In C32 cells, the fall in CD36 was associated with a corresponding decrease in cytoadherence of parasitised erythrocytes (figure 1). Ritonavir treatment resulted in a mean decrease in cytoadherence of 41% (SD 10·97, p=0·0017), and saquinavir resulted in mean decrease of 52% (28·8, p=0·0002). Nevirapine, which did not affect CD36 surface concentrations (mean decrease 7% [SD 22·5, p=0·73]), had no significant effect on cytoadherence of parasitised erythrocyte (mean decrease –12·3% [24·6, p=0·29].

Phagocytosis of parasitised erythrocytes by macrophages represents an essential first line of defence against malaria. We have previously shown a role for CD36 in the non-opsonic uptake of parasitised erythrocytes by macrophages, a potentially important mechanism of malaria clearance in non-immune individuals.[4] The effect of HIV-1 infection or antiretrovirals on macrophage function as it relates to clearance of malaria has not been addressed.

Figure 2 shows that human macrophages exposed to clinically achievable concentrations of ritonavir or saquinavir significantly decreased surface values of CD36 (mean 43% [SD 13·4, p=0·0006] and 41% [7·8, p=0·0099], respectively), compared with nevirapine-treated (7% [13·4, p=0·45]) or control macrophages. Both ritonavir-treated and saquinavir-treated macrophages phagocytosed about 50–60% fewer parasites than controls (mean decrease for ritonavir-treated macrophages compared with control 50% [SD 23·6, p=0·0002]; and for saquinavir-treated macrophages compared with control was 58% [14·8, p=0·0002]). Treatment of macrophages with nevirapine had no significant effect on the uptake of parasitised erythrocytes (mean decrease was 12% [8·2], p=0·2082).

Protease inhibitor-induced defects in phagocytosis were reversible with the use of peroxisome proliferator-activated receptor-γ agonists, including thiazolidinedione drugs such as troglitazone, which upregulates CD36 in macrophages (figure 2).[4] Troglitazone treatment of saquinavir-treated cells rescued the defects in CD36 surface concentrations and phagocytosis to control values. Troglitazone plus saquinavir treatment resulted in a mean increase of 52% (SD 33·4) in CD36 surface values compared with saquinavir-treated cells alone (p=0·0007), and a 41% (5·6) increase in phagocytosis compared with saquinavir alone (p=0·0003).

Little is known about the effect of antiretrovirals on the clinical course and outcome of malaria infections. We show that some antiretroviral drugs, ritonavir and saquinavir, but not nevirapine, induced CD36 deficiency, resulting in decreased CD36-mediated cytoadherence and phagocytosis of parasitised erythrocytes. Since protease inhibitors induce CD36 deficiency in some patients treated with antiretrovirals,[5] our results suggest that these drugs might also modify malaria sequestration in vivo. If interactions between CD36 and parasitised erythrocytes contribute to malaria pathophysiology as proposed by some investigators, antiretrovirals might positively affect outcome in co-infected individuals. If on the other hand, binding of parasitised erythrocytes to CD36 on endothelium in non-vital sites is protective against cerebral malaria, decreases in CD36-mediated sequestration in vivo might divert to receptors that are directly implicated in cerebral malaria, such as ICAM-1, and negatively affect clinical outcome. Similarly, if non-opsonic clearance mechanisms are important in the control of *P falciparum* malaria, particularly in non-immune individuals at greatest risk of severe malaria, antiretroviral-induced defects in phagocytic clearance might affect disease outcome. Collectively, these data suggest the potential for modifying host–parasite interactions in co-infected patients treated with antiretrovirals. However, these findings need to be further assessed in vivo.

Contributors

S Nathoo, L Serghides, and K C Kain conceived and designed the study, and wrote the report. S Nathoo and L Serghides did the experiments.

Conflict of interest statement

L Serghides and K C Kain hold a patent on intellectual property related partly to this investigation.

