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Acute Plant Poisoning and Antitoxin Antibodies

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Abstract

Plant poisoning is normally a problem of young children who unintentionally ingest small quantities of toxic plants with little resulting morbidity and few deaths. In some regions of the world, however, plants are important clinical problems causing much morbidity and mortality. While deaths do occur after unintentional poisoning with plants such as *Atractylis gummifera* (bird-lime or blue thistle) and *Blighia sapida* (ackee tree), the majority of deaths globally occur following intentional self-poisoning with plants such as *Thevetia peruviana* (yellow oleander) and *Cerbera manghas* (pink-eyed cerbera or sea mango). Antitoxins developed against colchicine and cardiac glycosides would be useful for plant poisonings - anti-digoxin Fab fragments have been shown to be highly effective in *T. peruviana* poisoning. Unfortunately, their great cost limits their use in the developing world where they would make a major difference in patient management. Therapy for some other plant poisonings might also benefit from the development of antitoxins. However, until issues of cost and supply are worked out, plant anti-toxins are going to remain a dream in many of the areas where they are now urgently required.

Globally, plants are an uncommon cause of significant poisoning. However, unintentional poisoning with plants is common in small children. Surveys of calls to Poison Information Centres in Germany and the USA show that ingestion of plants is responsible for a significant number of calls (10% of all inquiries), but that serious poisonings are rare.1,2 Plants were responsible for 5% of paediatric poisoning cases seen in Finnish hospitals and 28% of calls to a poison information centre.3 Of 71 children seen in hospital, 52 were sent home from the emergency department, two were sent briefly to an intensive care unit (ICU), none died and all were discharged home within 24hrs.3 Plant poisoning in the developed world is predominantly a problem of small children who put things in their mouth while exploring their environment. Few cases result in significant harm.

Deaths from plant poisoning are rare in the industrialised world - at least in those cases who reach medical attention. Of 24,950 cases of plant poisoning reported to the Swiss Toxicological Information Centre between 1966 and 1994, significant poisoning occurred in just 152 cases.4 Five deaths were noted - due to poisoning with *Colchicum autumnale* (meadow saffron, two cases), *Oenanthe crocata* (hemlock water dropwort), *Taxus baccata* (English or common yew) and *Narcissus pseudonarcissus* (daffodil) - although it appears uncertain whether the last death was actually due to the plant. A recent study from the USA

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reported 30 fatalities from plant poisoning over 18 years (1983-2000);5 seven were caused by various *Cicuta spp.* and five by *Datura stramonium* (jimson weed or thorn apple).

However, in parts of the developing world, plant poisoning is a major clinical problem. Poisoning with *Thevetia peruviana* (yellow oleander),6,7 *Datura stramonium*,8 *Cerbera manghas* (pink-eyed cerbera or sea mango, 9 and Eddleston, unpublished observations), and *Cleistanthus collinis* (a species of teak)10,11 cause significant numbers of deaths each year in south Asia. Almost all deaths result from suicide or homicide. In two studies of 631 poisoned patients admitted to Jaffna Hospital in northern Sri Lanka during 1983-4, 12-17% of cases were due to *T. peruviana* poisoning with a case fatality rate of 6-7%.12-14 Some 12-14 years later, further south in Sri Lanka, the problem had grown even bigger. Now in a study of 4361 poisoning patients over three years, 32-36% had ingested *T. peruviana* and 3-4% had died, while around 40% required transfer to a tertiary referral hospital.15,16

Unintentional deaths do occur in children in the developing world - for example, *Atractylis gummifera* (bird-lime or blue thistle) poisoning has a reported case fatality rate greater than 65% in the Magreb.17,18 Likewise, poisoning with unripe *Blighia sapida* (ackee tree) fruit in the Caribbean and West Africa probably causes 10s to 100s of deaths each year,19-21 and an acute ascending peripheral neuropathy following the ingestion of *Karwinskia humboldtiana* (*tullidora* or buckthorn) fruits is a common problem in Central America.22-24

A separate group of poisonings with significant mortality and morbidity occurs after women use plants to induce abortions - eg *Ruta chalepensis* in Uruguay 25 and *T. peruviana* in Brasil and India.26,27

Treatment for most plant poisonings is symptomatic and specific antidotes are used in only a few. For example, poisoning with plants containing belladonna alkaloids results in an anticholinergic syndrome that can be treated with physostigmine.

