Guideline for the Management of Tricyclic Antidepressant Overdose

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1. Executive Summary

- The Guidelines in Emergency Medicine Network (GEMNet) has been created to promote best medical practice in a range of conditions presenting to Emergency Departments (EDs) in the UK
- This guideline presents a summary of the best available evidence to guide the management of adult patients who present to the ED following an overdose of tricyclic antidepressant agents (TCA)
- The document has been developed following discussion amongst Emergency Physicians to decide which topics would benefit from the development of clinical guidelines
- The document is intended as a guideline for use in the ED by Emergency Physicians and is based on the review of the best existing evidence for the diagnostic tools and treatments used in this setting
- The document is summarised as a Clinical Decision Support Guideline that has been presented as an easy to follow algorithm
- The intention is for each guideline to be updated and reviewed as further evidence becomes available. The formal revision date has been set at 5 years from publication though the guideline is subject to continuous informal review.

2. Introduction

2.1 Responsibility for development

This document has been developed in response to a perceived need to improve clinical effectiveness for care in this field. The ED at the Manchester Royal Infirmary has been undertaking primary and secondary research for a number of years to achieve this aim. The intention is to distil this information into practical advice for clinicians working in the department. The information is presented in the form of Clinical Decision Support Guidelines, available on shop floor in the form of a Clinical Decision Support Manual and on individual A4 sized forms.

Departmental Consultants have considered clinical conditions that may benefit from evidence based guidelines and following discussion with other clinical staff have compiled a list of topics that included tricyclic antidepressant overdose.

2.2 Funding

Funding for the development for this guideline has been received from the College of Emergency Medicine.

2.3 The Guideline Working Group

A Guideline Working Group met to discuss this condition and decide on the clinical questions, consider the evidence available and develop the recommendations. The group process ensured that the working group had access to the relevant information and the required resources in order to develop in a constructive manner.

The guideline has been developed in accordance with the principles described by the National Institute for Health and Clinical Excellence guideline development methods.[1]

3. Topic Introduction

TCA's are prescribed in the UK for problems including depression, anxiety and chronic pain. Recent recommendations have meant that prescribing practices are changing and the availability of TCA is reducing[2]. Despite this TCA overdose still accounts for up to 18% of all poisoning deaths in the UK[3]. The toxicity of the TCA coupled with the high risk patient group means that self-poisoning episodes are more likely to be fatal[4]. In the UK in 2005 there were 272 deaths related to TCA overdose[5].

Patients presenting to the ED with significant overdose pose difficult management issues. TCA's block alpha-adrenergic receptors and have anticholinergic effects. This may lead to cardiovascular effects including sinus tachycardia, cardiac conduction abnormalities, vasodilatation, arrhythmias, hypotension and asystole[6-11]. The anticholinergic effects of TCA's may also lead to dry mouth, blurred vision, dilated pupils, hyperthermia and delayed gastric emptying[12;13]. Intestinal obstruction and perforation have been reported[14;15] as has pancreatitis[16]. Finally, TCA's exert a number of effects on the central nervous system, which may lead to drowsiness, coma, respiratory depression, seizures and delirium[17-20]. Opthalmoplegia has also been reported[21;22]. Many patients require intensive care support or hospital admission[19;20].

To date Toxbase has been the initial portal for treatment advice in TCA overdose[23]. This guideline does not aim to replace previous advice but to present a complementary structured guideline and evidence-based flowchart to aid the decision-making process for these patients within the ED. The document is presented as a series of clinical questions which have been answered using the previously described Best BETs methodology[24].

The aim of the guideline is to summarise the evidence supporting the various therapeutic options that have been advocated in the management of TCA overdose within the ED. It is hoped that this will help to optimise and standardise the standard of care that may be delivered to this patient group.

4. Scope

This guideline encompasses adult patients (>16 years of age) presenting to the ED with suspected lone TCA overdose. The key aspects this is designed to include are initial assessment, decontamination, active management and disposition of the patient from the ED. The initial assessment and management recommendations can be followed using resources available in any UK ED. Disposition may vary dependent on local resources but the guideline may be adapted as appropriate.

This document does not provide guidance regarding patients less than 16 years of age, patients with multiple drug overdose and those patients who present in cardiac arrest. The use of experimental or limited availability treatments such as extracorporeal mandatory oxygenation (ECMO) is also excluded because of limited availability throughout the country.

5. METHODOLOGY

This guideline was developed using a novel methodology that has recently been utilised in cardiothoracic surgery[25]. Many guidelines perform a single systematic review of the literature in order to answer all of the relevant clinical questions. In order to maximise sensitivity, we performed a separate short-cut systematic review of the literature for each clinical question identified.

Guideline development was structured into several stages. Initially the two lead guideline developers (TB and RB) met to discuss the scope of the guideline and to identify all clinical questions that may have been relevant. In order to answer the clinical questions identified we performed a series of structured short-cut systematic reviews (Best Evidence Topic Summaries, BETs), the principles of which have been previously described[26]. Where relevant BETs had already been created, the search strategies were checked and updated when necessary.

Having gathered and collated the evidence for each clinical question, the principle guideline developers met to create a series of guideline recommendations, which were used to create an evidence-based flowchart. Following consultation with the senior author (KMJ), modifications were made before the final guideline was agreed upon.

5.1 Levels of evidence and grading of recommendations

Studies included in this guideline were graded for level of evidence according to previously accepted definitions[27]. In summary, level 1 evidence comes from well-designed randomised controlled trials (RCT's), level 2 evidence from large cohort studies or poorly designed RCT's, level 3 evidence from small cohort studies or case-control studies and level 4 evidence from experimental studies, case series or case studies. The suffix 'a' implies that evidence at this level is from systematic review or meta-analysis, whereas the suffix 'b' implies that the evidence is from original research.

The recommendations that have been made were graded according to the level of evidence upon which they were based:
Grade A: Based upon multiple level 1a or 1b papers.
Grade B: Based upon individual level 1a or 1b papers or multiple level 2a or 2b papers.
Grade C: Based upon individual level 2a or 2b papers or multiple level 3a or 3b papers.
Grade D: Based upon individual level 3a or 3b papers or level 4 papers.
Grade E: Based on consensus guidelines or studies of expert opinion.

5.2 Definition of TCA overdose

For the purposes of this guideline TCA overdose is defined as suspected deliberate or accidental ingestion of TCA at above the recommended therapeutic dose.

6. Summary of Recommendations

6.1 Airway protection

Patients with GCS ≤8 should undergo rapid sequence induction at the earliest opportunity **(Grade C)**.

Some patients with GCS >8 may also need intubation, particularly in the presence of airway compromise, hypoventilation or refractory seizures **(Grade C)**.

Benzodiazepines may be considered to control agitation following TCA overdose **(Grade E).**

6.2 Gastric decontamination

Activated charcoal may be considered for use within 1 hour of TCA ingestion but only in patients with an intact or secured airway. The potential risk of aspiration should be strongly considered before use **(Grade D)**.

Multiple dose activated charcoal should not be considered **(Grade D)**.

Gastric lavage may be considered for potentially life-threatening TCA overdoses only when it can be delivered within 1 hour of ingestion and the airway is protected **(Grade D)**.

6.3 Initial assessment

An ECG should be recorded at presentation to the ED following TCA overdose **(Grade B)**.

The ECG should be used to risk stratify patients with TCA overdose and to guide subsequent therapy **(Grade B)**.

Serial ECG recordings should be examined for the presence of QRS prolongation (>100ms), QTc prolongation (>430ms) and R/S ratio >0.7 in lead aVR. These changes identify patients at high risk of developing complications following TCA overdose **(Grade B)**.

6.4 Blood pH for risk stratification

Blood gas analysis is an important part of the initial assessment and monitoring of patients who have taken a TCA overdose **(Grade E)**.

Venous sampling for blood gas analysis is an acceptable alternative to arterial sampling unless hypoxia or hypoventilation are suspected **(Grade D)**.

6.5 Treatment of haemodynamic instability

A bolus of intravenous fluids should be considered as a first-line therapy to treat hypotension induced by TCA overdose **(Grade D)**.

Sodium bicarbonate is indicated for the treatment of dysrhythmias or hypotension associated with TCA overdose. **(Grade C)**.

Sodium bicarbonate may be considered for the treatment of QRS prolongation (>100ms) associated with TCA overdose **(Grade E)**.
The treatment of dysrhythmias or hypotension should include alkalinisation to a serum pH of 7.45 to 7.55. **(Grade E)**.

Vasopressors should be used for hypotension following TCA overdose that has not responded to initial treatment (including sodium bicarbonate and intravenous fluids). **(Grade D)**.

Epinephrine may be superior to norepinephrine for treating refractory hypotension and preventing arrhythmias. **(Grade D)**.

It is not unreasonable to administer 10mg intravenous glucagon to treat life-threatening hypotension or arrhythmias refractory to other measures **(Grade D)**.

Magnesium sulphate may be considered for the treatment of TCA-induced dysrhythmias when other treatments have been unsuccessful. **(Grade D)**.

6.6 Management of seizures

Phenytoin should be avoided in patients with TCA overdose **(Grade D)**.

Benzodiazepines should be used to control seizures following TCA overdose **(Grade E)**.

6.7 Observation of asymptomatic patients

Following TCA overdose asymptomatic, stable patients with no significant ECG abnromalities six hours after ingestion may be safely discharged **(Grade B)**.

7. FINDINGS & RECOMMENDATIONS

Below are summaries of the short cut systematic reviews used to establish the recommendations for this guideline. The three part question and search details are presented with comments and clinical bottom line. The search strategies are summarised and can be found in full in the appendix.

7.1 Airway protection

7.1.1 Assessing the need for intubation following tricyclic antidepressant overdose in patients with reduced level of consciousness
7.1.2 Can sedation be safely used in agitated patients with TCA overdose?

7.1.1 Assessing the need for intubation following tricyclic antidepressant overdose in patients with reduced level of consciousness

Three part question

In [adult patients who present to the ED following a psychotropic drug overdose with a reduced level of consciousness] does [endotracheal intubation versus standard treatment alone] lead to [fewer respiratory complications, reduced mortality and reduced length of hospital stay]?

Search strategy

Ovid Medline 1950 – May Week 2 2008
Ovid Embase 1980 – 2008 Week 21

[Overdose filter] AND [Intubation filter] AND [Unconsciousness filter] limit to humans and English language.

Search outcome

62 papers were identified in Medline and 159 in Embase. Six were relevant to the three-part question (Table 1).

