

## REVIEW

## Tricyclic antidepressant overdose: a review

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**Abstract**

**Overdoses of tricyclic antidepressants are among the commonest causes of drug poisoning seen in accident and emergency departments. This review discusses the pharmacokinetics, clinical presentation and treatment of tricyclic overdose.**

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Keywords: tricyclic antidepressant; overdose

The first report of the adverse effects of tricyclic overdose was in 1959 and came within two years of their clinical usefulness having been recognised.<sup>1</sup> Now tricyclics are identified as one of the most frequently ingested substances in self poisoning along with paracetamol, benzodiazepines and alcohol.<sup>2</sup> They are second only to analgesics as the commonest drug taken in fatal drug overdose.<sup>3-4</sup> There is also evidence that the number of deaths relative to the number of prescriptions issued is significantly higher for tricyclics in comparison to other antidepressants.<sup>5</sup>

On average 268 people in Britain die each year after taking an overdose of tricyclic drugs.<sup>5</sup> Despite the introduction of newer and safer antidepressants the prescription of tricyclics is still widespread as they are cheaper and many still consider them to be the most effective group of antidepressants.

The commonest tricyclic taken in fatal overdose is dothiepin,<sup>5</sup> which, along with amitriptyline, has been shown to have comparatively greater toxicity than other tricyclics.<sup>5-6</sup>

**Pharmacokinetics**

Tricyclics are rapidly absorbed from the gastrointestinal tract and undergo first pass metabolism. They are highly protein bound and have a large volume of distribution, resulting in a long half life of elimination that generally exceeds 24 hours and in the case of amitriptyline is 31 to 46 hours.<sup>7</sup> After metabo-

lism by hepatic enzymes the metabolites, some of which have pharmacological activity themselves, are conjugated and excreted by the kidneys.

The ingestion of large quantities of tricyclics in self poisoning causes altered pharmacokinetics.<sup>8</sup> Gastrointestinal absorption may be delayed because of inhibition of gastric emptying and significant enterohepatic recirculation prolongs the final elimination. The amount of unbound tricyclic may also increase if the overdose causes respiratory depression resulting in an acidosis, which reduces protein binding.

The toxic effects of tricyclics are caused by four main pharmacological properties:

- 1 Inhibition of norepinephrine reuptake at nerve terminals.
- 2 Direct  $\alpha$  adrenergic block.
- 3 A membrane stabilising or quinidine-like effect on the myocardium.
- 4 Anticholinergic action.

**Clinical features**

The dose ingested, even if reliably confirmed, is a poor predictor of the subsequent clinical outcome. Doses of less than 20 mg/kg are unlikely to be fatal or cause severe complications<sup>9-10</sup> but individual variation in absorption, protein binding and metabolism limit any meaningful prediction.

The clinical features of tricyclic overdose can be grouped according to their effects on the peripheral autonomic system (anticholinergic effects), the cardiovascular system and the central nervous system (table 1).

**ANTICHOLINERGIC EFFECTS**

Anticholinergic features are common and may aid diagnosis in certain patients. Generally anticholinergic effects do not cause serious clinical problems but cases of toxic megacolon and intestinal perforation have been described.<sup>11-12</sup>

By impairing sweating heat dissipation is reduced and this can result in a fever, especially if seizures occur. Central cholinergic block can also alter thermoregulation.<sup>13</sup>

**CARDIOVASCULAR EFFECTS**

The commonest cardiovascular effect is a sinus tachycardia, which is attributable to the inhibition of norepinephrine reuptake and the anticholinergic action. However, the most important toxic effect of tricyclics is the slowing of depolarisation of the cardiac action potential by inhibition of the sodium current

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Table 1 Clinical features and complications of tricyclic antidepressant overdose

Cardiovascular system	Central nervous system	Anticholinergic effects
Sinus tachycardia	Drowsiness	Dry mouth
Prolonged PR/QRS/QT	Coma	Blurred vision
ST/T wave changes	Convulsions	Dilated pupils
Heart block	Pyramidal signs	Urinary retention
Vasodilatation	Rigidity	Absent bowel sounds
Hypotension	Delirium	Pyrexia
Cardiogenic shock	Respiratory depression	Myoclonic twitching
Ventricular fibrillation/tachycardia	Ophthalmoplegia	
Asystole		

and this delays propagation of depolarisation through both myocardium and conducting tissue.<sup>14</sup> This results in prolongation of the QRS complex and the PR/QT intervals with a predisposition to cardiac arrhythmias. This inhibition of sodium flux into myocardial cells can occur to such an extent that depressed contractility can result<sup>15 16</sup> and this, coupled with the reduction in peripheral resistance, contributes to hypotension.

