

Anti-digoxin Fab fragments in cardiotoxicity induced by ingestion of yellow oleander: a randomised controlled trial

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Summary

Background Severe cardiac glycoside cardiotoxicity after ingestion of yellow oleander seeds is an important problem in rural areas of Sri Lanka. Currently, patients must be transferred to the capital for temporary cardiac pacing. We did a randomised controlled trial to investigate whether anti-digoxin Fab could reverse serious oleander-induced arrhythmias.

Methods After a preliminary dose-finding study, 66 patients who presented to hospital with a serious cardiac arrhythmia were randomised to receive either 1200 mg of anti-digoxin Fab or a saline placebo. A 12-lead electrocardiogram, 3 min rhythm strip, and blood sample for measurement of electrolytes and cardiac glycosides were taken before treatment and at 12 timepoints thereafter.

Findings 34 patients received anti-digoxin Fab and 32 received placebo. The presenting arrhythmia had resolved completely after 2 h in 15 antibody-treated patients and two controls ($p < 0.001$); 24 and five patients, respectively, were in sinus rhythm at 8 h ($p < 0.001$). Kaplan-Meier analysis of time to first reversal showed a significant response to anti-digoxin Fab. The heart rate increased in cases, from 49.1 per min at baseline to 66.8 at 2 h, but not in controls (50.6 per min at baseline to 51.5; $p < 0.001$). Mean serum potassium concentrations decreased from 4.9 mmol/L to 4.1 mmol/L at 2 h in cases; no such decrease occurred in controls.

Interpretation Anti-digoxin Fab fragments are a safe and effective treatment for serious cardiac arrhythmias induced by yellow oleander. Their use in small rural hospitals in Sri Lanka should minimise costly transfer of patients and reduce the numbers of deaths; however, further study will be required to confirm this reduction.

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Introduction

Ingestion of sufficient quantities of any part of the common (*Nerium oleander*) or yellow (*Thevetia peruviana*) oleander can produce a syndrome similar to digoxin poisoning.^{1,2} Accidental oleander poisoning occurs throughout the tropics and subtropics: 303 cases were reported in Texas during 1994¹ and oleander caused 27% of the paediatric plant poisonings in Australia during 1972–78.³ Fatal poisonings have been reported from across the world.^{4–10}

Deliberate self-poisoning with yellow oleander is a recent phenomenon in Sri Lanka. The first cases occurred in Jaffna between 1981 and 1983, after publicity surrounding the suicide of two girls who ingested oleander seeds.¹¹ In some areas, 40% of self-poisoning cases are now linked to oleander seeds, particularly in teenagers, with an annual incidence of more than 150 per 100 000.^{12,13} This epidemic imposes a substantial burden on the Sri Lankan health services.

The most severely affected patients are transferred to the coronary-care unit (CCU) of the Cardiology Institute in Colombo for cardiac pacing.¹² The transfer is long and hazardous, commonly taking more than 4 h. Patients die before and during transfer to the CCU; some die soon after arrival. Standard therapy in the CCU is to observe patients and then insert a pacemaker in those with marked arrhythmias.

There is a pressing need for a treatment that can be used in small peripheral hospitals. Polyclonal anti-digoxin Fab fragments are recommended for the treatment of life-threatening cardiac glycoside poisoning.^{14,15} Although this recommendation for digoxin poisoning is based on a large open-label multicentre study,¹⁶ the use of these fragments in poisonings by other glycosides is based solely on case reports, commonly with poor results.^{17–22} We assessed the efficacy and safety of anti-digoxin Fab fragments in patients with cardiac arrhythmias induced by yellow oleander.

Methods

Patients

The study was designed in two parts: a dose-finding study to identify an effective dose of anti-digoxin Fab; and a randomised, double-blind, placebo-controlled trial of this dose in the treatment of oleander-induced cardiotoxicity. The trial was reviewed by the ethics review committee of Colombo University's Faculty of Medicine and done with the approval of the Sri Lankan Health Authorities.

Patients admitted to the Cardiology Institute with a history of yellow-oleander ingestion were included in the study if they showed electrocardiographic (ECG) evidence of sinus bradycardia (<40 per min), sinus arrest or block, atrial tachyarrhythmias, or second or third degree atrioventricular block. Patients were excluded if they had hypotension (systolic blood pressure <80 mm Hg), bradycardia, or ventricular tachycardia together with signs of shock. Excluded patients were given anti-digoxin Fab immediately on a compassionate basis.