Comments

In total we identified five retrospective analyses of patients who had been admitted following psychotropic drug overdoses and one prospective diagnostic cohort study that investigated the association between Matthew-Lawson coma grade and serious complications following tricyclic antidepressant overdose. Although the studies have significant weaknesses, a strong correlation has consistently been shown between level of consciousness and the development of serious complications including death, hypoventilation and aspiration pneumonia following drug overdose.

Of interest, both Hulten *et al*[28] and Emerman *et al*[29] showed that TCA drug levels are of little use for predicting complications especially when coma grade and QRS width were taken into account. Further it would seem that level of consciousness is a stronger independent predictor of complications than QRS width. The evidence strongly suggests that patients with GCS ≤8 should undergo intubation at an early stage in the ED. Results from the retrospective study by Liisanantti *et al*[30] suggest that intubation at the earliest possible opportunity may reduce complication rates. Further, in the study by Emerman *et al* GCS ≤8 was only 86.5% sensitive for prediction of hypoventilation or loss

of protective airway reflexes.[29] Thus intubation may still be necessary for some patients with GCS >8 from a pragmatic patient safety viewpoint.

Clinical bottom line

Patients who present to the ED following psychotropic drug overdose with GCS ≤8 should undergo intubation at the earliest opportunity. Some patients with GCS >8 may also need intubation.

Recommendation

Patients with GCS ≤8 should undergo rapid sequence induction at the earliest opportunity **(Grade C)**.

Some patients with GCS >8 may also need intubation, particularly in the presence of airway compromise, hypoventilation or refractory seizures **(Grade C)**.

7.1.2 Can sedation be safely used in agitated patients with TCA overdose?

Three part question

In [agitated adult patients who present to the Emergency Department after an overdose of tricyclic antidepressant drugs] does [the use of sedative agents] lead to [an acceptably low rate of pulmonary aspiration]?

Search strategy

Ovid MEDLINE 1950 – June Week 1, 2008
Ovid EMBASE 1980 - 2008 Week 24

[TCA filter] AND [Overdose filter] AND ([Benzodiazepine filter] OR ([Sedation filter] AND [Aspiration filter])) LIMIT to humans and English language.

Search outcome

1787 papers were identified (194 in Medline and 1593 in Embase). None were relevant to the three-part question.

Comments

There is no evidence of harm when intravenous sedation is administered in agitated patients who have taken an overdose of tricyclic antidepressant agents. The National Poisons Information Service recommends the use of benzodiazepines to control delirium in this situation.[31]

Because tricyclic antidepressant agents are known to delay gastric emptying and many patients who have taken an overdose have also consumed a large amount of alcohol it would be advisable to exercise caution when sedating these patients. When there is doubt regarding a patient's protective airway reflexes endotracheal intubation may be necessary.

However there is no evidence to suggest that sedation should not be attempted in these patients. **Clinical bottom line** There is no evidence of harm when sedating

agitated patients following tricyclic antidepressant overdose. National Poisons Information Service guidance advocates the use of benzodiazepines to control delirium in this situation. Caution should be exercised in view of the potential risks of pulmonary aspiration.

Recommendation

Benzodiazepines may be considered to control agitation following TCA overdose **(Grade E).**

7.2 Gastric Decontamination

7.2.1 Activated charcoal
7.2.2 Multiple dose activated charcoal
7.2.3 Gastric lavage

7.2.1 Activated charcoal

Three part question

In [adults who have taken a TCA overdose] is [activated charcoal] effective at [reducing drug absorption and reducing complication rates]? A short-cut systematic review to answer this three-part question has been documented within the literature.[32] This was updated.

Search strategy

Ovid Medline 1950 – 2008 May Week 3
Ovid Embase 1980 – 2008 Week 22

[TCA filter] AND [Overdose filter] AND [Charcoal filter] limit to humans and English language.

Search outcome

67 papers were found in Medline and 125 in Embase. Eight papers were relevant to the three-part question (Table 2).

Comments

Experimental volunteer studies have consistently shown that administration of activated charcoal to patients who have ingested TCA within 1 hour leads to a reduction in TCA absorption and biovavailability. However, it is not possible to extrapolate these results to the clinical situation of patients with TCA overdose. Larger doses of TCA may lead to delayed gastric emptying, which may alter the observed effects of activated charcoal. Further, the risk of pulmonary aspiration may be increased.

One small observational study demonstrated that time to charcoal administration was directly correlated with estimated plasma TCA half-life.[33] However, the study involved small numbers and had significant weaknesses, meaning that it is difficult to interpret the results. Three randomised controlled trials of charcoal have been reported.[33-35] None of these trials were able to demonstrate a significant improvement in clinical outcome following charcoal administration. Further, in one study of 51 patients 15.7% of patients aspirated.[34]

As pulmonary aspiration is a significant risk in patients with TCA overdose and a well-described complication of activated charcoal administration, caution should be exercised before prescribing activated charcoal in this patient group. [36-41]

Clinical bottom line

There is no clinical evidence that activated charcoal is of benefit in patients with TCA overdose. Experimental data suggest that drug absorption may be reduced. Activated charcoal may be considered within 1 hour of significant drug overdose but the potential for pulmonary aspiration should be strongly considered before use.

Recommendation

Activated charcoal may be considered for use within 1 hour of TCA ingestion but only in patients with an intact or secured airway. The potential risk of aspiration should be strongly considered before use **(Grade D)**.

7.2.2 Multiple dose activated charcoal

Three part question

In [tricyclic antidepressant overdose] is [Multiple dose Activated charcoal better than single dose Activated charcoal] at [reducing toxicity and improving clinical outcome]

Search strategy

Ovid Medline 1950 – 2008 May Week 3
Ovid Embase 1980 – 2008 Week 22

[TCA filter] AND [Overdose filter] AND [Charcoal filter] LIMIT to Humans and English language.

Search outcome

67 papers were found in Medline and 125 in Embase. Six were relevant to the three part question. One study was excluded due to insufficient quality (Table 3).

Comments

Multiple dose charcoal appears to increase elimination. However level of evidence is poor due to the use of volunteer studies. These studies are difficult to apply to the clinical setting of the ED as the patients did not receive the overdose amount and were treated more quickly than in the clinical setting.

The effect of multiple dose charcoal on clinical outcomes and complications such as arrhythmias and hypotension have not been studied, therefore the effect of multiple dose charcoal in the clinical setting cannot truly be assessed as the measurements are not clinically relevant. Studies used in the clinical setting have small number of patients.

There is a need for larger studies in the clinical setting.

Clinical bottom line

There is no convincing clinical evidence that multiple dose activated charcoal reduces toxicity and improves clinical outcome.

Recommendation

Multiple dose activated charcoal should not be considered **(Grade D)**.

7.2.3 Gastric lavage

Three part question

In [Tricyclic antidepressant overdose] which [method of gastric decontamination] is better at [reducing toxicity and improving clinical outcome]

Search strategy

Medline 1950 – 2008 June Week 1
Embase 1980 – 2008 Week 23

[TCA filter] AND [Overdose filter] AND [Lavage filter] LIMIT to Humans and English language.

Search outcome

MEDLINE: 58 papers were found. EMBASE: 141 papers were identified. 58 papers were identified in Medline and 141 in Embase. Two papers were directly relevant to the three part question and have been tabulated (Table 4).

Comments

There seems to be no significant difference between gastric lavage and activated charcoal. Kulig *et al*[42] did demonstrate that gastric lavage improved clinical outcomes after drug overdose (not specifically tricyclic antidepressant overdose) when performed within one hour compared to no treatment. The European toxicologists consensus statement is, at least in part, based upon this.[43] One small study of thirteen consecutive patients who presented to the ED with evidence of antidepressant overdose and underwent gastric lavage showed that, where estimated time of ingestion was available, none of the patients received gastric lavage within one hour of ingestion. The mean time to delivery of gastric lavage was six hours. Further, a mean of only 8.7% of the estimated dose ingested was recovered.[44]

Clinical bottom line

There is no clinical evidence for the benefit of gastric lavage in tricyclic antidepressant overdose. In a clinical setting gastric lavage is unlikely to recover a clinically significant amount of antidepressant. Its use should only be considered in the context of a potentially life-threatening overdose with a protected airway where lavage can be delivered within one hour of ingestion. Activated charcoal is less invasive and may be a preferable alternative in conscious patients.

Recommendation

Gastric lavage may be considered for potentially life-threatening TCA overdoses only when it can be delivered within 1 hour of ingestion and the airway is protected **(Grade D)**.

7.3 The Electrocardiogram

7.3.1 The ECG versus serum drug level as a predictive tool
7.3.2 ECG changes as predictors of severity of overdose

7.3.1 The ECG vs. serum drug level as a predictive tool

Three part question

In [tricyclic antidepressant overdose] is the [ECG a greater predictor than serum drug level] at predicting [seizures and arrhythmias]

Search strategy

Ovid Medline 2008 June Week 1
Ovid Embase 2008 Week 23

[TCA filter] AND [ECG filter] AND [Overdose filter].

Search outcome

388 studies were found including one systematic review that incorporated a meta-analysis of all other relevant studies that had been identified (Table 5).

Comments

The meta-analysis by Bailey *et al* demonstrates that QRS duration and serum drug levels are roughly equivalent for predicting complications including death, seizures and ventricular arrhythmias. The use of the ECG allows rapid and repeated measurement in the emergency setting. It may be immediately examined for multiple abnormalities, each of which may aid in the prediction of complications. While serum drug level provides comparable predictive value, it has the disadvantages of being more invasive, taking longer to obtain results and being less widely available in the ED.

Future research may concentrate on multivariate analysis to determine which variables are independent predictors of complications, ideally with a view to deriving a clinical decision rule to guide management and disposition of patients who have taken a TCA overdose.

Clinical bottom line

The ECG is preferable to serum drug level for the prediction of complications following TCA overdose.

Recommendation

An ECG should be recorded at presentation to the ED following TCA overdose **(Grade B)**.

The ECG should be used to risk stratify patients with TCA overdose and to guide subsequent therapy **(Grade B)**.

7.3.2 ECG changes as predictors of severity of overdose

Three part question

In [TCA overdose] which [ECG abnormalities] are [predictive of death, seizures and arrhythmias]?

Search strategy

Ovid Medline 2008 June Week 1
Ovid Embase 2008 Week 23
[TCA filter] AND [ECG filter] AND [Overdose filter].

