A randomized clinical trial of activated charcoal for the routine management of oral drug overdose

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Summary

Background: Activated charcoal (AC) is commonly used for the routine management of oral drug overdose.

Aim: To determine whether the routine use of activated charcoal has an effect on patient outcomes.

Design: Randomized controlled unblinded trial.

Methods: We recruited all adult patients presenting with an oral overdose at The Canberra Hospital, excluding only transfers, late presenters, those who had ingested drugs not adsorbed by activated charcoal or where administration was contraindicated, and very serious ingestions (at the discretion of the admitting physician). Patients were randomized to either activated charcoal or no decontamination.

Results: The trial recruited 327 patients over 16 months. Of 411 presentations, four refused consent, 27 were protocol violations and 53 were excluded from the trial. Only seven were excluded due to the severity of their ingestion. The most common substances ingested were benzodiazepines, paracetamol and selective serotonin reuptake inhibitor antidepressants. More than 80% of patients presented within 4 h following ingestion. There were no differences between AC and no decontamination in terms of length of stay (AC 6.75 h, IQR 4–14 vs. controls 5.5 h, IQR 3–12; p = 0.11) or secondary outcomes including vomiting, mortality and intensive care admission.

Discussion: Routine administration of charcoal following oral overdose did not significantly influence length of stay or other patient outcomes following oral drug overdose. There were few adverse events. This does not exclude a role in patients who present shortly after ingestion of highly lethal drugs.

Introduction

In 1997, the AACT/EAPCCT (American Academy of Clinical Toxicology and European Association of Poisons Centers and Clinical Toxicologists) published a Position Statement on Single-Dose Activated Charcoal. This recommended that activated charcoal (AC) should not be used routinely in the management of poisoned patients. However, it was suggested that based on the available volunteer studies, AC is more likely to produce benefit if it is administered within the first hour after ingestion.¹ The clinical evidence behind this position statement consisted of ten published studies. The first group of
studies compared various forms of gastric emptying (gastric lavage, ipecac, gastric aspiration) and administered AC to all patients. The second group compared AC with a combination of gastric emptying procedures. These studies were small (n = 62, 17, 60 and 77), studied selected drugs and the outcomes were various simple pharmacokinetic calculations, supported in two studies on tricyclic antidepressant poisoning by measures of the degree of coma and presence of toxic symptoms. One of these studies included a ‘no-treatment’ arm, but there were only five patients in this group. One study compared AC in a standard 50 g dose against no gastric decontamination treatment, but did not categorize patients according to time from ingestion, was not formally randomized, and excluded patients who ingested toxic doses of paracetamol and those who were symptomatic. Since the publication of the consensus document, another study has been published. This large trial was a prospective alternate-day trial completed in 1994. It showed no differences in outcome parameters. However, fewer than half those assigned to AC actually received the treatment, and intention-to-treat analysis was not used.

Clinical decision-making is based on available evidence. However, the change in the accepted standard of overdose patients has led to a ‘shifting sand scenario’. The AACT/EAPCCT position statement on AC aimed to aid practitioners in their management of these patients. This paper reviewed the topic thoroughly, to try to clarify the evidence available at the time and highlight its deficiencies. However, much of the evidence included was based on studies completed 10–15 years ago, when gastric decontamination methods such as lavage, induced emesis and aspiration were still routinely used. Now that these are rarely used, the trial evidence for AC is difficult to incorporate into clinical practice.

To summarize the evidence prior to this trial, charcoal was known to adsorb many drugs, and both animal and volunteer studies had shown an effect on drug blood levels. However, the routine use of charcoal had been compared in randomized clinical trials to other forms of gastric decontamination methods but not with supportive care alone. Despite this lack of published evidence for the use of AC, it remains widely administered to patients following oral overdose, and is often given more than one hour post ingestion. At our hospital, over 80% of overdose patients received AC prior to the trial. No studies have addressed its use in the routine management of oral drug overdose including paracetamol ingestions and symptomatic patients. In this clinical trial, we tested the hypothesis that the routine administration of AC to patients who present after a deliberate oral overdose would change clinical outcome.

