Deliberate self-poisoning in Sri Lanka – improving medical management through clinical research

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Sri Lanka has one of the highest suicide rates of any country in the world. More people have died from suicide during the last 15 years than have died in the war (75,000 vs 50,000). In the rural areas, such as Anuradhapura and Polonnaruwa, pesticide poisoning kills more people than ischaemic heart disease and tropical disease together[1].

However, Sri Lanka does not have a markedly higher rate of attempted suicide or, more accurately, deliberate self-harm (DSH)[2] compared to other countries. As pointed out by Hettiarachchi and Kodithuwakku[3,4], the high number of deaths here are simply due to much higher fatality rates: 10-30% compared to < 1% in the UK.

A reduction in the number of suicidal deaths must be a national priority. While reducing the incidence of acts of self-harm will obviously play an important part, improvements in acute medical management have the potential to rapidly reduce the current appallingly high fatality rate. This will be particularly true if these interventions are designed for use at the most peripheral level of the national health service. Unfortunately, while the scope for clinical research in Sri Lanka is almost boundless, there is currently a dearth of high quality clinical research, particularly clinical trials.

Studies on deliberate self-harm in Sri Lanka

Most studies of DSH have been carried out in Europe and the USA[2,5-7]. However, the problems of the developing world clearly differ from those of industrialised western countries and it is unclear whether the conclusions drawn from these Western studies are relevant to Sri Lanka.

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A number of descriptive studies of the situation in Sri Lanka have been published. Hospital-based studies of acute poisoning in Kandy[8], Galle[3], and Jaffna[9,10], and community-based studies centred on Kandy[11] and Galle[4], have all described the local methods of self-poisoning. These studies have particularly emphasised the importance of agricultural pesticides, in terms of both number of admissions and case fatality rate.

Three studies have specifically examined the pesticide poisoning problem in Sri Lanka[12-14]. They demonstrated that during the 1970s and '80s, approximately 13,000 persons were admitted to hospital each year for pesticide poisoning and 1000-1500 died. The study by Jeyaratnam and colleagues[12] showed that the majority of patients were male and between the ages of 11 and 30. The case fatality rate amongst patients was 22.4% with most of the deaths (74%) being due to organophosphate compounds. The authors urged at this time that measures be taken to minimise the extent of this problem[12]. Unfortunately, if anything, this problem has only become worse.

Our studies in Anuradhapura General Hospital during 1995 and 1996 focused on a different form of self poisoning[15,16]. The ingestion of cardiac glycoside-containing yellow oleander *(Thevetia peruviana)* seeds has become popular amongst young women in the North Central province over the last five years - it is now a significant problem as far south as Kurunegala. In Anuradhapura, it accounts for 40% of all poisoning admissions and 4% of deaths due to poisoning[17]. The case fatality rate for patients who reach a secondary hospital is 10%.

Psychiatric studies

Studies over the last 40 years have shown that many people who appear to attempt suicide do not actually want to die[2,5-7]. The Sri Lankan medical studies published thus far have not attempted to

understand the patients' reasons for taking poison. It is essential that answers are found since it will be difficult to develop effective strategies to prevent deliberate self-harm in Sri Lanka if we do not know why these people are harming themselves. Thus far, sociologists have lead the way in exploring these issues[18]. However, while these studies make tragic reading, they draw little light upon important clinical questions such as whether the patients were depressed and therefore medically treatable, or how many patients intended to die?

These questions are probably going to require collaboration between sociologists and medical researchers. An example of such a collaboration is the excellent work of researchers from *Sumithrayo* and the Universities of Peradeniya and Kelaniya[19].

Few Sri Lankan patients admitted with self-harm are currently referred to a psychiatrist or counsellor. During 1995 or 1996, the medical wards of Anuradhapura General Hospital began to refer self-harm patients to the psychiatry ward for assessment of mental illness. Unfortunately, the numbers are overwhelming for the psychiatry service since Anuradhapura sees over 1200 cases of deliberate self-harm each year. In addition, the patients do not like this transfer because of the stigma they associate with mental illness and the psychiatry ward.

Across the island, procedures for routinely assessing patients before discharge have only rarely been implemented, even though for some of these patients the ingestion of poisons was the culmination of difficult social and interpersonal problems. There is need for routine assessment of DSH patients - this will also allow systematic study of their reasons and seriousness of the attempt.

