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Antidotes for acute cardenolide (cardiac glycoside) poisoning (Review)

Roberts DM, Buckley N

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[Intervention Review]

Antidotes for acute cardenolide (cardiac glycoside) poisoning

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ABSTRACT

Background

Cardenolides are naturally occurring plant toxins which act primarily on the heart. While poisoning with the digitalis cardenolides (digoxin and digitoxin) are reported worldwide, cardiotoxicity from other cardenolides such as the yellow oleander are also a major problem, with tens of thousands of cases of poisoning each year in South Asia. Because cardenolides from these plants are structurally similar, acute poisonings are managed using similar treatments. The benefit of these treatments is of interest, particularly in the context of cost since most poisonings occur in developing countries where resources are very limited.

Objectives

To determine the efficacy of antidotes for the treatment of acute cardenolide poisoning, in particular atropine, isoprenaline (isoproterenol), multiple-dose activated charcoal (MDAC), fructose-1,6-diphosphate, sodium bicarbonate, magnesium, phenytoin and anti-digoxin Fab antitoxin.

Search methods

We searched MEDLINE, EMBASE, the Controlled Trials Register of the Cochrane Collaboration, Current Awareness in Clinical Toxicology, Info Trac, www.google.com.au, and Science Citation Index of studies identified by the previous searches. We manually searched the bibliographies of identified articles and personally contacted experts in the field.

Selection criteria

Randomised controlled trials where antidotes were administered to patients with acute symptomatic cardenolide poisoning were identified.

Data collection and analysis

We independently extracted data on study design, including the method of randomisation, participant characteristics, type of intervention and outcomes from each study. We independently assessed methodological quality of the included studies. A pooled analysis was not appropriate.

Main results

Two randomised controlled trials were identified, both were conducted in patients with yellow oleander poisoning. One trial investigated the effect of MDAC on mortality, the relative risk (RR) was 0.31 (95% confidence interval (CI) 0.12 to 0.83) indicating a beneficial effect. The second study found a beneficial effect of anti-digoxin Fab antitoxin on the presence of cardiac dysrhythmias at two hours post-administration; the RR was 0.60 (95% CI 0.44 to 0.81). Other benefits were also noted in both studies and serious adverse effects were

minimal. Studies assessing the effect of antidotes on other cardenolides were not identified. One ongoing study investigating the activated charcoal for acute yellow oleander self-poisoning was also identified.

Authors' conclusions

There is some evidence to suggest that MDAC and anti-digoxin Fab antitoxin may be effective treatments for yellow oleander poisoning. However, the efficacy and indications of these interventions for the treatment of acute digitalis poisoning is uncertain due to the lack of good quality controlled clinical trials. Given pharmacokinetic differences between individual cardenolides, the effect of antidotes administered to patients with yellow oleander poisoning cannot be readily translated to those of other cardenolides. Unfortunately cost limits the use of antidotes such as anti-digoxin Fab antitoxin in developing countries where cardenolide poisonings are frequent. More research is required using relatively cheap antidotes which may also be effective.

PLAIN LANGUAGE SUMMARY

Antidotes for acute cardenolide (cardiac glycoside) poisoning

Cardenolides are naturally occurring plant toxins which act primarily on the heart. While poisoning with the digitalis cardenolides (digoxin and digitoxin) are reported worldwide, cardiotoxicity from other cardenolides such as the yellow oleander are also a major problem, with tens of thousands of cases of poisoning each year in South Asia. Because cardenolides from these plants are structurally similar, acute poisonings are managed using similar treatments. The benefit of these treatments is of interest, particularly in the context of cost since most poisonings occur in developing countries where resources are very limited. The objectives of this review are to determine the efficacy of antidotes for the treatment of acute cardenolide poisoning, in particular atropine, isoprenaline (isoproterenol), multiple-dose activated charcoal (MDAC), fructose-1,6-diphosphate, sodium bicarbonate, magnesium, phenytoin and antidigoxin Fab antitoxin.

Two randomised controlled trials were identified; both were conducted in patients with yellow oleander poisoning. One trial investigated the effect of MDAC on mortality, the relative risk (RR) was 0.31 (95% confidence interval (CI) 0.12 to 0.83) indicating a beneficial effect. The second study found a beneficial effect of anti-digoxin Fab antitoxin on the presence of cardiac dysrhythmias at two hours post-administration; the RR was 0.60 (95% CI 0.44 to 0.81). Other benefits were also noted in both studies and serious adverse effects were minimal. Studies assessing the effect of antidotes on other cardenolides were not identified. One ongoing study investigating the activated charcoal for acute yellow oleander self-poisoning was also identified. There is some evidence to suggest that MDAC and anti-digoxin Fab antitoxin may be effective treatments for yellow oleander poisoning. However, the efficacy and indications of these interventions for the treatment of acute digitalis poisoning is uncertain due to the lack of good quality controlled clinical trials. Given pharmacokinetic differences between individual cardenolides, the effect of antidotes administered to patients with yellow oleander poisoning cannot be readily translated to those of other cardenolides. Unfortunately cost limits the use of antidotes such as anti-digoxin Fab antitoxin in developing countries where cardenolide poisonings are frequent. More research is required using relatively cheap antidotes which may also be effective.

