REVIEW ARTICLE

Toxicol Rev 2005; 24 (3): 181-186
1176-2551/05/0003-0181/$34.95/0

Tricyclic Antidepressant Poisoning

Central Nervous System Effects and Management

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Abstract

All tricyclic drugs are potentially able to cause the main acute CNS toxic syndromes of coma and convulsions. Dosulepin (dothiepin) seems more likely to cause convulsions than other drugs in this class, and amitriptyline also appears a more toxic tricyclic agent. Coma is the most useful sign indicative of toxic risk and appears to predict severe toxic complications (fits and arrhythmias) more reliably than ECG changes. Prophylactic therapy against convulsions has not been shown to be effective. Use of an anticholinesterase (physostigmine) is not recommended for management of coma. There is no good evidence base to support a particular anticonvulsant.

The tricyclic antidepressant (TCA) drugs have been in clinical use for >40 years, and first cases of poisoning were described in 1959.[1] Despite the introduction of newer classes of antidepressants, the importance of these agents as a cause of morbidity and mortality continues to be recognised.[2,3] In Australia, for example, in a cohort of 256 antidepressant poisonings, patients ingesting antidepressants in this class had longer median length of stay (23.1 vs 15.9 hours, $p = 0.0008$), greater need for endotracheal intubation (31% vs 4%; odds ratio [OR] = 11.5; $p < 0.0001$) and higher incidence of seizures (7.2% vs 0.7%; OR = 10.4; $p = 0.01$) than those ingesting newer agents. Forty-three percent of the series were cyclic antidepressants.[2] In the UK, similar concerns about relative toxicity are raised by post mortem data.[3]

1. Pharmacology

TCAs have three pharmacological effects that may potentially cause direct effects on the CNS, their main site of therapeutic action. The pharmacological property that is responsible for their antidepressant effect is recognised to be a blockade of monoamine reuptake, at both noradrenergic and serotinergic nerve endings. Tricyclic compounds also have anticholinergic effects at muscarinic receptors, and an action on sodium channels that is predominantly seen on the myocardium. These may all be relevant to their CNS effects in overdose. A fourth pharmacological property, that of α-adrenoceptor blockade may contribute to hypotension seen

after TCA poisoning, but is otherwise unlikely to have any direct relevance to effects seen in the brain after overdose.

2. CNS Features

2.1 Common Features

The clinical effects of TCAs following overdose were described in case series published from the 1960s[4] and in the 1970s.[5] The authors of these reports emphasised effects that were similar to clinical features associated with the anti-muscarinic compounds. These included dilated pupils, drowsiness and tachycardia. Early series also reported that myoclonic and choreoathetoid movements were common, with a frequency of up to 43%.[4] Later series[5] found far lower rates of these abnormalities, and a number of hypotheses have been advanced to account for this difference. One potentially important confounder is the change in availability of other drugs to co-ingest, in particular benzodiazepines, which would reduce the possibility of this event, the other is the magnitude and type of TCA ingested.

It was noted in 1976[6] that the duration of coma in TCA poisoning tended to be relatively short lived. In this series of patients presenting in coma, one-third were awake in 2 hours, and two-thirds in 24 hours.

Grand mal convulsions are the most serious CNS effect, and their incidence in case series is in the order of 4%.[5] Convulsions are recognised to be an early complication, and unlikely to arise *de novo* beyond 12 hours after overdose ingestion.[5]

2.2 Rarer CNS Complications

External ophthalmoplegia, manifesting clinically as divergent squint, is relatively frequently found if examined for during the course of coma in TCA poisoning. One such case associated with seizures and respiratory arrest was reported by Pulst and Lombroso.[7] Larger case series do not provide adequate data to calculate an incidence.

Internuclear ophthalmoplegia and gaze paralysis are other CNS features reported.[8,9] Further CNS effects that have been reported include dystonic reactions and serotonergic syndrome.[10] Since serotonin is also involved in the control of antidiuretic hormone (ADH) secretion, hyponatraemia relating to an inappropriate ADH release is a theoretical risk.[11]

Some authors have commented on the ability of TCAs to depress brain-stem reflexes in overdose. Thus, White[12] reported on three cases, two of which included a tricyclic compound, who had absent brain-stem reflexes. Yang and Dantzker[13] reported a 46-year-old patient who developed loss of brain-stem reflexes following an amitriptyline overdose of 9g. More recently, a case was reported of 5 days of coma associated with loss of brain stem reflexes but no features of cardiovascular toxicity[14] following ingestion of a combined overdose, which included amitriptyline and venlafaxine.

Fujino et al.[15] reported a patient who developed progressive cerebellar atrophy and cerebellar ataxia following what appeared to be the onset of a serotonin syndrome.