The overall incidence of serious cardiovascular arrhythmias is low. In one series four patients from 153 admitted to an intensive care unit had either a nodal or ventricular arrhythmia<sup>17</sup> and only 3 of 225 patients admitted to another intensive care unit developed arrhythmias.<sup>18</sup> Hypotension is more common with an incidence of 14% to 51% having been reported.<sup>19–21</sup>

#### CENTRAL NERVOUS SYSTEM EFFECTS

Coma was present in 53 patients (17%) of a series of 316<sup>22</sup> and the incidence is even higher (52%) in the initial presentation of overdoses with a fatal outcome.<sup>23</sup>

Twenty four patients (6.2%) from a series of 388 admitted to intensive care had seizures<sup>24</sup> and confirmed a previous report of seizures exacerbating hypotension.<sup>25</sup> This is thought to be caused by the metabolic acidosis associated with the seizures increasing the bioavailability of the tricyclic by decreasing the amount that is protein bound or altering the effect of tricyclics on the cardiac membrane sodium channels.

#### Investigations

Plasma tricyclic concentrations are not widely available and measured levels often lack sensitivity in detecting active metabolites. Petit *et al*<sup>26</sup> demonstrated an increased incidence of seizures, coma and cardiac arrest in patients with a total tricyclic level greater than 1000 µg/l but subsequently it has been shown that prolongation of the QRS duration (>0.16 seconds) is a better predictor of seizures or ventricular arrhythmias than the plasma drug concentration.<sup>27</sup> The QRS duration has also been associated with the probability of requiring ventilation<sup>18</sup> but it is possible for a patient with very high plasma concentrations to have a normal QRS duration<sup>28</sup> and the use of the QRS duration as a reliable indicator of poisoning severity is controversial.<sup>29 30</sup> Decreased R-R variation has been described as a method of identifying tricyclic overdose<sup>31</sup> and it has been suggested that a terminal R wave greater than 3 mm in lead aVR is a more useful predictor of seizures or arrhythmias than QRS duration.<sup>32</sup>

The most frequent acid base disturbance is acidosis.<sup>33</sup> This is often a mixed acidosis with both respiratory depression and myocardial impairment/hypotension resulting in reduced tissue perfusion and the production of lactate.

Hypokalaemia may be present and in a series of 295 patients 9% had a potassium concentration less than 3.0 mmol/l.<sup>34</sup>

#### Management

##### REDUCING ABSORPTION

The majority of papers regarding gastric lavage include many different types of overdose substances. Kulig *et al* showed that lavage only improved clinical outcome in obtunded patients if performed within one hour of ingestion in a study of 592 poisoned patients.<sup>35</sup> A subsequent study of over 800 patients failed to show any improvement in outcome from gastric lavage<sup>36</sup> and it may even move ingested drug into the small bowel.<sup>37</sup> The consensus statement of European toxicologists that gastric lavage should only be performed within one hour of the ingestion of a potentially life threatening dose is based on such papers.<sup>38</sup>

Where specifically tricyclic poisonings have been examined approximately 9% of the estimated ingested dose has been recovered<sup>39</sup> but a comparison of gastric lavage and activated charcoal versus charcoal alone showed no difference in clinical outcome.<sup>40</sup> There is no evidence to suggest that lavage should be considered outwith the one hour period in tricyclic poisoning.

Activated charcoal may reduce the absorption of tricyclics and the benefits of both single and multiple doses have been described.<sup>41 42</sup>

Although Crome *et al* reported that a single dose of activated charcoal reduces absorption of tricyclics, the 12 subjects were given charcoal only 30 minutes after a therapeutic dose of nortriptyline.<sup>41</sup> Others have also found a reduction when charcoal was given four hours after a therapeutic dose.<sup>43</sup> However, studies of tricyclic overdoses involving 77 and 17 patients failed to show any reduction in systemic absorption after a single dose of charcoal.<sup>44 45</sup> It should be noted that doses of 20 g or 10 g of charcoal were used respectively.

Crome<sup>41</sup> and Karkkainen<sup>46</sup> both studied the use of multiple dose activated charcoal in six patients and reported an acceleration of tricyclic elimination, but other small studies also involving therapeutic doses have failed to confirm this.<sup>47 48</sup> Two studies reported on multiple dose regimens in a total of six tricyclic overdose patients and neither provides evidence to support a significant effect on elimination.<sup>49 50</sup>

##### ALKALINISATION

The use of sodium bicarbonate in tricyclic poisoning has been shown to have beneficial effects. Brown *et al*<sup>51</sup> successfully treated five children with tricyclic induced arrhythmias by administering boluses of sodium bicarbonate and subsequently they confirmed this antiarrhythmic action in experimental work with dogs. Further work with dogs has demonstrated a reduction in QRS duration, conversion of arrhythmias and a rise in blood pressure following sodium bicarbonate.<sup>52</sup>

