In nature, a wide variety of cardiotonic steroids is found in plants, the insects that feed on them and in the parotid glands and skin of some toads (family Bufonidae; genera Bufo, Atelopus, Dendrophryniscus and Melanophryniscus). All these natural drugs contain a steroid nucleus with a lactone ring, five-membered in the case of cardenolides, six-membered in bufadienolides. The cardiac glycosides have a carbohydrate or sugar moiety attached through an oxygen bridge to carbon 3 of the ‘A’ ring of the steroid. The myocardial effects of these compounds are attributable to increased intracellular concentrations of Ca\(^{2+}\) and Na\(^{+}\) resulting from inhibition of the transmembrane Na\(^{+}/K\(^{+}\) ATPase pump. The digitals glycosides are by far the best known of the cardiac glycosides, but many hundreds of others have been identified in dozens of different species of plants from at least 12 different families. The Apocyanaceae (dog banes) are sources of African arrow poisons (for example *Carissa acokanthera*, ‘bushman’s poison’ and *Strophanthus hispidus*) and also contain many of the most beautiful but deadly tropical flowering shrubs such as *Plumeria rubra*, ‘frangipani’, *Nerium oleander*, ‘common, pink or white oleander’ and *Thevetia peruviana*, ‘yellow oleander’. The yellow oleander contains at least eight different cardiac glycosides, including Thevetin A, Thevetin B (cerberoside), thvetoxin, nerifolin, peruvoside and ruvoside. All parts of the plant are dangerous, especially the seeds.

Ingestion of oleander seeds or leaves is a common cause of accidental poisoning worldwide, particularly among children.\(^3,4\) Cases have been reported from places as diverse as Hawaii, the Solomon Islands, Southern Africa, Australia, Europe, the Far East and the United States.\(^1,2\) The oleanders have been used for suicide, homicide, abortion and as herbal remedies in India, Thailand, Brazil and elsewhere.\(^2,5,6\) Yellow oleander glycosides proved effective in patients with heart failure and atrial fibrillation in studies carried out in the 1930s\(^7\) and more recently in India. However, digitoxin or ouabain have been preferred because of less frequent gastrointestinal side-effects.

In Sri Lanka, cases of attempted suicide with yellow oleander were extremely rare before 1980. During that year, the deaths of two girls who intentionally ate yellow oleander seeds was widely reported in local newspapers. The practice suddenly became so popular that the number of cases admitted to Jaffna hospital increased from zero in 1979 to 103 in 1983.\(^8\) Since then it has continued to gain in popularity as a method of self-harm. Currently, several thousand cases occur each year; at least 10% of the patients die, mostly young women and children who have eaten the seeds in response to stressful events.\(^9\)

During 1995–7, we worked with the University of Colombo’s Department of Clinical Medicine to record the clinical and biochemical manifestations of oleander poisoning in more than 300 patients, to compare these with other forms of cardiac glycoside poisoning and to attempt to identify an effective treatment. Most cases of cardiac glycoside poisoning reported in the literature have been in patients overdosed during long-term digitalis therapy for cardiovascular disease.\(^10\) We found clear differences in the incidence of particular arrhythmias between oleander and digitalis poisoning.\(^11\) Ventricular ectopics and tachycardias are common in digoxin-poisoned patients, but are rare in oleander-poisoned patients, who are normally young and previously healthy. Among 89 seriously ill patients, 53% had AV node conduction block, while 62% had sinus node block; 30% had conduction block affecting both nodes. Only 1% had ventricular tachycardias and 8% had ventricular ectopics. These differences may be explained in part by serum potassium levels before glycoside ingestion. Most patients with severe digitals poisoning have pre-existing hypokalaemia attributable to the many other drugs that they are taking.\(^10\) Few of the patients who ingested yellow oleander were on any medication, and would have been normokalaemic before the poisoning. Severe oleander poisoning was associated with elevated serum potassium levels.\(^11\) A similar relationship has been found in patients taking large suicidal overdoses of digoxin\(^12,13\) and those ingesting toad skin poisons.\(^14\) This is explained by inhibition of the transmembrane

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Na\textsuperscript{+}/K\textsuperscript{+} ATPase pump by the cardiotonic steroids. We did not find any relationship between the severity of poisoning and the serum magnesium level.

At present, patients with oleander poisoning who come to rural health centres in Sri Lanka are transferred to the nearest secondary hospital for induced emesis and cardiac monitoring.\textsuperscript{9} Those showing evidence of cardiac conduction block are then transferred as quickly as possible to the CCU in Colombo for temporary cardiac pacing. It takes 1–2 h for an ambulance to be organized and a further 4–5 h for the patient to reach the CCU. Since the evolution of poisoning cannot be accurately assessed, around four patients are transferred to Colombo for every patient eventually requiring specialized management. The cost of transfers together with temporary pacemakers and CCU beds is very high. Around 5% of patients who arrive at a secondary hospital die before they can be transferred to Colombo. Others perish in the ambulance or soon after their arrival in Colombo. Since these patients are rarely monitored, it is difficult to know the exact form of their cardiorespiratory arrest. One patient who was monitored had a VF arrest which did not respond to multiple DC shocks. We presume that many of the others who died had ventricular arrhythmias, a hypothesis supported by the experience of the CCU staff.