Anti-muscarinic features of TCA poisoning may result in reduced ability to sweat. Central cholinergic muscarinic antagonism may also disturb thermoregulation and thus contribute to hyperpyrexia.[16] Since TCA poisoning has been associated with development of a serotinergic syndrome,[10] temperature disturbance may have more than one cause in TCA poisoning. Baca and Martinelli[17] reported the clinical course of a 50-year-old woman who developed features of hyperpyrexia and elevated creatine kinase activity in association with the therapeutic use of desipramine. This author considered the patient had developed neuroleptic malignant syndrome, but is much more likely to have been a case of serotonin syndrome.

Peripheral neuropathy has been reported to be associated with therapeutic use of amitriptyline.[18,19] Peripheral neuropathy has also been reported in a small number of cases in association with coma and skin blistering.[20] It is unclear as to whether these effects are truly a single clinical syndrome, as blistering is a feature seen in many types of coma. The authors of the report suggest a specific effect of amitriptyline on the neuronal microvasculature as a cause.[20]

2.3 Late Features

A feature recognised clinically but poorly reported in the literature is that of prolonged delirium in the recovery phase of TCA poisoning. This is a relatively common feature in patients who have had serious intoxication, and is in our experience accompanied by a typical clinical pattern of incoherent mumbling and plucking at the bed clothes. The cause of this syndrome is unclear, and it does not respond to treatment with physostigmine, a specific therapy for anticholinergic effects.[21] A similar although perhaps less severe pattern of behaviour has been reported following therapeutic use of antidepressants.[22,23] These observations suggest that the cause is most likely to be due to excess central monoamine activity, rather than anti-muscarinic effects.

2.4 Features in Children

Poisoning has been reported in children since the 1960s and the profile of adverse effects seems similar to that in adults. For example, convulsions and respiratory arrest occurred within 90 minutes of ingestion of 2.5g of imipramine in a 2.5-year-old boy. In a series of five further cases, Giles[24] reported that CNS manifestations had been dominant over cardiac effects in imipramine poisoning. Features in this series included agitation, coma, involuntary movements and convulsions.

2.5 CNS Symptoms and Poisoning Severity

Depression of conscious level presenting as drowsiness or sedation is a frequent complication of TCA poisoning. Of the 316 cases reported by Starkey and Lawson,[5] 53 were in coma, as defined using the Edinburgh coma scale. In cases with a fatal outcome, the proportion of patients in a coma at presentation is high (e.g. 52% in one series).[25] In view of this finding, the level of consciousness has been studied as a predictor of complications following overdose with tricyclic compounds. In a series of 92 patients, 37 developed serious complications including seizures, hypotension and haemodynamically significant arrhythmias, and all of these required intubation.[26] These authors reported that a Glasgow Coma Scale of <8 was the most sensitive predictor of serious complications. In a multicentre study of 67 patients, Edinburgh coma scores were compared with ECG changes and plasma levels as a predictor of toxicity as judged by complications, including convulsions, hypotension, arrhythmia, need for intubation and ventilation;[27] 30 of 67 patients developed complications. The authors concluded that an Edinburgh coma score of grade II or less (i.e. fully conscious or drowsy) in patients admitted after 6 hours was associated with a low risk of complications. Plasma drug concentration did not add to the strength of prediction.

2.6 CNS Effects and Other Features in Poisoning

As there is a close relationship between the cardiac and CNS toxicity of tricyclic compounds, several studies have examined the interrelationship of cardiovascular and ECG findings and CNS effects in acute overdose. Taboulet et al.[28] reported severe cardiovascular complications in association with seizures. They noted increasing abnormalities in the ECG, in particular broadening of the QRS, and hypotension, systolic pressure <80mm Hg prior to seizure occurrence in three patients with the most severe poisoning in their series. In such patients, convulsions have a major impact as they aggravate cardiovascular instability by causing acidosis and hence increasing the free fraction of the TCA. These authors also stressed the significance of seizures as a factor in QRS worsening (41%) and hypotension (29%) post-ictally in their case series of 24 patients who experienced seizures in the intensive-care unit (ICU).

Boehnert and Lovejoy[29] examined the relationship between serum drug level and QRS duration in predicting risk of a arrhythmias and seizures after acute TCA overdose. They used a QRS duration of 100ms as a cut-off, and no seizures occurred in patients with QRS less than this. In patients who had a longer QRS duration, 34% had seizures and 14% ventricular arrhythmias. Thus, while abnormal QRS is obviously a potential risk factor, it clearly does not necessarily accurately predict all patients who will have abnormalities subsequently. This may have led other workers to be more optimistic about the reliability of QRS alone as an indicator of poison severity.[30]

In contrast, Liebelt et al.[31] examined QRS duration and the shape of the R wave in lead aVR of the ECG. They found that the R wave was a more reliable measure than the QRS duration as a predictor of seizure and arrhythmia. Only an R wave of >3mm in lead aVR statistically significantly predicted these complications.

