Tricyclic antidepressant poisoning: cardiovascular and neurological toxicity


1 Department of Emergency medicine, St Antonius Hospital, Nieuwegein, the Netherlands
2 Department of Emergency Medicine, Medical Center Haaglanden, The Hague, the Netherlands
3 Department of Pharmacology, The Hague hospital pharmacy, The Hague, the Netherlands
4 Critical Care, Medical Center Haaglanden, The Hague, the Netherlands
5 Department of Clinical Pharmacy, Ikazia Hospital and Maasstad Hospital, Rotterdam, the Netherlands

Correspondence
F.C. Verbree – fcverbree1@gmail.com

Keywords - tricyclic antidepressants, Nortriptyline, overdose, intoxication

Abstract
Tricyclic antidepressant poisoning is a potentially lethal condition and treatment can be challenging. ECG findings are the most important risk stratification and should be used to guide subsequent therapy. Sodium bicarbonate is the main treatment along with activated charcoal. When high doses of a tricyclic antidepressant are ingested, the anticholinergic effect may be substantial.

Introduction
Tricyclic antidepressants (TCAs) were introduced in the 1950s.1 The first fatal overdose was reported in 1959.2 Although TCAs have been largely replaced by newer antidepressants with a less toxic profile in overdose, such as selective serotonin reuptake inhibitors (SSRIs), they are still frequently prescribed. In the Netherlands, with a total population of 16.8 million, more than 263,000 people used a TCA in 2013.3 The reported mortality of TCA overdose is approximately 1.3%.4,5 Nervous system toxicity and cardiovascular toxicity, resulting in decreased levels of consciousness, hypotension and dysrhythmias, are primarily responsible for mortality attributed to TCA overdose.6 We describe the presentation and management of severe toxicity following TCA overdose; we also provide a treatment algorithm, in order to help physicians managing this serious condition.

Case report
A 39-year-old woman (56 kg) was transferred to the emergency department after she was found unconscious with an empty bottle of nortriptyline beside her. Two hours earlier she was seen in good health. The amount ingested was unknown, but the bottle may have contained 100 tablets of nortriptyline 50 mg (89 mg/kg). The patient’s medical history documented depression and two previous suicide attempts, with medication. Her first attempt was three years earlier with morphine and TCAs, a second attempt was two years later with a combination of opioids.

On physical examination her Glasgow Coma Scale was E1M5V2. Respiratory rate was 14/min, oxygen saturation 98% on room air, heart rate 150 beats/min and blood pressure 80/40 mmHg. Her temperature was 36.6 °C. Other physical examination was unremarkable.

Immediately after arrival a tonic-clonic seizure occurred, ending spontaneously after 20 seconds. As the seizure ceased, the monitored heart rhythm had changed from narrow complex tachycardia to ventricular tachycardia and her blood pressure dropped to 60/30 mmHg (figure 1, QRS 184 ms). This was the first ECG to be obtained, and conduction times before the seizure were unknown.

Figure 1. First obtained ECG, QRS 184ms

Because of a high suspicion of nortriptyline ingestion, 100 ml of sodium bicarbonate 8.4% was administered. Additionally, synchronised electrical cardioversion was performed at 50
Tricyclic antidepressant poisoning: cardiovascular and neurological toxicity

Joules, resulting in conversion back to small complex tachycardia (figure 2). Her blood pressure remained low for which saline and noradrenalin were administered. The Glasgow Coma Scale remained low, rapid sequence intubation was performed with midazolam (2x5 mg) and rocuronium (50 mg) to prevent aspiration. The first arterial blood gas analysis was obtained after intubation and showed: pH 7.37, pO2 58.2 kPa, pCO2 7.7 kPa, base excess 6.9 mmol/l and bicarbonate 30.7 mmol/l.