BACKGROUND

Cardenolides, sometimes referred to as cardiac glycosides or cardioactive steroids, are naturally occurring plant toxins which act primarily on the heart (Hoffman 2002). The most well known are the digitalis cardenolides (digoxin and digitoxin) which are used therapeutically for the treatment of cardiac failure. Poisoning with digitalis cardenolides are reported worldwide and require admission to a coronary care unit (if available) to monitor for significant cardiotoxicity, and administration of antidotes such as anti-digoxin Fab antitoxin, as needed. Case fatality ratios up to 20% have been reported, and severe toxicity may not occur until 24 hours post-admission for digoxin, or up to five days for digitoxin poisonings (Taboulet 1993a).

Cardiotoxicity is reported from other cardenolides also, in particular yellow oleander (*Thevetia peruviana*) and pink or white oleander (*Nerium oleander*), as well as the sea mango tree (*Cerbera manghas*). The oleander plants are found commonly through much of the tropics and subtropics around houses and gardens (Langford 1996). These cardenolides are structurally similar to digitalis, and treatments for digitalis poisoning such as the anti-digoxin Fab antitoxin have been trialled in the management of acute poisoning with these cardenolides (Eddleston 2000). In parts of India and Sri Lanka, yellow oleander has become a popular means of self harm with tens of thousands of cases in South Asia each year, and probably hundreds of deaths given the case fatality ratio of 5 to 10%. Further, significant dysrhythmias may be delayed for up to 72 hours post ingestion, requiring prolonged hospital admissions (Roberts 2005). Unfortunately, because the anti-digoxin Fab antitoxin is expensive, it is not readily available worldwide, particularly in developing countries where poisonings with these cardenolides are common (Eddleston 2003). As such, the management of patients with severe cardenolide poisoning is generally difficult and costly in countries with limited resources.

Why it is important to do this review

A number of specific treatments for cardenolide poisoning have been either used or recommended, including atropine, isoprenaline (isoproterenol), multiple-dose activated charcoal, fructose-1,6-diphosphate, sodium bicarbonate, magnesium, phenytoin and anti-digoxin Fab antitoxins. The purpose of this systematic review is to evaluate the efficacy of all these treatments. The benefit of these treatments in the context of cost is also of high interest as most poisonings occur in developing countries where resources are very limited (Roberts 2005).

OBJECTIVES

To determine the efficacy of antidotes for the treatment of acute cardenolide poisoning, in particular atropine, isoprenaline (isoproterenol), multiple-dose activated charcoal (MDAC), fructose-1,6-diphosphate, sodium bicarbonate, magnesium, phenytoin and anti-digoxin Fab antitoxin.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials.

Types of participants

Patients with acute symptomatic cardenolide poisoning, in particular digitalis or oleander who present within 24 to 48 hours of poisoning.

Types of interventions

Interventions where antidotes are administered, in particular atropine, isoprenaline (isoproterenol), MDAC, frustose-1,6-diphosphate, sodium bicarbonate, magnesium, phenytoin and anti-digoxin Fab anti-toxin. Randomised controlled trials comparing these results to patients who do not receive the antidote were included. It is likely that all patients will continue to receive standard treatment in addition to the intervention.

Types of outcome measures

Primary outcomes

- Mortality

Secondary outcomes

- Occurrence of serious cardiac dysrhythmias (in particular second or third degree heart block or cardiac arrest)
- Time to reversal of dysrhythmias
- Occurrence of hyperkalaemia (serum K+ > 5.5mmol/L)
- Time to reversal of hyperkalaemia
- Requirement for pacemaker insertion
- Adverse effects of the treatment

Where information on cost of the intervention is available, the cost-benefit would be determined.

Search methods for identification of studies

The searches were not restricted by language or publication status.

Electronic searches

We searched the following electronic databases (details of the strategies used are presented in Appendix 1);

- CENTRAL (*The Cochrane Library*, issue 3, 2006)
- MEDLINE (1966 to October 2005)
- EMBASE (1980 to October 2005)
- Current Awareness in Clinical Toxicology (www.npis.org/cact/cact.htm) (to March 2006)
- Info Trac (to March 2006)
- http://www.google.com (to March 2006)

Searching other resources

We also searched the reference lists of relevant studies identified by the above search.

We consulted experts, including authors of textbook chapters and review articles on cardenolide poisoning, and other experts in the field of clinical toxicology. We made contact by e-mail, and encouraged each expert to forward the message to other experts knowledgeable in the area.

Data collection and analysis

Selection of studies

One author (DMR) reviewed the results of all searches and identified any article that may be eligible, given a reference to acute cardenolide poisoning and treatment with a potential antidote. Each study was then discussed between authors to confirm eligibility for inclusion in the systematic review.