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The study was explained to each patient and written informed consent obtained in Sinhalese or Tamil. Those patients not willing to join the study were offered standard therapy.

The duty cardiology medical officer inserted a temporary cardiac pacemaker in patients who had complete heart block; Mobitz type-II second-degree block; sinus bradycardia with heart rate of less than 40 beats/min; sinus arrest or block with sinus pauses longer than 2 s; or ST-segment depression greater than 2 mm at a point 80 ms from the J-point. These criteria, derived by the institute's cardiologists with their extensive experience of oleander poisoning, define patients at high risk of deterioration. However, to find out whether anti-digoxin Fab is effective without pacing is important, since this is the clinical situation throughout northern Sri Lanka where most patients present, and where a new therapy is urgently required. The pacemakers in this study were therefore set to be activated only when the R-R interval exceeded 2 s. If any patient deteriorated, pacing was increased to 70 per min and the patient was given open-label anti-digoxin Fab (DigiTab; Protherics, Macclesfield, UK)—a sterile, affinity purified, and lyophilised Fab product derived from the blood of sheep immunised with a digoxin conjugate.

Clinical history and results of physical examination were recorded on standard forms. Before treatment, a blood sample was taken and a 12-lead ECG and 3 min rhythm strip recorded to confirm the presence of an arrhythmia fulfilling the trial's criteria.

Dose-finding study

The first 16 patients recruited into the study received 400, 800, 1200, or 1600 mg of digoxin-specific Fab, administered by intravenous infusion over 20 min in 200 mL saline. Patients were closely observed for signs suggestive of an imminent anaphylactoid reaction: these patients were treated immediately with epinephrine (0.5 mg), hydrocortisone (100 mg), and chlorpheniramine (10 mg).

Patients were monitored with a 12-lead ECG machine; recordings were taken 5 min before (baseline) and at 10, 20, 30, 45, and 60 min, and 2, 4, 8, 12, 24, 36, and 48 h after treatment. Blood pressure and cardiac and respiratory rates were also measured at these times. Blood was withdrawn via indwelling intravenous catheters at all timepoints except at 45 min. Patients were discharged at 48 h if clinically well and in normal sinus rhythm.

A full biochemical screening was done at Homerton Hospital, London, by means of standard automated techniques. The oleander-derived cardiac glycosides in this baseline blood sample were measured by cross-reactivity with a digoxin polarisation fluoroimmunoassay (Innofluor-Digoxin assay system, Oxix International, Portland, OR, USA) on an TDx machine (Abbot, Chicago, IL, USA). Administration of Fab therapy interfered with this assay, preventing measurement of free versus bound cross-reactive digoxin-like substances.

The trial

A trial size of 80 patients was calculated to achieve a power of 95% and a type-I error of 1%, assuming that the specific Fab fragments would be 50% effective and that 10% of patients would show spontaneous reversion within 2 h. The Sri Lankan ethics committee requested an interim analysis after 60 patients had been treated.

On recruitment into the trial, patients were randomly assigned to receive either anti-digoxin Fab or saline. Randomisation was done in the UK by someone not associated with the care or assessment of the patients by means of a random number table in blocks of 40.²³ Allocations were concealed in sequentially numbered, opaque, sealed envelopes lined with carbon paper. The patient's name and study number and the date were written on the envelope before it was opened. One investigator (ME or SJ) prepared the infusion in a separate area away from the other investigators and CCU staff—this investigator had no role in the patient's assessment or clinical management. To confirm correct randomisation, the 30 min serum samples were assayed blind for Fab fragments using a radioimmunoassay.

Outcome

Outcome was assessed masked by a senior ECG technician in the UK. He examined the patients' ECGs taken at baseline, 2 h, and 8 h to assess whether at 2 h the original arrhythmia had been reversed and whether at 8 h there was sinus rhythm at a rate of more than 44 bpm. The 3 min rhythm strip was inspected and the treatment deemed to have failed if a single abnormal complex was found.

