

Activated Charcoal in Resource Poor Settings: Reviewing the Evidence

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Abstract

Background: Poisoning is unfortunately a common occurrence worldwide with relatively higher mortality in resource-poor settings, and oral activated charcoal (AC) is a standard therapy both for gastrointestinal decontamination as well as enhancement of elimination. AC is an inexpensive, widely available decontaminant with a favorable side effect profile. However, recent clinical trial results have called into question its benefit. This review was done to examine the recent clinical evidence evaluating standard AC decontamination in international resource-poor settings.

Methods: A review of the recent literature was conducted on both single dose activated charcoal, (SDAC) and multidose activated charcoal (MDAC) looking for the clinical evidence that supports its use. EMEDLINE Pubmed, Cochrane Databases, Clinicaltrials.gov, and Google Scholar were searched for published studies in the English language in the last 20 years using an exhaustive search methodology.

Results: Out of all eligible studies published in the past 20 years, 64 total studies met criteria for inclusion. Of these, there were 4 MDAC trials (3 prospective, 1 retrospective) and 7 SDAC trials (5 prospective, 2 retrospective) with analyzable efficacy data. Of these, two studies showed mortality benefit, while most were underpowered to show a benefit. Subgroup analysis suggested greatest benefit for organophosphorus pesticides and cardiac glycosides.

Conclusion: This review of the past two decades of literature evaluating the efficacy of AC in RPS found support for SDAC in undifferentiated overdose presenting in RPS. MDAC administration demonstrated benefit for selected poisonings, particularly cardiac glycosides and organophosphorus pesticides. In addition, adverse events associated with AC administration appear to be extremely rare.

Keywords: Activated charcoal; Poisoning; Resource-poor settings

Introduction

The use of charcoal-like mixtures dates back to Ancient Greece to lessen the effects from food poisoning [1]. Oral activated charcoal (AC) is a fine, black, odorless, insoluble carbon-based powder that is processed to achieve an extremely high surface area [2], and is used around the world as a decontaminant to toxic drug exposure and oral overdose. Charcoal can be made from a variety of materials including wood, coconut, or petroleum by a two-step process beginning with pyrolysis by thermochemical decomposition at high temperatures in the absence of oxygen. The “activation” process involves an oxidizing agent such as carbon dioxide or steam to create a maze-like internal porous structure with very high internal surface area [1].

The mechanism of action of AC involves decontamination of the gastrointestinal (GI) tract via adsorption as well as enhanced elimination in some poisonings. Adsorption is believed to rely on hydrogen bonding, ion-ion, dipole, and van der Waals forces to adsorb material within the gut lumen, thus preventing the toxic effects of systemically absorbed molecules and chemicals [1,3]. When mixed as a slurry and given orally, AC begins to work within one-minute and reaches an equilibrium in about 10-25 minutes [4]. Efficacy of AC for GI decontamination was first studied in the 1940s, showing that AC, is a powerful adsorbent both in vitro [5], and in vivo [6].

The position statement by the American Academy of Clinical Toxicology (AACT)/European Association of Poison Centres and Clinical Toxicologists (EAPCCT) recommends its use within the first hour after drug exposure for maximum benefit [3]. However, although its ability to prevent GI absorption reduces as time elapses between exposure and decontamination there is evidence that AC may be of benefit up to 4 hours [7,11], or even at 9-12 hours [12].

Many reports in the recent literature have investigated the use of AC internationally in resource-poor settings (RPS). An RPS is widely defined as an environment where the use of routine antidotes (e.g., NAC for acetaminophen and anti-digoxin Fab antibody fragments for Digoxin) is either unavailable or prohibitively expensive [13]. Although the rate of suicidal intent is not necessarily higher [14], self-poisoning in industrialized countries, most commonly from pharmaceuticals like acetaminophen/ paracetamol (APAP), benzodiazepenes and tricyclic antidepressants have a much lower mortality (0.5% UK) than self-poisonings in developing countries, 10-20% mortality [14,15]. Patients in RPS typically have limited access to mental health services and are demographically young and otherwise productive. Such patients commonly present following consumption of highly toxic pesticides or poisonous plants, as opposed to over-the-counter medication more common to non-RPS [14,16].