Methods

The study was performed between July 1999 and October 2000 on sequential presentations to the Emergency Department at The Canberra Hospital, Australia. This is a 400-bed tertiary referral teaching hospital in an urban setting.

We included all patients aged 16 years or older who presented within 12 h following a deliberate oral overdose and were thought to have ingested a substance adsorbed by AC. Patients could be excluded at the discretion of the treating physician if they had ingested a potentially toxic modified release preparation, or presented within 1 h of an ingestion of a highly lethal substance (e.g. large doses of tricyclic antidepressants, antineoplastic medications, aspirin, cardioactive agents). In addition, patients were excluded if they had ingested substances not significantly adsorbed by AC (hydrocarbons, acids, alkanes) or had contraindications (unprotected airway, non-intact gastrointestinal tract).

Patients were randomized to AC or no gastrointestinal decontamination, as indicated by the sealed sequentially numbered envelope contents. AC was administered (Norit C 50 g in 200 ml of water as slurry) either orally or via a naso-gastric tube. Other treatment appropriate to the substances ingested was then instigated, and patients were either discharged home after an appropriate monitoring period with psychiatric follow-up, or admitted to a medical ward or ICU/CCU for continued monitoring or treatment. Psychiatric services were consulted while the patient was medically admitted, and care was transferred to them once the patient was determined to be medically fit for discharge. The primary outcome measure for the trial was the medical length of stay of the patient (LOS, hours). Secondary outcomes, such as the requirement for ventilation, vomiting after admission, occurrence of aspiration and death were also recorded. Medical LOS was calculated as the time of presentation to the emergency department until the patient was declared medically fit for discharge, on the basis of standard clinical criteria (i.e. normal level of consciousness, no need for antidote or other intervention, normal vital signs and no symptoms). This decision was made by a senior member of the medical staff, but this was not usually a toxicologist or any other member of the study team. The treating medical staff

...
were not blinded to the administration of AC, as this would be very difficult to achieve. The coordinator and data manager of the study was never involved in the decision to medically discharge the patient.

Data were collected by means of a Toxicology Admission Form. This was a systematic record of the examination and results for each toxicological presentation. Data were then entered into a Microsoft Access database that was password-protected, and access was available only to the researchers. The Australian Capital Territory Department of Health and Community Care Ethics Committee approved the trial. Consent was obtained if the patient was competent. Non-competent patients (e.g. unconscious, delirious, psychotic, etc.) were randomized without prior consent. There was information available to patients and the next of kin about the trial, and there was a display in the waiting area of the Emergency Department describing the trial.

For this trial to be able to detect a 33% reduction in LOS for patients who received AC, it was calculated that a sample size of 300 was required (power 0.8, \( p < 0.05 \), two-sided). Data were analysed using the Mann-Whitney test for continuous variables and Fisher’s exact or \( \chi^2 \) tests for categorical variables using Prism Software. Analysis was based on intention to treat.

Results

There were 411 presentations following oral drug ingestion. Of these, 53 were excluded from the trial, four refused consent and 27 were protocol violations. This left a population of 327 presentations to randomize to AC or no gastrointestinal decontamination (Figure 1).

Of the patients who were excluded from the trial, the majority were late presenters (>12 h after ingestion) or transfers from other hospitals where treatments had already been instigated. The treating physicians excluded seven severe ingestions from the trial. Three had ingested slow-release cardiac agents. The other four were patients with Glasgow Coma Score (GCS) <7 at presentation, with clinically serious poisoning and unclear information on the drugs or time of ingestion. These seven were given AC but not randomized. Protocol violations (failure to randomize eligible patients) occurred in 8% of overdose patients. Most of these were early in the trial, when staff were unfamiliar with the trial, or when there was confusion about the presenting diagnosis.

Overall, the two arms of the trial were well matched, and showed no differences in baseline characteristics of randomized subjects (Table 1). About a third of patients in each arm of the trial had a decreased level of consciousness. Presentation occurred within 4 h of ingestion in more than 80% of patients where the time of overdose was known. Presentation occurred within 2 h in 57.8%. Benzodiazepines and paracetamol were the most commonly ingested substances, followed by the selective serotonin reuptake inhibitor (SSRI) antidepressants. Multiple drug ingestion was common.