Search outcome

388 papers were found (143 in Medline and 245 in Embase) including one systematic review that incorporated a meta-analysis of all other relevant studies that had been identified (Table 5).

Comments

The ECG has long been used to aid in the risk stratification and management of patients who have taken a TCA overdose. The meta-analysis by Bailey *et al* demonstrates that ECG abnormalities are fairly good predictors of serious complications including death, seizures and ventricular arrhythmias. A QRS width >0.1s would appear to be the strongest predictor of complications. Indeed the wider the QRS complex the greater is the apparent risk of arrhythmias, with one group reporting a 50% incidence of arrhythmias when the QRS complex is >0.16s in duration.[45] However the results of one study also suggest that QTc >430 ms predicts ventricular arrhythmias with reasonable sensitivity (78%) but lower specificity (56%) than QRS prolongation. Further, one study demonstrated that R/S ratio >0.7 in lead aVR has a high positive predictive value (positive likelihood ratio 15.7) for predicting ventricular arrhythmias.

Importantly it is recognised that the timing of ECG recording is important and serial recordings should be considered.

Clinical bottom line

QRS width >100ms is a good predictor of complications following TCA overdose. Further, QTc >430ms and R/S ratio >0.7 in lead aVR may be useful for predicting complications.

Recommendation

Serial ECG recordings should be examined for the presence of QRS prolongation (>100ms), QTc prolongation (>430ms) and R/S ratio >0.7 in lead aVR. These changes identify patients at high risk of developing complications following TCA overdose **(Grade B)**.

7.4 Blood pH for risk stratification

7.4.1 pH versus ECG for risk stratification
7.4.2 Arterial or venous pH in conscious patients with TCA od

7.4.1 Arterial pH versus the ECG for risk stratification

Three part question

In [TCA overdose] is [ECG or blood PH] superior for [predicting seizures, reduced cardiovascular function and death]?

Search strategy

Ovid Medline 2008 June Week 1
Ovid Embase 2008 Week 23
[TCA filter] AND [ECG filter] AND [Overdose filter].

Search outcome

388 studies were identified (143 in Medline and 245 in Embase), none of which were relevant to the three part question.

Comments There is no evidence that can assist in answering this question. The use of ECG as a predictor of complications in tricyclic overdose has been proven, however this has never been compared to the pH. More research is required in this area.

Clinical bottom line

Local advice should be followed.

7.4.2 Arterial or venous blood gas estimation for monitoring and risk stratification following tricyclic antidepressant overdose

Three part question

In [patients who have taken an overdose of tricyclic antidepressants] does [measurement of arterial or venous blood gases] lead to [superior risk stratification and monitoring of blood pH]?

Search strategy

Ovid Medline 1950 - 2008 June Week 1
Ovid Embase 1980 - 2008 Week 23

[TCA filter] AND [Blood gas filter] limit to humans and English language.

Search outcome

A total of 81 papers were identified (65 in Medline, 18 in Embase). One paper was directly relevant to the three-part question (Table 6).

Comments

Assessment of acid-base balance is an essential part of the initial assessment and monitoring of patients who have taken a significant overdose of tricyclic

antidepressants. An important part of the management of these patients is alkalinisation, which has been reported to result in profound alkalaemia and high mortality.[46] However arterial blood sampling is often painful. In alert patients who do not have suspected hypoventilation, venous blood gas analysis would be preferable if it could be shown to be equivalent for risk stratification and monitoring.

The only relevant paper did seek to directly answer this question and had an appropriate sample size. Although statistically significant differences were detected in all relevant parameters between arterial and venous blood gas analysis, the clinical effects of the differences in bicarbonate and pH (in particular) are questionable. Further, a fairly strong linear relationship was demonstrated between arterial and venous pH measurements.

The study did not attempt to determine which sampling method enabled superior prediction of complications. However the evidence is sufficient to recommend that venous blood gas analysis is likely to be acceptable for the initial assessment and subsequent monitoring of these patients, so long as hypoxia or hypoventilation are not suspected.

Clinical bottom line

Venous blood gas analysis is an acceptable alternative to arterial blood gas analysis following tricyclic antidepressant overdose unless hypoxia or hypoventilation are suspected.

Recommendation

Blood gas analysis is an important part of the initial assessment and monitoring of patients who have taken a TCA overdose **(Grade E)**.

Venous sampling for blood gas analysis is an acceptable alternative to arterial sampling unless hypoxia or hypoventilation are suspected **(Grade D)**.

7.5 Adjunctive therapies

7.5.1 Intravenous fluids
7.5.2 Sodium bicarbonate
7.5.3 Vasopressors
7.5.4 Glucagon
7.5.5 Magnesium sulphate

7.5.1 Intravenous fluids

Three part question

In [patients who have taken an overdose of tricyclic antidepressants and have developed hypotension] does [the administration of normal saline, colloid or no intravenous fluid] lead to [superior success in treating hypotension, quicker resolution of hypotension, fewer arrhythmias and quicker recovery]?

Search strategy

Ovid MEDLINE 1950 – 2008 June Week 1
Ovid EMBASE 1980 – 2008 Week 23

[Tricyclic antidepressant filter] AND [Hypotension filter] AND [Intravenous fluids filter] limit to English language.

Search outcome

158 papers were identified (118 in Embase and 40 in Medline). None were relevant to the three-part question.

Comments

There is no direct evidence for the use of intravenous fluids to treat hypotension in tricyclic antidepressant overdose. However, the absence of evidence does not equate to evidence of absence.

Tricyclic-induced hypotension is likely to result from a combination of myocardial depression and reduced systemic vascular resistance. While intravenous fluids will not counter either of these effects, they may optimise cardiac preload thus improving the chances that a sufficient cardiac output will be achieved.

It is unlikely that a cautious fluid bolus will cause harm in this situation. Where concern exists about potential volume overload, invasive haemodynamic monitoring may be prudent.

The age-old argument of colloid versus crystalloid cannot be answered even for this well-defined situation. Colloid is believed to remain in the intravascular compartment for longer than crystalloid. Of note, however, there is some evidence that sodium loading may be important in reversing tricyclic antidepressant toxicity[47], which may lead the undecided clinician to favour saline infusion.

Clinical bottom line

There is no evidence within the literature that intravenous fluids counter tricyclic-induced hypotension. As there is a sound physiological rationale for their use, they may still be considered as a useful first line treatment.

Recommendation

A bolus of intravenous fluids should be considered as a first-line therapy to treat hypotension induced by TCA overdose **(Grade D)**.

7.5.2 Use of sodium bicarbonate for arrhythmias and hypotension

Three part question

In [Tricyclic antidepressant overdose] does [sodium bicarbonate] improve [arrhythmias and hypotension]?

Search strategy

Ovid Medline 1950 – 2008 June Week 1
Ovid Embase 1980 – 2008 Week 23

[TCA filter] AND [Bicarbonate filter] limit to humans and English language.

Search outcome

357 papers found (86 in Medline, 271 in Embase). One systematic review was relevant to the three-part question.[48] While this incorporated all other relevant papers the data was not suitable for meta-analysis. Four relevant papers are therefore tabulated (Table 7). Individual case reports are discussed but not tabulated. One survey of expert opinion is discussed.

Comments

The use of sodium bicarbonate to treat the complications of TCA overdose is so well established in everyday clinical practice that it is perhaps surprising to discover that its use is not based upon high level evidence. The evidence to supports its use is of a low level including only experimental animal studies, case reports and retrospective analyses.

In addition to the tabulated papers the meta-analysis by Blackman *et al* cites a total of eight case reports where bicarbonate therapy has reportedly led to beneficial effects including resolution of QRS prolongation, recovery of hypotension, successful treatment of arrhythmias and spontaneous return of circulation following cardiac arrest.[48] Further they cite a case series of 10 patients with QRS prolongation following TCA overdose, in whom the QRS duration normalised during periods of hypocapnoea and worsened during periods of normocapnoea.[49]

Given the available evidence it would be prudent to use sodium bicarbonate to treat major toxicity following TCA overdose, including arrhythmias and refractory hypotension. Further, as QRS prolongation is associated with a high risk of arrhythmias the use of sodium bicarbonate would also be reasonable in this situation.

Most of the relevant studies provide few details regarding the target pH for successful alkalinisation therapy. However, in the largest published study the recommended regime was alkalinisation to a pH between 7.50 and 7.55.[50] It would appear that the absence of acidosis need not preclude the use of sodium bicarbonate in this situation. The successful use of bicarbonate to treat TCA-induced arrhythmias has been reported

in a patient with alkalosis.[51] Notably, however, a case series of two patients reported the aggressive use of bicarbonate and hyperventilation in two patients with QRS prolongation and ventricular arrhythmias resulting in profound alkalosis (peak pH of 7.83 and 7.66 respectively) and death.[46]

A 2003 survey asked 58 medical directors of United States Poisons Centres to specify the clinical situations in which they would recommend the use of sodium bicarbonate. 100% recommended sodium bicarbonate to treat QRS prolongation, 62% to treat hypotension, 53% to treat seizures, 31% to treat tachycardia, 16% to treat ventricular dysrhythmias and 3% to treat acidosis. 53% would use a QRS width threshold of 100ms to recommend bicarbonate. Finally, 62% believed that the minimum target pH for alkalinisation should be 7.45 and 66% considered 7.55 to be the maximum pH target for alkalinisation therapy.[52]

Current practice in many centres is to use 50-100ml 8.4% (50mmol sodium bicarbonate); however in stable patients the use of 500ml 1.26% (75mmol) is safer in the event of extravasation.

Clinical bottom line

Sodium bicarbonate may be used to treat arrhythmias, hypotension and significant ECG abnormalities to a pH of 7.45-7.55 in tricyclic antidepressant overdose even in the absence of initial acidosis.

Recommendation

Sodium bicarbonate is indicated for the treatment of dysrhythmias or hypotension associated with TCA overdose. **(Grade C)**.

Sodium bicarbonate may be considered for the treatment of QRS prolongation (>100ms) associated with TCA overdose **(Grade E)**.

The treatment of dysrhythmias or hypotension should include alkalinisation to a serum pH of 7.45 to 7.55. **(Grade E)**.

7.5.3 Vasopressors

Three part question

In [TCA overdose with refractory hypotension] does the use of [catecholamines] improve [hypotension and survival]?

Search strategy

Ovid Medline 1950 – 2008 June Week 1
Ovid Embase 1980 – 2008 Week 23

[TCA filter] AND [Overdose filter] AND [Vasopressor filter] limit to English language.