**Figure 2.** ECG after cardioversion

After securing the airway by intubation, a nasogastric tube was inserted and activated charcoal (50 grams) was administered. Four hours after presentation, while checking for gastric residual volumes, activated charcoal was still seen. A gastroscopy was performed in order to position a duodenal tube to enable activated charcoal to be administered beyond the stomach. Large amounts of pills were seen, five hours after ingestion. Aspiration of pill remains was not possible. Infusion of sodium bicarbonate 1.4% (2 litres/24 hours) was stopped when the second blood gas analysis, two hours later, showed a pH of 7.66. One day after admission the cardiac conduction times normalised (QRS 98 ms). Two days later her ECG normalised (figure 3), sedation was stopped and she was extubated. Neurological examination showed no abnormalities. The patient complained about some abdominal pain and constipation, which were treated. The patient was transferred to the psychiatric ward, without any sequelae. Toxicological analysis showed elevated serum levels of nortriptyline (2.1 mg/l) and its active metabolite OH-nortriptyline (0.78 mg/l).

**Figure 3.** ECG two days after admission

Discussion

**Pharmacodynamics and pharmacokinetics**

Nortriptyline is a second-generation tricyclic antidepressant and is the active metabolite of amitriptyline. The progression of clinical toxicity with an overdose of TCAs is unpredictable. Due to slow absorption in overdose, decreased by the anticholinergic effects of TCA, patients without initial symptoms may develop life-threatening cardiovascular and central nervous system toxicity within the next hours.[7] Nortriptyline is primarily metabolised in the liver by CYP2D6 to the pharmacologically active metabolite 10-OH-nortriptyline and to inactive metabolites which are eliminated by the kidneys. The average half-life of nortriptyline is 26 hours (16-38 hours). Therapeutic levels of nortriptyline are 0.05-0.15 mg/l. In normal dosage the maximum concentration is reached within approximately five hours, in overdose this is prolonged. The ingested dose is a poor predictor of clinical outcome, just as serum levels are.[4,8] In general, signs of toxicity start above a sum concentration of nortriptyline and OH-nortriptyline of 0.5 mg/l, and toxicity is usually severe in patients with a sum concentration of >1 mg/l.[9] Toxicity usually starts mildly with anticholinergic effects but can develop into serious toxicity with seizures, coma, hypotension and QRS prolongation with ventricular dysrhythmias. Serum concentrations were measured to confirm the suspected diagnosis, and to evaluate severity. When measured levels are <0.5 mg/l, the chance of a life-threatening intoxication is small. Serum levels in our patient were almost six times the toxic serum concentration. Furthermore, TCAs are highly protein bound (93% at normal pH), lipophilic and have a high volume of distribution (17-25 l/kg). Bioavailability is 51%.

**Clinical presentation**

The clinical presentation usually starts with mild symptoms such as agitation, which may worsen over time to convulsions, coma and death. Anticholinergic effects of TCA include delirium, widened pupils, decreased gut motility and urine retention. Cardiovascular effects include alpha-receptor blockage resulting in vasodilatation, sodium channel blocking resulting in increased depolarisation time and the inhibition of potassium channels causing increased repolarisation time and dysrhythmias. Neurological symptoms can include lowered levels of consciousness, due to antihistaminic effects, and seizures due to TCA antagonist effects on the GABA-A receptor.

**ECG use in risk stratification**

ECG findings are used for risk stratification and to guide subsequent therapy.[10] The typical ECG changes that can be found in a TCA overdose are QRS width >100 ms, QTc prolongation >430 ms and R/S ratio 0.7 in lead aVR.[10] Also an R in aVR of >3 mm and right axis deviation of 130 to 270 degrees in the terminal 40 ms of the QRS are typical findings in TCA overdose. These ECG findings are identified as the most
important risk stratification, more important than serum drug levels for the prediction of complications (seizure, dysrhythmias such as torsade de pointes) following a TCA overdose. Our patient showed all the ECG findings listed above.

**Therapeutic options**

First the dosage of the ingested tablets has to be estimated. It is important to know whether the tablets are immediate- or slow-release tablets, the main difference being the prolonged observation time.