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Tropical Disease Unit, Division of Infectious Diseases, Department of Medicine, University Health Network–Toronto General Hospital and the University of Toronto, ON, Canada (S Nathoo MSc, L Serghides PhD, Prof K C Kain MD)

Correspondence to: Prof Kevin C Kain, Tropical Disease Unit, Toronto General Hospital, 200 Elizabeth Street, Toronto, ON, Canada M5G 2C4 (e-mail: kevin.kain@uhn.on.ca)

Deaths due to absence of an affordable antitoxin for plant poisoning

Michael Eddleston, Lalith Senarathna, Fahim Mohamed, Nick Buckley, Edmund Juszczak, M H Rezvi Sheriff, Ariaranee Ariaratnam, Senaka Rajapakse, David Warrell, K Rajakanthan

There is a severe shortage of affordable antivenoms and antitoxins in the developing world. An anti-digoxin antitoxin for oleander poisoning was introduced in Sri Lanka in July, 2001, but because of its cost, stocks ran out in July, 2002. We looked at the effect of its introduction and withdrawal on case fatality, and determined its cost-effectiveness. The antitoxin strikingly reduced the case fatality; its absence resulted in a three-fold rise in deaths. At the present price of US$2650 per course, every life saved cost $10 209 and every life year cost $248. Reduction of the antitoxin's price to $400 would reduce costs to $1137 per life gained; a further reduction to $103 would save money for every life gained. Treatments for poisoning and envenoming should be included in the present campaign to increase availability of affordable treatments in the developing world.

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Yellow oleander (*Thevetia peruviana*) seed self-poisoning is common in Sri Lanka.[1,2] Findings of a trial of digoxin-specific antibodies showed resolution of oleander-induced

dysrhythmias.[3] Before these results were published, patients were treated with atropine and transferred to a tertiary hospital for temporary cardiac pacing, with a case fatality of 5–10%.[1]

Digoxin-specific antibodies were purchased for use in four hospitals that admit most oleander patients. Criteria for their use were drawn up: third or second degree atrioventricular block, bradytachycardia syndrome, ventricular dysrhythmias, and concentration of potassium greater than 5·5 mmol/L.[3] Patients were first treated in July, 2001, with a subsequent decline in deaths and transfers reported by doctors. Unfortunately, because of their high cost, supplies were intermittent and finally, in July, 2002, stocks ran out. Thus, we looked at the effect of using the antitoxin for treatment of oleander poisoning.

Kurunegala Hospital, Sri Lanka, a tertiary hospital with a coronary care unit and facilities for cardiac pacing, receives transfers from secondary hospitals (including Anuradhapura and Polonnaruwa Hospitals). We traced patients admitted to Kurunegala Hospital with oleander poisoning by cross-checking hospital records, the coronary care unit pacing record book, and the poisoning admission register. Oleander poisoning has a typical presentation: only three of 351 patients suspected to have ingested oleander in one study had undetectable serum cardiac glycosides.[4] As part of a prospective study presently underway in the North Central Province of Sri Lanka, the outcome was recorded of patients who were admitted with a diagnosis of poisoning to Anuradhapura Hospital from March 31, 2002, to Oct 31, 2002, or Polonnaruwa Hospital from June 5, 2002, to Oct 31, 2002. Availability of antitoxin (DigiFab, Protherics, TN, USA) was determined by review of pharmacy and ward stock books.