Questions and problems in medical management of poisoning

Attempts to improve medical management of acute poisoning, particularly at the peripheral levels of the health system, have the potential to markedly reduce the condition's fatality rate. The case fatality rate of 12% that we found in Anuradhapura, although low in comparison to other studies from Sri Lanka[3,8,11], contrasts strongly with the rate of < 1% typical of the UK. The reasons for this higher rate probably include the greater toxicity of local poisons, the lack of a specific antidote for many of them, and the long distances over which patients must be transferred to receive specialised care. In spite of these great problems, there are still many aspects of acute management which could be re-evaluated and assessed for efficacy – see Table 1.

Reducing absorption, increasing excretion

After the ingestion of any poison, toxicity can potentially be reduced at four points:

- removing the poison by emesis or gastric lavage
- decreasing absorption of the poison in the GI tract
- interrupting the enteroheptic circulation
- encouraging poison excretion via the GI tract

1. Gastric lavage or forced emesis

In Anuradhapura district, all patients receive either forced emesis or gastric lavage on admission to any hospital, regardless of the time elapsed or previous management. It is also often used as a punishment for the patient. Some patients receive forced emesis for more than 30 minutes, delaying their initial medical assessment by the ward doctor and in some cases endangering the patient. I have seen yellow oleander-poisoned patients arrest during forced emesis.

There are currently no consistent guidelines for removing poisons from the stomach. The British National Formulary (BNF) states that neither gastric lavage nor forced emesis is useful more than 1-2 hours after ingestion of a poison (except perhaps in the case of salicylates[20]). Multiple clinical trials failed to produce evidence for the efficacy of either[21-24], although all the trials have major design flaws, particularly in terms of their randomisation[25-27]. It is possible however that gestric lavage may be suitable for the Sri Lankan situation, for example, for the removal of large pieces of yellow oleander seeds.

2. Reducing absorption with activated charcoal

Instead, the BNF recommends the use of activated charcoal if the patient presents within a few hours of ingestion. Its efficacy later than this is unclear.

Simulated human overdoses studies indicate that, while activated charcoal is highly effective if given within minutes of ingestion, its efficacy

Table 1

Poison	Current medical management[20,53,54]	Questions
General	Gastric lavage or forced emesis is recommended for almost all poisonings in Sri Lanka[53]. However, there is increasing evidence that gastric lavage is not as good as activated charcoal and only delays the administration of charcoal.	In which types of poisoning is gastric lavage or forced emesis effective? Should activated charcoal alone be given to poisoned patients? Is gastric lavage more useful in plant poisonings where large pieces may be present hours after ingestion?
General	Activated charcoal or Fuller's earth can be used for most poisonings (the BNF recommends activated charcoal). Give 50-100g activated charcoal with a laxative (to encourage diarrhoea), then repeat at least every 4 hours until it is seen in the stool.	In which types of poisoning is activated charcoal effective? Should it be given to all patients presenting with a *Hx* of poisoning, regardless of the poison which has been ingested? Which patients require multiple doses? Are cathartics effective? How can it be given as early as possible? Should it be given on initial presentation to any health care centre?[32]
Dipyridylium compounds (eg paraquat)	Symptomatic treatment only. At presentation give gastric lavage, and administer either Fuller's earth or activated charcoal together with a laxative eg magnesium sulphate.	Might early high dose therapy with methylprednisolone (1g days 0,1,2) and cyclophosphamide (1g days 0,1) prevent lung fibrosis in moderately poisoned patients?[45,46]
Organochlorines (eg Endosulfan)	Symptomatic treatment after gastric lavage plus prophylactic phenytoin to prevent convulsions. If convulsions occur but do not respond to diazepam, intubation, curarization and assisted ventilation are necessary.	Should all patients who have an organochlorine be given prophylactic phenytoin immediately on first presentation? Are there better drugs for management of Endosulfan-induced *status epilepticus* which could be used in peripheral hospitals?
Organophosphates	After gastric lavage and administration of activated charcoal/Fuller's earth, muscarinic effects are countered with atropine and nicotinic effects with pralidoxime.	Does activated charcoal decrease organophosphate absorption? Is pralidoxime ineffective in organophosphate poinsoing - should organophosphate poisoning be treated with atropine alone?[47,48]
Yellow oleander	Currently, symptomatic treatment: atropine (or isoprenaline) for bradycardia, temporary cardiac pacing for AV dissociation and severe sick sinus syndrome. Anti-digoxin Fab fragments may be introduced into clinical practice in the near future.	Should all patients receive multi-dose activated charcoal?[37,38] If anti-digoxin Fab fragments come into clinical practice, which patients should be receiving them in peripheral units? At which level of health service facility should patients receive this drug? What is the best indicator of a poor prognosis - could serum K^+ done rapidly on admission supply such an indicator?