These deaths indicate that a form of treatment appropriate for rural hospitals is urgently required. An open-label trial has shown that polyclonal anti-digoxin Fab fragments are effective in digitalis poisoning.\textsuperscript{15} Their use has been recommended in the USA for life-threatening intoxications with other cardiotonic steroids,\textsuperscript{16} but this is not based on a clinical trial, but rather on the treatment of just six patients with natural cardiac glycoside or bufadienolide poisoning. One study of common oleander poisoning in dogs\textsuperscript{17} did show a good response to anti-digoxin Fab, but there are no reports of their use in yellow oleander poisoning. Since the cost of the Fab fragments will preclude their use in Sri Lanka without good evidence of efficacy, we set up a randomized controlled double-blind trial to assess whether ‘DigitTab’ (Therapeutic Antibodies Ltd, London) could reverse yellow oleander-induced cardiotoxicity.\textsuperscript{18}

Patients presenting to the Colombo CCU with sinus bradycardia < 40 bpm, sinus arrest or exit block, atrial tachyarrhythmia, and second- or third-degree AV block were recruited to the study. Those with cardiogenic shock were excluded and given open-label Fab. There was a highly significant response to Fab: 15/33 patients reverted to sinus rhythm at 2 h compared to only 2/32 control patients. There was also a marked and rapid increase in heart rate in treated patients, and a significant decline in serum potassium concentration. This study demonstrated that anti-digoxin Fab rapidly reverses yellow oleander-induced arrhythmias, bradycardia, and hyperkalaemia. The Sri Lankan government is planning to supply this treatment to secondary hospitals. This implementation will have to be closely monitored to see whether the Fab actually prevents deaths as well as reversing cardiotoxicity.

This hypothesis is challenged by the biochemical findings in four patients who died. Blood was taken from two of three severely ill patients treated with Fab outside the trial. Both had relatively low serum cardiac glycoside levels (< 2.1 nmol/l vs. a mean of 2.83 nmol/l for seriously ill cases) but marked electrolyte disturbances (potassium 8.1 mmol/l, or potassium 2.8 mmol/l and magnesium 0.47 mmol/l). Similar electrolyte disturbances were found in two of three patients who died before they could be transferred from Anuradhapura: one had a serum potassium concentration of 8.3 mmol/l and magnesium of 1.34 mmol/l, the second a serum potassium of 10.8 mmol/l and magnesium of 1.05 mmol/l. These electrolyte disturbances could have been present before intoxication and may have predisposed to severe disease. These results suggest that rapid correction of electrolyte disturbances may be more important than neutralizing cardiotonic glycosides (and therefore preventing further problems) in severely ill patients. Although it is often difficult to get rapid measurement of serum electrolyte concentrations in secondary hospitals in Sri Lanka, future studies will need to assess the importance of these values in management.

The efficacy of treatment with anti-digoxin ovine Fab fragments in our patients with yellow oleander poisoning should encourage their use in victims of poisoning by other cardiotonic steroids, as there is growing evidence of a wide cross-neutralization of these poisons. There are anecdotal reports suggesting efficacy in poisoning by common oleander,\textsuperscript{19,20} yew (Taxus bacata)\textsuperscript{21} and toad-skin bufadienolides.\textsuperscript{22} Fatal poisoning has been reported in people who ingested Chinese herbal remedies containing toad parotid and sebaceous gland secretions, known as ch’an su\textsuperscript{23} and, most remarkable, a group of men in New York City, who ate a topical aphrodisiac consisting of toad poisons, marketed under the name of ‘Lovestone’ or ‘Rockhard’.\textsuperscript{22} There is evidence from animal studies and from therapeutic success in a few human cases that anti-digoxin ovine Fab are effective against these toad-derived cardiotonic steroids.\textsuperscript{22,24}

Deliberate self-poisoning is an important problem in the developing world, where the case fatality rate is far higher than in industrialized countries — 20% vs. < 1% in the UK.\textsuperscript{25} One reason for this large difference is the lack of antidotes for many of the poisons used in poor agricultural communities. If activated charcoal could non-specifically reduce the absorption of these poisons, its use could make a
large difference. Unfortunately, currently there is no good evidence for its clinical efficacy, the American and European Poisons Centres stating in 1997 that they could not recommend its use, due to a complete lack of this.\textsuperscript{29} Since multiple-dose regimens of activated charcoal increase excretion of digoxin in humans,\textsuperscript{27,28} activated charcoal may well improve the outcome in oleander poisoning and reduce the need for expensive Fab. A large randomized clinical trial is needed to assess the value of this cheap intervention in the developing world. It may be found to improve the clinical outcome in all overdoses, not just oleander poisoning.

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