LOS was not different between the groups, regardless of the time to presentation or the severity of ingestion as measured by the GCS at presentation (Table 2). There were no differences between AC and no decontamination in terms of LOS (AC 6.75 h, IQR 4–14 vs. controls 5.5 h, IQR 3–12; \( p = 0.11 \)). AC also had no significant effects on the secondary outcomes of aspiration, vomiting or ventilation (Table 3). There was only one death during the trial (0.3% mortality). This patient presented 2.5 h following ingestion of a combination of turpentine, benzodiazepines, boracic acid and a large quantity of alcohol, and had aspirated outside hospital. If the history of ingestion had been obtained prior to randomization then this patient would not have been included in the trial, due to the ingestion of hydrocarbons.

Discussion

This trial highlights the low toxicity of most drug ingestions in recent times, in developed countries. Drugs taken in overdose now differ from those ingested 10–20 years ago. The most common agents ingested in our study were benzodiazepines, paracetamol and the newer antidepressants that have very low case-fatality rates. In contrast, past studies investigated gastric decontamination procedures following agents that had much higher case-fatality rates such as tricyclic antidepressants and barbiturates, and excluded paracetamol. Intentional overdose of orally ingested agents as a cause of death in hospital is rare in Australia, although the use of toxic oral recreational drugs may affect this in the future. There have been advances in supportive care, resuscitation and retrieval, and new antidotes have become available. Management of the severely ill patient has been optimized through the use of advanced cardiac life support. There was only one death (0.3%) in our study, which is consistent with other recent studies.
(from about 80% before the trial to 10% in a recent audit), and deaths in hospital have remained very infrequent. Death from overdose in the developed world usually occurs out of hospital, or as a result of complications occurring prior to hospitalization.\textsuperscript{23,24}

The trial continued for 16 months, and we demonstrated that it is possible to recruit patients rapidly into a toxicology trial. However, a major limitation is the size of the study. It should also be acknowledged that our study was designed to assess superiority, not equivalence. Less frequent outcomes, such as death, aspiration and ventilation would require a very much larger trial to detect clinically meaningful differences. Our trial was deliberately designed to assess usual clinical practice in adult overdose patients, and thus the results may not be generalizable to all poisonings.

The typical patients in our trial presented within 1–4 h after ingestion of pharmaceuticals with relatively low toxicity such as paracetamol, SSRIs and benzodiazepines. Most importantly, there were seven severe ingestions that were excluded (around 2% of the total), and results should not be generalized to the most severe ingestions. Very early presentations (<1 h) after ingestion were uncommon in our study, and our study was not large enough to detect a benefit confined to this sub-group. Also, our trial was completed in a developed country and in an urban environment where facilities were centralized and supportive care of a high standard. Translation of these results to the severe poisonings that are more common in developing countries may be inappropriate.\textsuperscript{25}

We endeavoured to eliminate potential sources of bias in the trial design, with true randomization,
prevention of subversion in allocation and intention to treat analysis including all randomized patients. However, our trial was not blinded: due to the nature of charcoal, this is very difficult. One trial attempted single blinding, but did not report on the success of this attempt.26

Our results provide the only randomized clinical trial evidence to support the recommendation of the AACT/EAPCCT Position Statement that AC should not be given routinely for overdose.1 If the benefit of AC is primarily limited to the first hour after an ingestion as volunteer studies indicate, there are implications for future studies. Our study would have needed to have been at least ten times larger to detect a difference in this sub-group, for it is uncommon to present this quickly, and enrolment and administration of AC within an hour would be even more difficult to achieve.

It could also be argued that there is a need for a trial to determine the optimum approach for the management of oral overdoses of highly toxic substances that present within 1 h or are ingested as slow-release preparations. Such ingestions are uncommon (only 2% of overdose patients in our study), and only a very large multi-centre trial would provide a definitive result. Such a trial seems unlikely to get the necessary widespread clinical support and ethical approvals. Given that adverse effects of AC occur rarely, we believe its use should continue in this very high-risk population. However, we have shown that the routine use of activated charcoal for the management of all overdoses, particularly those presenting after 1 h, did not lead to any statistically significant change in length of stay or other outcomes. We suggest activated charcoal should be used far more selectively. Specifically, it should be restricted to those situations where there is a substantial risk from the poisoning and a significant amount of the poison is likely to still be present in the gut.