Antitoxin antibodies are available for only two plant families and for just one of these are antitoxin antibodies in current clinical practice. Unfortunately, the great cost of the antitoxins means that their use in developing countries, where they are currently most needed, is severely limited. The widespread availability of affordable antitoxin antibodies would revolutionise management of *T. peruviana* poisoning in particular and would likely save hundreds of lives each year.

The following text concentrates on the plant families for which antitoxins are available. It is not a comprehensive review of plants that cause serious poisoning for which readers are referred to texts such as Schvartsman27 and Frohne.28

PLANT ANTITOXIN ANTIBODIES

Polyclonal Fab fragments have been developed against colchicine and digoxin (table 1). These antibodies could be used for plant colchicine and cardiac glycoside poisoning, respectively, markedly improving current management options.

Anti-colchicine antibodies

Gloriosa superba (glory lily) poisoning has been reported from Sri Lanka and south India. 29-33 The plant contains the alkaloids colchicine and gloriosine.34 Colchicine has antimitotic properties and causes vomiting and severe diarrhoea, dehydration, haemodynamic instability, renal failure and eventually multiorgan failure. A retrospective study of poisoning in western Sri Lanka found that it was responsible for 44% of plant poisonings with a 15% case fatality rate.35 *Colchicum autumnale* (meadow saffron) also contains colchicine. It appears to be a rare cause of poisoning in many countries but

occasional and even fatal cases are currently observed in Europe 36,37 and *C. autumnale* poisoning is reported to be common in Turkey.38

Antibodies against colchicine have been developed in France for the management of acute poisoning with the drug form of colchicine. Animal studies have shown good efficacy.39,40 Use of the antitoxin has been reported in one human case in France.41

A 25yr old woman was admitted to ICU after ingesting 60mg of colchicine (~0.8mg/kg). There she continued to deteriorate with hypotension unresponsive to fluid resuscitation and acute renal failure. In view of her poor condition, she was infused with 240mg colchicine-specific Fab fragments over one hour followed by a further 240mg over six hours. Her haemodynamic state made a rapid improvement and she began to pass urine. Free colchicine blood levels fell from 7.5ng/ml before infusion to undetectable after 10 minutes. She was discharged from the ICU on day 10 and from the hospital on day 25. At followup nine months later, she was well and without sequelae.41

Anti-colchicine antibody fragments are not in commercial production. If they could be made available at a price affordable to local health systems, they might make a significant difference in the management of *G. superba* and *C. autumnale* poisoning.

Anti-digoxin antibodies

Such antibodies were first used in 197642 and a subsequent multicentre study showed that they were highly effective for the management of digoxin toxicity.43 They are now considered first line therapy for severe digoxin poisoning in patients with life-threatening dysrhythmias, cardiogenic shock and hyperkalemia.44,45 Adverse events for the most part are anaphylactoid reactions to the infused Fab fragments. These reactions are treatable and not common. They occurred in less than 1% of cases in the original multicentre study and post-marketing surveillance.43,46

Until the late 1990s, no clinical trials had been reported and it was unclear how effective the antibodies would be for the wide range of cardiac glycosides found in plants. One animal study had shown that antibodies could reverse *Nerium oleander*-induced cardiac dysrhythmias;47 three of four human cases of *N. oleander* poisoning also suggested a beneficial effect.48-51 Mixed responses have occurred in cases of *Digitalis lanata* (woolly foxglove),52 *Apocyneacea cannabinum* (Indian hemp),53 *Taxus baccata*, 54 and toad bufoglycoside poisoning,55 although in the last case subsequent animal studies 56 do indicate that early administration of anti-digoxin Fab fragments would be beneficial.

