis type movements are commonly seen.
- Myoclonus and/ or **seizures.**

2. CVS:

- **Sinus tachycardia is a common finding,** (anticholinergic effect)
- Hypotension, (due to alpha blocking effects and direct myocardial depression)
- In more serious ingestions broad complex tachyarrhythmias or bradyarrhythmias are seen.

3. Other anticholinergic effects:

- Mydriasis
- Ileus
- Urinary retention.
- Dry warm, flushed skin.

Investigations

Blood tests:

1. **Serum TCA concentrations**

- These can be done and are useful to detect the presence of TCA.

  Levels do correlate with the clinical severity of the intoxication, however the **ECG** together with the clinical signs have a better correlation with eventual outcome.

2. U&Es and glucose

3. Consider co-ingestions, paracetomol, alcohol, and salicylates

12 lead ECG:

This is very important in the setting of TCA overdose.

1. The commonest finding will simply be a sinus tachycardia.

2. Prolongation of the P-R interval.

3. **Prolongation of the QRS interval:**

   - This reflects the degree of fast sodium channel blockade.
   - The degree of prolongation of the **QRS complex** is the best predictor of risk of both ventricular arrhythmias and seizures in the acute overdose.
     - ♥ A QRS of greater than 100 ms (or 0.1 second or 2.5 small squares) in the setting of a TCA overdose is predictive of seizures.
     - ♥ A QRS of greater than 160 ms (or 0.16 seconds or 4 small squares) in the setting of a TCA overdose is predictive of VT.
   - The QRS can become extremely widened and come to resemble a sine wave, which may preface asystole, VT or VF.

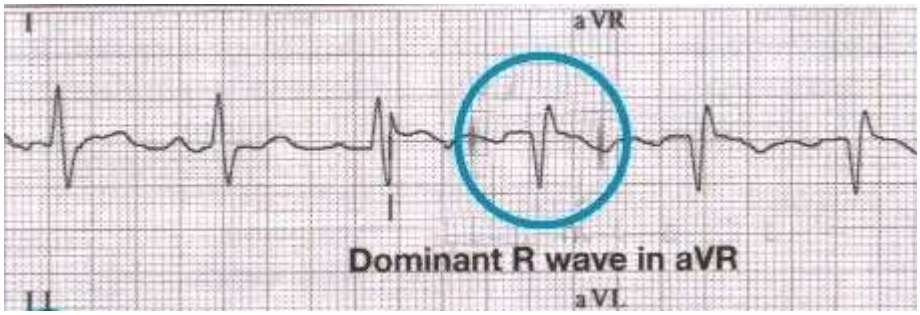
4. Prolongation of the Q-T interval:

   - Prolongation of the QT interval may predict the risk of development of torsade de points, VT or VF

5. Lead AVR abnormalities:

   Diagnostic features of TCA poisoning (and sodium channel blockade in general) in lead AVR include:

   - A large terminal R wave in aVR
   - An increased R/S ratio, (>0.7)



5. Note that a patient can have significant **CNS** toxicity despite a normal ECG.

Management

1. Immediate attention to ABC issues:

- Intubation is necessary in patients with significantly reduced conscious state and will allow for the safe administration of activated charcoal.

- If the patient is ventilated pCO_2 levels should be kept below 40 mmHg (to help maintain an alkalosis) with appropriate ventilation settings.

2. Establish monitoring:

   - Continuous ECG monitoring

   - Pulse oximetry

   - Continuous blood pressure monitoring.

3. Charcoal:

   - Is best avoided in *unintubated* patients or those with ECG changes, as the risk from aspiration is significant with sudden reduction in conscious state and/ or sudden development of a "malignant" arrhythmia or sudden onset of seizures. This is a more serious consideration than any theoretical benefit of charcoal.

   - Intubated patients *should* receive **repeat** charcoal dosing.

4. Hypotension:

   - This usually responds well in the first instance to IV fluids.

   - In more severe and refractory cases **bicarbonate** should be tried, even in the presence of a normal QRS.

   - If there is still no response inotropes will be needed. **Noradrenaline** is the agent of choice for its alpha-adrenergic effects and its minimal effect on beta-receptors.

5. Confusion and agitation:

   - These are best treated with IV diazepam.

6. Seizures:

   - Are treated in the usual manner with IV benzodiazepines.

7. **Sodium bicarbonate:**

   Sodium Bicarbonate is regarded as the specific anti-dote for the treatment of TCA induced cardiac toxicity.

It is thought to act by providing a large source of **sodium** which competitively overcomes the sodium channel blockade. pH alterations into the range of 7.5-7.55 is also beneficial for sodium channel *function*.

Indications:

It is indicated for patients with:

- Widened QRS complexes.
- Cardiac arrhythmias.
- Hypotension not responsive to fluids.

Dosing:

- A loading dose of 1 mmol / kg IV (= 1 ml / kg of 8.4% solution) is given over 15 minutes, or **quicker over several minutes** if the patient is very unstable, (eg. arrhythmias).
- If arrhythmias persist, then the bicarbonate doses should be repeated, it is a common pitfall to not provide enough sodium bicarbonate in cases of refractory arrhythmias in the setting of TCA overdose. Doses can be repeated within several minutes if necessary
- This may be followed by an infusion of 25 mmol/ hr to aim for a blood pH of 7.50-7.55. (100 mls of sodium bicarbonate can be added to 1 liter of normal saline and infused at 250 mls/hour).

8. Anti-arrhythmics:

- If arrhythmias persist despite bicarbonate therapy type 1a and type 1c anti-arrhythmics (procainamide/ amiodarone/ flecainide) should be avoided, because of their aggravating effects on sodium channel blockade.
- Lignocaine may be tried, but is unlikely to be effective.
- The best treatment will be repeated doses of bicarbonate.

8. Cardioversion/ defibrillation:

- These can be performed when required, but are unlikely to be effective without adequate bicarbonate therapy.

9. Flumazenil:

- This agent should be avoided in the setting of a TCA overdose because its action may precipitate refractory seizures.

10. Hemodialysis:

- TCA is highly bound to serum proteins and tissues, with a consequently large volume of distribution. Therefore hemodialysis will **not** be effective and is **not** recommended.

Disposition

- Patients who show no signs of toxicity and have a normal ECG after 6 hours of observation may be medically cleared.

- All patients with significant CVS or CNS manifestations should be admitted to HDU/ICU.

References:

1. TCA Overdose in L Murray et al. Toxicology Handbook 2nd ed 2011.

Further reading:

Gould S. J. The Flamingo's Smile: Reflections in Natural History, W.W Norten 1985.

Dr J. Hayes
Reviewed May 2011.