THE CEYLON MEDICAL JOURNAL

Established 1887

The Official Publication of the Sri Lanka Medical Association
Volume 53, No.2, June 2008
Quarterly ISSN 0009–0875

All communications should be addressed to **The Editors, CMJ**

Continued overleaf

Efficacy of activated charcoal in yellow oleander poisoning

Conflicting data perpetuate the debate

Deliberate self-poisoning with yellow oleander (*Thevetia peruviana*) seeds continues to be a major problem in Sri Lanka, especially in rural areas, and results in many deaths annually. The amount of cardioactive toxins absorbed from a seed varies between individuals, and the number of seeds ingested does not always correlate with the degree of toxicity [1]. The treatment of yellow oleander poisoning (YOP) in Sri Lankan hospitals includes gastric lavage, administration of activated charcoal (AC), and intravenous atropine or isoprenaline, or both, for bradyarrhythmias. Temporary cardiac pacing is done if patients develop life-threatening bradyarrythmias; this is often done in a tertiary care hospital. An anti-digoxin antitoxin for YOP was introduced to Sri Lanka in 2001. The antitoxin, antidigoxin antibody Fab fragments, reduces case fatality [2], but because of cost it is used sparingly.

AC, which is inexpensive and widely available, benefits patients with YOP by reducing absorption and facilitating elimination of toxic glycosides contained in oleander seeds [3]. After yellow oleander seed ingestion and absorption of glycosides into the systemic circulation, oleander glycosides are re-secreted into the gut lumen [4, 5]. In the gut, the secreted glycoside binds to AC and encourages further secretion, thus increasing glycoside excretion [4]. In volunteers early administration of a single dose of activated charcoal (SDAC) has been shown to adsorb poison in the stomach and reduce its absorption [6]. However, the severity of poisoning in this group was very mild. Animal studies have shown that multiple doses of activated charcoal (MDAC) reduce the half-life of intravenous digoxin from 65 to 17 hours and increase clearance from 2·3 ml/min/kg to 7·1 ml/min/kg [7]. In 10 healthy volunteers who received intravenous digoxin, repeated doses of activated charcoal increased total body clearance from 12 l/h to 18 l/h and reduced the half-life from 37 to 22 hours [8]. The effect of activated charcoal on the pharmacokinetics of *Thevetia* cardenolides has also been studied; patients who were given activated charcoal were found to have a reduction in 24-hour mean residence time and apparent terminal half-life compared to those not given activated charcoal [9]. This effect was nearly equal in patients given SDAC and MDAC. It has also been suggested that AC may work long after ingestion of poison by interrupting the enterohepatic and enterovascular cycling of the poison [10]. MDAC has, therefore, been administered to some patients, irrespective of the delay in presentation, to increase elimination of poison [11].

Despite this evidence, the debate on whether SDAC or MDAC is beneficial in YOP continues. Conflicting mortality rates have been reported in two recent randomised controlled trials which assessed the efficacy of AC

Samiran Nundy FRCS, FRCP
New Delhi, India

N Medappa MD
New Delhi, India

Jane Smith BA, MSc
London, UK

Anita KM Zaidi MMBS, SM
Karachi, Pakistan

David Warrell MD, FRCP
Oxford, UK

Published by

The Sri Lanka Medical Association
Wijerama House
6, Wijerama Mawatha
Colombo 7
Sri Lanka

Tel: +94 11 2693324

Fax: +94 11 2698802

Internet home page
http://www.cmj.slma.lk

e-mail: office@cmj.slma.lk

Printed by

Ananda Press
82/5, Sir Ratnajothi Saravanamuttu
Mawatha, Colombo 13
Sri Lanka

Tel: +94 11 2435975

Fax: +94 11 2385039

e-mail: anpress@sltnet.lk

This journal is indexed in BIOSIS, CAB International, EMBASE, and Index Medicus

[12,13]. De Silva et al reported a reduction in mortality from 8% to 2.3% with MDAC compared to SDAC [12]. The corresponding figures in a study done by Eddleston et al were 4.7% to 4.3% [13]. It is well accepted that mortality in YOP is about 10%. This figure was used both by groups in their power calculations. Even though the mortality was slightly lower (8%) in the former study it is unlikely to have seriously affected the validity of their results. However, in the case of the latter study, the actual mortality was only 47% of the initial assumption. This casts serious doubts on the suitability of their control group for comparison with the treatment group. The low mortality in their control group may have been due to their selection criteria; recruitment for up to 72 hours after ingestion of yellow oleander, and only patients with a Glasgow Coma Scale of more than 13 which would have eliminated patients with more severe poisoning. They report that most deaths occurred within the first 24 hours of ingestion of the poison. Including patients for up to 72 hours after ingestion of yellow oleander may have diluted their mortality rate. De Silva et al included subjects only up to 24 hours after ingestion of the poison, and included patients irrespective of the severity of poisoning.

Important differences between these two contradictory studies deserve comment. Eddleston et al gave AC 4-hourly for only 24 hours, while de Silva et al continued AC 6-hourly for 72 hours. De Silva et al justify the longer use of AC on the long half-lives of oleander glycosides (median of 43 hours) [9], and the increased frequency of life-threatening cardiac arrhythmias after 24 hours in their placebo group. Eddleston et al have considered only death as an end-point. This may be inappropriate in YOP as cardiac arrhythmias can lead to considerable morbidity and treatment costs. Administration of AC for longer periods in YOP has been shown to reduce absorption and increase glycoside excretion, a fact acknowledged by Eddleston et al. It is worth emphasizing here that even if all patients with YOP are administered AC for long periods, this would cost less than having to subject even a few to temporary cardiac pacing or administration of antidigoxin antibody Fab fragments. The other issue is compliance. Eddleston et al estimate adherence to MDAC as 80% for the first dose and 60% for the sixth dose, that is 20% of their patients in the MDAC group may not have received any AC. De Silva et al claim that study-independent medically qualified trial staff directly observed the patients, who either drank the charcoal themselves or had it administered by nasogastric tube, ensuring adherence to therapy in all cases.