AC was once called the “ultimate antidote” (due to its safety, favorable side effect profile, low cost, and wide availability) [16-20], however recent literature evidence has challenged this notion. The goal

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Received November 12, 2011; **Accepted** January 02, 2012; **Published** January 04, 2012

Citation: Abrass A, Manini AF (2012) Activated Charcoal in Resource Poor Settings: Reviewing the Evidence. J Clin Toxicol S1:006. doi:10.4172/2161-0495.S1-006

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of this review was to review new evidence regarding the clinical efficacy of AC in RPS, with less focus on pill ingestions [3,7,13,21], which may not be relevant for the majority of poisonings in RPS. We hypothesized a favorable risk-benefit ratio would be found given its high safety profile, theoretical mechanism, and general ease of use.

Methods

Study type

This review was performed by two independent reviewers to evaluate the clinical evidence supporting the use of single dose activated charcoal (SDAC) and multiple dose activated charcoal (MDAC) in clinically suspected poisoning.

Definitions of terms

An RPS is widely defined as an environment where the use of routine antidotes (e.g., NAC for APAP overdose) is either unavailable or prohibitively expensive [2,7,13,16]. Clinical Trials in this study were defined as research studies using consenting human subjects that tests the effectiveness and safety of AC as a study intervention. Overdose was defined as exposure to a therapeutic agent, drug, or narcotic, in excess of that required to produce the desired effects which may or may not produce harm. Poisoning was defined as harm due to exposure from any chemical, substance, drug or toxin. Mean-residence-time (MRT) was defined as a dose-independent, non-compartmental method for measuring the time a drug spends in the body [22].

Abstraction method

EMEDLINE Pubmed, Cochrane Databases, Clinicaltrials.gov, and Google Scholar were searched for published studies in the English language using the search terms “activated charcoal” and any of the following: “poison” or “overdose” or “ingestion” “activated charcoal” or “gastric decontamination” or “intestinal dialysis” or “SDAC” or “single dose activated charcoal” or “MDAC” or “multi-dose activated charcoal” or “multiple-dose activated charcoal”. Exclusion criteria were any of the following: lack of AC decontamination data, non-English language, animal studies, healthy human volunteer trials, and studies that incorporated the use of hemodialysis. Articles evaluating SDAC were limited to those evaluating, in at least one study-arm, one single dose of AC. Articles evaluating MDAC were limited to those evaluating, in at least one study-arm, the administration of 2 or more doses of AC [2].

Results

Search results

Using the specified search terms in the last 20 years of literature, 64 studies were included for analysis after applying inclusion/exclusion criteria. Of these, four studies looked only at adverse events and applicability of AC and were excluded.

Efficacy of SDAC

Overall there were 45 studies found regarding SDAC, of which 31 were excluded (10 reviews of literature, 7 human volunteer studies, 9 animal studies, 5 case series/reports), leaving 14 human studies (8 prospective, 6 retrospective) and only 7 with suitable efficacy data. These 7 included studies evaluating the efficacy of SDAC are summarized in Table 1.

Two large prospective studies of SDAC vs. no treatment in adults with undifferentiated drug overdose (Cooper 2005 and Merigian 2002) were unable to show differences in length of stay (LOS), vomiting, or mortality (only one death between both studies). One small pediatric study (Kornberg 1991) demonstrated shorter LOS and less emesis in the AC group and there were no deaths. Two large studies (Spiller 2006, Spiller 2007) evaluated SDAC v. no treatment in APAP ingestions and demonstrated a modest mortality benefit as well as a beneficial effect on transaminases. One large retrospective study of adult APAP ingestions evaluated three arms (SDAC vs. gastric lavage plus SDAC vs. no treatment) and found a beneficial effect on transaminases in both SDAC arms but had no deaths.

Efficacy of MDAC

Overall there were 7 studies found regarding MDAC efficacy (human non-volunteer), of which 2 were excluded (2 case series/reports), leaving 4 human studies (3 prospective, 1 retrospective) and all 4 with suitable efficacy data. The largest prospective study (Eddleston 2008) evaluated undifferentiated overdoses with 3 arms (SDAC, MDAC, no AC) in Sri Lanka and found a non-significant trend towards improved in-hospital mortality with MDAC (6.3%) vs. SDAC (7.1%) vs. no AC (6.8%). Three additional studies evaluated MDAC for cardiac glycoside poisoning, two of which evaluated MDAC vs. SDAC conducted in RPS (Sri Lanka). The results are summarized in Table 2. One large subgroup analysis was performed (Eddleston 2008) which demonstrated mortality benefit in pesticide poisoning (see Table 3).

