Multiple-dose activated charcoal for treatment of yellow oleander poisoning: a single-blind, randomised, placebo-controlled trial

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Summary

Background Deliberate self-poisoning with yellow oleander seeds is common in Sri Lanka and is associated with severe cardiac toxicity and a mortality rate of about 10%. Specialised treatment with antidigoxin Fab fragments and temporary cardiac pacing is expensive and not widely available. Multiple-dose activated charcoal binds cardiac glycosides in the gut lumen and promotes their elimination. We aimed to assess the efficacy of multiple-dose activated charcoal in the treatment of patients with yellow-oleander poisoning.

Methods On admission, participants received one dose of activated charcoal and were then randomly assigned either 50 g of activated charcoal every 6 h for 3 days or sterile water as placebo. A standard treatment protocol was used in all patients. We monitored cardiac rhythm and did 12-lead electocardiographs as needed. Death was the primary endpoint, and secondary endpoints were life-threatening cardiac arrhythmias, dose of atropine used, need for cardiac pacing, admission to intensive care, and number of days in hospital. Analysis was by intention to treat.

Findings 201 patients received multiple-dose activated charcoal and 200 placebo. There were fewer deaths in the treatment group (five [2·5%] *vs* 16 [8%]; percentage difference 5·5%; 95% CI 0·6–10·3; p=0·025), and we noted difference in favour of the treatment group for all secondary endpoints, apart from number of days in hospital. The drug was safe and well tolerated.

Interpretation Multiple-dose activated charcoal is effective in reducing deaths and life-threatening cardiac arrhythmias after yellow oleander poisoning and should be considered in all patients. Use of activated charcoal could reduce the cost of treatment.

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Introduction

Deliberate self-poisoning with the seeds of yellow oleander (*Thevetia peruviana*) is an important problem in Sri Lanka.[1,2] Ingestion usually produces severe glycoside toxicity, characterised by nausea, vomiting, and cardiac arrhythmias, and results in about 2000 deaths each year. Treatment in Sri Lankan hospitals is gastric lavage and one oral dose of activated charcoal on admission, followed by intravenous atropine, isoprenaline, or both for bradyarrhythmias.[3] Patients who do not respond to this treatment are given temporary cardiac pacing, often in a special unit, to which they must be transferred.[4] Eddelston and colleagues[5] have shown that antidigoxin antibody Fab fragments can reduce life-threatening cardiac arrhythmias and the need for cardiac pacing. However, their study was too small to determine whether treatment with the antibody had an effect on death rates. Furthermore, use of the antibody is limited by its high cost and because it is rarely available in the rural and secondary care hospitals in which patients with yellow oleander poisoning seek treatment.

Yellow oleander seeds contain highly toxic cardiac glycosides, including thevetin A, thevetin B, neriifolin, and peruvoside.[6,7] Between individuals, there is a large amount of variation in the amount of absorption of cardioactive toxins from a seed, and the number of seeds ingested does not always correlate with the degree of toxicity.[1] After absorption into the systemic circulation, cardiac glycosides such as digoxin are secreted into the gut lumen by the action of P-glycoprotein.[8,9] In the gut, activated charcoal binds the secreted glycoside and encourages further secretion, thereby causing a rise in glycoside excretion.[8] In pigs, repeated doses of activated charcoal reduced the half-life of digoxin given intravenously from 65 h to 17 h and increased clearance from 2·3 mL/min/kg to 7·1 mL/min/kg.[10] In ten healthy volunteers who received intravenous digoxin, repeated doses of activated charcoal increased total body clearance from 12 L/h to 18 L/h and reduced the half-life from 37 h to 22 h.[11]

Activated charcoal is inexpensive and widely available. Through interruption of the enteric recirculation of the glycosides in yellow oleander, multiple-dose activated charcoal could improve the outcome in yellow oleander poisoning and reduce the need for expensive interventions such as cardiac pacing and antidigoxin antibody Fab fragments.