These two major studies raise many issues regarding the management of YOP. Clinical sciences need to be combined with basic sciences so that the many unanswered questions are addressed before recommending adjustments in treatment protocols [14]. It is now imperative that toxicokinetic studies be combined with randomised controlled trials to establish a dose-response effect in relation to the YOP dose ingested and the frequency of administering AC, before drawing any definitive conclusions regarding the efficacy of AC in YOP. In the de Silva et al study, 18 of the 21 deaths occurred within 48 hours of hospital admission. There is a need to test the hypothesis whether administration of AC for 48 hours, and not 72 hours, is sufficient. As two dosing regimens have been used, 4-hourly and 6-hourly, it is essential to establish the one that is most effective and acceptable standard protocols in resource poor settings. Another area that needs to be further investigated is whether better monitoring can reduce mortality, as claimed by Eddleston et al.

The benefit in clearance of glycosides, even though this was at "subtoxic doses", as shown by pharmacokinetic studies, and the reductions in admissions to intensive care and incidence of life-threatening arrhythmias reported by de Silva et al, both indicate some benefit of MDAC in patients with YOP. Eddleston et al too agree to a "non-significant trend towards benefit with charcoal" in their most ill patients.

If activated charcoal does improve the outcome in YOP and reduces the need for expensive interventions such as cardiac pacing, administration of antidigoxin antibody Fab fragments and ICU care, the economic benefit to the health care sector in this country will be considerable. Case fatality should not be the only factor to decide whether AC (MDAC or SDAC) is effective or not in YOP, when even here the evidence is inconclusive. Clearly, trying to write the epitaph for MDAC with the evidence available is unwise.

References

1. Eddleston M, Ariaratnam CA, Meyer WP, Perera G, Kularatne SAM, et al. Epidemic of self-poisoning with seeds of the yellow oleander tree (*Thevetia peruviana*) in northern Sri Lanka. *Tropical Medicine and International Health* 1999; **4:** 266-73.
2. Eddleston M, Senarathna L, Mohamed F, Buckley N, Juszczak E, et al. Deaths due to absence of an affordable antitoxin for plant poisoning. *Lancet* 2003; **362:** 1041-4.
3. Ardagh M, Flood D, Tait C. Limiting the use of gastro-intestinal decontamination does not worsen the outcome from deliberate self-poisoning. *New Zealand Medical Journal* 2001; **114:** 423-5.
4. Caldwell JH, Caldwell P, Murphy JW, Beachler CW. Intestinal secretion of digoxin in rat. Augmentation by feeding activated charcoal. *Naunyn-Schmiedeburgs Archives of Pharmacololgy* 1980; **312:** 271-5.
5. Stephens RH, O'Neill CA, Warhurst A, Carlson GL, Rowland M, et al. Kinetic profiling of P-glycoprotein-mediated drug efflux in rat and human intestinal epithelia. *Journal of Pharmacology and Experimental Therapeutics* 2001; **296:** 584-91.
6. Chyka PA, Seger D, Krenzelok EP, Vale JA; American Academy of Clinical Toxicology; European Association of Poison Centres and Clinical Toxicologists. Position paper: single-dose activated charcoal. *Clinical Toxicology* 2005; **43:** 61-87
7. Chyka PA, Holley JE, Mandrell TD, Sugathan P. Correlation of drug pharmacokinetics and effectiveness of multiple-dose activated charcoal therapy. *Annals of Emergency Medicine* 1995; **25:** 356-62.
8. Lalonde RL, Deshpande R, Hamilton PP, McLean WM, Greenway DC. Acceleration of digoxin clearance by activated charcoal. *Clinical Pharmacology and Therapeutics* 1985; **37:** 367-71.
9. Roberts DM, Southcott E, Potter JM, Roberts MS, Eddleston M, et al. Pharmacokinetics of digoxin cross-reacting substances in patients with acute yellow oleander (*Thevetia peruviana*) poisoning, including the effect of activated charcoal. *Therapeutic Drug Monitoring* 2006; **28:** 784-92.
10. Levy G. Gastrointestinal clearance of drugs with activated charcoal. *New England Journal of Medicine* 1982; **307:** 676-8.
11. Bradberry SM, Vale JA. Poisons: initial assessment and management. *Clinical Medicine* 2003; **3:** 107-10.
12. De Silva HA, Fonseka MMD, Pathmeswaran A, Alahakone DGS, Ratnatilake GA, et al. Multiple-dose activated charcoal for treatment of yellow oleander poisoning: a single-blind, randomised, placebo-controlled trial. *Lancet* 2003; **361:** 1935-8
13. Eddleston M, Juszczak E, Buckley N A, Senarathna L, Mohamed F, et al. Multiple-dose activated charcoal in acute self-poisoning: a randomised controlled trial. *Lancet* 2008; **371:** 579-87
14. Eyer P, Eyer F. Is this the epitaph for multi-dose activated charcoal? *Lancet* 2008; **371:** 538-9.

R J Peiris-John, *Department of Physiology, Faculty of Medical Sciences, University of Sri Jayewardenepura, Nugegoda,* and **A R Wickremasinghe**, *Department of Public Health, Faculty of Medicine, University of Kelaniya, Ragama, Sri Lanka.*

Correspondence: RJP-J, *e-mail: <roshipj@hotmail.com>. Competing interests: none declared.*