Data extraction and management

Data from studies meeting inclusion criteria were entered into a computer spreadsheet. The authors performed this process independently and the results were compared. We extracted data on the following:

- number of participants;
- method of allocation;
- type of study;
- participant selection;
- treatment regimen of the antidote;
- details of concurrent treatments;
- outcome measures listed above, including standard deviations if applicable.

Assessment of risk of bias in included studies

Since there is evidence that the quality of allocation concealment particularly affects the results of studies (Schulz 1995), the authors scored quality on the scale used by Schulz as shown below, assigning C to poorest quality and A to best quality:

- A = trials deemed to have taken adequate measures to conceal allocation (that is, central randomisation; serially numbered, opaque, sealed envelopes; or other description that contained elements convincing of concealment).
- B = trials in which the authors either did not report an allocation concealment approach at all or reported an approach that did not fall into one of the other categories.
- C = trials in which concealment was inadequate (such as alternation or reference to case record numbers or to dates of birth).

The overall quality of each trial was independently assessed by both authors according to the method of Jadad using the following criteria, where the maximum possible score for any study is 5/5: (Jadad 1996)

- Randomly assigned: A method to generate the sequence of randomisation will be regarded as appropriate if it allowed each study participant to have the same chance of receiving each intervention and the investigators could not predict which treatment was next. This criteria is scored when the method to generate the sequence of randomisation was described (one point) and it was appropriate (table of random numbers, computer generated, etc) (one point).
- Double blind: A study must be regarded as double blind if the word "double blind" is used. The method will be regarded as appropriate if it is stated that neither the person doing the assessments nor the study participant could identify the intervention being assessed, or if in the absence of such a statement the use of active placebos, identical placebos, or dummies is mentioned. This criteria is scored when the method of double blinding was described (one point) and it was appropriate (one point).
- Withdrawals and dropouts described: Participants who were included in the study but did not complete the observation period or who were not included in the analysis must be described (one point).

Assessment of heterogeneity

If the data were suited to meta-analysis, we proposed to use a random-effects model to pool the data given that heterogeneity between studies was considered likely. The presence of heterogeneity of the observed treatment effects was to be assessed using the I^2 statistic, which describes the percentage of total variation across studies due to heterogeneity rather than chance. A value of 0% indicates no observed heterogeneity, and larger values show increasing heterogeneity. Where heterogeneity appears significant, pooled results were to be interpreted with caution.

Data synthesis

Relative risk (RR) of death plus 95% confidence interval (CI) was calculated such that a RR of more than one indicated a higher risk of death (or serious dysrhythmias, etc) in the first group named. RR was used because it is more readily applied to the clinical situation. For continuous data the weighted mean difference (WMD) plus 95% CI was used.

Subgroup analysis and investigation of heterogeneity

We planned the following subgroup analyses.
If there were sufficient appropriate data we would have undertaken the following subgroup analyses;

- type of intervention
- type of cardenolide poisoning (digitalis versus oleander)
- time to presentation. Following acute poisoning the sooner that management is initiated the more likely it is to be effective;
- severity of toxicity (symptomatic patients versus those with severe toxicity as defined in Roberts 2005). There is a wide range of severity - trivial poisonings where no effect is possible are relatively common. Conversely, many patients present in a moribund state where any intervention is unlikely to have time to be effective. Patients with severe poisoning who are not about to expire are those who are most likely to benefit from a treatment.

However, there were insufficient data to enable such analyses.

RESULTS

Description of studies

We identified a total 24 studies for this systematic review, but 21 were excluded from further consideration because that they were not randomised controlled trials in patients with acute cardenolide poisoning (see 'Characteristics of excluded studies' table for more details).

Of the three studies fulfilling inclusion criteria (de Silva 2003; Eddleston 2000; Eddleston 2005), only two (de Silva 2003; Eddleston 2000) were included in the analyses (see 'Characteristics of

included studies' table for more details) as the third (Eddleston 2005) is presently ongoing (see 'Characteristics of ongoing studies' table for more details). Patient recruitment to the ongoing study has been completed and data are being analysed with final results being expected by late 2006.

Both of the included studies were conducted in patients with acute yellow oleander poisoning, one (de Silva 2003) assessed the effect of MDAC and one (Eddleston 2000) assessed the effect of anti-digoxin Fab antitoxin.

No other studies assessing the effect of antidotes on other cardenolides were identified.

Risk of bias in included studies

de Silva 2003
Allocation concealment was not adequately described (Schulz = B).
The overall quality received 2/5 on the Jadad scale as the method of concealing the next allocation in the random sequence was not described (randomisation 1/2) and it was a single blind study (double blinding 0/2). However, it is acknowledged it would be nearly impossible to conduct a double blind study when the intervention is orally administered activated charcoal.

Eddleston 2000
Appropriate randomisation procedures were reported (Schulz = A), suggesting adequate allocation concealment.
The overall quality was rated as 5/5 according to the Jadad scale (high quality).

Effects of interventions

As the two included studies assessed the outcomes from different antidotes, the data were not suited to meta-analysis.