Author/Yr	Study type	Study vs. Control	N	Mortality	Secondary Endpoint(s)	Significance
Spiller 2007	Retrospective APAP	AC+NAC vs. NAC	97,960	0.5% vs. 0.8%	↓ AST/ALT>1000 AC 2.9% vs. 12%	SDAC saves lives, ↓ liver damage
Spiller 2006	Prospective APAP divided by time to NAC	AC+NAC vs. NAC 4-8hrs, 9-12hrs and 13-16hrs	145	None	↓ AST or ALT >1,000 4-8h 0% vs. 11.7% 9-12h 2.7% vs. 52% 13-16h 10% vs. 45%	↑ Effect of AC when NAC started later
Cooper 2005	Prospective All ODs	AC vs. No AC	327	0.3%	1° LOS, no dif 2° vomit/asp/ICU no dif	Low acuity, severe ODs and <1hr excluded
Merigian 2002	Prospective All OD	AC vs. No AC	1479	None	1° LOS, no dif 2° clinical worse/emesis ↓Emesis- AC 25% v no AC 14%	Subjective endpt. Low acuity 86% discharged,
Buckley 1999	Retrospective APAP	AC 1-2g/kg vs. GL+AC vs. control	981	None	↓ risk of hepatotoxicity AC 12.9% AC+GL 14.2% control 29.9%	AC↓ serum toxicity, GL no benefit
Kornberg 1991	Prospective Children	AC vs. SOI + AC	70	None	Less emesis and shorter LOS w AC	SOI ↑ side effects, delays AC
Underhill 1990	Prospective APAP	AC vs. GL vs. SOI	60	None	% fall in serum [APAP] AC 52 GL39 SOI 41	AC > GL or SOI if <2hrs

Abbreviations: AC:Activated Charcoal; APAP:Acetaminophen/Paracetamol; AST/ALT:Transaminases; G:Grams; GL:Gastric Lavage; H:Hours; ICU:Intensive Care Unit; Kg:Kilograms; LOS:Length of Stay; N:Number of Patients; NAC:N-Acetylcysteine; OD:Overdose; SOI:Syrup of Ipecac; ↑:Increase; ↓:Decrease

Table 1: Studies evaluating efficacy of single dose activated charcoal (SDAC).

Author/Yr	Study type	Intervention	Patient pop.	Mortality	Secondary	Significance
Eddleston 2008	Prospective	No AC SDAC 50g MDAC 50g q4h x6	4632 Sri Lanka all ODs	MDAC 6.3% SDAC 7.1% No AC 6.8%	↓ Adverse events	↓ Trend mortality: early AC ↓ Trend need for Tx
Roberts 2006	Prospective	SDAC 50g MDAC 50g q4h x6	254 Sri Lanka cardiac glycosides	None	↓ MRT and t _{1/2}	Small study no deaths.
De Silva 2003	Prospective	SDAC 50g MDAC q6h x72h	401 Sri Lanka cardiac glycosides	SDAC 8% MDAC 2.5%	↓ Arrhythmia, atropine, pacing, ICU admits	↓ Mortality ↓ Need for Tx
Ibanez 1995	Retrospective	MDAC vs. no AC	39 Digoxin	None	↓ t _{1/2} 36h vs. 68h ↑ CI 98 vs. 55	Small study, benefit in renal failure, 78% ↑ elimination

Abbreviations: AC:Activated Charcoal; G:Grams; H:Hours; ICU:Intensive Care Unit; LOS:Length of Stay; MRT:Mean Residence Time; N:Number of Patients; NAC:N-Acetylcysteine; OD:Overdose; SDAC:Single Dose Activated Charcoal; Tx: Treatment; ↑:Increase; ↓:Decrease

Table 2: Studies evaluating multiple dose activated charcoal (MDAC) mortality benefit.

Author/year	Study type	Study vs. control	Patient population	Mortality Rate	Point Estimate	Significance
Eddleston 2008	Prospective subset Pesticides	MDAC vs. SDAC vs. No AC	2037	10% v 13.7%	ARR 3.7% NNT 27	↓ Trend mortality with MDAC

Abbreviations: ARR:Absolute Risk Reduction; MDAC:Multiple Dose Activated Charcoal; NNT:Number Needed to Treat; SDAC:Single Dose Activated Charcoal.

Table 3: Mortality benefit of activated charcoal (AC) for pesticide poisoning.