In response to this lack of good quality evidence for efficacy, and the significant number of deaths due to *T. peruviana* in Sri Lanka, a randomised controlled trial (RCT) was set up in 1997 in the Coronary Care Unit (CCU), Colombo, to assess the ability of anti-digoxin Fab fragments to reverse *T. peruviana*-induced cardiac dysrhythmias and hyperkalaemia.57

This study showed that anti-digoxin Fab fragments were highly effective in treating oleander-induced dysrhythmias and electrolyte disturbances. Sixty six patients were randomized to receive saline placebo (32) or 1200mg of anti-digoxin Fab fragments (34). The dysrhythmias had completely resolved by two hours in 2/32 control patients and 15/34 treated patients. Eight hours post-treatment, 5/32 control patients and 24/33 treated patients had reverted to sinus rhythm with heart rate >44bpm. The time to 50% reversal was 3hrs for active treatment and 30hrs for saline treatment. The Fab fragments also increased the cardiac rate and controlled hyperkalaemia.57

Although the role and effectiveness of anti-digoxin antibodies in cases of poisoning with other cardiac glycoside-containing plants has not been as well studied, they may also be effective in these other poisonings. Further studies are required.

Antitoxins for plant poisoning - learning from the Sri Lankan experience of snake envenomation and T.peruviana *poisoning*

The successful system of treating snake bite in the periphery that has been established in Sri Lanka over the last two decades could serve as a model for the management of serious plant poisoning.

Current management of snake bite involves admission of patients to rural single-doctor hospitals and observation for signs of systemic envenoming. As soon as such signs are noted, antivenom is given and the patient transferred to a secondary hospital either during or soon after the infusion. In this way, specific treatment has already been given by the time the patient arrives in a hospital with ICU facilities and specialist physicians. Since the widespread introduction of snake antivenom into the rural hospitals during the 1980s and early 1990s, there has been both a marked increase in the number of patients coming to the Western medical hospitals for treatment of their snake bite and a significant fall in case fatality rate - from 1,564 admissions in 1982 to 37,801 in 1996, with the case fatality rate falling from 5.4% to 0.51% (Health Statistics Unit, Colombo and ref. 58).

In contrast, *T.peruviana* poisoning in Sri Lanka is managed in secondary and tertiary hospitals. Patients presenting to small rural hospitals are subject to potentially hazardous gastric decontamination and then transferred to a secondary hospital. They receive no specific treatment other than atropine or isoprenaline for bradycardia. The number of ambulances is limited and the transfer often delayed by several hours. Patients die from oleander poisoning before arriving at the rural hospital, while waiting for transport, and during transport. There are no official figures for these deaths - if they occur during transit or before presentation to hospital, they do not figure in the hospital statistics; when they do occur in hospital, they are then hidden amongst ‘other causes of poisoning’ in the records.

On arrival at a secondary hospital, the patients are sent to the medical ward where procedures for gastointestinal decontamination are often repeated. Patients are observed on a heart monitor by the nursing staff and medical staff notified of any dysrhythmias. Previously the patients were then, if necessary, further transported with a nursing attendent to Colombo for insertion of a temporary pacing wire. Again, this meant a life-threatening situation should serious dysrhythmias occur in the secondary hospital or during transfer to Colombo - during a one month period in 1997, the team carrying out the RCT were aware of at least two deaths immediately on admission to the CCU and two deaths during transfer (Eddleston, unpublished observations). Other deaths would definitely have occurred in transit without the study team in Colombo being notified.

Since this RCT was reported, anti-digoxin antibodies have been made available in four secondary hospitals that see most patients. Patients are treated symptomatically but, once dysrhythmias or hyperkalaemia pass certain thresholds, they are then treated with anti-digoxin Fab fragments. There has been a marked fall in transfers to the Colombo CCU for pacing and physicians report a reduction in deaths (table 2).

In secondary hospitals with access to pacing facilities, seriously poisoned patients are treated with a combination of antitoxin and pacing. A study of 168 patients presenting to Polonnaruwa hospital during May to August 1999 when pacing, but not antitoxin, was available reported a 2.4% death rate.59 This low death rate, if confirmed from other hospitals, suggests that the antivenom may be unnecessary in hospitals where pacing

facilities are available and that the answer to the Sri Lankan problem may be to make such facilities more widely available across the island. But this is unlikely to be the ultimate solution.45 Some people die well before they reach a secondary hospital that could be fitted with a pacing laboratory. Pacing, unlike the antitoxin, does not treat serious hyperkalaemia and is not always effective, with multiple iatrogenic complications.60

Taking the management of snake bite as a model, the current practice of making antitoxin available only in secondary hospitals is far from ideal. The immense cost means that stocks are small - typically 800mg (one dose) per ward. Cost and small stocks mean that the Fab fragments must be used sparingly, sometimes to the detriment of the patient. During April 2002, two young men who were treated at Anuradhapura General Hospital died because ward stocks were used up and they were not able to be treated in time with further essential courses of antitoxin.

