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Citation for published version:

Digital Object Identifier (DOI):
10.1016/S0140-6736(08)60270-6

Link:
Link to publication record in Edinburgh Research Explorer

Published in:
The Lancet

Publisher Rights Statement:
Available under Open Access

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Multiple-dose activated charcoal in acute self-poisoning: a randomised controlled trial

Michael Eddleston, Edmund Justszczak, Nick A Buckley, Lalith Senarathna, Fahim Mohamed, Wasantha Dissanayake, Ariyasena Hittarage, Shifa Azher, K Jeganathan, Shaluka Jayamanne, M H Rezvi Sheriff, David A Warrell for the Ox-Col Poisoning Study collaborators

Summary

Background The case-fatality for intentional self-poisoning in the rural developing world is 10–50-fold higher than that in industrialised countries, mostly because of the use of highly toxic pesticides and plants. We therefore aimed to assess whether routine treatment with multiple-dose activated charcoal, to interrupt enterovascular or enterohepatic circulations, offers benefit compared with no charcoal in such an environment.

Methods We did an open-label, parallel group, randomised, controlled trial of six 50 g doses of activated charcoal at 4-h intervals versus no charcoal versus one 50 g dose of activated charcoal in three Sri Lankan hospitals. 4632 patients were randomised to receive no charcoal (n=1554), one dose of charcoal (n=1545), or six doses of charcoal (n=1533); outcomes were randomised to 4629 patients. 2338 (51%) individuals had ingested pesticides, whereas 1647 (36%) had ingested yellow oleander (Thevetia peruviana) seeds. Mortality was the primary outcome measure. Analysis was by intention to treat. The trial is registered with controlled-trials.com as ISRCTN02920054.

Findings Mortality did not differ between the groups. 97 (6·3%) of 1531 participants in the multiple-dose group died, compared with 105 (6·8%) of 1554 in the no charcoal group (adjusted odds ratio 0·96, 95% CI 0·70–1·33). No differences were noted for patients who took particular poisons, were severely ill on admission, or who presented early.

Interpretation We cannot recommend the routine use of multiple-dose activated charcoal in rural Asia; although further studies of early charcoal administration might be useful, effective affordable treatments are urgently needed.

Introduction

Treatment of self-poisoning involves resuscitation, antidotes, gastric decontamination, and supportive care.1 2 However, no evidence of benefit from gastric decontamination exists, resulting in widespread debate about the role of forced emesis, gastric lavage, and activated charcoal in the management of poisoned patients.3 4 Since few self-poisoning patients die in hospital in developed countries,5 decontamination seems unlikely to offer much benefit and its routine use is no longer recommended in these regions.3 6

Self-poisoning in the rural developing world, however, is quite different. Highly toxic pesticides and plants are ingested rather than pharmaceuticals and the resulting case-fatality is 10–50-fold higher than in developed countries.7 8 Self-poisoning causes more than 300000 deaths each year in the Asia Pacific region alone.9 10 Effective therapies to improve treatment outcomes are urgently needed.

Activated charcoal is the only form of gastrointestinal decontamination that is still widely used.11 It is regarded as safe and volunteer studies show that early administration of one dose of activated charcoal can adsorb poison in the stomach and reduce absorption.12 Charcoal might also work long after ingestion, by interruption of enterohepatic and enterovascular cycling of poison.13 Multiple doses of activated charcoal are therefore given to some patients, irrespective of delay in presentation, to increase poison elimination.14 No evidence for clinical benefit from single-dose or multiple-dose activated charcoal regimens exists.15 16 Few patients present to hospital within 1–2 h in rural Asia; therefore, only one dose of activated charcoal is unlikely to offer benefit. By contrast, since charcoal might increase poison elimination several hours after its ingestion, several doses of activated charcoal might prove beneficial in such regions. Most Sri Lankan patients ingest either organophosphorus pesticides or yellow oleander (Thevetia peruviana) seeds, both of which are known to bind to activated charcoal.17 18 We therefore set up a trial to assess whether multiple doses of activated charcoal, compared with no charcoal, would reduce the rate of death and complications in self-poisoned patients in rural Sri Lanka. To distinguish whether any effect seen with multiple doses was a result of the first dose or all six doses, a third group of single-dose activated charcoal was added to the study.