Although clinical evidence for the use of sodium bicarbonate is poor, it is advised as standard therapy. Sodium bicarbonate acts at three levels. First, it raises the sodium gradient across the affected sodium channel, accelerating the rise of the action potential, counteracting the drug-induced side effect of sodium channel blocking. Second, sodium bicarbonate increases the pH; a higher pH promotes dissociation of TCA from cardiac sodium channels and decreases TCA-induced blockade, primarily causing arrhythmias. Third, TCAs are bound to protein in a pH-dependent fashion; in the higher pH range TCAs bind more easily to protein resulting in a lower pharmacologically active TCA concentration. Alkalisation to a pH of 7.45-7.55 is advised until normalisation of the QRS interval, even in the absence of initial acidosis. When the pH becomes >7.6 the risk of dysrhythmias increases.

Metabolic and electrolyte disturbances need to be corrected. Administration of magnesium sulphate at a range of 0.7-1.05 mmol/l is advised to stabilise the myocardial cell membrane and the potassium serum level should range between 4.5 and 5.0 mmol/l, to shorten the QT interval.

TCA are easily absorbed from the gastrointestinal tract, but the anticholinergic effect may slow gastrointestinal tract motility. Repeated activated charcoal and laxation is advised to prevent delayed absorption and re-uptake via the entero-hepatic cycle. It is not advised to perform gastric lavage after the first hour following TCA poisoning, because it is thought to be unlikely that a significant amount of antidepressant will be recovered. The risk of aspiration, seizure and tachycardia should also be taken into account. Bosse et al. compared three different gut decontamination modalities: activated charcoal alone, gastric lavage followed by activated charcoal and activated charcoal followed by gastric lavage, followed by a final dose of activated charcoal. In this study no difference with respect to outcome was found. For these reasons, initially gastric lavage was not performed and only activated charcoal was administered, but residual volume was found four hours after presentation and a gastroscopy was performed. Five hours after presentation the stomach still contained a large amount of pill remains and activated charcoal. Given these observations, a duodenal tube was inserted and activated charcoal administered through this tube. We believe that with exceptionally high doses of TCA ingestion, the anticholinergic effect should be taken into consideration regarding gastrointestinal motility. Our patient complained about abdominal pain and constipating during the days following ingestion, in our opinion due to anticholinergic side effects.

Our patient had a seizure shortly after arriving, which ceased spontaneously. Seizures are usually brief. Recurrent seizures require prompt treatment with benzodiazepines or barbiturates. Phenytoin should be avoided as there is doubt regarding the safety in these patients. Some TCA may increase phenytoin levels; this is problematic because of the narrow therapeutic range of phenytoin. Furthermore phenytoin has class 1a antiarrhythmic actions, and in animal models the likelihood of ventricular arrhythmias was increased.

In the case of hypotension unresponsive to volume expansion, the use of catecholamines is advised. Because TCAs theoretically block neurotransmitter reuptake, norepinephrine (a direct-acting vasopressor) is believed to be more efficacious than an indirect-acting catecholamine such as dopamine. Our patient received norepinephrine, with good response. Haemodialfiltration and haemoperfusion have limited efficacy because TCAs have a large volume of distribution and are largely protein bound.

Lipid emulsion can be used when standard therapeutic options such as repeated activated charcoal and sodium bicarbonate have no effect. Lipid is assumed to decrease the unbound free-

---

**Figure 4.** Treatment algorithm useful in patients with TCA intoxication
drug concentration by redistribution of the lipophilic TCA from the aqueous plasma, known as ‘lipid sink.’ However, there are no human studies to support this theory and animal studies show contradicting results.[17,18]

Several treatment options have been discussed. Figure 4 shows the algorithm for the treatment of a suspected severe TCA overdose, with immediate release tablets.

**Disclosures**
All authors declare no conflict of interest. No funding or financial support was received.

**References**