In this single-blind, randomised, placebo-controlled trial, we aimed to assess the efficacy and safety of multiple-dose activated charcoal after one dose of activated charcoal in the treatment of patients with yellow oleander poisoning.

Methods

Patients

We recruited patients from the accident and emergency department of the Kurunegala Teaching Hospital, Kurunegala, Sri Lanka. Patients aged 12–70 years who were admitted within 24 h of ingestion of yellow oleander seeds were eligible for inclusion.

We excluded patients who had taken another drug (such as alcohol, organophosphates, paracetamol, or sedatives), had other debilitating diseases (diabetes mellitus, hepatic or renal disease, heart failure, or malignant disease), or had had abdominal surgery within the past year. Patients with known hypersensitivity to activated charcoal, those with severe infections, and pregnant and lactating women were also excluded.

We gave patients verbal and written information about the nature, objectives, importance, expected benefits, and possible adverse effects of the treatment. If we could not gain consent from the patient, we sought permission from a parent, spouse, or guardian. Patients were told that they were free to withdraw from the trial at any time if they wished to do so, without any prejudice to subsequent management. Written consent was obtained in Sinhalese or Tamil. The ethics committee of the Faculty of Medicine, University of Kelaniya, and local health authorities approved the study.

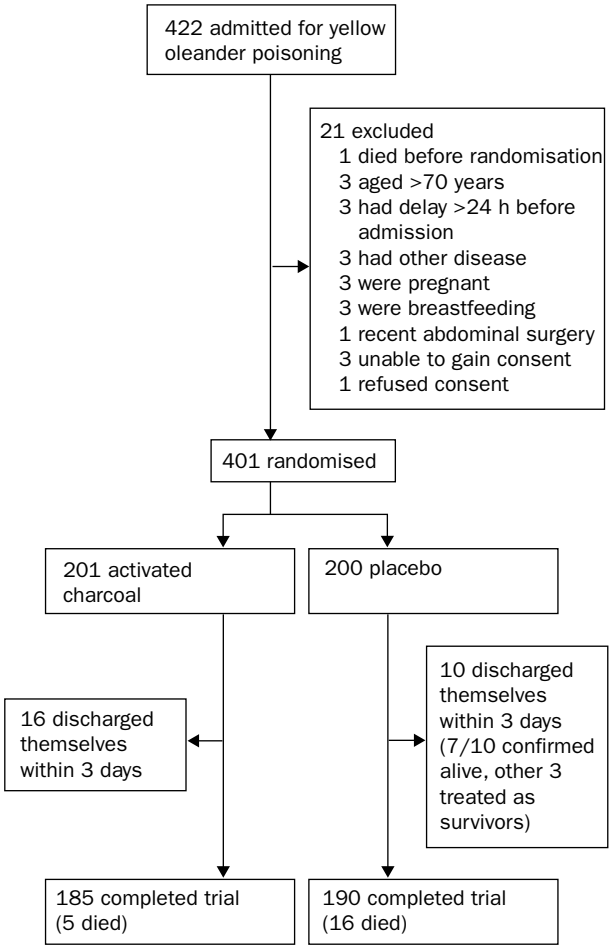
Procedures

On admission, all patients were assessed and received standard treatment for yellow oleander poisoning—ie, gastric lavage, one 50g dose of activated charcoal, and atropine as needed. Cardiopulmonary resuscitation was given when required. We measured concentrations of potassium in serum at baseline, did electrocardiographs, and recorded cardiac rhythms for at least 24 h after admission. Two investigators (GAR and DGSA) assessed patients and continued to assess and treat patients throughout the trial in accordance with a standardised management protocol (panel).

6 h after admission, an investigator (AP) used a computer-generated random-allocation table to allocate patients either multiple doses of activated charcoal (Haycarb, Sri Lanka) or placebo (sterile water) every 6 h. This investigator was not involved in care or assessment of patients. We asked patients to drink the activated charcoal or sterile water, and used a nasogastic tube for those who were unable to do so. Investigators were unaware of patients' treatment allocation. Three medically qualified research assistants supervised administration of activated charcoal or sterile water, but they did not participate in clinical assessment or management of patients. To facilitate blinding, research assistants also ensured that patients and their bedclothes were cleaned thoroughly after each treatment.