Methods

Participants and procedures The protocol for this randomised, controlled trial has been published.19 The trial was done in secondary referral hospitals in Anuradhapura, Polonnaruwa, and Kurunegala, Sri Lanka. We approached all patients with poison ingestion admitted to adult wards. The exclusion criteria were: age less than 14 years; treatment with
charcoal during this episode; known pregnancy; ingestion of a corrosive or a hydrocarbon alone; need for medicine given orally; inability of medical staff to intubate the patient with a Glasgow coma score (GCS) less than 13; presentation more than 72 h after ingestion; and previous recruitment. All patients with poisoning presenting to hospital were admitted to the wards. The poison was identified from the patient, relatives, or referring doctor’s letter, or by the clinical syndrome expressed by the patient. We have noted that such historical reporting of poison ingested is highly accurate in this cohort.19,21,22

The primary aim was to determine whether routine treatment with multiple-dose activated charcoal reduced death and complications after acute self-poisoning compared with no charcoal. We also wanted to assess whether any effect noted with multiple-dose activated charcoal was a result of the first or subsequent doses of charcoal, therefore a single-dose activated charcoal treatment was added to the trial. We examined whether any benefit was consistent across the prespecified subgroups—organophosphorus or carbamate pesticides, yellow oleander,23 and pharmaceutical drugs—and whether any effect was dependent on time from ingestion to treatment or severity on admission (asymptomatic, symptomatic with GCS 14 or 15, or symptomatic with a GCS <14).

Patients were randomised (with equal probability) to receive no charcoal, one 50 g dose of activated charcoal (Carbonmix, Norit, Amersfoort, Netherlands; 2000 m2/g) dissolved in 300 mL of water, or 50 g every 4 h for six doses. Stratified block randomisation was done with the following strata: (1) substance ingested; (2) time between poisoning and recruitment (<1 h; 1–4 h; >4 h; unknown); (3) status on admission (asymptomatic, symptomatic [GCS 14 or 15], symptomatic [GCS <14]); and (4) hospital site. For each stratum, computer generated random allocation sequences with variable block sizes (3, 6, 9) were concealed within a Microsoft Access programme written for patient recruitment, randomisation, and event recording. The allocation sequence was generated independently by the study statistician and programmer. Randomisation occurred after patients’ details had been entered and receipt of consent noted, and could not be manipulated by recruiting doctors. Study doctors administered the charcoal; conscious patients drank the charcoal, and unconscious patients with protected airways received it by nasogastric tube. The study was not masked.

Primary outcome was all-cause mortality during hospital admission. Secondary outcomes were identified a priori as relevant to specific poisons. For organophosphorus or carbamate pesticides,24 secondary outcomes were intubation, time ventilated, and seizures. For oleander, outcome was occurrence of cardiac dysrhythmias needing digoxin-specific antibody fragments25 or serum potassium greater than 6.0 mmol/L. Digoxin-specific antibody fragments became unavailable after 3–4 months25 and...
patients were then transferred for temporary pacing with the same criteria. Therefore, this secondary outcome was then modified to become need for digoxin-specific antibody fragments or transfer for pacing.

Patients were seen by study doctors within 30 min of admission. Their airway was stabilised and oxygen, atropine, fluids, and antidotes given as necessary. Gastric decontamination was only started when patients were stable. Gastric lavage or emesis, but not charcoal, was previously given in hospital clinical practice. In accordance with position papers about ipecac-induced forced emesis and gastric lavage published by the international associations of clinical toxicology, we initially did not give either to recruited patients. However, from patient number 1905 onwards, after much discussion within the national doctors union, all patients presenting less than 2 h after ingestion of large amounts of moderate-toxicity to high-toxicity pesticides or high doses of toxic medications (eg, tricyclic antidepressants) received gastric lavage with 300 mL of water three times at the request of the consultant physicians.