Both of the included studies reported a benefit in the primary outcome from their respective interventions and their effect on outcomes pre-defined for this review are shown under 'Analyses'.

de Silva 2003
The administration of MDAC (compared to single dose activated charcoal (SDAC)) indicated beneficial effects in terms of mortality (RR 0.31, 95% CI 0.12 to 0.83), occurrence of severe arrhythmias (RR 0.21, 95% CI 0.06 to 0.71) and requirement for temporary pacing (RR 0.09, 95% CI 0.01 to 0.70).

The reported adverse effects were minor in nature (nausea, abdominal discomfort, diarrhoea) and uncommon.

Eddleston 2000
Administration of anti-digoxin Fab antitoxin reduced the presence of cardiac dysrhythmias two hours post-administration (RR 0.60, 95% CI 0.44 to 0.81) and increased the mean heart rate at two hours (WMD 16.00, 95% CI 8.18 to 23.82) and at eight hours (WMD 15.00, 95% CI 7.50 to 22.50) post-administration. Fab antitoxin also reduced the mean serum potassium at two hours post-administration (WMD -0.60, 95% CI -1.02 to -0.18]) although this effect was not observed at 48 hours post-administration (WMD 0.00, 95% CI -0.19 to 0.19).

Adverse effects were reported to be more frequent from anti-digoxin Fab antitoxin (13% of patients administered Fab), and while some potentially severe reactions were reported (including bronchospasm in two patients and mild angioedema in one patient), the reactions all responded promptly to standard treatment with epinephrine, antihistamines and corticosteroids.

DISCUSSION

Few high quality studies have been conducted to assess the efficacy of antidotes for the treatment of acute cardenolide poisoning. In particular there are no randomised controlled trials in acute digitalis poisoning, despite the widespread therapeutic use of digitalis cardenolides and the relative frequency of poisonings. Instead, the evidence supporting antidotes for digitalis poisoning (where they have been assessed) is limited to observational and retrospective studies. While these studies have demonstrated an apparent reversal of cardiotoxicity, the role of the antidote in causing this response, independent of the effects of confounding variables such as other treatments and the natural history of the cardiotoxicity, cannot be clearly defined.

The suboptimal study design is of particular importance when considering the effect of the anti-digoxin Fab antitoxin. Because the Fab antitoxin is expensive, clear guidelines on indications for its use and quantified benefits would be of interest to clinicians and others. However, because of the favourable outcomes from the observational studies and widespread use of this antidote, it would now be considered unethical to conduct a randomised controlled trial. Similarly, given the widespread use of atropine for cardenolide-induced bradycardia, and clinical experience suggesting its efficacy, it seems unlikely that a randomised controlled trial will be conducted to define its efficacy.

Fortunately, randomised controlled trials have been conducted on antidotes for the treatment of acute yellow oleander poisoning (see 'Characteristics of included studies' table for more details). Yellow oleander poisoning is a particular problem in developing countries where resources are limited and therefore more information on the efficacy of antidotes is required to determine if it should be available. Unfortunately, in the case of antidotes such as anti-digoxin Fab antitoxin, despite this data the cost of the drug limits its use in developing countries such as Sri Lanka (Eddleston 2003). Given pharmacokinetic differences between individual cardenolides, the effect of antidotes administered to patients with yellow oleander poisoning cannot be readily translated to those of other cardenolides.

The final interim report of the ongoing randomised controlled trial into the efficacy of activated charcoal in acute poisoning did not report a difference in terms of the primary outcome (death) for the subgroup of patients with yellow oleander poisoning (n = 1515 patients) and secondary analysis data is not yet available (Eddleston 2005). This is in contrast to the included study which reported improvements in mortality from MDAC. The data from this ongoing study are undergoing final analysis and the results are eagerly awaited.

There are other potentially useful antidotes for cardenolide poisoning which have not yet been assessed. Of particular interest is fructose-1,6-diphosphate which appears to be useful in dogs poisoned with nerium oleander (Markov 1999). A phase II clinical trial is currently underway in Sri Lanka to assess the effect of this antidote in patients with acute yellow oleander poisoning (Dawson 2006).

With the exception of two studies conducted in patients with acute yellow oleander poisoning (Eddleston 2003; Roberts 2006), the excluded studies were all conducted on subjects exposed to digitalis cardenolides (many included patients with both acute and chronic toxicity). A limited range of antidotes were considered in the excluded studies, notably anti-digoxin Fab antitoxin (15), activated charcoal (4), glucagon (1), phenytoin (1). This highlights the gap in the available data, inviting further research into antidotes for the management of acute cardenolide poisoning.

AUTHORS' CONCLUSIONS

Implications for practice

There is some evidence to suggest that MDAC and anti-digoxin Fab antitoxin may be effective treatments for yellow oleander poisoning. However, the efficacy and indications of these interventions for the treatment of acute digitalis poisoning is uncertain due to the lack of good quality controlled clinical trials. The evidence base supporting the current treatment of acute cardenolide poisoning, in particular digitalis, is limited.

Considering the findings of the two included studies and their limitations, the current treatment recommendations for antidotes may include MDAC and anti-digoxin Fab antitoxin for patients with yellow oleander poisoning. However due to the absence of high quality controlled trials, the effectiveness of other antidotes for cardenolide poisoning (such as isoprenaline (isoproterenol), frustose-1,6-diphosphate, sodium bicarbonate, magnesium, phenytoin) is unknown.