Statistical analysis

Final data analyses were done with SAS (version 6.12), and checked by SPSS (version 7.5). Treatment group comparisons were deemed significant at or below 5% alpha level with two-tailed tests. Kaplan-Meier estimates were constructed to estimate the cumulative incidence over time. The generalised Wilcoxon test was used to test the overall difference between treatments for all observation times. Time-to-event data were right-censored if the event did not occur during the study, follow-up period, either because of discontinuation or because the patient did not have an event by 48 h. The χ^2 test and Fisher's exact test were used inferentially to analyse categorical data. Student *t* test and univariate ANOVA were used for continuous data (heart rate and electrolyte concentrations).

Results

Dose-finding study

Four groups of four consecutive patients fulfilling the entry criteria were recruited to the study. We expected the clinical severity and serum cardiac glycoside concentrations of the patients to vary substantially within these small groups. However, a dose-finding study was deemed essential as a basis for choosing an appropriate dose for the controlled trial and for identifying times at which to measure outcome.

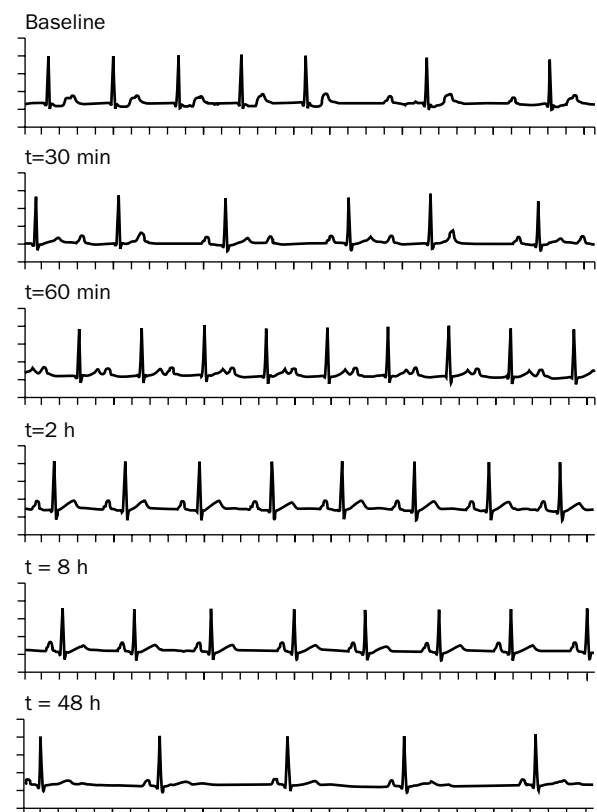


Figure 1: Resolution of atrioventricular conduction block after treatment with 1200 mg of digoxin-specific Fab fragments