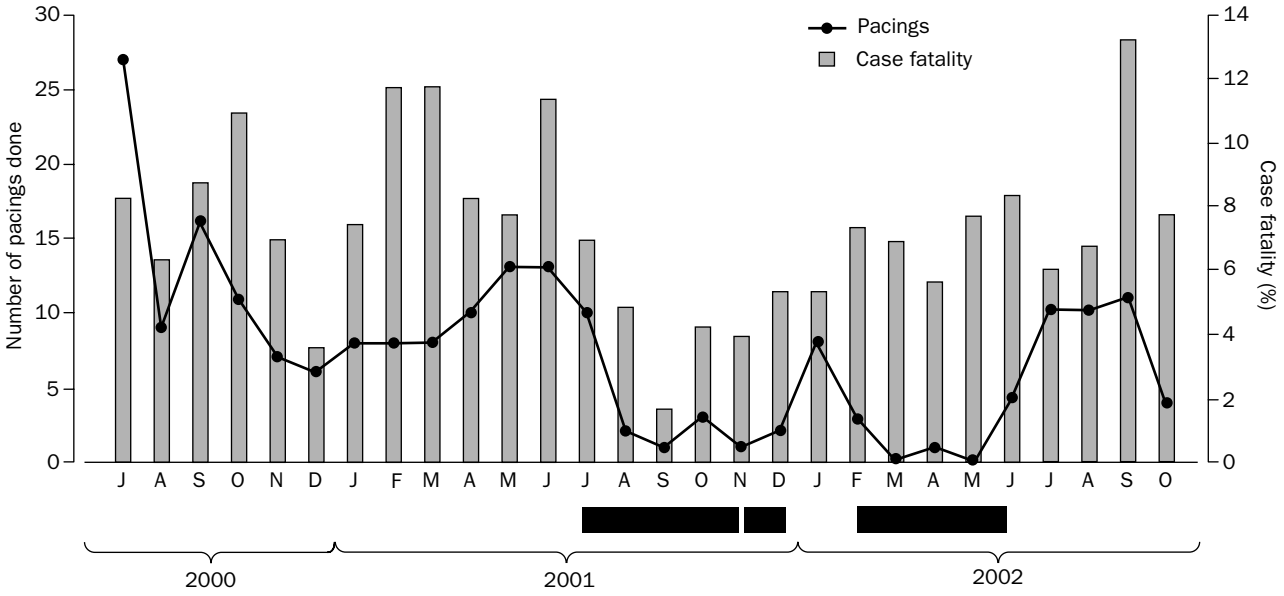
The effect of antitoxin introduction was studied retrospectively in Kurunegala. During the 12 months before introduction of the antitoxin (July 1, 2000, to June 30, 2001; figure), 1217 patients were admitted for oleander poisoning (101 per month). 136 (11·2%) needed temporary pacing. 105 (8·6%) patients died (35 after receiving a pacemaker). During the next 5 months (July 1, 2001, to Nov 30, 2001), when antitoxin became available in Kurunegala and the two referring hospitals, fewer patients were treated in Kurunegala (78 admissions per month). Only nine (2·4%) of 381 patients needed pacing (absolute risk reduction with antitoxin 8·8%, 95% CI 6·2–11·0; p<0·0001) and 16 (4·2%) died (absolute risk reduction 4·4%, 1·5–6·8; p=0·004).

Hospital stocks of antitoxin in Kurunegala and the other hospitals were intermittent after Nov 30, 2001, and the case fatality rose (figure). Antitoxin was finally used up in Kurunegala on June 9, 2002; during the next 4 months (July 1, 2002, to Oct 31, 2002), 42 (11%) of 383 patients who were admitted died.

The effect of antitoxin withdrawal was studied prospectively in Anuradhapura and Polonnaruwa district hospitals. The last dose of antitoxin was given in Anuradhapura on June 28, 2002, and in Polonnaruwa on July 19, 2002. 194 patients with oleander poisoning were admitted to these hospitals during the study before the antitoxin ran out; four (2·1%) needed transfer to Kurunegala and 41 received a total of 49 doses (800 mg) of antitoxin. Six (3·1%) of 194 patients died; every death was due to an inability to give further doses.

From these dates until Oct 31, 2002, a further 279 patients were admitted to the two hospitals; 54 (19·4%) needed transfer for possible cardiac pacing (absolute risk increase with withdrawal of antitoxin 17·3%, 95% CI 12·1–22·5; p<0·0001). 26 (9·3%) of 279 patients died (absolute risk increase 6·2%, 1·7–10·5; p=0·008), 12 before they could be transferred. When antitoxin was present, treatment courses were given on 49 occasions for 194 patients. Therefore, four courses of antitoxin were needed to save one life (95% CI 2·4–14·7).

We generated a simple cost-effectiveness model with these prospective data from Anuradhapura and Polonnaruwa (table). Details of methods used to calculate treatment costs and life-years saved are given in the appendix. Antitoxin was priced at US$132·5 per vial ($2650 per treatment). Using antitoxin in the secondary hospitals and transferring only 2% of patients cost $10 209 for every life saved. Since many patients who died were young—with a conservative mean life expectancy of 70 years for males and 75 years for females—cost per life-year saved was much less, at $248.