falls off rapidly over a couple of hours[28-30]. Again, there have been no good clinical trials to assess the effectiveness of activated charcoal in decreasing absorption – the trials listed above have tended to find activated charcoal to be better than gastric lavage but the trials need repeating. Randomised controlled trials (RCT) are urgently needed to determine whether this relatively safe procedure[31] is effective in reducing the absorption of poisons such as oleander and pesticides.

These studies should also attempt to find out how late it can be used and whether all overdose patients should receive it. If activated charcoal is found to work, then it will be important to find ways of giving it even earlier. A pilot study in California is looking to evaluate the benefits of giving charcoal in the ambulance[32]. In the Sri Lankan situation, it may be possible to distribute activated charcoal free to shops throughout the community, perhaps to those which sell the pesticides, so that relatives can get hold of it and give it early to the poisoned patient, before the patient even comes into contact with the health services.

Other relevant questions include whether high-surface-area activated charcoals give an extra benefit which is worth their increased cost[33,34] and whether the cheaper Fuller's earth is just as effective as the popular activated charcoal[35].

3. Interruption of a poisons's enterohepatic circulation using multi-dose activated charcoal regimens

Some drugs are secreted in the bile into the GI tract before being reabsorbed lower down in the ileum - in this way, 30% of the body's digoxin is secreted and reabsorbed each day. Interruping this circulation is a powerful way of increasing the excretion of any poison from the body.

Multiple doses of activated charcoal can be used to interrupt it [36]. Charcoal has been shown to work for digoxin and digitoxin[37,38] but not imipramine[39], amiodarone, or chloroquine[40]. Unfortunately, these studies have been laboratory based and there is currently no evidence that increasing drug clearance using multi-dose activated charcoal regimens actually produces a cilinical benefit[36].

One human simulated overdose study has suggested that more frequent administrations of smaller quantities of activated charcoal is at least as effective as the regular four-hourly dose of 50g[41]. This may have relevance for deciding how much should be given both before and after admission to hospital.

4. Increasing excretion in the GI tract

The excretion of some other drugs which do not have an enterohepatic circulation has also been promoted by multi-dose activated charcoal regimens. The best studied example is phenobarbital[42-44] – unfortunately clinical studies have yet to show clinical benefit from increasing phenobarbital excretion[43].

Paraquat poisoning

The case fatality rate after paraquat poisoning is appallingly high[45] - 68% in one study from Galle[4]. Around 30% of patients survive the first few days but then die during subsequent weeks due to lung fibrosis. A study from Taiwan using historical controls suggested that early pulse immunosuppressive treatment with cyclophosphamide and methyl-prednisolone prevented the later onset of fibrosis[46]. It was not a RCT and it is unclear whether this expensive treatment really is as effective as was claimed by the authors[45]. A RCT is urgently required to determine whether it is worth using - a late, fully conscious deaths from paraquat-induced lung fibrosis must be a most appalling way to die.

Endosulphan-induced status epilepticus

A common presentation in Anuradhapura is *status epilepticus* due to the ingestion of an organochlorine pesticide called Endosulfan. The convulsions do not respond to diazepam and often require the patient to be paralysed and ventilated. Patients die in the rural areas or soon after admission to a secondary hcspital, because assisted ventilation is available in very few centres and their arrival at these centres is often delayed. New treatments which can be used before the patient is admitted to a secondary hospital are urgently required.

Pralidoxime in organophosphate poisoning

As Professor Senanayake pointed out in his Oration to the 1997 Sri Lankan Medical Society meeting, we do not know if pralidoxime is at all effective in organophosphate poisoning, even

though its use is recommended. The evidence from his study[47] and that of Singh and colleagues[48] should be sufficient to stimulate the setting up of a RCT to address this question. Another Indian study has reported that continual infusions of atropine rather than the usual bolus injections markedly improved survival[49] - again not a RCT but provocative nonetheless.