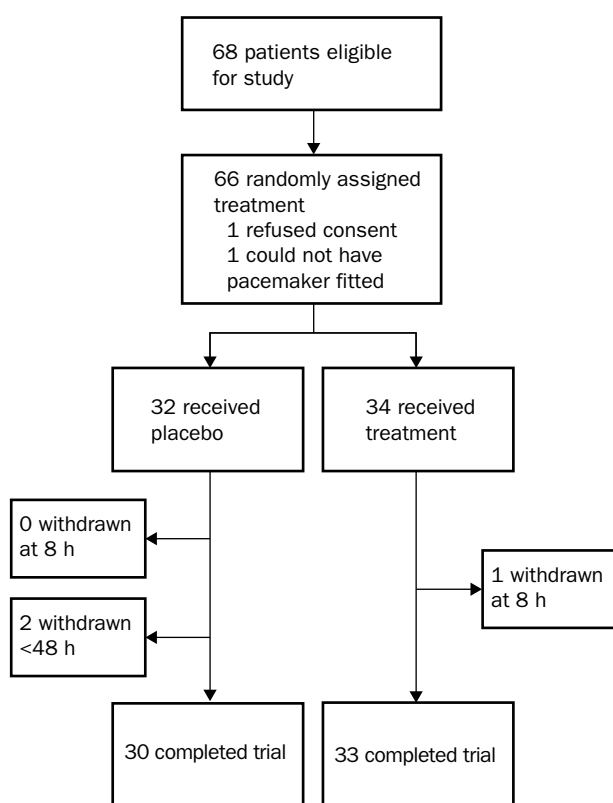


Figure 2: Trial profile

There was a good clinical response in all patients who received 1200 mg of anti-digoxin Fab and three of four patients who received 800 or 1600 mg, compared with only one of those who received 400 mg. 1200 mg was the dose chosen for the randomised controlled trial; the ECG of one patient who received 1200 mg is given in figure 1. This patient, a 20-year-old man, presented in intermittent third-degree atrioventricular block with serum cardiac glycoside concentration of 3.35 nmol/L and potassium of 5.8 mmol/L. His cardiac rhythm had improved to first-degree atrioventricular block 1 h after treatment with DigiTab. By 2 h he was in regular sinus rhythm in which he remained for 48 h. His serum potassium had fallen to 4.4 mmol/L by 2 h and was 4.1 mmol/L at discharge. The timecourse of response in these patients, and previously reported patients,^{14,24} suggested that 2 h and 8 h would be good primary endpoints. A full biochemical screening was done at all 13 timepoints. Differences over time were noted only for K⁺ and Mg²⁺. We therefore decided to measure only K⁺ and Mg²⁺ in the trial patients at regular intervals until 4 h, and then at 48 h. The other biochemical assays were done at baseline and 48 h for each patient.

The Fab was initially distributed into a volume similar to that of the vascular compartment (71 mL per kg; SD 30), and then gradually redistributed into the interstitial fluid with a half-life of 64 min (SD 25). The distribution volume at steady state was similar to the extracellular fluid volume (268 mL per kg; 91). The elimination half-life was 16.0 h (5.2) and systemic clearance 24 mL per kg every hour (5).

The trial

Between April 19 and Oct 20, 1997, 205 patients admitted to the Colombo CCU with oleander poisoning were reviewed by the study physicians. 68 fulfilled the

entry criteria (figure 2). One patient could not be entered into the trial because a pacemaker could not be fitted and one patient refused consent. All received the intervention to which they were randomised. No patient died during the study period and none was withdrawn after randomisation to be treated with anti-digoxin Fab on compassionate grounds. The study team did not take blood samples from one patient in the treatment group at 8 h. Two controls discharged themselves before 48 h.

The trial was stopped after 66 patients had been recruited because the interim analysis, initiated after 60 patients, provided evidence that anti-digoxin Fab was effective. Six patients were recruited during the analysis.

The two groups were similar at baseline (table). The commonest symptoms were persistent vomiting, diarrhoea, weakness, dizziness, and abdominal pain. Most patients presented with sinus bradycardia, exit block or arrest, and/or atrioventricular conduction block. Six of 32 controls and six of 34 cases had heart rates of less than 40 per min; four of 32 controls and six of 34 cases had third-degree atrioventricular block.

The arrhythmias had completely resolved by 2 h in two of 32 controls and 15 of 34 cases ($p < 0.001$; Fisher's exact test). 8 h after treatment, five of 32 controls and 24 of 33 cases had reverted to sinus rhythm with heart rates greater than 44 beats/min ($p < 0.001$). Kaplan-Meier analysis of the time to first reversal of arrhythmia showed that treated patients reverted to sinus rhythm earlier than control patients ($p < 0.001$; Wilcoxon score $p = 0.0003$; figure 3). The time to 50% reversal was 3 h for active treatment and 30 h for saline treatment.

Seven patients who received anti-digoxin Fab and two patients who received saline, who had initially responded, developed a recurrent arrhythmia. Three other treated patients developed a sinus bradycardia of 40–44 per min at 48 h. All were observed without further treatment until the arrhythmia had resolved. One of the cases developed recurrent symptoms of oleander poisoning with vomiting, abdominal pain, and diarrhoea. None of the other patients had recurring symptoms.

The cardiac rate increased rapidly in patients who received anti-digoxin Fab (figure 4). The mean cardiac rate 5 min before treatment was 50 (SD 13) and 49 (11) in the control and treatment groups, respectively. In the