Monthly case fatality, and number of temporary cardiac pacemakers inserted for yellow oleander poisoning at Kurunegala Hospital, before and after introduction of anti-digoxin antitoxin

Availability of antitoxin in Kurunegala Hospital is indicated by black bars.

	Antitoxin available (n=194)				Antitoxin not available (n=279)			
	Number of patients	Unit cost (US$)	Days	Total cost (US$)	Number of patients	Unit cost (US$)	Days	Total cost (US$)
Activity								
Rural hospital admission	68	2	NA	136	68	2	NA	136
Transfer to district hospital	68	5	NA	340	68	5	NA	340
District hospital admission	100	8	2·5	2000	100	8	2·5	2000
Atropine	80	0·91	1	72·8	80	0·91	1	72·8
Antitoxin	25	2650	NA	66 250	NA	NA	NA	NA
Transfer for coronary care unit/pacing	2	20	NA	40	19	20	NA	380
Pacing	0·5	300	NA	150	4·5	300	NA	1350
Coronary care unit/pacing admission	0·5	30	3	45	4·5	30	3	405
Medical ward (post pacing)	0·5	8	2	8	4·5	8	2	72
Coronary care unit/no pacing admission	1·5	30	2	90	14·5	30	2	870
Medical ward (post no pacing)	1·5	8	2	24	14·5	8	2	232
Total cost (US$)	..	..	..	69 155·8	..	..	..	5857·8
Deaths	6 (3·1%)	..	..	..	26 (9·3%)	..	..	..

NA=not applicable.

Cost-effectiveness analysis of treatment costs for 100 patients admitted to a district hospital when antitoxin was and was not available

Antivenoms in Asia and South America cost several hundred US dollars per treatment; an antitoxin priced at US$400 would cost $1137 per life saved and $28 per life-year saved. The break-even price is $103; below this amount, use of antitoxin saves both lives and money compared with standard treatment.

Our finding of a reduced case fatality at the time the antitoxin was introduced is limited by the retrospective nature of the study. However, no other change in management of patients with oleander poisoning during the middle of 2001 might have accounted for the reduction seen: one of us (KR) was the consultant cardiologist in Kurunegala throughout the period. Doctors working in both Kurunegala and the secondary hospitals all attributed the antitoxin's introduction to the fall in number of deaths. The rise in the case fatality after withdrawal of the antitoxin in Kurunegala is consistent with the antitoxin reducing the number of deaths. The prospective nature of the withdrawal study in Anuradhapura and Polonnaruwa makes it more reliable than retrospective data, which is why we used these data for the cost-effectiveness analysis.

The antitoxin is presently perceived to be too expensive for use in South Asia. The World Bank judges health-care interventions to be cost effective if they buy a year of healthy life for less than the national per person gross domestic product.[5] This amount for Sri Lanka is US$811, substantially higher that the $248 cost per life-year gained in our model at the present cost. Nevertheless, since the local opportunity cost matters, antitoxin at its present price remains expensive. Reductions in price to near that of other antivenoms—eg, US$100 per treatment course—would save money and lives.

Antitoxins could be made affordable by simplification of their preparation—eg, caprylic acid suspended whole IgG rather than Fab or $F(ab')_2$ fragments prepared by enzyme digestion—or by supplying larger vials.[6] These approaches might have disadvantages: patients' advocates, Ministries of Health, and clinicians would need to debate the importance of quality, availability, and price.

Digoxin-specific antibodies can be administered outside of tertiary hospitals.[2] They have none of the complications of pacemakers, do not need specialist doctors or equipment, treat oleander-induced hyperkalaemia and severe diarrhoea, and can be given in small rural hospitals without cardiac monitors, with gastrointestinal signs as markers of toxic effects.[2,7]

There is presently a worldwide effort to develop and make available affordable drugs for tropical diseases;[8] however, this effort seems to be passing poisoning and envenoming by. Treatments for poisoning and envenoming should be included in the campaign to increase the availability of affordable treatments. Both are significant problems in poor rural areas of the tropics, yet there is a dearth of affordable antivenoms for snake bite[6] and antitoxins for plant poisoning.[2] Although digoxin-specific antibodies were not patented on ethical grounds when developed in 1975, they are now unavailable in Sri Lanka because of their cost.