Oleander poisoning

The Ox-Col collaboration's work in Anuradhapura and Colombo has shown that anti-digoxin Fab fragments are highly effective in reversing potentially fatal oleander-induced cardiac arrhythmias[50]. If the Sri Lankan Drug Regulatory Authority decides that they should be brought into clinical practice, guidelines detailing who should receive this expensive drug must be drawn up. For this, an indicator of poor prognosis is required.

Gaultier and colleagues have shown that hyperkalaemia is associated with more severe arrhythmias and increased mortality in acute dignoxin poisoning[51]. They proposed that serum potassium concentrations should be measured on admission in these patients and used to guide decisions about treatment. Since hyperkalaemia is also associated with more severe arrhythmias in oleander poisoning, this may be a test which could be used in secondary hospitals in Sri Lanka.

However, if we find that multi-dose activated charcoal works as well for oleander cardiac glycosides as it does for digoxin, effective early therapy may reduce the incidence of the serious arrhythmias which require Fab fragment administration.

Clinical research in Sri Lanka

There is an urgent need in Sri Lanka for high quality clinical research on questions relevant to the local situation. Management strategies need to be designed for the most distant elements of the health service since it is there that most patients live and first come into contact with a doctor. There is currently little clinical research carried out by physicians in Sri Lanka. As the system is set up, no-one has the time to dedicate themselves to research. High quality research requires full time commitment.

As part of their clinical training in the UK, many registrars do one to three years of research in either the wards or laboratory. This exposes them to the culture of asking questions and attempting to improve clinical practice. The potential for this type of work in Sri Lanka is phenomenal. It should be possible to set up a system in which registrars being trained in Colombo spend a year at one of the peripheral base or district hospitals, working with one of the consultants as a research registrar. The consultant with her or his local knowledge should be well placed to choose highly relevant questions which could help transform local medical practice, quickly improving efficiency and reducing the workload. The registrars would also gain research experience which would benefit them during their own consultant years and in turn allow them to effectively supervise their own research registrars.

There is a large and ready audience for high quality clinical research, both in Sri Lanka and the international medical community. In addition to the Sri Lankan journals, international journals such as the *Lancet* and *New England Journal of Medicine* regularly publish clinical studies from the tropics. Specialised tropical medicine journals publish clinical research - in July this year the editor of *Tropical Medicine and International Health* bemoaned the paucity of clinical studies coming from the developing world. He actively encouraged such studies to be submitted to this excellent new journal[52].

Conclusions

Acute poisoning results in over 1000 tragic deaths each year in Sri Lanka. While less than 1% of patients admitted to hospital with acute poisoning in the UK die, the figure is nearer 20 or 30% here. Simple management options have been proposed in the literature but no where in the world has the clinical research been carried out to evaluate whether these possible interventions are effective.

Sri Lanka can only gain by increasing the amount of cilinical research performed in its hospitals, as long as this research is relevant to the local situation. Well designed trials can not only reduce the number of deaths and health service costs, but also reduce the workload of the already stretched Sri Lankan health service.