Treatment protocol for yellow oleander posioning

1 Routine treatment after poisoning—gastric lavage, one dose of activated charcoal, IV access, cardio-pulmonary resuscitation
2 Randomly allocate patients who meet inclusion criteria to either activated charcoal or placebo
3 Administer drug or placebo orally or via nasogastric tube
4 Treatment schedule:
  A Metoclopramide 10 mg intravenously as required
  B Atropine three 2 mg intravenous boluses at 5–10 min intervals, or infusions of 12 mg/h for:
    a) sinus bradycardia <50 per min
    b) sinus bradycardia <60 per min and systolic blood pressure
    c) All other bradyarrhythmias
  C If no response or deterioration in cardiac rhythm, transfer to intensive care unit. Criteria for admission to intensive care: haemodynamic instability, life threatening arrhythmias, or both
5 Discharge criteria—sinus rhythm with rate >60 per min for 24 h



Trial profile

Activated charcoal was given in a dose of 50 g dissolved in water to 400 mL every 6 h for 3 days. An equivalent amount of sterile water was given to those on placebo. Patients who had nausea or vomiting after the trial began were given 10 mg of intravenous metoclopramide as required. We monitored patients for abnormalities in cardiac rhythm, and electrocardiograms were done if arrhythmias were detected. We monitored patients until discharge from hospital or death.

We used death as the primary endpoint. Secondary endpoints were the need for admission to an intensive care unit, temporary cardiac pacing, administration of antidigoxin antibody Fab fragments, doses of atropine used, and duration of hospital stay. We also assessed the frequency of life-threatening cardiac arrhythmias (second-degree heart block, third-degree heart block, sinoatrial block, nodal bradycardia, ventricular tachycardia, and ventricular fibrillation).

We assessed patients' tolerance of charcoal by recording response to treatment. Bowel sounds were monitored regularly, and we took precautions to help patients to avoid aspiration of activated charcoal, especially in those who received treatment via a nasogastric tube.

Statistical analysis

We assumed a 10% death rate in patients admitted with yellow oleander poisoning on the basis of previously published results.[1] We expected treatment to reduce the death rate to 2·5%. Thus, we calculated that a sample size

	Placebo (n=200)	Activated charcoal (n=201)
Age (years)	24·1 (8·7)	23·5 (9·6)
Height (cm)	156 (8·1)	154 (8·5)
Weight (kg)	52·2 (8·6)	50·1 (9·3)
Time after ingestion (h)	10·4 (6·3)	9·4 (6·3)
Number of seeds	4 (2–5)	3 (2–5)
Respiratory rate (breaths per min)	21 (18–23)	20 (18–22)
Systolic blood pressure (mm Hg)	115 (13)	116 (15)
Diastolic blood pressure (mm Hg)	75 (8·1)	75 (9·3)
Serum potassium (mmol/L)	4·15 (0·51)	4·12 (0·46)
Number presenting with life-threatening arrhythmias (%)	10 (5%)	7 (4%)
Male sex (%)	111 (56%)	87 (43%)
Number (%) of direct admissions*	54 (27%)	60 (30%)

Data are mean (SD) or median (IQR) unless stated otherwise. *Patients presenting directly to the study hospital, rather than those who were referred from a rural or secondary care hospital.

Table 1: **Patients' baseline characteristics**

of 376 was needed to give the study 80% power at α=0·05. We used SPSS (version 10) and did z tests to assess differences between percentages and difference between means. For quantitative variables that had skewed distributions, we used the Mann-Whitney U test. Analysis was by intention to treat.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between November, 2001, and June, 2002, 422 patients were admitted to Kurunegala Teaching Hospital with yellow oleander poisoning. Of these, 401 fulfilled entry criteria and were randomly allocated to a treatment group (figure). 26 (16 in the treatment group) patients discharged themselves within 72 h of admission; all had normal heart rates at the time they left hospital, and 23 (16 in the treatment group) reported being well when contacted at their homes within 1 week of leaving hospital.