If antitoxin can be made available affordably - at say $50-100 per treatment - then it could also be made available in rural hospitals. Some of these hospitals will not have facilities for cardiac monitoring, but in our experience gastrointestinal signs are often the first indication of intoxication. Therefore patients could be held at a rural unit and observed regularly for GI or cardiac signs and symptoms. Symptomatic patients would then be given a small dose of antitoxin and transferred urgently to the nearest secondary hospital. Here second doses could be given according to need in a CCU. It is important to note that only a minority of patients will require the antitoxin - many will be treatable with just adrenalin or isoprenaline.59

The use of less than maximal doses of Fab fragments is clearly not ideal but the practice may be better than the current situation where patients do not receive any at all before transfer. Such an approach would have to be studied carefully to determine whether small doses of Fab fragments do reduce the number of deaths or simplify further patient management. It would allow specific treatment of *T.peruviana* poisoning at a much earlier stage and might mean a significant reduction in the number of deaths. In such resource poor locations, it is surely worth trying.

Conclusions

Although plant poisoning is a worldwide problem, most deaths occur in the developing world where highly toxic plants have entered practice as methods for self-harm or are mistaken for edible plants in areas where food supply is short. A single study in South Asia has shown that antitoxins can be used effectively for plant poisoning but their high cost limits the use of what should be a successful therapy. In other parts of the world, plant poisoning is not well studied and possible targets for antitoxins have not been explored.

The Sri Lankan model for treating snake bites has shown the importance of having lifesaving antitoxins readily available near to the patients, irrespective of where they live. The successful introduction of anti-digoxin antibodies in oleander poisoning, as well as the limited but promising experiences of anti-colchicine antibodies, should stimulate the development of specific antibodies against other important plant toxins.

The debate in Sri Lanka should now move away from the question of the best treatment for *T. peruviana* poisoning and towards finding ways of making the antitoxin more widely available and affordable. The introduction of facilities for pacemaker insertion in some secondary hospitals may reduce the need for antitoxin but will not remove it. There are thousands of oleander poisoning cases across South Asia each year and many deaths could be prevented with an antitoxin. The task now is to approach pharmaceutical companies with details of the size of the market and interest them in making such antibodies.

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Table 1

List of antitoxins for plant poisonings.

Name (source)	Target Species	Route	Country/Continent	Manufacturer
Anti-colchicine antibodies (goat)	*Gloriosa superba, Colchicum automnale*	IV	France	Not commercially available
DigiBind anti-digoxin antibodies (sheep)	Plants containing cardiac glycosides including: *Cerbera manghas, Convalleria majalis, Digitalis grandiflora, D.lanata, D. purpurea Nerium oleander, Strophanthus gratus, Thevetia peruviana, Urginea maritima, U.indica.*	IV	USA	GlaxoSmithKline NC, USA
DigiFab anti-digoxin antibodies (sheep)	As above	IV	Australia/UK	Protherics, TN, USA
Digitalis-Antidot BM anti-digitoxin antibodies (sheep)	As above	IV	Germany	Roche, Switzerland

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Table 2

The effect of the introduction of anti-digoxin Fab fragments into clinical practice in Anuradhapura, north central Sri Lanka, on deaths and transfers.

Period	Fab available?	Patients	Deaths	Transfers to CCU
June-Sept 1995	No	78	5	40
April-May 2002	Yes	88	2 *	3 **

* Both deaths occurred in patients who had received one treatment course of anti-digoxin Fab fragments (800mg) but whose second course was delayed until cardiac arrest had already occurred. One was transferred but died in CCU.

** Two transfers occurred after Fab administration because no further Fab was available in the hospital and the patients were still symptomatic.