Patients remained under the care of consultant physicians using management protocols that had been agreed with the study team. The ward team made decisions about intubation and transfer of patients to intensive care or for cardiac pacing independently of study doctors. Patients were first managed on the medical ward; those needing intubation or inotropes were transferred to intensive care as a bed became available. All who died had a judicial post mortem.

Ethics approval was received from the Oxfordshire Clinical Research Ethics Committee and Faculty of Medicine Ethics Committee, Colombo. Written informed consent was obtained from each patient, or their relative (for patients unconscious or <16 years of age), in their own language. An independent data monitoring and ethics committee (IDMEC) was established for the trial.

Interim analyses were to be supplied by the trial physicians using management protocols that had been agreed with the study team. The ward team made decisions about intubation and transfer of patients to intensive care or for cardiac pacing independently of study doctors. Patients were first managed on the medical ward; those needing intubation or inotropes were transferred to intensive care as a bed became available. All who died had a judicial post mortem.

Statistical analysis
We calculated that to detect whether multiple-dose activated charcoal reduced the case fatality from 10% to 7%, with a significance of 5% and power of 80%, a minimum of 1400 patients was needed in each group (4200 patients overall).

Demographic factors and clinical characteristics were summarised with counts (percentages) for categorical variables, mean (SD) for normally distributed continuous variables, or median (IQR) for other continuous variables. We did an intention-to-treat analysis on all patients with available outcomes data (loss to follow-up of three [<1%] patients) analysed in the groups to which they were assigned.
Figure 2: Forest plot of mortality for multiple-dose activated charcoal versus no activated charcoal

Figure 3: Forest plot of mortality for single-dose activated charcoal versus no activated charcoal
allocated. For the primary analysis, we reported the number and proportion of patients having an event. To establish the magnitude and direction of the treatment effect, we calculated the odds ratio (OR; plus exact 95% CI). We used logistic regression to compare the groups, estimate the OR (95% CI), and adjust for stratification factors and for geographical centre and baseline value (where appropriate).

The use of logistic regression was extended for the primary outcome to investigate the effects of potentially important prognostic factors such as previous administration of gastric lavage and forced emesis (by test of interaction), perform prespecified subgroup analyses with the test of interaction to examine whether the treatment effects were consistent across poison subgroups (suspected and confirmed), and test for trends in treatment effects for reported time from ingestion to randomisation and illness severity on admission. Poison-specific analyses were initially done for the groups identified on admission. Since the poison was sometimes identified only after randomisation (eg, patients randomised in the unknown poison group), analyses were then repeated including all patients identified as having ingested the poison.

Role of the funding source
The funding source had no role in study design, data collection, data analysis, and data interpretation; or writing of the report; or in the decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Patients were enrolled from March 31, 2002, in Anuradhapura and June 04, 2002, in Polonnaruwa, and from Nov 23, 2002, to Feb 03, 2003, in Kurunegala. The target sample size was reached in September, 2004. Data were then reviewed by IDMEC at its final planned analysis. Recruitment was stopped on Oct 16, 2004, as per IDMEC recommendation.

Figure 1 shows the trial profile. Table 1 shows baseline demographic and clinical characteristics in the three groups. Median time from ingestion to randomisation was similar. Although patients were eligible up to 72 h after ingestion, very few presented after 24 h—108 (2%) of 4632 presented between 24 h and 48 h and 11 (<1%) of 4632 between 48 h and 72 h. 2338 (51%) patients had ingested pesticides—1310 had ingested organophosphorus or carbamate pesticides and received multiple-dose activated charcoal (figure 3) and multiple-dose activated charcoal did not reduce mortality for patients who had ingested dimethyl organo phosphorus poisoning (webfigure 1). We did not note a consistent trend between treatment effect and time from ingestion to treatment. Reduction in mortality for patients who had ingested organophosphorus or carbamate pesticides and received multiple-dose activated charcoal was not significant (OR 0·78, 95% CI 0·51–1·19), this reduction was greater for diethyl organophosphorus poisoning than for dimethyl organophosphorus poisoning (webfigure 1).