Baseline characteristics are shown in table 1. Although the median numbers of seeds ingested in the placebo and treatment group was four and three, respectively, there was much variation in the number of seeds ingested. Those who died in the placebo group took two to eight seeds and those who died in the treatment group took two to twelve seeds, data which do not differ greatly from those for patients who survived (placebo group one to ten, treatment group two to ten). The slight difference in sex balance between the two groups is unlikely to have had an effect on cardiac complications of poisoning in such a young population. Furthermore, results of multivariate analyses adjusted for differences in baseline characteristics showed no difference in primary and secondary endpoints.

Fewer patients died in the treatment group than did on placebo (five [2·5%] *vs* 16 [8%]; p=0·025). We also noted differences in favour of the treatment group for all secondary endpoints other than the number of days in hospital (table 2).

Of the 21 deaths, 14 occurred within 24 h of admission, and another four took place in the next 24 h. 11 patients (three in the treatment group) had sudden cardiac events, such as ventricular fibrillation or asystole, that led to death, preceded by sinus rhythm, sinus bradycardia, or first-degree heart block at the last monitoring. None of these patients had second-degree or third-degree heart block after admission. Ten patients (two in the treatment group) who died had heart block (four had second-degree Mobitz type-I; three second-degree Mobitz type-II heart block; three third-degree heart block). The six patients with third-degree heart block or second-degree Mobitz type-II heart block had temporary cardiac pacing. Two patients with third-degree heart block were given anti-digoxin antibody Fab fragments.

At admission, the frequency of life-threatening cardiac arrhythmias between the treatment group and the placebo group was much the same (table 1). However, 24 h after randomisation, the frequency of life-threatening cardiac arrhythmias rose substantially in the placebo group, but had decreased in the treatment group (table 2).

27 patients who had severe nausea after starting the trial were given 10 mg of intravenous metoclopramide. The most frequent adverse effects of treatment with multiple doses of activated charcoal were diarrhoea and abdominal discomfort. Three patients had diarrhoea and 13 complained of abdominal discomfort during treatment. These side-effects were transient and resolved without any specific treatment. Although most patients found the charcoal unpalatable, none refused to take it. Three patients were given activated charcoal via a nasogastric tube because they were too ill to take it orally. None developed aspiration or intestinal obstruction.

Discussion

Treatment of patients who had yellow oleander poisoning with multiple doses of activated charcoal over 72 h reduced the death rate by 69%. Thus, only 18 patients had to be treated with activated charcoal after yellow oleander poisoning to prevent one death (number needed to treat=18 patients [95% CI 10–90]). The treatment also significantly reduced the number of patients who needed admission to intensive care, insertion of a temporary pacemaker, or antidigoxin antibody Fab fragments. The dose and number of boluses of atropine needed to treat

	Placebo (n=200)	Activated charcoal (n=201)	Difference (95% CI)	p
Primary endpoint				
Death	16 (8%)	5 (3%)	5·5 (0·6–10·3)	0·025
Secondary endpoints				
ICU admission	16 (8%)	5 (3%)	5·5 (0·6–10·3)	0·025
Patients given anti-digoxin antibody Fab fragments	7 (4%)	0	3·5 (0·6–6·6)	0·022
Cardiac pacing	11 (6%)	1 (<1%)	5·0 (1·2–8·8)	0·008
Life-threatening arrhythmias at 24 h	14/190 (7%)	3/195 (2%)	5·9 (1·7–10·6)	0·010
Mean dose of atropine in mg (SD)	5·2 (3·8)	3·6 (2·7)	1·6 (0·9–2·2)	<0·0001
Boluses of atropine (median [range])	2 (1–12)	1 (1–6)	0 (0·0–1·0)	<0·0001*
Time in hospital (days) (median [range])	3 (0·5–10)	3 (0·25–24)	0 (0·0–0·0)	0·902*

*p values calculated with Mann-Whitney U test.