Search outcome

810 papers were identified (699 in Embase and 111 in Medline). Five were relevant to the three-part question (Table 8).

Comments

There is no published evidence of the effectiveness of catecholamines to treat refractory hypotension following tricyclic antidepressant overdose. Perhaps importantly, however, there were no reports of harmful or potential pro-arrhythmic effects of catecholamines in this situation. Experimental studies in animals suggest that epinephrine may be more effective than norepinephrine in this situation with epinephrine potentially reducing some of the cardiotoxic effects of tricyclic antidepressants.

Clinical bottom line

There is no published evidence of benefit or harm with intravenous catecholamines following tricyclic antidepressant overdose. They may be a useful adjunct in the treatment of refractory hypotension in this situation. Animal evidence suggests that epinephrine may be preferable to norepinephrine.

Recommendation

Vasopressors should be used for hypotension following TCA overdose that has not responded to initial treatment (including sodium bicarbonate and intravenous fluids). **(Grade D)**.

Epinephrine may be superior to norepinephrine for treating refractory hypotension and preventing arrhythmias. **(Grade D)**.

7.5.4 Glucagon

Three part question

In [overdose with tricyclic antidepressants] does [the addition of glucagon to standard treatments] improve [clinical outcome]?

Search strategy

Ovid Medline 1950 – 2008 June Week 1
Ovid Embase 1980 – 2008 Week 23

[TCA filter] AND [Glucagon filter] limit to human and English language.

Search outcome

84 papers were identified (71 in Embase, 13 in Medline). Three papers were relevant to the three-part question (Table 9).

Comments There have been three case reports of the successful use of glucagon to treat refractory hypotension and arrhythmias and correct QRS prolongation following TCA overdose. In each of these cases the patient had received several other treatments although the authors state that the improvement in clinical condition was temporally related to glucagon administration. If it is effective a 10mg intravenous bolus may be necessary to elicit clinical improvement.

No reports of failure to respond to glucagon therapy were identified within the literature although this is most probably attributable to reporting bias. Further research is necessary.

Clinical bottom line

There is not enough evidence currently available to support the routine use of glucagon in tricyclic overdose. It is not unreasonable to administer 10mg intravenous glucagon to treat life-threatening hypotension or arrhythmias refractory to other measures.

Recommendation

It is not unreasonable to administer 10mg intravenous glucagon to treat life-threatening hypotension or arrhythmias refractory to other measures **(Grade D)**.

7.5.5 Magnesium sulphate

Three part question

In [patients who have taken an overdose of tricyclic antidepressants and develop dysrhythmias] does [magnesium sulphate or standard treatment] lead to [improved rates of cardioversion to sinus rhythm and haemodynamic stability]?

Search strategy

Ovid Medline 1950 – 2008 June Week 1
Ovid Embase 1980 – 2008 Week 23

[TCA filter] AND [Magnesium filter] AND [Dysrhythmias filter] limit to humans and English language.

Search outcome

111 papers identified (102 in Embase, 9 in Medline). No relevant comparative trials were identified. Three case studies were identified and have been tabulated (Table 10). An experimental animal study was identified and is discussed.

Comments

There are three reports of the successful use of magnesium sulphate for dysrhythmias associated with tricyclic antidepressant use, two of which are from Turkey and have striking similarities. The effects have not been scientifically validated. Knudsen and Abrahamsson[53] reported that magnesium sulphate was superior to lignocaine for the successful cardioversion of amitriptyline-induced ventricular tachycardia in rats. There are no reports of potential adverse effects of magnesium sulphate in this context.

Clinical bottom line

It is reasonable to consider the use of magnesium sulphate for refractory dysrhythmias causing haemodynamic instability in the context of tricyclic antidepressant overdose.

Recommendation

Magnesium sulphate may be considered for the treatment of TCA-induced dysrhythmias when other treatments have been unsuccessful. **(Grade D)**.

7.6 Management of seizures

7.6.1 Phenytoin
7.6.2 Benzodiazepines

7.6.1 Phenytoin

Three-Part Question

In [patients with TCA overdose who develop prolonged seizures] does [phenytoin or benzodiazepines] lead to [quicker and more reliable termination of seizures with fewer complications]?

Search strategy

Ovid MEDLINE 1966 – 2007 June Week 1
Ovid EMBASE 1980 – 2007 Week 24
[TCA filter] AND [Overdose filter] AND [Phenytoin filter] limit to human and English language.

Search outcome

710 papers were identified (293 in Medline and 417 in Embase). None directly answered the three-part question. Several papers discussed the use of phenytoin in TCA overdose. These are discussed.

Comments

Intravenous phenytoin is licensed for use in status epilepticus. Its use in the context of TCA overdose is controversial. There have been sporadic case reports of the successful use of intravenous phenytoin for the treatment of patients with severe TCA overdose who have developed cardiac conduction abnormalities[54;55]. It is proposed that this may result from its class Ia antiarrhythmic action. However, there is evidence of interaction between the two drugs, with TCA's increasing phenytoin levels[56;57]. Due to the narrow therapeutic window of phenytoin, this interaction is of concern. Further, in an animal model phenytoin was found to increase the likelihood of ventricular arrhythmias when TCA's were also infused[58]. In light of this potential interaction, guidelines from the National Poisons Information Service state that phenytoin should be avoided in patients who have taken a TCA overdose[59].

Clinical bottom line

Phenytoin has not been compared to benzodiazepines in patients with TCA overdose. Evidence for the benefit of phenytoin in TCA overdose comes only from sporadic case studies. As there are doubts regarding the safety of phenytoin in these patients, it should be avoided.

Recommendation

Phenytoin should be avoided in patients with TCA overdose. **(Grade D)**.

7.6.2 Benzodiazepines

Three part question

In [adult patients who develop seizures following tricyclic antidepressant overdose] does [the use of [benzodiazepines] lead to [safe and effective termination of seizures]?

Search strategy

Ovid MEDLINE 1950 - May Week 2, 2008
Ovid EMBASE 1980 - 2008 Week 21

[TCA filter] AND [Overdose filter] AND [Benzodiazepine filter] LIMIT to English language.

Search outcome

1743 papers were identified (186 in Medline and 1557 in Embase). None were relevant to the three-part question.

Comments

There were no studies found that were relevant to the three part question. Notably there have been no reports of harmful interactions when benzodiazepines are used in tricyclic antidepressant overdose. The National Poisons Information Service recommend the use of intravenous benzodiazepines to control seizures associated with tricyclic antidepressant overdose[60].

Clinical bottom line

There is no evidence of benefit or harm when benzodiazepines are used to control seizures associated with tricyclic antidepressant overdose. As there is no evidence of harm National Poisons Information Service guidance, which advocates the use of benzodiazepines in this situation, ought to be followed.

Recommendation

Benzodiazepines should be used to control seizures following TCA overdose **(Grade E)**.

7.7 Observation of asymptomatic patients

Three part question

In [a clinically stable patient following TCA overdose] what [period of observation] enables [safe discharge]?

Search strategy

Ovid Medline 1950 - 2008 June Week 1
Ovid Embase 1980 – 2008 Week 24

[TCA filter] AND [Overdose filter] AND [Observation filter] limit to Humans and English language.

Search outcome

592 papers were identified (156 in Medline, 436 in Embase). Seven were relevant to the three-part question (Table 11).

Comments

Late complications including cardiac arrhythmias have been reported to occur as long as several days after TCA overdose.[61-64] However in all of these cases there were significant signs of toxicity at a much earlier stage. There are no reports of late complications occurring in clinically stable patients who are alert, normotensive and have had no ECG abnormalities after six hours of observation.

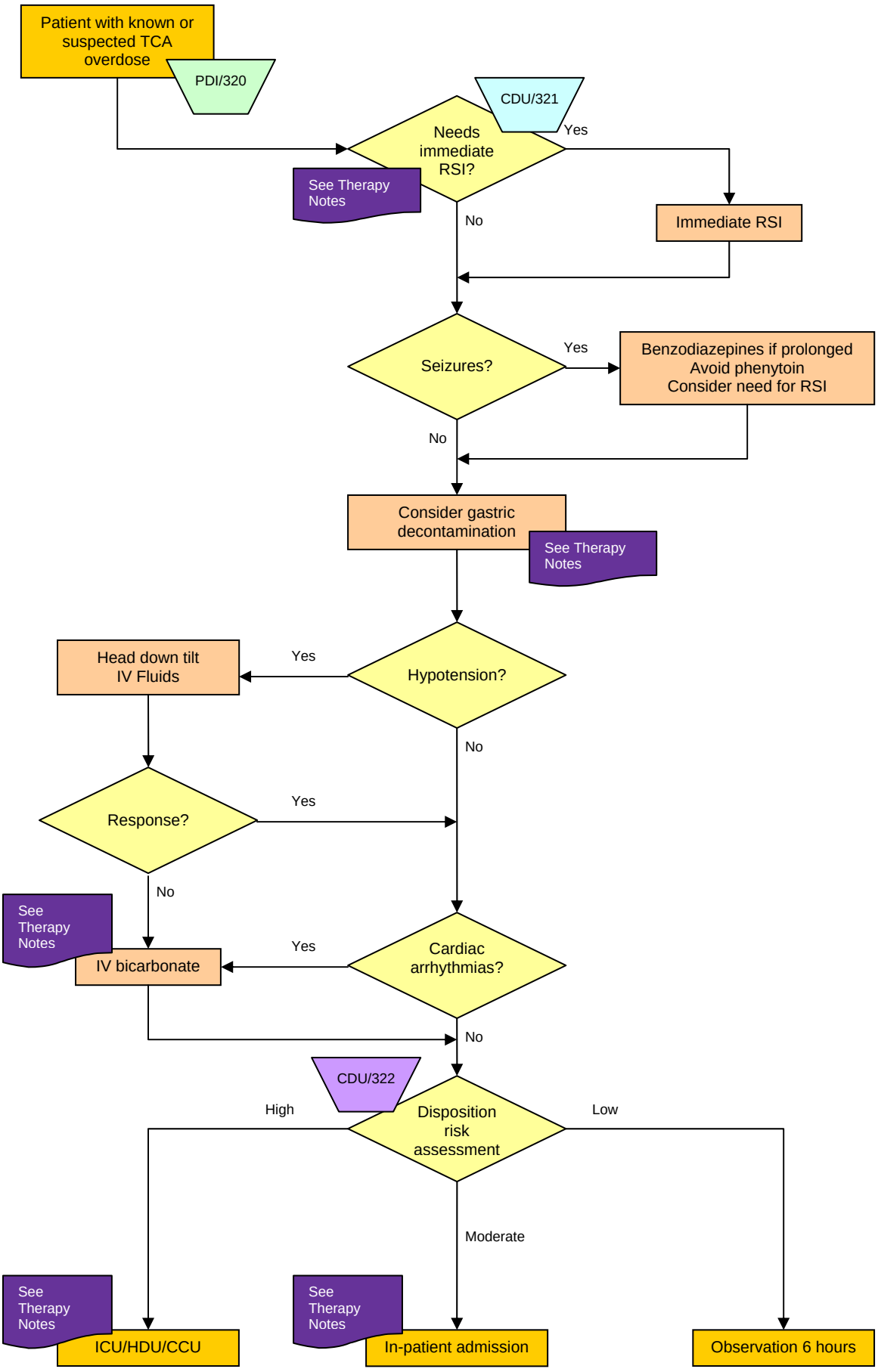
Clinical bottom line

Stable patients with tricyclic antidepressant overdose who show no sign of toxicity and have had no significant ECG abnormalities (including QRS<0.10s) for 6 hours can safely be discharged.