Contributors

M Eddleston set up the prospective poisoning study in Sri Lanka, designed the study, did the analysis, and wrote the first draft of the report. L Senarathna and F Mohamed run the two trial centres and together with M Eddleston extracted data for analysis. N Buckley and E Juszczak designed the prospective study and contributed to the analysis. M H R Sheriff and D A Warrell are senior coordinators of the Ox-Col Collaboration; S Rajapakse, A Ariaratnam, and M H R Sheriff drew up guidelines for antitoxin use and organised its introduction into Sri Lankan clinical practice; all had substantial input in setting up the prospective study. K Rajakanthan contributed to design of this study and extracted data from Kurunegala Hospital records. All authors reviewed and edited the final version of the report.

Conflict of interest statement

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Centre for Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK (M Eddleston, Prof D Warrell)**; Ox-Col Collaboration, Department of Clinical Medicine, University of Colombo, Colombo, Sri Lanka** (M Eddleston, L Senarathna, F Mohamed, Prof M H R Sheriff, A Ariaratnam, S Rajapakse)**; Department of Clinical Pharmacology and Toxicology, Canberra Clinical School, Canberra, ACT, Australia** (N Buckley)**; Centre for Statistics in Medicine, Institute of Health Sciences, Oxford** (E Juszczak)**; and Department of Cardiology, Kurunegala Teaching Hospital, North Western Province, Sri Lanka** (K Rajakanthan)

Correspondence to: M Eddleston, Department of Clinical Medicine, Faculty of Medicine, University of Colombo, PO Box 271, 25 Kynsey Road, Colombo-08, Sri Lanka (e-mail: eddlestonm@eureka.lk)

Appendix

Method of calculation of treatment costs

We took patients' data for analysis from the prospective study presently underway. These data were used to establish the number of patients needing every intervention except pacing.

Costing information was obtained through discussion with administrative and coronary care unit staff. We used 25% as the proportion of patients transferred for pacing who actually received pacing.[5] This value could be an underestimate, since more patients probably died on the 4–5 h journey to Colombo coronary care unit than on the 2 h journey to Kurunegala coronary care unit, thus reducing the number who would have needed pacing in Colombo.

No data are available on the costs of bed occupancy in different types of government hospital in Sri Lanka. Coronary care unit and general medical bed occupancy costs US$100 and $28 per day, respectively, in private hospitals in Sri Lanka. An estimate of 30% of these costs was made for government hospitals; these prices include interventions such as intravenous cannula and infusions and staffing costs. Admission to a rural hospital, where investigations are few, was informally costed at US$2 by the Sri Lankan Ministry of Health.

No data are available on the costs of patients' transfer in the government health service. A private ambulance from Anuradhapura to Kurunegala costs US$30; a figure of $20 for this transfer in a government ambulance and $5 for shorter rural to district hospital transfers were determined. Atropine costs 7 c per 0·6 mg vial. Patients receive a 0·6 mg bolus on admission and then an infusion of 0·3 mg/h for an average of 24 h. Consumables for temporary cardiac pacing cost US$300; this costing does not include depreciation on the pacing units, which cost $750 each.

Calculations for life-years saved

There were 32 deaths in Anuradhapura and Polonnaruwa during the prospective study.

Male deaths: n=21
Mean age 34·5 years (SD 16·4; range 15–60)
Mean life expectancy=70 years
Life-years expected 70×21=1470
Life-years lived 34·5×21=724·5
Life-years lost 1470–724·5=745·5

Female deaths: n=11
Mean age 23·2 years (SD 12·9; range 15–60)
Mean life expectancy=75 years
Life years expected 75×11=825
Life years lived 23·2×11=255·2
Life years lost 825–255·2=569·8

Total life years lost=745·5+569·8=1315·3
Mean life-years lost for every patient dying from oleander poisoning=41·1