Implications for research

Further research is required to confirm the efficacy of antidotes which have been suggested to be useful for acute cardenolide poisoning. In particular, research into antidotes which are relatively cheap (for example, magnesium, fructose-1,6-diphosphate, sodium bicarbonate and phenytoin) should be encouraged, given the high incidence of yellow oleander poisoning in developing countries.

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Taboulet P, Baud FJ, Bismuth C. Clinical features and management of digitalis poisoning - rationale for immunotherapy. *Journal of Toxicology - Clinical Toxicology* 1993;**31**(2):247-60.

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

de Silva 2003

Methods	Randomised controlled trial.
Participants	All patients with a history of acute yellow oleander poisoning.
Interventions	50g SDAC or MDAC (50g every 6 hours for 12 doses).

de Silva 2003 *(Continued)*

Outcomes	Death, admission to intensive care unit, temporary cardiac pacing, administration of anti-digoxin Fab antitoxin, dose of atropine, duration of hospital stay and frequency of life-threatening cardiac arrhythmias.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Eddleston 2000

Methods	Randomised controlled trial.
Participants	Patients with acute yellow oleander poisoning and clinical evidence of severe toxicity.
Interventions	1200mg of anti-digoxin Fab antitoxin or placebo.
Outcomes	Reversal of cardiac arrhythmia within 2 hours, heart rate, potassium, time to first reversal of cardiac arrhythmia.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Albrecht 1988	Uncontrolled case series.
Antman 1990	Uncontrolled case series.
Eddleston 2003	No randomisation - outcomes in patients included in a prospective observational study were compared to patients identified by a retrospective review of hospital records.
Hickey 1991	Uncontrolled surveillance study.
Ibanez 1995	Retrospective study.
Kirkpatrick 1991	Uncontrolled study of adverse reactions.
Lavaux 2004	Uncontrolled retrospective study.
Love 1998	Uncontrolled case series of patients ingesting multiple poisons.

Study	Reason for exclusion
Montoya 1995	Uncontrolled case series of patients ingesting multiple poisons.
Oliveri 1971	Uncontrolled case series.
Reissell 1982	Volunteer study in patients on maintenance digoxin (no acute poisoning).
Roberts 2006	Convenience sample from a randomised controlled trial in patients with acute poisoning.
Schaumann 1986	Uncontrolled case series.
Smith 1982	Uncontrolled case series.
Smith 1991	Uncontrolled case series.
Smolarz 1984	Uncontrolled case series.
Taboulet 1993b	Non-randomised case series.
Wenger 1985	Uncontrolled case series.
Wenger 1991	Patients were a subgroup from an uncontrolled case series.
Woolf 1991	Patients were a subgroup from an uncontrolled case series.
Woolf 1992	Patients were a subgroup from an uncontrolled case series.

Characteristics of ongoing studies *[ordered by study ID]*

Eddleston 2005

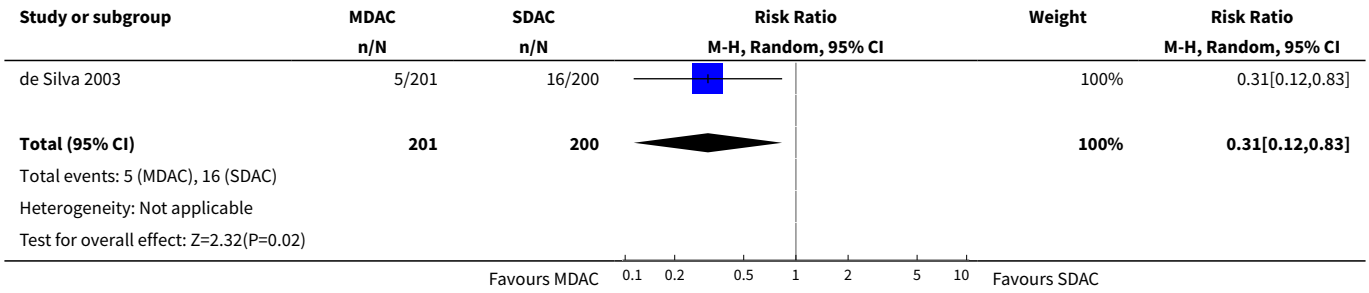
Trial name or title	A randomised controlled trial of single or multiple dose activated charcoal for acute self-poisoning. (ISRCTN02920054)
Methods	
Participants	All patients with acute poisoning; 30% present with yellow oleander.
Interventions	No activated charcoal or 50g SDAC or MDAC (50g every 4h for 6 doses).
Outcomes	Death, proportion of patients receiving anti-digoxin Fab or requiring transfer for tertiary care (temporary cardiac pacing).
Starting date	31st March 2002
Contact information	Dr Michael Eddleston eddlestonm@eureka.lk
Notes	Patients were allocated via a stratified block randomisation procedure using the following strata: (i) ingested toxin; (ii) time between poisoning and recruitment; and (iii) clinical status on admission.