Comparison of single-dose activated charcoal versus no charcoal (figure 3) and multiple-dose activated charcoal versus single-dose activated charcoal did not provide any evidence that charcoal affected mortality (webfigures 2–4). We did not note a consistent trend between treatment effect and either severity on admission or time from ingestion to treatment. We did not find any evidence of a significant (p=0·1).
We saw no evidence of an interaction with either forced emesis or gastric lavage for each of the treatment comparisons (data not shown).

439 patients were admitted within 2 h of poison ingestion and allocated to either multiple-dose (n=214) or single-dose activated charcoal (n=225; figures 2 and 3). The demographic and clinical baseline characteristics of early and late arrivals (defined as before or after 2 h, respectively) were very similar with respect to age, blood pressure, sex, severity of symptoms, intubation, and seizures. Oleander poisoning featured more commonly in late arrivals (497 [38%] of 3919) than in early arrivals (141 [21%] of 664). Most patients who presented late were transfers from other hospitals in which they had received forced emesis or gastric lavage. Comparison of these 439 patients with 225 who were admitted within 2 h of poison ingestion and allocated to no charcoal (figure 5) did not show evidence of benefit on death of early charcoal administration (34 of 439 vs 15 of 225; OR 1.18 [95% CI 0.61–2.38]; test of interaction p=0.5). Additionally, there was no evidence of an interaction between early charcoal administration and any of the secondary outcomes.

Administration of charcoal seemed safe. Despite 2957 patients ingesting poisons (1647 oleander and 1310 organophosphorus or carbamate pesticides) that are treated with atropine, which would reduce bowel motility, only two were referred for surgical review for acute abdomen. None of the patients who died in the study had substantial quantities of charcoal in their lungs at judicial post-mortem examination.

The number of patients with absent bowel sounds on abdominal auscultation was small—17 (1.1%) of 1531 receiving multiple-dose activated charcoal, seven (0.5%) of 1310 organophosphorus or carbamate pesticides) that are treated with atropine, which would reduce bowel motility, only two were referred for surgical review for acute abdomen. None of the patients who died in the study had substantial quantities of charcoal in their lungs at judicial post-mortem examination.

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Discussion

This randomised, controlled trial showed no benefit from routine administration of multiple-dose activated charcoal in Sri Lankan district hospitals. Most patients had ingested yellow oleander seeds or pesticides. Both poisons have major effects that are delayed for several hours, most deaths from oleander seeds occurred after 12 h (data not shown), and the median time to intubation and death after admission for all poisoned patients was 12–24 h (figure 4), potentially giving multiple-dose activated charcoal time to work. Absence of benefit was seen irrespective of the poison ingested or time to presentation. A non-significant trend towards benefit with charcoal was seen in the most ill patients at admission.

In 2003, de Silva and co-workers30 published the results of a single-blind, randomised, placebo-controlled trial investigating the effect of multiple-dose activated charcoal in yellow oleander poisoning. They reported a beneficial effect of charcoal on time to death (figure 4) and most of the deaths occurred within the first 24 h in all poison groups. Multivariable logistic regression showed no effect (no evidence of an interaction) of our change in gastric lavage policy 12 months into the trial (in which all patients presenting within 2 h of a serious ingestion received lavage; data not shown).

Neither multiple-dose nor single-dose activated charcoal reduced the need for intubation, the rate of seizures, or (in oleander poisoning) cardiac dysrhythmias (tables 2 and 3). A similar proportion of patients needed intubation in each group: no difference was recorded in the time to first intubation (figure 4). Median duration of ventilation (excluding deaths) was similar with multiple-dose activated charcoal (83.8 [IQR 35.0–173.0] h) and no charcoal (88.5 [38.5–203.1] h), but longer with single-dose activated charcoal (112.0 [36.6–234.9] h). Analyses were repeated, as stated in the protocol, after reclassification of cases in which the poison was identified after randomisation. Reallocation of these cases did not tangibly affect the findings for any analysis (figures 2 and 3; webfigures 1–4).