In a review of 91 patients treated with sodium bicarbonate, hypotension was corrected in 20 of 21 patients (96%) within one hour and QRS prolongation was corrected in 39 of 49 patients (80%).<sup>53</sup> Similar effects have been described after alkalisation by hyperventilation<sup>54 55</sup> but the combined use of both

techniques has resulted in profound alkalosis, which is associated with higher rates of mortality.<sup>56</sup>

The mechanism of this effect is a subject of debate. Brown *et al*<sup>51</sup> demonstrated that the plasma protein binding of amitriptyline increased with a more alkali pH and this was confirmed by a later study.<sup>57</sup> This reduction in the pharmacologically active unbound fraction and a direct effect on myocardial contractility by correcting the metabolic acidosis present, were thought to be the causes. It is not surprising therefore that sodium bicarbonate has a therapeutic effect in patients with an acidosis. However, it has also been found to be effective in the absence of acidosis<sup>58 59</sup> and even in a patient with a preceding alkalosis.<sup>60</sup>

The administration of hypertonic sodium chloride to rats with desipramine toxicity has been shown to be as effective as sodium bicarbonate in reversing QRS prolongation and hypotension while respiratory alkalosis had little effect.<sup>59</sup> McCabe *et al* used a large animal swine model, which confirmed these findings and actually demonstrated that hypertonic saline had significantly more effect on these parameters than sodium bicarbonate.<sup>61</sup> From these experiments it has been suggested that increasing the extracellular sodium concentration is the major mechanism. Other experimental work on the depolarisation of purkinje fibres has shown that the effects of increasing the extracellular sodium concentration and of raising the pH are distinct and additive.<sup>62</sup>

#### ANTIARRHYTHMIC TREATMENT

In general antiarrhythmic drugs should be avoided and the correction of hypotension, hypoxia and acidosis will reduce the cardiotoxic effects of tricyclics. Where antiarrhythmic agents are used it is important to avoid certain drugs that exacerbate the cardiac effects of tricyclics. Class 1a (quinidine, procainamide, disopyramide) and class 1c drugs such as flecainide, prolong depolarisation in a similar fashion to tricyclics. Likewise class 3 drugs (bretium, amiodarone) also prolong the QT interval and may predispose to arrhythmias.

Lignocaine (lidocaine) has been reported as being effective in the treatment of frequent ventricular ectopics in 13 overdose patients but in some patients the ectopics persisted for up to 72 hours.<sup>21</sup> Experiments with four dogs failed to show any significant effect on the treatment of arrhythmias<sup>63</sup> and other research with rats found that lignocaine only successfully treated one case from ten with tricyclic induced ventricular arrhythmias.<sup>64</sup>

Phenytoin is a class 1b agent, which, unlike 1a and 1c drugs, can increase the rate of phase 0 depolarisation. Boehnert described the successful treatment of ventricular arrhythmias in three patients with the use of phenytoin.<sup>65</sup> When phenytoin was used in a study of 10 patients it was found to correct conduction defects in five patients within 46 minutes and in the remaining five within 14 hours.<sup>66</sup> However, these patients were stable with no arrhythmias and phenytoin did not change their clinical outcome. Animal experiments

have failed to show any significant benefit from phenytoin in the prevention or management of arrhythmias.<sup>63 67</sup>

The use of  $\beta$  blockers may further reduce myocardial contractility and although reported as being effective in treating arrhythmias both in humans<sup>68</sup> and animals,<sup>63</sup> in all cases there was an marked decrease in blood pressure associated.

The use of glucagon in one patient was reported to increase blood pressure and reduce the QRS duration but sodium bicarbonate had also been given shortly before the glucagon.<sup>69</sup> An animal experiment with glucagon found no beneficial effect on blood pressure or arrhythmias.<sup>63</sup>

Magnesium sulphate has been used successfully in an overdose patient with refractory ventricular fibrillation.<sup>70</sup> Although an early experiment with two dogs found no benefit with magnesium,<sup>63</sup> Knudsen reported that magnesium sulphate converted ventricular tachycardia to sinus rhythm in 9 of 10 rats.<sup>71</sup>

Physostigmine is a short acting cholinesterase inhibitor that was proposed in the 1970s as a treatment for arrhythmias. Since then, however, it has been described as causing asystole<sup>72</sup> and seizures.<sup>73</sup> There is no role for its use in the management of tricyclic toxicity.