Characteristics	Placebo (n=32)	Anti-digoxin Fab (n=34)
Sex		
F	19	13
M	13	21
Age (years)	26.9 (14.1)	25.0 (10.0)
Weight (kg)	48.2 (8.9)	46.6 (8.1)
Height (cm)	159.2 (8.1)	162 (8.7)
Number of seeds ingested	4.8 (3.1)	4.4 (3.0)
Vomiting (%)	100	100
Diarrhoea (%)	81	79
Abdominal pain (%)	53	65
Time from ingestion to CCU admission (h)	16.7 (11.4)	18.2 (10.9)
Time from CCU admission to start of therapy (h)	15.6 (24.8)	11.0 (8.8)
Pulse rate (per min)	50 (13)	50 (13)
Systolic blood pressure (mm Hg)	104 (10)	108 (13)
Diastolic blood pressure (mm Hg)	63 (14)	59 (11)
Respiratory rate (per min)	23 (3)	24 (3)
Oral temperature (°C)	37.1 (0.3)	37.0 (0.3)
Serum digoxin-like substances (nmol/L)	2.8 (0.7)	2.9 (0.7)
Serum potassium (mmol/L)	4.7 (1.0)	4.9 (1.1)
Serum magnesium (mmol/L)	0.78 (0.12)	0.77 (0.15)

All data are mean (SD), unless where indicated.

Characteristics of 66 trial patients at baseline

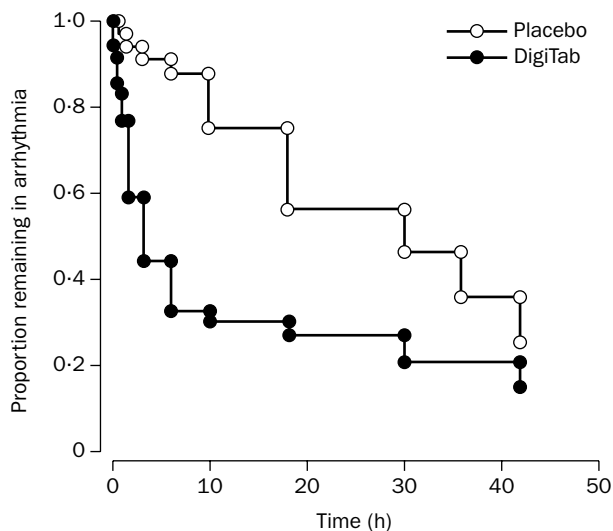


Figure 3: **Kaplan-Meier analysis of first reversal to sinus rhythm**

treatment group, this had increased to 67 (19) at 2 h and 69 (17) at 8 h compared with 51 (13) and 54 (14) in the control group ($p < 0.001$ at both timepoints). The increase in heart rate over time in the treatment group was significant (ANOVA, $p < 0.001$).

Serum K^+ concentrations had decreased significantly by 2 h in patients receiving anti-digoxin Fab (figure 4). At this time, there was also a significant difference in mean serum K^+ between cases (4.1 mmol/L; SD 0.7) and control patients (4.7 mmol/L; SD 1.0). By 48 h, the serum concentrations had fallen in both groups to 4.0 mmol/L (SD 0.4). Serum Mg^{2+} concentration fell in both groups soon after treatment (data not shown) but was substantially lower in cases than in controls at 4 h and 48 h. There were no other significant differences in the biochemical screening between the two groups or between samples at baseline and discharge for each group.

Compassionate treatment

Seven patients received anti-digoxin Fab outside the trials on compassionate grounds. Four women and three men, mean age 23 years, had ingested 2–15 seeds (mean seven). Four presented with shock and systolic blood pressure of less than 80 mm Hg. Two presented with decreased consciousness but a stable cardiovascular system; these are atypical presentations of oleander poisoning, although both patients had denied taking anything other than oleander seeds. One patient had third-degree atrioventricular block; temporary cardiac pacing was indicated but, because of a nursing strike, the necessary equipment was unavailable and he was treated with open-label Fab. A temporary pacemaker was inserted in six patients. Five patients received 800 mg of anti-digoxin Fab, one 1600 mg and one 3200 mg. Four patients recovered fully; three (including the two with atypical presentations) died following cardiorespiratory arrest.