### Table 1 Baseline characteristics of treatment groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No gastrointestinal decontamination (n = 161)</th>
<th>Charcoal (n = 166)</th>
<th>p (Mann Whitney)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (IQR)</td>
<td>28.5 (21.5–42.5)</td>
<td>31.5 (21–42)</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>113 (70%)</td>
<td>116 (70%)</td>
<td></td>
</tr>
<tr>
<td>Vomited out of hospital</td>
<td>11 (7%)</td>
<td>19 (11%)</td>
<td></td>
</tr>
<tr>
<td>GCS &lt;15</td>
<td>43 (27%)</td>
<td>50 (30%)</td>
<td></td>
</tr>
<tr>
<td><strong>Time to presentation</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (5%)</td>
<td>21 (13%)</td>
<td></td>
</tr>
<tr>
<td>≤2</td>
<td>95 (59%)</td>
<td>94 (57%)</td>
<td></td>
</tr>
<tr>
<td>2–4</td>
<td>32 (20%)</td>
<td>25 (15%)</td>
<td></td>
</tr>
<tr>
<td>&gt;4</td>
<td>26 (16%)</td>
<td>26 (16%)</td>
<td></td>
</tr>
<tr>
<td><strong>Most common drugs ingested</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>60 (37%)</td>
<td>60 (36%)</td>
<td></td>
</tr>
<tr>
<td>Paracetamol</td>
<td>46 (29%)</td>
<td>43 (26%)</td>
<td></td>
</tr>
<tr>
<td>SSRIs</td>
<td>26 (16%)</td>
<td>35 (21%)</td>
<td></td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>16 (10%)</td>
<td>19 (11%)</td>
<td></td>
</tr>
<tr>
<td>Tricyclic</td>
<td>11 (7%)</td>
<td>6 (4%)</td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>5 (3%)</td>
<td>10 (6%)</td>
<td></td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>56 (35%)</td>
<td>52 (31%)</td>
<td></td>
</tr>
<tr>
<td>More than one drug ingested</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

GCS, Glasgow coma score.

### Table 2 Primary outcome of length of stay (LOH, hours): overall and in subgroups according to time to presentation and Glasgow Coma Score (GCS)

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No gastrointestinal decontamination (n = 161)</th>
<th>Charcoal (n = 166)</th>
<th>p (Mann Whitney)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>5.5 (3.0–12.0)</td>
<td>6.8 (4.0–14.0)</td>
<td>0.11</td>
</tr>
<tr>
<td>Unknown ingestion time (n = 29)</td>
<td>5.0 (3.0–9.0)</td>
<td>7.0 (4.0–24.0)</td>
<td>0.24</td>
</tr>
<tr>
<td>≤2 h post ingestion (n = 189)</td>
<td>5.0 (3.0–9.8)</td>
<td>6.0 (4.0–12.0)</td>
<td>0.33</td>
</tr>
<tr>
<td>2–4 h post ingestion (n = 57)</td>
<td>8.0 (3.0–16.0)</td>
<td>6.0 (4.0–16.5)</td>
<td>0.50</td>
</tr>
<tr>
<td>&gt;4 h post ingestion (n = 52)</td>
<td>7.5 (3.3–14.0)</td>
<td>9.5 (4.5–18.5)</td>
<td>0.36</td>
</tr>
<tr>
<td>GCS 15 (n = 234)</td>
<td>5.0 (3.0–11.5)</td>
<td>5.8 (4.0–12.0)</td>
<td>0.09</td>
</tr>
<tr>
<td>GCS &lt;15 (n = 93)</td>
<td>9.0 (5.0–28.0)</td>
<td>12.0 (4.5–36.0)</td>
<td>0.52</td>
</tr>
</tbody>
</table>

Data are medians (IQR).
Acknowledgements

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References