Stern et al.[32] reviewed 72 consecutive cases of TCA poisoning admitted to an ICU between 1977 and 1982. Of these patients, 70% were comatose prior to admission and 68% were intubated, with 61% requiring mechanical ventilation. In patients without ECG abnormalities or requiring ventilator support, further complications did not develop. When the clinical records of 30 patients who had seizures as a result of TCA toxicity were examined, it was found that mortality was 10%. In all but two patients, seizures occurred within 1.5 hours of admission, and in these two co-ingestion of alcohol may have been a factor in seizure delay. Twenty-three percent of seizures occurred in patients who were alert, but the majority of seizures were brief, self-limiting and terminated without anticonvulsant therapy. In this series, four patients developed marked cardiovascular deterioration following seizure occurrence. All these patients had a QRS duration of >200ms during their in-patient stay.[33]

Shannon[34] reported on a series of 22 patients in whom ten developed seizures. No seizures occurred in these patients when the QRS was <100ms.

3. Concentration-Effect Relationships

Measurement of plasma levels of TCAs has generally been thought to be a poor predictor of clinical outcome. In a case series of 40 patients, Biggs et al.[35] examined the relationship between the stated ingested dose, plasma concentration and clinical features of poisoning. The stated dose correlated with plasma concentration ($r = 0.58$) but there was considerable inter-individual variation. In this series, grand mal seizures occurred in 20% of cases and unconsciousness in 47%, with 40% requiring ventilation. Plasma level correlated with seizure occurrence and unconsciousness.

Nicotra et al.[36] studied 47 patients with documented TCA ingestion in whom the overdose was confirmed by a plasma concentration measurement. They correlated neurological parameters with concentrations of the parent TCA and the total of parent and desmethyl metabolites. Duration of abnormal mental status was most strongly correlated with blood level, although depth of coma did not significantly relate to concentration. The need for, and length of ventilator support also correlated with TCA concentration. In this series there was poor correlation between cardiac toxicity as reflected in the QRS duration and neurological abnormalities on admission.

In a detailed study of a case series of nine patients with amitriptyline poisoning, there was a good correlation between the Edinburgh coma scale value and both total and free amitriptyline concentrations.[37] This may seem paradoxical in view of other

reports in which single concentrations did not correlate well with outcome. It is most likely due to the very wide range of plasma drug concentration observed both within and between individuals. Timing from ingestion, absorption delay due to anticholinergic actions, absorption and distribution kinetics and hysteresis between plasma concentration and effect together make clinical prediction from a single plasma concentration measurement almost impossible. Thus, a study from South Africa examining gastric emptying using scintigraphic techniques has illustrated clearly the significant delays in gastric emptying that can occur in this situation further emphasising this issue.[38]

4. Relative Toxicity

The relative toxicity of TCA drugs has been examined in a number of different ways. From the theoretical perspective, different compounds might be expected to exhibit different profiles of adverse effect in overdose based on understanding of the differences in their primary pharmacology. Thus, Hollister[39] reported a 100-fold difference in the *in vitro* binding of different antidepressants to the receptor sites upon which these drugs act. From the point of view of CNS effects, at high concentrations TCAs interact with muscarinic histamine H_1, catecholamine reuptake, α receptors and membrane sodium channels. All of these actions could contribute to CNS effects. Sedation would be due to H_1 and antimuscarinic effects, and convulsions relate to an increase in amine availability, antimuscarinic action, or effects on membrane stability relating to sodium channel action. It is possible that in an individual patient all of these separate actions may be present at the same time. Animal data have suggested that, at least initially, an increase in amine activity may be associated with protection from convulsions.[40] At high doses these protective effects are lost.

In a prospective study, seizures were shown to vary with the agent ingested with the rates being apparently greater with amoxapine, maprotiline and desipramine. In this series, coma and arrhythmias were of equal frequency with all drugs.[41] Buckley et al.,[42] in a retrospective study of cases submitted to their unit in Australia, examined the relative frequency of fits in antidepressant poisoning. They found an increased rate of convulsions in patients ingesting dosulepin (dothiepin) [9 of 67 cases] compared with all other antidepressants (5 of 220). The OR without adjustment for age, sex and dose, was 6.7 (95% CI 2.2, 20.7) and adjusted for these additional factors were 7.1 (95% CI 2.2, 23.2). In this study, the OR of increased convulsions with dosulepin was far greater than that of increased risk of arrhythmias. A number of interpretations could be placed on this difference, one being that the pharmacological effects responsible for the arrhythmia are different to those causing the convulsion. If the convulsions themselves were a risk factor for arrhythmias this might be confounding, but it would tend to make arrhythmias more likely to occur in patients who have fits. There is little evidence from the literature that the converse applies, i.e. that arrhythmias themselves predispose to fits.