Table 2: **Primary and secondary endpoints**

bradycardia were also reduced in the treatment group. However, there was no difference in the number of days spent in hospital.

The need for early treatment to prevent death after poisoning with yellow oleander is emphasised by the fact that 18 of 21 deaths occurred within 48 h of admission. Furthermore, 11 of these patients had sudden cardiac events that were not preceded by arrhythmias suggestive of the need for temporary cardiac pacing or antidigoxin antibody Fab fragments. All patients in our study were treated within 24 h of poisoning.

It is noteworthy that in yellow oleander poisoning, activated charcoal acts not only through prevention of the initial absorption of the toxic glycosides, but also by preventing toxin reabsorption after intestinal secretion from the systemic circulation. The effectiveness of activated charcoal in treatment in reducing the severity of yellow oleander poisoning is lent support by the fact that death in the treatment group was less common both in patients with sudden cardiac events and in those who had warning arrhythmias. Furthermore, multiple-dose activated charcoal was also associated with a reduction in the number of patients who developed life-threatening cardiac arrhythmias 12–24 h after admission, and this trend continued in the next 24 h.

We did not design this trial as a double-blind study, because it would not have been possible to conceal treatment allocation from patients in an open medical ward in the absence of a placebo identical in appearance to activated charcoal. However, the cleaning of patients after treatment with activated charcoal helped to conceal treatment allocation from physicians who did patient assessment. Furthermore, to avoid the risk of bias in patient assessment of treatment, endpoint measures were objective, and physicians followed the same strict protocol for the management of yellow oleander poisoning for every patient. Despite this potential unblinding, we noted a significant reduction in a hard endpoint—namely, death. Additionally, the amount of intervention was higher in the placebo group, indicating that it is extremely unlikely that the beneficial effect of multiple-dose activated charcoal could have been attributable to patients' knowledge of their treatment allocation, or bias on the part of the clinicians who managed these patients. A limitation of the study was that once patients were transferred to intensive care, decisions about treatment were made by physicians there, not trial physicians.

In Sri Lanka, patients from rural areas who need temporary cardiac pacing for life-threatening bradyarrhythmias after yellow oleander poisoning are usually transferred to a tertiary care centre. Such transfers are costly and have resulted in deaths during transit. A single treatment (1200 mg) of anti-digoxin antibody Fab fragments costs 254 000 Sri Lankan rupee (US$2650), and some patients need more than one dose. Thus, there is a pressing need for an inexpensive and effective treatment that can be used in non-urban hospitals. The cost of treatment with 12 doses of activated charcoal was about $6.70 per patient.

Multiple-dose activated charcoal is safe and effective in reducing death and life-threatening cardiac arrhythmias after yellow oleander poisoning, and should be given to all patients who have ingested yellow oleander seeds. Expensive interventions such as cardiac pacing and antidigoxin antibody Fab fragments could be reserved for patients who have dangerous arrhythmias at the time of presentation with poisoning (there were 17 such cases in our study), or those who develop arrhythmias despite treatment with activated charcoal.

Our results suggest that multiple-dose activated charcoal could also be of use in the treatment of patients who have been poisoned with other cardiac glycosides. A previous study in 23 patients[12] and a few anecdotal reports[13] have shown that charcoal increases the clearance rate of digoxin, and experimental evidence shows much the same effect on digitoxin clearance.[13]

Contributors

H A de Silva, M M D Fonseka, C D Ranasinha, S B Gunatilake, and H J de Silva designed and supervised the study, and wrote the manuscript. A Pathmeswaran analysed and interpreted data and helped write the manuscript. D G S Alahakone and G A Ratnatilake had overall responsibility for care of the patients. D G Lalloo supervised study design and revised the paper. J K Aronson suggested the study, supervised the study design, and revised the paper.

Conflict of interest statement

None declared.

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