Recommendation

Following TCA overdose asymptomatic, stable patients who have had no significant ECG abnormalities six hours after ingestion may be safely discharged. **(Grade B).**

8. EVIDENCE-BASED FLOWCHART



PDI/320: SUITABILITY FOR PROTOCOL DRIVEN INVESTIGATION (ALL YES)

Over 16 years old	Yes
Known or suspected TCA overdose	Yes
No other agents ingested	Yes

Order: T, P, R, BP, SpO2
Immediate ECG and cardiac monitor
Blood gas (venous or arterial)

CDU/321: NEED FOR IMMEDIATE RSI (ANY YES)

Airway compromise	Yes
Inadequate respiration (bradypnoea, hypoxia, significant hypercapnia)	Yes
GCS ≤8/15	Yes
Unmanageable agitation	Yes

CDU/322: DISPOSITION RISK ASSESSMENT
(HIGH IF ANY H, LOW IF ALL L AND NO H, OTHERWISE MODERATE)

Indications for RSI present	HIGH	
Persistent hypotension or inotrope/vasopressor support required	HIGH	
GCS <14/15	HIGH	
Cardiac arrhythmias	HIGH	
Alert (GCS 15/15)		LOW
Normal ECG (including QRS width <0.10s and no right axis deviation)		LOW
Normal heart rate (60-100bpm)		LOW
Systolic blood pressure ≥100mmHg		LOW
>2 hours since ingestion		LOW

THERAPY NOTES

Indications for RSI: TCA overdose delays gastric emptying and may cause vomiting, increasing aspiration risk, particularly in patients with reduced level of consciousness. A low threshold for early intubation should be adopted and the need should be continually reassessed. It is imperative to ensure the availability of adequate expertise during rapid sequence induction.

Gastric decontamination: Activated charcoal may be considered for use within 1 hour of TCA ingestion but only in patients with an intact or secured airway. The potential risk of aspiration should be strongly considered before use. Gastric lavage may be considered for potentially life-threatening TCA overdoses only when it can be delivered within 1 hour of ingestion and the airway is protected.

Hypotension: TCA overdose causes hypotension by reducing preload and afterload as well as direct effects on the myocardium. Optimising the preload may reverse hypotension. This may be achieved by head-down tilt and bolus of intravenous fluid. Sodium bicarbonate may reverse hypotension even in the absence of acidosis and is indicated if hypotension is persistent. If hypotension still persists, vasopressors/inotropes should be used. There is some evidence that epinephrine may be preferable to norepinephrine in this situation.

Arrhythmias: Administration of sodium bicarbonate, even in the patient without acidosis, may reverse TCA-induced arrhythmias. If arrhythmias are persistent, magnesium sulphate may be given, although there is limited available evidence for its efficacy.

ECG abnormalities: QRS prolongation (>0.10s) and right axis deviation are associated with increased risk of cardiac arrhythmias. The use of sodium bicarbonate should be strongly considered in this situation.

Sodium bicarbonate: For life-threatening toxicity use 50-100ml 8.4% sodium bicarbonate. The dose can be repeated with blood gas monitoring to a target pH of 7.45-7.55. For more stable patients 500ml 1.26% sodium bicarbonate carries less risk of skin necrosis in the event of extravasation.

Seizures: Prolonged seizures should be treated initially with benzodiazepines. Phenytoin should be avoided because of a possible interaction with TCA's. If there is no response to benzodiazepines RSI should be considered.

ECG monitoring is essential for all patients at moderate/high risk. Serial 12-lead ECG recording is recommended in all patients to monitor for changes in QRS duration.

APPENDIX 1: RELEVANT PAPERS

Table 1: Assessing the need for intubation in semiconscious patients presenting to the ED following psychotropic drug overdose

Author, date & country	Study type	Patient group	Outcomes	Key results	Study weaknesses
Chan *et al*, 1993 Australia[65]	Retrospective analysis	393 patients who presented to the ED with a history or evidence of overdose (of a drug with no antidote) who had GCS documented at presentation	GCS ≤8/15 for prediction of intubation	67% of patients with GCS ≤8/15 were intubated. GCS ≤8/15 had sensitivity 90% (95% CI 81-99%) and specificity 95% (93-97%) for prediction of intubation	Study only assesses what actually happened (whether patients were intubated or not). We do not know whether it was actually necessary to intubate the patients with GCS ≤8/15. No reporting of complications in semi-conscious patients who were/were not intubated
			Relationship between GCS and intubation (logistic regression analysis)	Odds ratio 0.48 (95% CI 0.4-0.59), P<0.0001 (i.e. odds of intubation increase approximately two-fold for every point decrease in GCS)	
Emerman *et al*, 1987 USA[29]	Retrospective analysis	All 92 patients age ≥17 years who were admitted to Cleveland Metropolitan General Hospital with TCA overdose between 1975 and 1985	Association between GCS and complications (hypoventilation, loss of protective airway reflexes, hypotension, seizures, haemodynamically significant arrhythmias or death	Significant association (P<0.001). GCS was significantly better than QRS interval (P<0.001)	Retrospective 38 patients had a mixed drug overdose (although subgroup analysis of patients with pure TCA overdose yielded similar results) Only 92 patients included over a 10 year period
			GCS <=8 for prediction of serious complications	Sensitivity 89%, specificity 88%. GCS<=8 was significantly more sensitive than QRS >=100ms (P<0.05)	
			Sensitivity of GCS <=8 for prediction of individual complications	Hypoventilation or loss of protective airway reflexes: 86.5%; Death, hypotension, seizures, haemodynamically significant arrhythmias: 100%	
			Logistic regression model for prediction of complications	Only GCS was a significant independent predictor of complications	

Cont.

Table 1 cont.

Author, date & country	Study type	Patient group	Outcomes	Key results	Study weaknesses
Hulten *et al*, 1992 Sweden[28]	Prospective diagnostic cohort study	67 patients >= 14 years from four centres with suspected TCA overdose. Excluded if mixed overdose detected and TCA was not the major cause of symptoms. Matthew-Lawson coma grade recorded	Matthew-Lawson coma grade >=3 for prediction of serious complications (seizures, hypotension (systolic BP <100mmHg), arrhythmias, need for intubation)	Sensitivity 65%, specificity 94%	Matthew-Lawson coma grade not universally accepted for assessing conscious level (GCS not recorded) Need for intubation included as an outcome. Physicians may have decided to intubate on the basis of coma grade alone, thus introducing significant bias
			Matthew-Lawson coma grade >=2 for prediction of serious complications	Sensitivity 81%, specificity 77%	
			Matthew-Lawson coma grade vs. QRS duration and plasma TCA level for prediction of serious complications	Matthew-Lawson coma grade was the strongest predictor in logistic regression model. QRS duration >100ms was more sensitive for prediction of complications (86%) but less specific (75%)	
Liisanantti *et al*, 2003 Finland[30]	Retrospective analysis	257 patients admitted to ICU with self-poisoning of psychopharmaceutical drugs between November 1989 and October 2000 Classed as conscious (GCS 8-15) or unconscious (3-7) based on 'approximate GCS' 73 patients (28.4%) met criteria for aspiration pneumonia	Unconsciousness on discovery for prediction of aspiration pneumonia	OR 2.9 (95% CI 1.2 – 7.0)	Retrospective 'Approximate GCS' used due to lack of universal use of GCS in Finland Selection bias: Only patients admitted to ICU included GCS at time of initial contact with medical services not recorded in 20.6% of cases Possible reporting bias – this centre may have noticed a particularly high rate of aspiration pneumonia in patients intubated late, prompting this analysis
			Unconsciousness in ED for prediction of aspiration pneumonia	2.2 (0.9 – 5.4)	
			Unconscious when found and intubated on discovery for prediction of aspiration pneumonia	1.8 (0.6 – 5.7)	
			Unconscious when found and intubated in ED	3.4 (1.3 – 8.7)	
			Unconscious when found and intubated in ICU for prediction of aspiration pneumonia	3.5 (1.1 – 10.7)	
			Mean length of hospital stay	Aspiration pneumonia 6.5 days (95% CI 5.3 – 7.6); No aspiration pneumonia 2.8 days (2.5 – 3.1)	
			Mean length of ICU stay	Aspiration pneumonia 1.9 days (1.3 – 2.6); No aspiration pneumonia 0.9 days (0.8 – 0.9)	

Cont.

Table 1 cont.