#### HYPOTENSION

Hypotension is thought to result from a combination of decreased myocardial contractility and peripheral vasodilatation. In cases refractory to the use of intravenous fluids the use of inotropic agents may be required. In theory pure  $\alpha$  agonist agents should be used to avoid unopposed  $\beta$  receptor stimulation.<sup>74</sup>

Norepinephrine has been found to be more effective than dopamine in the management of hypotension, possibly as the effect of dopamine partially depends on the release of endogenous norepinephrine stores that are depleted in tricyclic overdose because of reuptake inhibition.<sup>75</sup> A study with amitriptyline poisoned rats has suggested that the use of epinephrine is less likely to cause arrhythmias in comparison with norepinephrine.<sup>76</sup> Its use may be preferable because this and further experiments have demonstrated an additional benefit from the combined use of sodium bicarbonate and epinephrine.<sup>77</sup>

Extracorporeal circulation has been used in patients who have not improved with the use of inotropes<sup>78 79</sup> and experimental work in pigs has demonstrated increased survival with this technique.<sup>80</sup>

#### CARDIAC ARREST

Where patients have a cardiac arrest after ingestion of tricyclics recovery is possible even after prolonged resuscitation. Patients have recovered after three and five hours of external cardiac massage.<sup>81-83</sup> This may be attributable to metabolism and redistribution of the tricyclic during this time with a subsequent reduction of its effect on the myocardium.



## CNS COMPLICATIONS

Seizures are usually self limiting but where treatment is necessary benzodiazepines are the treatment of choice.<sup>9</sup> Although some recommend the use of phenytoin its efficacy has never been proven<sup>67</sup> and in a rat model was found to be of no benefit.<sup>84</sup> Patients with decreased conscious level and respiratory depression may require intubation.

## DRUG ELIMINATION

Tricyclic specific antibody fragments have been developed and their effectiveness at reversing cardiovascular toxicity in animals has been demonstrated by several studies.<sup>85–86</sup> However, experimental work has shown that extremely large amounts are required and at present the use of Fab fragments is limited by cost and the possibility of renal toxic effects. A case report of their clinical use indicates an improvement in QRS and QT intervals but sodium bicarbonate had also been given.<sup>87</sup>

Tricyclics have a very large volume of distribution and this restricts the role of methods designed to increase drug clearance from the intravascular space. The treatment of eight patients with resin haemoperfusion removed no more than 3.1% of the estimated ingested dose<sup>88</sup> and others have also described how only small amounts of tricyclic are extracted by haemoperfusion.<sup>89</sup> Other techniques such as forced diuresis, peritoneal dialysis and haemodialysis do not seem to be any better.<sup>90</sup>

## MONITORING

Several reports have found that all major complications will be apparent within six hours of ingestion<sup>23–91–92</sup> and that the incidence of late complications is extremely low.<sup>93–94</sup> It has been shown that arrhythmias do not occur after cardiovascular toxicity has resolved.<sup>93–95</sup> There have been reports of ventricular arrhythmias and fatalities occurring up to five days after ingestion but these events were in patients who displayed continuing signs of toxicity.<sup>96–97</sup>

Patients should have cardiac monitoring until the electrocardiogram has been normal for 12 to 24 hours.<sup>98</sup>

## Conclusion

It has been reported that the advice from the British poisons centres concerning the management of tricyclic overdose is not uniform.<sup>99</sup> Differences in the management strategies of the poisons centres reflect the quality of the evidence available. There are limited data and much of the evidence quoted is derived from animal studies, case reports or small series of healthy subjects. The quality of this information results in variable interpretations and seems to cause some ambiguity in the advice given. In the absence of further evidence a consensus approach to the management of tricyclic overdose with national guidelines could avoid confusion when medical staff seek advice from the poisons centres.

## Contributors

Gary Kerr initiated the review, performed the original literature search and wrote the first draft. Crawford McGuffie and Stewart

Wilkie undertook literature searches, edited and wrote further drafts. Gary Kerr, Crawford McGuffie and Stewart Wilkie edited and wrote the final draft. Gary Kerr will act as guarantor.

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## Appendix: management plan for treatment of tricyclic overdose

- 1 Assess and treat ABCs as appropriate.
- 2 Examine for clinical features
  - Check urea and electrolytes—look for low potassium
  - Check arterial blood gases—look for acidosis
  - Perform electrocardiograph—look for QRS>0.16 seconds
- 3 Consider gastric lavage only if within one hour of a potentially fatal overdose.
- 4 Give 50 grams of charcoal if within one hour of ingestion.
- 5 Give sodium bicarbonate (50 ml of 8.4%) if:
  - a pH <7.1
  - b RS >0.16 seconds
  - c Arrhythmias
  - d Hypotension
- 6 Arrhythmias: Avoid antiarrhythmics
  - Correct hypoxia, hypotension, acidosis, hypokalaemia
  - Give sodium bicarbonate.
- 7 Hypotension: Give intravenous fluids
  - Consider inotropes
- 8 Cardiac arrest: Prolonged resuscitation may be successful
- 9 Monitoring: Patients who display signs of toxicity should be monitored for a minimum of 12 hours.

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