Although routine forced emesis and gastric lavage are no longer recommended internationally for self-poisoned patients, most had received mechanical forced emesis (2503 [54.0%] of 4632) or gastric lavage (347 [7.5%] of 4632), or both (64 [1.4%] of 4632), in a peripheral hospital before transfer. We used logistic regression analysis to assess whether previous gastric decontamination at the referring hospital affected the results of this study for the primary outcome—ie, death.
case fatality with multiple-dose activated charcoal of five (2.5%) of 201 patients versus 16 (8%) of 200 with single-dose activated charcoal (p=0.025, relative risk [RR] 0.31, 95% CI 0.12–0.83). The corresponding comparison in our study showed deaths in 23 (4.3%) of 540 patients given multiple-dose activated charcoal versus 26 (4.7%) of 549 given single-dose activated charcoal; a result showing a small non-significant benefit in favour of multiple-dose activated charcoal (0.90, 0.52–1.56). A longer regimen was given in de Silva and co-workers’ study—50 g every 6 h for 12 doses during 72 h—than in our study—50 g every 4 h for six doses during 20–24 h. However, 87% of oleander-induced deaths occurred within 24 h of admission, indicating that the continuation of charcoal therapy after 24 h could not account for the major difference in effectiveness of multiple-dose activated charcoal between studies.

We do not think that absence of benefit in our study was caused by poor compliance. Although we could not objectively measure it, we did estimate compliance in 1103 patients receiving charcoal in two study hospitals. Overall, patients ingested 80% of their first dose; and thereafter compliance decreased for further doses until 60% of the sixth dose was ingested. Compliance was not formally measured in de Silva and colleagues’ study, but they reported that “none refused to take it”. This finding contrasts with our absolute refusal rates of 2% for the first dose, increasing to 12% by the sixth dose. However, such differences are unlikely to have caused the effect we report. Nor does it seem likely that the difference was caused by the charcoal used—Carbomix is used widely worldwide and has a surface area of 2000 m²/g compared with Haycarb (Hayes, Colombo, Sri Lanka; 1600 m²/g), which de Silva and colleagues used. Overall, the combined evidence does not suggest a major effect of charcoal administration in oleander poisoning.

No benefit was noted from single-dose activated charcoal (or from the first dose of multiple-dose activated charcoal). Our study was not specifically designed to look at patients presenting within 2 h, in whom single-dose activated charcoal is proposed to have its major effect on reduction of poison absorption. The median time to admission in our trial was longer than 2 h; only 664 patients presented within 2 h. However, many patients had ingested oleander seeds, which are slowly absorbed over many hours and single-dose activated charcoal was worse than no charcoal in these patients (figure 3).

The absence of effect of single-dose activated charcoal in our study contrasts with studies of volunteers receiving pharmaceutical drugs that reduced absorption when single-dose activated charcoal was given early and also contrasts with a pharmacokinetic study that showed increased clearance in patients with moderate oleander poisoning. However, subtoxic doses of pharmaceutical drugs were given to the volunteers and these doses were probably far less than those that produced clinical outcomes in our study. Furthermore, charcoal is most likely to be effective with highly toxic poisons that cause clinical effects at small doses. Sri Lanka has banned the most toxic WHO class I pesticides, leaving only a few moderately toxic pesticides. The pharmacokinetic study that showed differences in oleander poisoning did not include patients with major clinical outcomes occurring within 24 h, suggesting that higher doses of poison were ingested by patients in our randomised controlled trial.

Mortality in the control no charcoal group was lower than predicted for two main reasons. First, frequent careful monitoring by the study team, its use of protocols, and administration of gastric lavage during resuscitation to only a few patients resulted in a substantial reduction in deaths for the patients recruited to the trial (data not shown). Second, because of poor outcome after paraquat ingestion, hospital doctors were not in equipoise for

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**Figure 5: Forest plot of effect of time to recruitment on mortality for multiple-dose or single-dose activated charcoal versus no activated charcoal, with detailed breakdown of less than 4 h**

AC=activated charcoal.
patients with paraquat poisoning and wanted to give Fuller’s earth or single-dose activated charcoal. Therefore few paraquat-poisoned patients were recruited, lowering overall mortality.