Author, date & country	Study type	Patient group	Outcomes	Key results	Study weaknesses
Unverir *et al*, 2006 Turkey[66]	Retrospective analysis	356 patients who presented to the ED with antidepressant ingestion between 1993 and 2004	Relationship between GCS and intubation rates	34 (9.6%) patients were intubated. Low GCS was cited as the reason for intubation in 58.8% of cases. 100% of patients with GCS <=8 were intubated compared with 5.6% of patients with GCS >8	Retrospective Obvious bias in outcome reporting: Almost 60% of patients were intubated primarily because of low GCS. There was no attempt to correlate low GCS with incidence of complications
			Logistic regression model for prediction of the need for intubation	GCS the strongest independent predictor of need for intubation (OR 29.4, 95% CI 8.1 – 106.4). Presence of seizures was also an independent predictor of intubation. Age, gender and QRS prolongation were not independent predictors	
Yanagawa *et al*, 2006 Japan[67]	Retrospective analysis	175 patients who were intubated following psychotropic drug overdose between January 2000 and December 2005 Patients were divided into an "early group" (extubated within 2 days) and a late group (not extubated within 2 days)	Mean GCS (on arrival) in early and late groups	Early group 6.2 (SE 0.2); Late group 4.5 (SE 0.3), P=0.001	Retrospective Significant selection bias: only intubated patients included No analysis of different GCS cut-offs for prediction of late extubation
			Logistic regression model for prediction of "late" extubation (>2 days)	GCS on arrival was an independent predictor of late extubation (OR 0.78, 95% CI 0.65 – 0.95)	

Table 2: Single dose activated charcoal in tricyclic antidepressant overdose

Author, date & country	Study type	Patient group	Outcomes	Key results	Study weaknesses
Bosse *et al* 1995 USA[34]	51 patients presenting to the ED with TCA overdose. Block randomisation to three groups: (1) 50g charcoal, 10oz magnesium citrate (2) Gastriclavage followed by 50g charcoal and 10oz magnesium citrate (3) 25g charcoal, gastric lavage, followed by 25g charcoal and 10oz magnesium citrate	PRCT	Mean serum TCA levels	No significant differences (p=0.797)	Block randomisation No sample size calculation – unknown power
			Seizures	No significant difference (p=1.000)	
			Wide QRS (>0.1s)	No significant difference (p=0.472)	
			Hypotension (□90 systolic)	No significant difference (p=0.874)	
			Sinus tachycardia (rate >100)	No significant difference (p=0.280)	
			Ventricular dysrhythmias	None in any group	
			Median GCS	Mean 8.5 in group 1; 8 in group 2; 12 in group 3 (p=0.242)	
			Mean length of stay in hospitalised patients	No significant difference (p=0.473)	
			Mean length of ICU stay	No significant difference (p=0.436)	
			Mean duration of sinus tachycardia	No significant difference (p=0.594)	
			Incidence of aspiration	15.7% of patients aspirated (no difference between groups, p=0.501)	
Dawling *et al* 1978 England[68]	6 fasted healthy volunteers given 75mg nortriptyline, allocated to four groups on different occasions: (1) No treatment (2) 10g Medicoal after 30min (3) 10g Medicoal after 2h (4) 10g Medicoal after 4h	Experimental, volunteer study, crossover design	Mean reduction in peak plasma nortriptyline concentrations	77% in group (2), 37% in group (3), 19% in group (4) (p<0.001)	Conducted in fasted volunteers Small dose of notrtiptyline
			Mean reduction in plasma nortriptyline availability (area under time-concentration curve)	74% in group (2), 37.5% in group (3), 13% in group (4). (p<0.001)	
Hedges *et al* 1986 USA[33]	9 patients with TCA overdose who clinically required hospitalisation All patients had gastric lavage and charcoal, the timing and dosing of which were performed at the treating physician's discretion	Prospective observational cohort	Correlation between estimated plasma amitriptyline concentration half-life and time to charcoal	Directly proportional (r=0.78, p<0.05)	Small numbers No data on time to gastric lavage 5 patients received a second dose of charcoal, which may have affected the results Dose of charcoal not standardised
			Correlation between estimated plasma amitriptyline concentration half-life and dose of charcoal	Weak inverse correlation (r=0.44, p=0.25)	

Cont.

Table 2 cont.

Author, date & country	Study type	Patient group	Outcomes	Key results	Study weaknesses
Scheinin *et al* 1985 Finland[69]	8 healthy volunteers given 50mg doxepin followed by 15g activated charcoal after 30min.	Experimental, volunteer study	Peak serum doxepin concentration	Reduced by 70%	Volunteer study, small numbers Small dose of TCA and charcoal
			Total doxepin availability	Reduced by 49%	
			Apparent elimination half-life of doxepin and its metaboilte	Prolonged by 350 and 140% respectively following single dose charcoal	
Crome P *et al* 1977 UK[70]	Health volunteers given 75mg nortriptyline. Control session: no intervention Treatment session: 10g medicoal at 30 min Plasma nortriptyline levels measured after 2, 4, 6, , 10, 24, 32 and 48 hours	Experimental, crossover design	Plasma nortriptyline level	60% (range 30-81%) average reduction in peak levels (P=0.01)	Small dose of TCA and charcoal. Study in fasted volunteers. The results cannot be directly extrapolated to the population with TCA overdose
Crome P *et al* 1983 UK[71]	48 patients with suspected TCA overdose. All had gastric lavage. 10g medicoal vs nothing	PRCT	Plasma TCA concentration	No difference in rate of fall noted	Small numbers with complications. Small charcoal dose. 18 patents excluded. Time from ingestion to charcoal not investigated No data on numbers also given gastric lavage
			Clinical signs	No significant difference	
Karkkainen S and Neuvonen PJ 1986[72]	6 healthy volunteers. Each took 75mg amitriptyline. 50g charcoal within 5 min	Experimental	Plasma TCA bioavailability (area under the concentration-time curve)	Decreased by 99% compared to controls	Small dose of TCA. Unrealistic time to charcoal
Hulten BA *et al* 1988 Multinational[35]	77 patients over 14 years old with TCA overdose. Randomised to receive either gastric lavage alone (control, n=43) or gastric lavage and activated charcoal 20g (n=34)	PRCT	Plasma TCA concentration	No significant difference in peak or half-life	Control group differed from charcoal group at baseline. No data regarding the timing of charcoal administration
			Toxic symptoms	Fewer in control group (not statistically significant)	

Table 3: Multiple dose activated charcoal following TCA overdose

Author, date & country	Study type	Patient group	Outcomes	Key results	Study weaknesses
Crome P 1977 UK[70]	12 healthy volunteers administered 75mg nortriptyline 5 received single dose activated charcoal (5g) 7 received single dose activated charcoal plus multidose regimen (4 x 5g) the following week. All participants were in control group which received nothing	PRCT	% Reduction Peak plasma levels	Multidose > Single dose (72% reduction vs 58% respectively) p < 0.05	Volunteers used, hence results may not be valid since patient did not take overdose levels Activated charcoal administered 30min following Nortriptyline, however in clinical setting, most patients do not present within 30 mins Not randomised, Not blinded Small Number
			% Reduction Nortriptyline Availability	Multidose > Single dose (70% reduction Vs 55% respectively) p < 0.05	
Schwartz CM *et al* 1984 USA[73]	3 randomly selected patients with Amitriptyline overdose Gastric Lavage performed. Given 40-50g Activated Charcoal, followed by 20-25g Activated Charcoal repeatedly via nasogastric tube	Observational	Half Life	Reduced half life below 10 hours for each patient to as low as 4 hours	Only half life measured No control group very small number
Scheinin M *et al* 1985 Finland[69]	8 healthy volunteers given 50mg doxepin Control group- received nothing vs Single dose 15g Activated Charcoal & Repeated dose- 15g Activated charcoal at 3 hours and 10g after 6, 9, 12 and 24 hrs	Non randomised controlled trial	Total plasma clearance (doxepin)	Repeated dose > clearance than control;Repeated dose > single dose (significance not available)	Small group Lack of description in methods Single group receives charcoal at 30 min, which explains it low peak concentration in comparison to other groups however this is not mentioned as a potential confounding variable. Comparison of variables between groups is difficult due to the weakness mentioned above Investigators not blinded, No randomisation. Did not receive overdose amounts of doxepin, hence implications of validity Received charcoal after 30min, in clinical setting not many patients will receive charcoal within 30 min, hence can this be applied to the clinical setting of an emergency department?
			Half life (desmethyldoxepin)	Repeat dose (16.2 +/-2.3) < Single dose (80.6 +/-20.5) (p<0.05)	
			Half life (doxepin)	Repeat dose (20.7 +/-3.1) < Single dose (67.9 +/-12.9) (p<0.01)	

Table 3 cont.

Author, date & country	Study type	Patient group	Outcomes	Key results	Study weaknesses
Karkkainen S *et al* 1986[72]	Amitriptyline 75 mg administered orally to 6 fasted volunteers Activated charcoal 50 g given 6 hours after amitriptyline dose and further doses (12.5 g) of charcoal at 12, 18, 24, 30, 36, 42, 48, and 54 hours	PRCT	Half life	Reduced half life by 20%from 27.4 +/- (SE) 4.8 hours (control) to 21.1 +/- 3.3 hours (charcoal group)	Small number Volunteers used, hence difficult to apply result to the clinical setting
Ilett KF *et al* 1991[74]	3 patients with Dothiepin overdose. Treated with repeated activated charcoal	Observational study	Mean Half life	12.1 +/- (SD) 1.3 hours. Compared to literature range of 18.5-24 hours	Small number No control group

Table 4: Gastric lavage following TCA overdose

Author, date & country	Study type	Patient group	Outcomes	Key results	Study weaknesses
Hulten BA *et al* 1988 Sweden[35]	91 patients with suspected TCA overdose 43 Gastric Lavage only 34 Gastric Lavage + 20g Activated Charcoal	PRCT	Peak plasma concentrations	No difference	Only 20g of charcoal utilised All patients received gastric lavage as standard (no comparison of charcoal versus lavage)
			Plasma half-lives	No difference	
			Plasma drug concentration versus time curve	No difference	
			Toxic symptoms	Toxic symptoms greater in gastric lavage only group, however this was not statistically significant	
Bosse GM *et al* 1995 USA[34]	51 TCA overdose Group 1=50 gm Charcoal only (n=22) Group 2=Lavage followed by 50 gm Charcoal (n=14) Group 3=25 gm Charcoal Followed by Lavage then 25 gm charcoal (n=15)	PRCT	Mean Length stay in Hospital (hrs)	No significant difference (1) 93.3; (2) 107.2; (3) 66.7 (p=0.473)	Not blinded Small numbers Variations between presenting GCS and drug levels between groups
			Mean Length Stay in ICU (hrs)	No significant difference (1) 66.9; (2) 54.1; (3) 34.4 (p=0.436)	
			Mean duration sinus Tachycardia (hrs)	No significant difference (1) 20.8; (2) 30.8; (3) 32.2 (p=0.594)	
			Mean mechanical ventilation time (hrs)	No significant difference (1) 43.4; (2) 24.1; (3) 17.8 (p=0.321)	
			Aspiration	No significant difference (1) 2/22; (2) 3/14; (3) 15/3 (p=0.501)	