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References

1. Ministry of Health. Annual health bulletin, Sri Lanka, 1995. Colombo, Sri Lanka: Ministry of Health, 1997.
2. Hawton K. Deliberate self-harm. *Medicine* 1997; **24**: 77-80.
3. Hettiarachchi J, Kodithuwakku GCS. Self-poisoning in Sri Lanka: factors determining the choice of the poisoning agent. *Human Toxicol* 1989; **8**: 507-510.
4. Hettiarachchi J, Kodithuwakku GCS. Pattern of poisoning in rural Sri Lanka. *Int J Epidemiol* 1989; **18**: 418-422.
5. Hawton K, Catalan J. Attempted suicide: a practical guide to its nature and management. 2nd ed. Oxford: Oxford Medical Publications, 1987.
6. Hawton K. Suicide and attempted suicide among children and adolescents. Developental clinical psychology and psychiatry series; v.5. Newbury park, CA: Sage Publications, Inc, 1986: 9-157.
7. Meredith TJ. Epidemiology of poisoning. *Pharmac Ther* 1993; **59**: 251-256.
8. Senewiratne B, Thambipillai S. Pattern of poisoning in a developing agricultural country. *Br J Prev Soc Med* 1974; **28**: 32-36.
9. Ganeswaran T, subramaniam S, Mahedevan K. Suicide in a nothern town of Sri Lanka. *Acta Psychiatr Scand* 1984; **69**: 420-425.
10. Ganeshamoorthy R. Spectum of acute poisoning in Jaffna - a one year survey. *Jaffna Med J* 1985; **20**: 3-12.
11. Senanayake N, Peiris H. Mortality due to poisoning in a developing country: trend over 20 years. *Hum Exp Toxicol* 1995; **14**: 808-811.
12. Jeyaratnam J, De Alwis Seneviratne RS, Copplestone JF. Survey of pesticide poisoning in Sri Lanka. *Bull World Health Organ* 1997; **60**: 615-619.
13. de Alwis LB, Salgado MS. Agrochemical poisoning in Sri Lanka. *Forensic Sci Int* 1988; **36**: 81-89.
14. Fernando R, Fernando D. Pesticide poisoning in Sri Lanka. Review of the eighties and the outlook for the nineties. Colombo: National Poisons Information Centre, 1995
15. Saravanapavananthan N, Ganeshamoorthy J. Yellow odeander poisoning - a study of 170 cases. *Forensic Sci Int* 1988; **36**: 247-250.
16. Sreeharan N, Putharasingam S, Ranjadayalan K, Satkurunathan K, Ganeshamoorthy J. Yellow oleander poisoning - clinical manifestations and prognostic criteria. *Jaffna Med J* 1985; **20**: 100-101.
17. Eddleston M, Sheriff MHR, Hawton K. Deliberate self-harm in the developing world - an overlooked tragedy. *BMJ* 1998; (in press)
18. Suicide in Sri Lanka. De Silva P, ed. Kandy: Institute of Fundamental Studies, 1989.
19. Kasturiaratchi ND, de Silva HJ, Ellawala NS, Senaratne DC, Premawardene AP, Seneviratne SL. A study of suicide in Sri Lanka, 1997: unpublished.
20. British National Formulary, Number 34 (September 1997). London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 1997.
21. Pond SM, Lewis-Driver DJ, Williams GM, Green AC, Stevenson NW. Gastric emptying in acute overdose: a prospective randomised controlled trial. *Med J Aust* 1995; **163**: 345-349.
22. Albertson TE, Derlet RW, Foulke GE, Minguillon MC, Tharratt SR. Superiority of activated charcoal alone compared with ipecac and activated charcoal in the treatment of acute toxic ingestions. *Ann Emerg Med* 1989; **18**: 56-59.
23. Merigian KS, Wodard M, Hedges JR, Roberts JR, Stuebing R, Rashkin MC. Prospective evaluation of gastric emptying in the self-poisoned patient. *Am J Emerg Med* 1990; **8**: 479-483.
24. Tenenbein M, Cohen S, Sitar DS. Efficacy of ipecac-induced emesis, orogastric lavage, and activated charcoal for acute drug overdose. *Ann Emerg Med* 1987; **16**: 838-841.
25. Whyte IM, Buckley NA. Progress in clinical toxicology: from case reports to toxicopidemiology (Editorial). *Med J Aust* 1995; **163**: 340-341.
26. Schulz KF. Subverting randomization in controlled trials. *JAMA* 1995; **274**: 1456-1458.
27. Begg C, Cho M, Eastwood S, et al. Improving the quality of reporting of randomised controlled trials: the CONSORT statement. *JAMA* 1996; **276**: 637-639.
28. Laine K, Kivisto KT, Pelttari S, Neuvonen PJ. The effect of activated charcoal on the absorption of fluoxetine, with special reference to delayed charcoal administration. *Pharmacol Toxicol* 1996; **79**: 270-273.
29. Laine K, Kivisto KT, Laasko I, Neuvonen PJ. Prevention of amlodipine absorption by activated charcoal: effect of delay in charcoal administration. *Br J Clin Pharmacol* 1997; **43**: 29-33.
30. Laine K, Kivisto KT, Neuvonen PJ. Effect of delayed administration of activated charcoal on the absorption of conventional and slow-release verapamil. *J Toxicol Clin Toxicol* 1997; **35**: 263-268.
31. Mauro LS, Nawarskas JJ, Mauro VF. Misadventures with activated charcoal and recommendations for safe use. *Ann Pharmacother* 1994; **28**: 915-924.
32. Crockett R, Krishel SJ, Manoguerra A, Williams SR, Clark RF. Prehospital use of activated charcoal: a pilot study. *J Emerg Med* 1996; **14**: 335-338.
33. Roberts JR, Gracely EJ, Scoffstall JM. Advantage of high-surface-area charcoal for gastrointestinal decontamination in a human acetaminophen ingestion model. *Acad Emerg Med* 1997; **4**: 167-174.
34. Krenzelok EP, Heller MB. Effectiveness of commercialy available aqueous activated charcoal products. *Ann Emerg Med* 1987; **16**: 1340-1343.