The fewer than predicted number of events reduced the power of our trial. However, at the third planned interim analysis, when the prespecified recruitment target had been reached, the IDMEC considered the likelihood of finding a clinically meaningful benefit from giving charcoal if the trial was extended over and beyond the original target sample size. After assessment of the accumulating evidence from this trial, the IDMEC recommended that the trial terminate recruitment.

Another limitation was the absence of masking. We believed that masking was difficult because of the impossibility to conceal from a reviewing doctor whether a patient had received any charcoal. An absence of masking might have allowed for performance bias for the secondary outcomes. To counter this potential bias, the medical team made decisions about intubation and transfer of patients independently of the study doctors. This pragmatic response to an issue of internal validity was regarded as acceptable since the primary outcome—death during the admission—was unambiguous.

The poisons ingested by our study patients were typical of rural Asia. Unlike western countries, where patients generally ingest pharmaceuticals with varying mechanisms of action, most patients in our study took two types of poisons—anticholinesterase pesticides (28·3%) and cardenolides (35·6%). The large number of patients ingesting these two types of poisons suggests that the results are especially applicable to them.

We believe our study is relevant to rural Asia because it shows that routine multiple-dose activated charcoal administration is unlikely to be beneficial even in locations with high case-fatality rates in which an intervention might be expected to offer greatest benefit. Our study shows that multiple-dose activated charcoal is not indicated for oleander poisoning or for organophosphorus and carbamate pesticides—all common and highly toxic poisons across the region.

We were not able to assess the effect of early administration of single-dose activated charcoal on outcome since few patients presented within 2 h. The OR 95% CI stretched from 0·61 to 2·38, suggesting little likelihood of benefit. However, our results might be useful in establishing a cluster randomised controlled trial in rural hospitals with the aim of recruiting large numbers of patients presenting within 2 h, especially those with a GCS of less than 14 on admission.

Intentional self-poisoning continues to kill many people throughout rural Asia. We have little evidence on which to base medical therapy of pesticide poisoning and effective treatments for oleander poisoning are often unaffordable.25 Clinical trials to identify effective therapy and new therapeutic interventions with which to prevent these unnecessary deaths are urgently needed.

Contributors
ME designed and set up the randomised controlled trial, and wrote the first draft of the report. EJ helped design the study and did the statistical analysis. NB helped design and set up the trial. LS and FM ran the trial centres, and together with ME extracted and checked patient data for analysis. WD, AH, SA, KJ, and Sj had clinical responsibility for the patients in the study. MHRs and DAW are the senior coordinators of the Ox-Col Collaboration. All authors had a role in improving the study design and in reviewing and editing the final version of the report.

Conflict of interest statement
We declare that we have no conflict of interest.

Acknowledgments
We thank Palitha Abeykoon and Kan Tun (WHO), Lakshman Karalliedde, D G S Alahakoon, and W M T B Wijekoon, and the Directors, medical and nursing staff of the study hospitals for their help and support, the IDMEC, Robin Ferner, and Doug Altman for advice, Geoff Iobister, Simon Thomas, Lewis Nelson, and Nick Bateman for critical review, Ly-Mee Yu and Nicola Alder for statistical support, Shukry Zawahri, and Chathura Palagasinghe for help with the final patient audit; and the Ox-Col study doctors for their work in the face of many pressures. ME is a Wellcome Trust Career Development Fellow; this work was funded by grant 06/3560 from the Wellcome Trust’s Tropical Interest Group to ME. The South Asian Clinical Toxicology Research Collaboration is funded by a Wellcome Trust/National Health and Medical Research Council International Collaborative Research Grant 07/6659.

Ox-Col poisoning study collaborators

Independent data monitoring and ethics committee
Mike Clarke (Director, UK Cochrane Centre, Oxford; Chair); Keith Hawthon (Department of Psychiatry, Oxford); Julian Higgins (MRC Biostatistics Unit, Cambridge University; Statistician); Saroj Jayasinghe (Department of Clinical Medicine, Colombo); Nimal Senanayake (Department of Clinical Medicine, Peradeniya); Kris Weerasuriya (WHO/SEARO, New Delhi).

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