Table 5: ECG and serum drug level for predicting complications

Author, date & country	Study type	Patient group	Outcomes	Key results	Study weaknesses
Bailey B *et al* 2004[75]	Papers identified from Medline and Cochrane register for studies that investigated criteria for predicting outcomes in TCA overdose. Papers assessed by 2 investigators. Studies included if possible to construct 2x2 table from TCA concentration or ECG abnormalities against clinical outcomes. The following diagnostic tests were evaluated (1)TCA concentration (2)QRS>0.10 seconds (3)QTc>430 ms (4)R/S ratio >0.7 (5)Right axis deviation of 120-270 degrees in the terminal 40ms frontal plane QRS vector (T40)	Systematic review & meta analysis	Number Studies	941 studies found, 18 studies were included in the review	All but one studies retrospective, most non blinded, time between ingestion and measurement not reported
			Pooled Sensitivity & Specificity to predict Death	QRS=0.81 & 0.62; TCA conc= 0.76 & 0.60; QTc= 0.50 & 0.68; T40= 0.33 & 0.71 respectively	
			Pooled Sensitivity & Specificity to predict Seizures	QRS=0.69 & 0.69; TCA conc= 0.75 & 0.72; T40= 0.50 & 0.72 respectively	
			Pooled Sensitivity & Specificity to predict Ventricular arrhythmias	QRS=0.79 & 0.46; TCA conc= 0.78 & 0.57; QTc= 0.78 & 0.56;T40= 0.33 & 0.71; R/S ratio= 0.47 & 0.97 respectively	
			Positive & Negative Likelihood ratios for Death	QRS= 2.13 & 0.31; TCA conc= 1.90 & 0.57; QTc= 1.56 & 0.74; T40= 1.14 & 0.94 respectively	
			Positive & Negative Likelihood ratios for Seizures	QRS= 3.18 & 0.38; TCA conc= 2.39 & 0.46; T40= 1.79 & 0.69 respectively	
			Positive & Negative Likelihood ratios for Ventricular arrhythmias	QRS=1.46 and 0.46; TCA conc= 1.81 & 0.39; QTc= 1.77 & 0.39; T40= 1.14 & 0.94; QTc= 1.77 & 0.39; R/S ratio= 15.7 & 0.55 respectively	

Table 6: Venous versus arterial blood gas sampling

Author, date & country	Study type	Patient group	Outcomes	Key results	Study weaknesses
Eizadi-Mood *et al* 2005 Iran[76]	50 patients with clinical manifestations of tricyclic antidepressant poisoning who presented to the Emergency Department. Samples for arterial and venous gas analysis were obtained at presentation and 30 minutes after bolus sodium bicarbonate therapy	Prospective diagnostic cohort study	Mean (SD) pH on admission	Venous 7.34 (0.0049); Arterial 7.37 (0.0052). P=0.00	Small statistically significant differences in parameters identified but clinical significance of the difference in parameters not assessed. No attempt to correlate blood gas parameters with the incidence of complications
			Mean (SD) HCO3 30 min after bicarbonate	Venous 25.24 (3.35); Arterial 23.78 (3.11). P=0.23	
			Mean (SD) pH 30 min after bicarbonate	Venous 7.34 (0.049); Arterial 7.37 (0.042). P=0.12	
			Mean (SD) PCO2 on admission	Venous 43.79 (6.39); Arterial 38.47 (7.10). P=0.00	
			Mean (SD) PO2 on admission	Venous 42.50 (10.78); Arterial 79.94 (15.94). P=0.00	
			Mean (SD) HCO3 on admission	Venous 23.26 (3.23); Arterial 22.19 (3.28). P=0.01	
			Linear regression model (arterial and venous pH measurements)	Significant relationship (P<0.001). r squared = 0.60	

Table 7: Sodium bicarbonate following TCA overdose

Author, date & country	Study type	Patient group	Outcomes	Key results	Study weaknesses
Brown TC *et al* 1973 Australia[77]	4 children 18 months to 3 years	Case series	Blood pressure	Normalised	Case series only Causal relationship between sodium bicarbonate and clinical improvement not established
			Reversion of dysrhythmias to sinus rhythm	Normalised	
Brown TC 1976 Australia[78]	12 children 15 months to 12 years with arrhythmias Sodium bicarbonate 0.5 - 2 mEq/kg	Case series	Reversion of dysrhythmias to sinus rhythm	9/12 reverted to sinus rhythm	Case series only Causal relationship between sodium bicarbonate and clinical improvement not established
Koppel C *et al* 1992 Germany[79]	184 cases of overdose. 8 patients with cardiac disturbance. 100 mmol of sodium bicarbonate administered	Retrospective cohort study	Rhythm	4/8 reverted to sinus rhythm	Small numbers No comparison with control group In some cases mixed overdose with chlordiazepoxide
Hoffmann JR *et al* 1993 USA[50]	91 patients with overdose Sodium bicarbonate to a pH of 7.55	Retrospective cohort study	Blood pressure	20/21 normalised (>90mmHg systolic)	No adequate control group Physicians not blinded Data may be missing from notes since retrospective study
			QRS prolongation (>0.11s)	39/49 improved	

Table 8: Intravenous catecholamines to treat hypotension following TCA overdose

Author, date & country	Study type	Patient group	Outcomes	Key results	Study weaknesses
Teba L *et al* 1988 Nov USA[80]	Case 1: 47 year old Female BP 66 mmHg Case 2: 56 year old Female BP 52 mmHg Both treated with sodium bicarbonate and dopamine without significant improvement in hypotension	Case report	Systemic Systolic BP (SBP)	Case 1: Continuous infusion of norepinephrine increased SBP from 68 mmHg to >100 mmHg. Case 2: Following Norepinephrine infusion SBP increased from 52 mmHg to 130 mmHg	Only 2 case reports These may be exceptional cases
Vernon D *et al* 1991 USA[81]	15 Dogs infused with amitriptyline HCL Received Dopamine 5,15 and 30 micrograms sequentially or Norepinephrine 0.25,0.5 and 1.0 micrograms sequentially Haemodynamic measurements after each dose.	Experimental Randomised Controlled Trial	Mean Arterial Pressure (mmHg)	All doses of norepinephrine > MAP compared to Control ($p<0.05$). 2 higher dopamine doses > MAP compared to Control ($p<0.05$). At highest does no significant difference between Norepinephrine and Dopamine	Animal Study Not blinded Randomisation questionable Small number Each catecholamine infusion given sequentially
			Cardiac Output (CO) L/min	All doses of norepinephrine > CO than Control ($p<0.05$). 2 higher Dopmaine doses > CO than Control ($p<0.05$). At highest does no significant difference between Norepinephrine and Dopamine	
			Peak Left Ventricular dP/dt (rate of change of LV pressure)	All doses of norepinephrine > LV dP/dt than Control ($p<0.05$). 2 higher dopamine doses > LV dP/dt than Control ($p<0.05$). At highest does no significant difference between Norepinephrine and Dopamine	
			Mixed Venous Oxygen Saturation (SVO2)	All doses of norepinephrine > SVO2 than Control ($p<0.05$). 2 higher dopamine doses > LV SVO2 than Control ($p<0.05$). At highest does no significant difference between Norepinephrine and Dopamine	
			Systemic Vascular Resistance (SVR)	All doses of norepinephrine > SVP than Control ($p<0.05$). At highest does no significant difference between Norepinephrine and Dopamine	

Cont.

Table 8 cont.

Author, date & country	Study type	Patient group	Outcomes	Key results	Study weaknesses
Knudsen K, Abrahamsson J 1994 Sweden[82]	86 Male Wistar Rats infused with amitriptyline HCl Treated with: Epinephrine Norepinephrine Epinephrine + magnesium Norepinephrine + magnesium Milrinone	Nonrandomised, controlled intervention trial	Survival	Epinephrine + norepinephrine > survival than control (P<0.001). Epinephrine>Norepinephrine survival rate	Animal study- can it be useful in humans? Not blinded Small number Raw data absent in some measurements
			Increase in QRS duration	Epinephrine significantly lower increase in QRS compared to control + norepinephrine groups	
			Onset Arrhythmia	Epinephrine delayed onset of arrhythmias compared to control (p<0.01)	
			Duration Sinus rhythm	Epinephrine>control (p<0.01). Epinephrine> Norepinephrine (p<0.05)	
Knudsen K, Abrahamsson J 1997 April Sweden[83]	91 Male Sprague-Dawley rats. All given amitriptyline HCl infusion at@ 2mg/kg/min for 60 mins. After 5 mins given either: (a)Epinephrine infusion + 5 min bolus of sodium bicarbonate (b)Norepinephrine infusion +5 min bolus sodium bicarbonate (c)Epinephrine infusion + 5 min bolus placebo (d)Norepinephrine infusion + 5 min bolus placebo (e)Placebo infusion + 5 min bolus sodium bicarbonate (f)Placebo infusuion + 5 min bolus placebo Placebo infusion= Glucose 5% Placebo bolus= sodium chloride (9 mg/mL) 1mL/Kg/min	Non-randomised, Animal controlled intervention trial	Survival	Epinephrine + sodium bicarbonate > survival rate than other groups (p<0.01). Epinephrine treatment groups > survival rates than Norepinephrine treatment groups (p<0.01). Treatment groups > survival rate than control groups (p<0.01). Epinephrine + Sodium bicarbonate treatment > survival rate than Epinephrine alone (p < .01). Norepinephrine + Sodium bicarbonate treatment > survival rate than Norepinephrine alone (p < .01)	Animal study hence extrapolation to humans may be difficult Not blinded Raw data unavailable in some measurements
			Arrhythmias	Epinephrine treated rats had a longer time to onset of arrhythmias than Norepinephrine treated rats (21.5 Vs 11.6 mins) (p<0.05). Epinephrine + sodium bicarbonate treated rats had the longest time in sinus rhythm	
			QRS duration	Epinephrine treatment associated with shorter QRS interval than Norepinephrine treatment (p<0.05)	

Cont.

Table 8 cont.