Other studies have looked at mortality in association with overdose, and examined the relationship between the numbers of prescriptions of different antidepressant drugs and mortality rates. Using this approach most deaths are associated with dosulepin and amitriptyline, and when account is taken of the numbers of prescriptions for these drugs they still appear to be significantly more toxic than some other antidepressants. Using the same approach, amoxapine and desipramine appear most toxic, but the number of deaths small and, therefore, the confidence of these estimates are less rigorous.[3,43,44] Evidence from North America supports the excess risk from desipramine and the authors consider this is due to an inappropriately high marketed dose.[45]

5. Other Factors in Seizure Occurrence

Ingestion of more than one epileptogenic compound is known to increase the risk of convulsions, but there are no data to quantify this risk.

The availability of antidotes for benzodiazepine poisoning may have changed the epidemiology of fit occurrence in patients with coma relating to poisoning. A number of case reports in a case series have indicated that patients who convulse having received flumazenil are often those in whom co-ingestion of a TCA has occurred but not been suspected or detected by the admitting physician. An example is reported in a child by McDuffee and Tobias,[46] and a fatal case in an adult by Haverkos et al.[47] The latter case had a QRS duration of 136ms at admission. Although some authors have suggested that an ECG should be performed and that if this is normal administration of flumazenil would be appropriate, as already discussed the relationship between ECG abnormalities and TCA toxicity is not as specific as that of depth of coma. While it is therefore sensible to advise that an ECG be done, the normality of that ECG cannot exclude the possibility of significant TCA ingestion. It is for this reason that flumazenil should not be used routinely as a treatment of patients presenting to hospital with suspected multi-ingestion overdose.

6. Management

The principles of care of the CNS effect of TCA poisoning reflect the principles of care of all medical patients. Initially it is important to protect the airway and monitor conscious level. A formal coma scale assessment, usually the Glasgow Coma Scale or similar, is helpful, since it provides a numerical assessment of patients progress, and can be repeated at regular intervals over time. Changes in level of consciousness over the first few hours after TCA ingestion are an important clinical feature. Patients who become rapidly unconscious are obviously more likely to experi-

ence fits and cardiovascular complications and, therefore, need more intensive monitoring.

Present evidence does not support the need for prophylactic therapy for patients deemed at potential risk of convulsions. There are no comparative trials of therapy in TCA-induced fits, but common practice is to administer a dose of intravenous benzodiazepine, usually diazepam. Clinicians, however, need to be aware that benzodiazepines have respiratory depressant effects, and these, together with the hypoxic- and acidotic-inducing effects of convulsions, may make the risk of arrhythmia temporarily increased. Such patients, therefore, need to be adequately oxygenated and have acid-base balance managed appropriately. Since the binding of TCAs to plasma proteins is in part pH dependent, an increase in acidity in blood will result in displacement of bound TCA and may potentially result in increased pharmacological effects.

6.1 Management of Seizures

Most seizures in TCA poisoning are of short duration and as such do not require specific therapy. Although animal work examined the usefulness of prophylactic anticonvulsants, and phenytoin has been cited as an example, in human cases of poisoning such prophylactic approaches are not generally recommended. From a theoretical perspective, phenytoin is to be avoided as it has membrane actions on the heart that could potentiate arrythmogenic effects of TCAs.[48]

As has already been demonstrated,[25-27] one of the most accurate predictors of major seizure activity is depth of coma, and administration of anticonvulsants, which are themselves more likely to increase this coma depth, may remove potentially important clinical signs. Patients who convulse do, however, need to be monitored very carefully in view of the potential risks of cardiac arrhythmias.

7. Conclusions

The effects of TCAs on the CNS following overdose are important in clinical management, as depth of coma is a particularly useful indicator of clinical risk. Present evidence suggests presence of coma predicts risk of convulsions and arrhythmias more reliably than ECG changes. Since these are the two complications that usually cause death, this is a key clinical message.

Other syndromes that can be observed include both internal and external ophthalmoplegias, and less commonly dystonia. Temperature regulation disturbance may be due to both central actions and peripheral effects on sweat production. A toxic confusional state is a well recognised clinical complication during the first 48 hours of recovery.

Prophylactic anticonvulsant therapy is not advised, and the optimum drug not defined by clinical trials. Most clinicians managing convulsions in TCA poisoning would use a benzodiazepine as first line therapy. Serotonin syndrome is a possibility with those agents that have an antidepressant action predominantly via serotonin mechanisms.

Acknowledgements

The authors declares no conflict of interest and has received no funding relevant to the content of this review.

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