35. Idid SZ, Lee CY. Effects of Fuller's earth and activated charcoal on oral absorption of paraquat in rabbits. *Clin Exp Pharmacol Physiol* 1996; 23: 679-681.

36. Bradberry SM, Vale JA. Multiple-dose activated charcoal: a review of relevant clinical studies. *J Toxicol Clin Toxicol* 1995; 33: 407-416.

37. Reissell P, Mannien V. Effect of administration of activated charcoal and fibre on absorption, excretion and steady state blood levels of digoxin and digitoxin. Evidence for investinal secretion of glycosides. *Acta Med Scand Suppl* 1982; 668: 88-90.

38. Lalonde RL, Deshpande R, Hamilton PP, McLean WM, Greenway DC. Acceleration of digoxin clearance by activated charcoal. *Clin Pharmacol Ther* 1985; 37: 367-371.

39. Goldberg MJ, Park GD, Spector R, Fischer LJ, Feldman RD. Lack of effect of oral activated charcoal on imipramine clearance. *Clin Pharmacol Ther* 1985; 38: 350-353.

40. Laine K, Kivisto KT, Neuvonen PJ. Failure of oral activated charcoal to accelerate the elimination of amiodarone and chloroquine. *Hum Exp Toxicol* 1992; 11: 491-494.

41. Ilkhanipour K, Yealy DM, Krenzelok EP. The comparative efficacy of various multiple-dose activated charcoal regimens. *Am J Emerg Med* 1992; 10: 298-300.

42. Berg MJ, Berlinger WG, Goldberg MJ, Spector R, Johnson GF. Acceleration of the body clearance of phenobarbital by oral activated charcoal. *N Eng J Med* 1982; 307: 642-644.

43. Pond SM, Olson KR, Osterloh JD, Tong TG. Randomised study of the treatment of phenobarbital overdose with repeated doses of activated charcoal. *JAMA* 1984; 251: 3104-3108.

44. Frenia ML, Schauben JL, Wears RL, Karlix JL, Tucker CA, Kunisaki TA. Multiple-dose activated charcoal compared to urinary alkalinization for the enhancement of phenobarbital elimination. *J Toxicol Clin Toxicol* 1996; 34: 169-175.

45. Newstead CG. Cyclophosphamide treatment of paraquat poisoning. *Thorax* 1996; 51: 659-660.

46. Lin J-L, Wei M-C, Liu Y-C. Pulse therapy with cyclophosphamide and methylprednisolone in patients with moderate to severe paraquat poisoning: a preliminary report. *Thorax* 1996; 51: 661-663.

47. de Silva HJ, Wijewickrema R, Senanayake N. Does pralidoxime affect outcome of management in acute organophosphate poisoning? *Lancet* 1992; 339: 1136-1138.

48. Singh S, Batra YK, Singh SM, Wig N, Sharma BK. Is atropine alone sufficient in acute severe organophosphate poisoning? Experience of a North West Indian hospital. *Int J Clin Pharmacol Ther* 1995; 33: 628-630.

49. Ram JS, Kumar SS, Jayarajan A, Kuppuswamy G. Continuous infusion of high doses of atropine in the management of organophosphorus compound poisoning. *J Assoc Physicians India* 1991; 39: 190-193.

50. Eddleston M, Rajapakse S, Rajakanthan K, et al. A randomised controlled trial of anti-digoxin Fab fragments in acute yellow oleander poisoning. QJM 1998; (abstract)

51. Bismuth C, Gaultier M, Conso F, Efthymiou ML, Hyperkataemia in acute digitalis poisoning: prognostic significance and therapeutic implications. *Clin Toxicol* 1973; 6: 153-62.

52. Hall A. Clinical research in the tropics. *Trop Med Int Health* 1997; 2: 511-512.

53. Fernando R. Management of acute poisoning. Colombo, Sri Lanka: National Poisons Information Centre, 1991.

54. Proudfoot AT, Vale JA. Pesticides. In: Weatherall DJ, Ledingham JGG, Warrell DA, eds. Oxford Textbook of Medicine. 3rd ed. Oxford: Oxford University Press, 1996: 1120-1124.