Author, date & country	Study type	Patient group	Outcomes	Key results	Study weaknesses
Knudsen K, Abrahamsson J Sept 1993[84]	101 Male wistar rats poisoned with amitriptyline Given either 0.1, 0.5 or 5.0 mg/Kg/min of Epinephrine or Norepinephrine. Control group received Glucose infusion	Non-Randomised, Animal controlled intervention trial	Mean arterial Blood Pressure	All doses of Norepinephrine and 2 higher doses of Epinephrine increased MAP. Norepinephrine>Epinephrine at low & intermediate doses	Animal study-difficult to apply data to humans Experiment not Blinded Raw data absent from study No significant Difference between treatment according to Fischer's exact test
			Mortality at 75 min(%)	Control group=75%; Norepinephrine=45%; Epinephrine=27%. At intermediate dose Epinephrine group has lowest death risk (p=0.012)	
			Arrhythmia	Intermediate dose: Norepinephrine>arrhythmia than Epinephrine (p<0.05)	

Table 9: Glucagon to treat haemodynamic instability after TCA overdose

Author, date & country	Study type	Patient group	Outcomes	Key results	Study weaknesses
Ruddy JM *et al*, 1972, Australia[85]	4 year old ingested approx 1000mg imipramine, episode of PEA 1.5 hours duration	Case report	Cardiac status	Improved with 1 mg boluses glucagon	Case report Pt also received pyridostigmine, sodium bicarbonate, isoprenaline, digoxin, lignocaine and mannitol
Sener EK *et al*, 1995, UK[86]	25 year old woman. Plasma toxicology - imipramine 3.0mg/l, desipramine 0.18 mg/l, diazepam 2.9mg/l, nordiazepam 2.2mg/l, chlorpromazine 0.3mg/l, temazepam 0.25mg/l	Case report	Blood pressure	No response to 1mg bolus glucagon. 40mmHG systolic rise after glucagon	Multiple drugs ingested in overdose Pt also received sodium bicarbonate, phenytoin and isoprenaline and fluid resuscitation
			Cardiac rhythm	No response to 1mg bolus glucagon. Broad complex reverted to sinus after 10mg bolus	
Sensky PR *et al*, 1999, UK[87]	36 year old OD-admission toxicology dothiepin 2.58mg/l, desmethyldothiepin 0.51mg/l, paracetamol 135mg/l, diazepam 0.33mg/l, nordiazepam 0.12mg/l	Case report	Blood pressure	No response to 1mg bolus glucagon. 30mmHG systolic rise after glucagon	Case Report Multiple drugs ingested in overdose Pt also received n-acetylcysteine, adrenaline, noradrenaline, ephedrine, dobutamine, and aminophylline with fluid restriction
			Cardiac rhythm	No response to 1mg bolus glucagon. Broad complex reverted to sinus after 10mg bolus	

Table 10: Magnesium sulphate to treat dysrhythmias following TCA overdose

Author, date & country	Study type	Patient group	Outcomes	Key results	Study weaknesses
Knudsen and Abrahamsson 1997 Sweden[53]	A 44 year-lady who was admitted after an overdose of amitriptyline. She suffered a cardiac arrest (ventricular fibrillation) after 12 hours	Case Study	Observed effect of cardiopulmonary resuscitation, sodium bicarbonate, defibrillation (four attempts), lignocaine and epinephrine ("several doses")	Patient remained in ventricular fibrillation	This is only a case study The observed effects may or may not have been partly due to the effect of magnesium sulphate
			Observed effect of magnesium sulphate 20mmol x2 and further defibrillation	Spontaneous return of circulation; "Stable regular heart rhythm". Haemodynamic performance normalised	
Citak *et al* 2002 Turkey[88]	A 23 month-old boy who had taken 36mg/kg of amitriptyline and had been successfully resuscitated from cardiac arrest after 70 minutes. Following return of circulation, he was in ventricular tachycardia (VT)	Case Study	Observed effect of lignocaine, bicarbonate and attempted electrical cardioversion	No effect	Case study. The observed effects may or may not have been partly due to the effects of magnesium sulphate
			Observed effect of magnesium sulphate	Cardiac rhythm normalised without side-effects	
Sarisoy *et al* 2007 Turkey	4 year old boy who had taken 70mg/kg amitriptyline GCS 3/15, bradycardia and hypotension on arrival. Cardiac arrest (VF) despite epinephrine, bicarbonate, lignocaine & normal saline. VT after 'synchronised cardioversion' of VF. Then loaded with 2g magnesium sulphate followed by infusion of 3mg/min	Case report	Reversion of VT	After a magnesium infusion a 'normal cardiac rhythm' was obtained	Case report Magnesium infusion may not have caused termination of VT (multiple other therapies given; may have resolved spontaneously) Some unusual features regarding the management of this patient

Table 11: Observation of asymptomatic patients following TCA overdose

Author, date & country	Study type	Patient group	Outcomes	Key results	Study weaknesses
Greenland P and Howe TA 1981 USA[89]	62 patients with TCA overdose	Retrospective Cohort Study	Cardiac arrhythmias	No cardiac arrhythmias occurred after the first 24 hrs in any patient free of such complication earlier	Lack of raw data important details may be missing in retrospective study
Pentel P, Sioris L 1981 USA[90]	Patients with TCA overdose All underwent Gastric emptying	Retrospective Cohort Study	Development of Complication	All patients who developed complications did so within 1 hour of hospitalisation. No patients developed arryhthmias after being alert and having a normal ECG for 1 hour	Does not mention the exact number of patients in the study Vital data may be missing from notes due to retrospective study
Goldberg *et al* 1985 USA[91]	75 patients with TCA overdose	Retrospective Cohort Study	Cardiac complications	No new complications after 24 hrs	Data may be missing due to retrospective study No actual data on times of complications following overdose
Emerman C *et al* 1987 USA[92]	92 patients with TCA overdose admission from 1975-85	Retrospective Cohort Study	Development of complications (26/37 patients had documentation)	19/26 developed complications within 30 mins. 7/26 developed complications between 30-120 mins	Data may be missing due to retrospective study
Tokarski GF. Young MJ 1988 USA[93]	Reviewed 45 TCA overdose patients from 1982-1985 and applied algorithm	Retrospective Cohort Study	Patient discharged using Algorithm (No major signs toxicity/QRS<0.10 in 6hrs)	20 patient would have been discharged since no signs of major toxicity or QRS was <0.10s within 6 hours of admission. None of these patients developed any complications	Small sample retrospective study hence vital data from notes may be missing
Banahan B, Schelkun P 1990 USA[94]	Reviewed 33 patients with an admission diagnosis of TCA overdose between January 1985-December 1988. Applied algorithm by Tokarski and Young (see above)	Retrospective Cohort Study	Patients discharged under Algorithm (by Tokarski *et al*. See above)	11 patients did not show signs of Major toxicity or QRS>0.10s within 6 hours. Using the Algorithm these patient could have been discharged. None developed any complications	Small sample retrospective study, hence data may be missing
Hulten *et al* 1992 Sweden[95]	67 TCA overdose Patients	Cohort study	Development of Complications	All patients who developed complications did so within 6 hours of admission	Lack of raw data No sample size estimation performed

APPENDIX 2: SEARCH FILTERS

TCA Filter: (exp Antidepressive Agents, Tricyclic/ OR tricyclic.mp. OR amitriptyline.mp. OR exp Amitriptyline/ OR desipramine.mp. OR exp Desipramine/ OR clomipramine.mp. OR exp Clomipramine/ OR doxepin.mp. OR exp Doxepin/ OR dothiepin.mp. OR exp Dothiepin/ OR imipramine.mp. OR exp Imipramine/ OR lofepramine.mp. OR exp Lofepramine/ OR nortriptyline.mp. OR exp Nortriptyline/ OR trimipramine.mp. OR exp Trimipramine/)

Charcoal Filter: (exp Charcoal/ OR charcoal.mp.)

Lavage Filter: (gastric lavage.mp. OR exp Gastric Lavage/ OR irrigation.mp. OR exp Irrigation/ OR lavage.mp. OR exp Decontamination/ OR gastric decontamination.mp. OR washout.mp. OR gut decontamination.mp OR exp Stomach Emptying/ OR exp Stomach Lavage/)

Overdose Filter: (exp Overdose/ OR exp Poisoning/ OR overdose.mp. OR exp Drug Overdose/)

ECG Filter: (ECG.mp. OR exp Electrocardiography/ OR electrocardiogram.mp. OR EKG.mp.)

Vasopressor Filter: (exp Catecholamines/ OR exp Epinephrine/ OR exp Norepinephrine/ OR exp Dopamine/ OR (catecholamine OR epinephrine OR norepinephrine OR dopamine OR adrenaline OR noradrenaline).mp.)

Bicarbonate Filter: (exp Sodium Bicarbonate/ OR exp Bicarbonates/ OR (sodium bicarbonate OR bicarbonates).mp.)

Observation Filter: (exp Monitoring, Physiologic/ OR exp Patient Admission/ OR (admission OR monitoring).mp.)

Benzodiazepine Filter: (exp Benzodiazepines/ OR exp Diazepam/ OR exp Clonazepam/ OR exp Midazolam/ OR exp Temazepam/ OR exp Nitrazepam/ OR (benzodiazepin$ OR diazepam OR clonazepam OR nitrazepam OR clonazepam OR midazolam OR temazepam).mp.

Phenytoin Filter: (exp Phenytoin OR phenytoin.mp. OR epilim.mp.)

Seizure Filter: (exp Seizure/ OR (seizur$ OR convuls$ OR fitting OR fit OR fits).mp.)

Intubation Filter: (exp Intubation, Intratracheal/ OR (rapid sequence induction).mp OR rsi.mp OR intubation.mp OR (crash induction).mp OR airway management.mp)

Sedation filter exp "Hypnotics and Sedatives"/ OR sedation.mp. OR sedat$.mp. OR hypnotic$.mp.

pH filter (exp Hydrogen Ion Concentration/ OR pH.mp.)

Blood gas filter (Exp Blood Gas Analysis/ OR exp Blood Gas/ OR blood gas$.mp.)

Unconsciousness filter (Glasgow Coma Scale.mp. OR exp Coma/ OR exp Glasgow Coma Scale/ OR exp Unconsciousness/ OR (unconscious$ or semiconscious$ or obtund$ or unresponsive$).mp.)

Hypotension filter (exp Hypotension/ OR (hypotension OR hypotensive).mp.)

Intravenous fluids filter (exp Infusion/ OR exp Infusion Fluid/ OR exp Colloid/ OR exp Polygeline/ OR exp Gelatin Succinate/ OR exp Sodium Chloride/ OR (infusion OR colloid OR gelofusine OR haemaccel OR saline).mp.)

Magnesium filter (exp Magnesium/ OR exp Magnesium Sulfate/ OR magnesium.mp.)

Dysrhythmias filter (exp Heart Ventricle Tachycardia/ OR exp Heart Arrhythmia/ OR exp Arrhythmias, Cardiac/ OR (dysrhythmias$ OR arrhythmia$).mp.)

Glucagon filter (exp Glucagon/ OR glucagon.mp.)

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