DATA AND ANALYSES

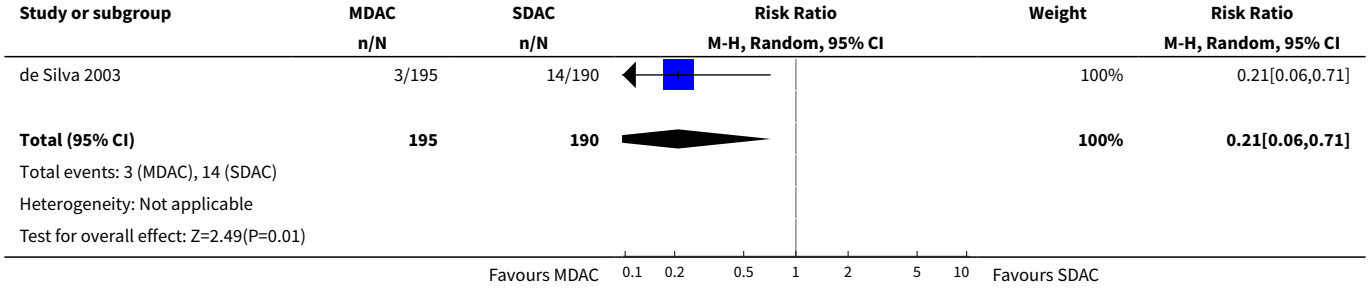
Comparison 1. Activated charcoal for yellow oleander

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality	1	401	Risk Ratio (M-H, Random, 95% CI)	0.31 [0.12, 0.83]
2 Presence of serious cardiac dysrhythmias	1	385	Risk Ratio (M-H, Random, 95% CI)	0.21 [0.06, 0.71]
3 Patients requiring temporary cardiac pacing	1	401	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.01, 0.70]

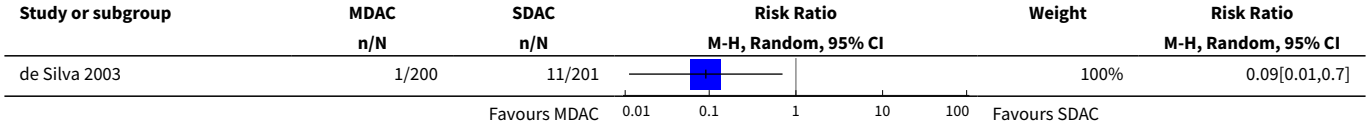
Analysis 1.1. Comparison 1 Activated charcoal for yellow oleander, Outcome 1 Mortality.

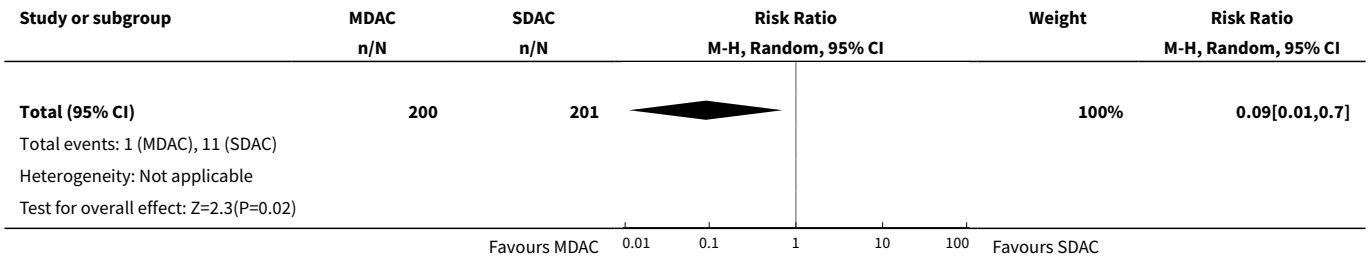


Analysis 1.2. Comparison 1 Activated charcoal for yellow oleander, Outcome 2 Presence of serious cardiac dysrhythmias.



Analysis 1.3. Comparison 1 Activated charcoal for yellow oleander, Outcome 3 Patients requiring temporary cardiac pacing.