Blood samples could not be taken from one of the patients who died. In the other six, digoxin-like substance concentrations varied from 1.33 to 4.62 (mean 3.30) nmol/L. Both fatalities had concentrations of less than 2.1 nmol/L whereas three patients who survived had concentrations greater than 4.0 nmol/L; the fourth had a blood concentration of 3.4 mmol/L. The patients who died had either severe hyperkalaemia (8.1 mmol/L), or hypokalaemia (2.8 mmol/L) and hypomagnesaemia

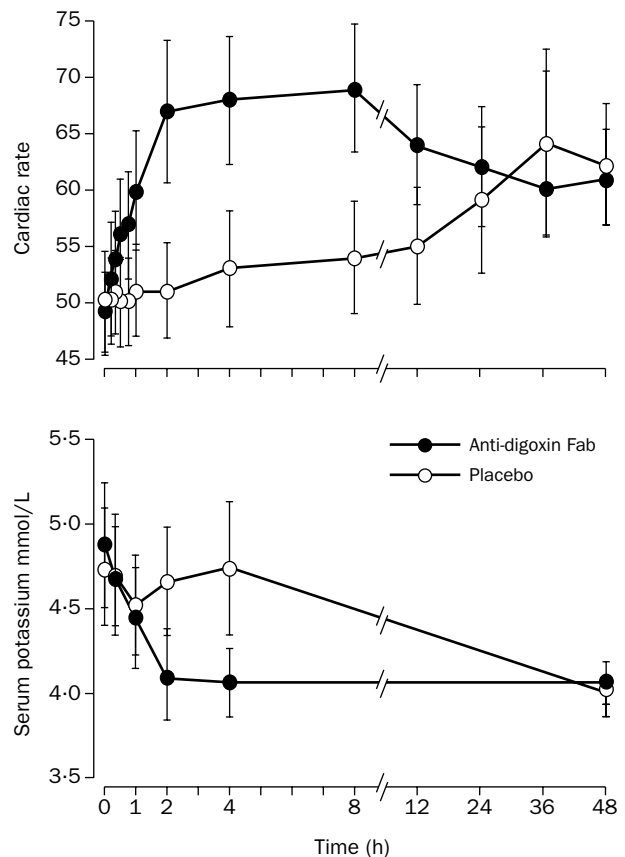


Figure 4: **Cardiac rate response to therapy and changes in serum potassium concentrations after therapy**

Bars are 95% CIs.

(0.47 mmol/L). Two of three responsive patients had moderate hyperkalaemia and/or hypomagnesaemia.

Safety data

Every patient was observed carefully by one of the study physicians for the first signs of an anaphylactoid reaction during the first 2 h after therapy. Patients showing such signs were immediately treated with epinephrine, chlorpheniramine, and hydrocortisone.

Of 57 patients who received anti-digoxin Fab during the study (34 in the trial, 16 in the dosing study, seven compassionate), 13 (23%) had reactions. Of 11 who began to itch, nine went on to develop urticarial rashes ranging from one to five papules (six patients) to widespread rashes over the trunk and arms (three patients). Two patients developed bronchospasm and a third developed mild angio-oedema of the lip. Of three patients with a history of atopy, one asthmatic patient developed itching of the head, chest, and arms after treatment. The reactions all responded promptly to therapy.

Discussion

The oleanders are common causes of accidental poisoning worldwide. Their leaves and seeds are eaten intentionally in the USA, Germany, and Australia.^{1,2} However, it is in Sri Lanka and south India that deliberate self-poisoning with yellow oleander has become an important problem, resulting in hundreds of deaths each year.¹² In certain areas of Sri Lanka, ingestion of yellow oleander has become the method of choice for self-harm, particularly among women and children.

Currently, about 10% of patients poisoned by yellow oleander in Sri Lanka die after reaching hospital.¹² Most of these previously healthy young people present with bradycardia which, initially, may be palliated with atropine. However, this treatment soon becomes less effective and patients must be transferred rapidly to the capital's CCU. These transfers are hazardous and expensive, and some patients will die during the 4 h transfer. A safe treatment that can be used in peripheral hospitals is urgently required.

Three case reports¹⁷⁻¹⁹ and one animal study²⁵ have suggested that anti-digoxin Fab fragments reverse common oleander-induced cardiotoxicity. We have shown in this randomised controlled trial that anti-digoxin Fab rapidly and safely reverses yellow oleander-induced arrhythmias, restores sinus rhythm, and rapidly corrects bradycardia and hyperkalaemia.