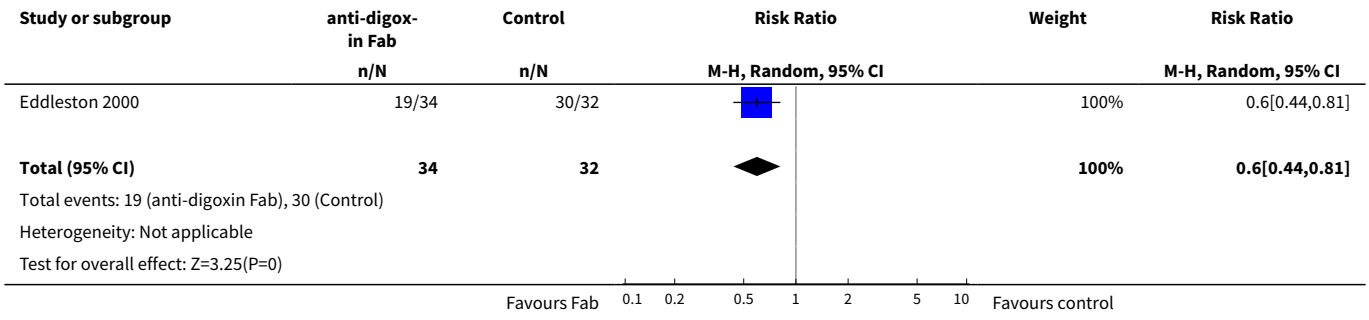




Comparison 2. Anti-digoxin Fab antitoxin for yellow oleander

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Persistence of presenting dysrhythmia at two hours	1	66	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.44, 0.81]
2 Heart rate at two hours	1	66	Mean Difference (IV, Random, 95% CI)	16.0 [8.18, 23.82]
3 Heart rate at eight hours	1	66	Mean Difference (IV, Random, 95% CI)	15.0 [7.50, 22.50]
4 Mean serum potassium at two hours	1	66	Mean Difference (IV, Random, 95% CI)	-0.60 [-1.02, -0.18]
5 Mean serum potassium at 48 hours	1	66	Mean Difference (IV, Random, 95% CI)	0.0 [-0.19, 0.19]

Analysis 2.1. Comparison 2 Anti-digoxin Fab antitoxin for yellow oleander, Outcome 1 Persistence of presenting dysrhythmia at two hours.



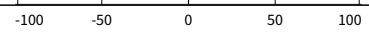
Analysis 2.2. Comparison 2 Anti-digoxin Fab antitoxin for yellow oleander, Outcome 2 Heart rate at two hours.

Study or subgroup	anti-digoxin Fab N	anti-digoxin Fab Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Eddleston 2000	34	67 (19)	32	51 (13)		100%	16[8.18,23.82]
Total ***	**34**		**32**			**100%**	**16[8.18,23.82]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.01(P<0.0001)							

Favours control — Favours Fab

Analysis 2.3. Comparison 2 Anti-digoxin Fab antitoxin for yellow oleander, Outcome 3 Heart rate at eight hours.

Study or subgroup	anti-digoxin Fab N	anti-digoxin Fab Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Eddleston 2000	34	69 (17)	32	54 (14)		100%	15[7.5,22.5]
Total ***	**34**		**32**			**100%**	**15[7.5,22.5]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.92(P<0.0001)							



Favours control — Favours Fab

Analysis 2.4. Comparison 2 Anti-digoxin Fab antitoxin for yellow oleander, Outcome 4 Mean serum potassium at two hours.

Study or subgroup	anti-digoxin Fab N	anti-digoxin Fab Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Eddleston 2000	34	4.1 (0.7)	32	4.7 (1)		100%	-0.6[-1.02,-0.18]
Total ***	**34**		**32**			**100%**	**-0.6[-1.02,-0.18]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.81(P=0)							

Favours Fab — Favours control

Analysis 2.5. Comparison 2 Anti-digoxin Fab antitoxin for yellow oleander, Outcome 5 Mean serum potassium at 48 hours.

Study or subgroup	Treatment N	Treatment Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Eddleston 2000	34	4 (0.4)	32	4 (0.4)		100%	0[-0.19,0.19]
Total ***	**34**		**32**			**100%**	**0[-0.19,0.19]**
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							

Favours Fab — Favours control

APPENDICES

Appendix 1. Search strategy

MEDLINE (1966 to October 2005)

#1 explode "Antidotes-" / all SUBHEADINGS in MIME,MJME
#2 explode "Antitoxins-" / all SUBHEADINGS in MIME,MJME
#3 explode "Antibody-Affinity" / all SUBHEADINGS in MIME,MJME
#4 explode "Immunoglobulins-" / all SUBHEADINGS in MIME,MJME
#5 explode "Charcoal-" / all SUBHEADINGS in MIME,MJME
#6 explode "Atropine-" / all SUBHEADINGS in MIME,MJME
#7 explode "Phenytoin-" / all SUBHEADINGS in MIME,MJME
#8 explode "Magnesium-" / all SUBHEADINGS in MIME,MJME
#9 explode "Fructosediphosphates-" / all SUBHEADINGS in MIME,MJME
#10 explode "Isoproterenol-" / all SUBHEADINGS in MIME,MJME
#11 explode "Sodium-Bicarbonate" / all SUBHEADINGS in MIME,MJME
#12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
#13 ((antidote* or antitoxin* or antibod* or immunoglobulin* or charcoal* or atropine* or phenytoin* or magnesium* or fructosediphosphate* or isoproterenol* or sodium?bicarbonate*) in TI)or((antidote* or antitoxin* or antibod* or immunoglobulin* or charcoal* or atropine* or phenytoin* or magnesium* or fructosediphosphate* or isoproterenol* or sodium?bicarbonate*) in AB)
#14 #12 or #13
#15 explode "Cardenolides-" / all SUBHEADINGS in MIME,MJME
#16 explode "Apocynaceae-" / all SUBHEADINGS in MIME,MJME
#17 explode "Cardiac-Glycosides" / all SUBHEADINGS in MIME,MJME
#18 explode "Thevetia-" / all SUBHEADINGS in MIME,MJME
#19 explode "Nerium-" / all SUBHEADINGS in MIME,MJME
#20 explode "Digoxin-" / all SUBHEADINGS in MIME,MJME
#21 explode "Digitoxin-" / all SUBHEADINGS in MIME,MJME
#22 #15 or #16 or #17 or #18 or #19 or #20 or #21
#23 ((cardenolide* or cardiac?glycoside* or apocynacae* or thevetia* or nerium* or digoxin* or digitoxin*) in TI)or((cardenolide* or cardiac?glycoside* or apocynacae* or thevetia* or nerium* or digoxin* or digitoxin*) in AB)
#24 #22 or #23
#25 #14 and #24
#26 #25 and the 'MEDLINE highly sensitive search strategy' outlined in the Cochrane Handbook for Systematic Review of Interventions (Higgins 2005).

EMBASE (1980 to October 2005)

((explode 'isoprenaline-' / all subheadings in DEM,DER,DRM,DRR) or (explode 'fructose-bisphosphatase' / all subheadings in DEM,DER,DRM,DRR) or (explode 'immunoglobulin-' / all subheadings in DEM,DER,DRM,DRR) or (explode 'drug-antibody' / all subheadings in DEM,DER,DRM,DRR) or (explode 'bicarbonate-' / all subheadings in DEM,DER,DRM,DRR) or (explode 'antitoxin-' / all subheadings in DEM,DER,DRM,DRR) or (explode 'antidote-' / all subheadings in DEM,DER,DRM,DRR) or (explode 'atropine-' / all subheadings in DEM,DER,DRM,DRR) or (explode 'activated-carbon' / all subheadings in DEM,DER,DRM,DRR) or (explode 'charcoal-' / all subheadings in DEM,DER,DRM,DRR) or (charcoal) or (atropine) or (phenytoin) or (magnesium) or (FDP) or (fructose) or (isoprenaline) or (isoproterenol) or (sodium-bicarbonate) or (Fab)) AND (explode 'Apocynaceae-' / all subheadings in DEM,DER,DRM,DRR) or (explode 'digitoxigenin-' / all subheadings in DEM,DER,DRM,DRR) or (explode 'peruvoside-' / all subheadings in DEM,DER,DRM,DRR) or (explode 'Nerium-oleander-extract' / all subheadings in DEM,DER,DRM,DRR) or (explode 'digitoxin-' / all subheadings in DEM,DER,DRM,DRR) or (explode 'acetyldigoxin-' / all subheadings in DEM,DER,DRM,DRR) or (explode 'alpha-acetyldigoxin' / all subheadings in DEM,DER,DRM,DRR) or (explode 'metildigoxin-' / all subheadings in DEM,DER,DRM,DRR) or (explode 'digoxin-' / all subheadings in DEM,DER,DRM,DRR) or (explode 'cardenolide-derivative' / all subheadings in DEM,DER,DRM,DRR) or (explode 'cardenolide-' / all subheadings in DEM,DER,DRM,DRR) or (nerium) or (thevetia) or (digoxin) or (cardenolide) or (oleander) or (cardiac-glycoside) or (apocynacae) or (digitoxin))

Current Awareness in Clinical Toxicology (www.npis.org/cact/cact.htm) (to March 2006)

CACT was searched using the following terms: cardenolides, cardiac glycoside, apocynacae, oleander, thevetia, nerium, digoxin and digitoxin.

Info Trac (to March 2006)

(cardenolide OR cardiac glycoside OR apocynacae OR oleander OR thevetia OR nerium OR digitalis OR digoxin OR digitoxin) AND (poison* OR toxic*)

http://www.google.com (to March 2006)

(cardenolide OR digitalis OR digoxin OR digitoxin OR oleander OR cardiac-glycoside OR thevetia OR nerium) AND (antidote OR antitoxin OR Fab OR antibody OR immunoglobulin OR charcoal OR atropine OR isoprenaline OR isoproterenol OR phenytoin OR fructose OR bicarbonate OR magnesium). The first 500 entries were reviewed.

WHAT'S NEW

Date	Event	Description
26 March 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

DMR designed the search criteria and drafted the review with the assistance of NAB.

DECLARATIONS OF INTEREST

NAB is an investigator in the above-mentioned ongoing RCT (Eddleston 2005) investigating the effect of single or multiple dose activated charcoal for acute self-poisoning with yellow oleander. He is also an investigator in the phase II study investigating the effect of fructose-1,6-diphosphate for acute self-poisoning with yellow oleander (Dawson 2006).

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- National Health and Medical Research Council, Australia.
- Wellcome Trust, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Antidotes [*therapeutic use]; Cardenolides [*poisoning] [therapeutic use]; Cardiac Glycosides [poisoning]; Charcoal [*therapeutic use]; Phytotherapy; Poisoning [drug therapy]; Randomized Controlled Trials as Topic; Thevetia [*poisoning]

MeSH check words

Humans