The dose of Fab fragments required for digoxin poisoning can be calculated from the serum digoxin concentration and/or known dose of digoxin.¹⁴ This calculation is impossible in oleander poisoning because digoxin assays are at best semiquantitative for other digoxin-like substances.^{6,20} An empirical dose of 400 mg of Fab fragments is recommended for non-digoxin cardiac-glycoside poisoning in the USA.¹⁵ Although our dose-finding study was small, we did not find such a dose to be clinically effective and would recommend an initial dose of at least 800 mg. Lower affinity of digoxin-specific Fab for the non-digoxin cardiac glycosides in oleanders probably explains the greater quantity of Fab required.

23% of patients had an adverse response to therapy. This proportion is much higher than that reported from either the original multicentre trials or post-marketing survey,^{16,26} and may be because one study physician always spent the first 2 h after treatment with each patient looking carefully and specifically for the first signs of a reaction. These signs were noted and immediately treated. Such a level of examination is unlikely in the other studies. In addition, larger doses of Fab were used for oleander poisoning than in other studies.

Yellow oleander seeds are usually eaten whole or in chunks in Sri Lanka. Fragments of seeds can be seen in the stomach contents of patients who present early to hospital. Continued absorption of cardiac glycosides from kernels remaining in the gastrointestinal tract explains the recurrent arrhythmias seen in some patients and also the long delay between ingestion and the appearance of serious arrhythmias in a few patients (eg, 92 h in one of our patients).

The pharmacokinetics are similar to those reported for ovine Fab, which is used in treatment of digoxin intoxication.^{27,28} The short half-life of anti-digoxin Fab (16 h) might have allowed recurrent cardiac arrhythmias in some patients. A slower infusion rate may reduce the amount of unbound Fab excreted in the urine, increase the half-life^{27,28} and might also reduce the incidence of infusion-related anaphylactoid reactions.

Activated charcoal is not used routinely in Sri Lanka since there is no evidence that this treatment improves clinical outcome.²⁹ However, multiple doses of activated charcoal can reduce plasma levels of digoxin by decreasing absorption and later by interrupting its enterohepatic circulation.³⁰ Therefore, a possible role in oleander poisoning should be investigated. If effective, activated charcoal could reduce the need for anti-digoxin Fab.

Hyperkalaemia is a well-recognised complication of cardiac glycoside poisoning in healthy people.^{20,31-34} This study shows that anti-digoxin Fab can reverse the hyperkalaemia. Displacement by Fab of the cardiac glycosides from the Na⁺/K⁺ ATPase and restoration of pump activity could account for this effect.

There were no deaths among the patients recruited to this trial. Most deaths occur before patients get to the CCU or in the first couple of hours after their arrival. During the first 2 months of our study, at least two patients died en route and two died immediately after arrival. Six patients presented in poor condition and were treated with anti-digoxin Fab and inotropes outside the study; of these, three died. Blood samples, which could be taken from only two of these three patients, showed electrolyte abnormalities rather than particularly high cardiac glycoside concentrations. Further studies will be required to look at the importance of pre-existing electrolyte disturbances.

This study did not look at mortality. When we designed the study, we were unclear whether anti-digoxin antibodies would cross-react sufficiently to be clinically effective as a treatment for oleander poisoning. It was considered prudent to address first the efficacy against the common arrhythmias and hyperkalaemia. However, since deaths following oleander ingestion are associated with cardiac arrhythmias and hyperkalaemia, it seems probable that their reversal will reduce mortality. Other therapeutic antibodies—eg, those effective against tetanus toxin, rabies virus, and animal venoms, are produced in some less-developed countries at the reasonable cost of US\$1.00 per treatment. Now that the Sri Lankan Ministry of Health is considering supplying anti-digoxin Fab to the northern hospitals, it will be essential that the introduction of this treatment is monitored to find out whether early treatment of cardiac arrhythmias in oleander poisoning does, in fact, save lives.

Contributors

The original hypothesis was generated by DA Warrell and M H R Sheriff. M Eddleston designed and set up the study, recruited the first 50 patients, analysed the data, and wrote the first draft. S Rajapakse, Rajakanthan, and S Jayalath recruited and treated the patients. W Santharaj and P N Thenabadu had overall responsibility for the clinical care of the patients. L Sjöström coordinated the study in the UK, organised the biochemistry, and helped analyse the data. M H R Sheriff and D A Warrell were the primary investigators and supervised the study design and implementation. All investigators were involved in the study design and reviewing of the paper.

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