Discussion

Despite the American Academy of Clinical Toxicology (AACT) recommendations of administering AC only within 1 hour of ingestion [3], the use of AC is believed to be safe and is still quite common [11,20,23]. A recent review in the US showed only 16% of toxic ingestions presented within 1hour, and only 3% of the late presenters (>1hr) were withheld AC [24], showing health care providers' reluctance to be limited strictly by the AACT guidelines. Historically, the dose of AC is 50g in adults, and 1g/kg in children derived from theoretical palatability and a therapeutic ratio [2] from a study in 1985 with human volunteers showing increased efficacy when the AC-to-drug ratio increased from 1:1 to10:1(g/g) [25]. Although new super-activated charcoal has a higher adsorptive capacity, surface area up to 2000m²/g, [26] a recent meta-analysis showed the therapeutic dose maybe as high as 40:1 [11]. This AC-to-drug ratio can be difficult to achieve as the exact amount of toxin ingested is often unknown [3] Studies have shown good compliance and toleration/tolerability of single doses up to 75g [9] and 100g, [3,27] although most trials involve the more common 50g dose in adults [2,3,11,20,21] Palatability and compliance are shown to increase when administered with cold cola and in an opaque container [28]

Enhanced elimination

Suggested indications for MDAC include ingestions with increased time of toxins within the gut, either large toxic ingestions,[2,3] ingestions known to cause concretions or bezoars, enteric-coated and slow-release tablets,[2,32] and decreased GI motility from either co-ingestion with dysmotility agents like opioids [33] or treatment with atropine [34,35]. Drugs with a low intrinsic clearance are likely to benefit from enhanced elimination with AC [3]. For example, drugs that take a long time to excrete may benefit from the enhanced elimination of MDAC. There are several reasons MDAC works to reduce tissue exposure, (by evidence of decreased t_{1/2} and MRT, or mean-residence-time) [34,36] and increase elimination beyond single dose AC. While there is excellent animal [37-38] and human volunteer [38] data in this area, we were unable to find any prospective clinical trials evaluating enhanced elimination or "gut dialysis" aside from scattered case reports [32,40].

Cardiac Glycosides

AC has been shown to statistically reduce mortality from cardiac

glycosides in one study (De Silva 2003) but failed to show similar benefit in a subgroup analysis from another large well-done study (Eddleston 2008). In the former, MDAC was shown to reduce the need for expensive treatments likely not available in RPS including anti-digoxin antibody Fab fragments, cardiac pacing and ICU admissions [7] in cardiac glycoside poisonings.

De Silva et al. showed a reduction in mortality for yellow oleander (cardiac glycoside) deliberate self-poisoning from 8% (control) to 2.5% with MDAC. All patients received gastric lavage and one dose 50g of AC regardless of time to presentation followed by MDAC 50g every six hours for 72hours in the treatment group. Being done solely at a tertiary care center, they included more transfer patients from other hospitals who the authors noted were "probably more severely poisoned" [7,35]. Reductions in secondary outcomes in the MDAC group include ICU admission, patients receiving cardiac pacing or anti-digoxin Fab antibody fragments, and life-threatening cardiac arrhythmias[7,35]. It is noted that bradycardic patients received high doses of atropine, known to induce dysrhythmias which could potentially increase mortality [16]. Atropine also increases the gut transit time, and it is unclear whether this resulted in greater systemic absorption of toxin in the control arm or enhanced elimination in the MDAC arm via increased charcoal-toxin interaction time. The reduction in mortality and life-threatening cardiac arrhythmias in the MDAC group was also noted even after 24 hours of admission, suggesting its potential benefit long after the initial ingestion of toxin [7].

MDAC vs. SDAC

The largest study to date on AC conducted in RPS (Eddleston 2008) included 4,629 patients and randomized them to receive MDAC, SDAC or no AC, with most of the patients ingesting either pesticides (51%) or cardiac glycosides, (36%) [16]. Investigators used 50g every 4hours for six doses as the MDAC regimen. They supported this shorter duration and lower total amount of AC given by stating that 87% of oleander-induced deaths occurred within 24hours of admission [16]. The primary outcome of in-hospital mortality was less with MDAC (6.3%) but not statistically significant vs. SDAC (7.1%) and no AC (6.8%). A further analysis of all patients in the Eddleston trial arriving within 90min of ingestion showed a non-significant reduced odds ratio for death (0.77, CI 0.35-1.70) with any AC [20] Another non-significant trend toward decreased mortality with MDAC treatment was noted in patients with

increased severity on admission overall (GCS<14) in the same study. There was a trend towards decreased need for cardiac pacing and antitoxin (anti-digoxin Fab antibody fragments) with MDAC vs. SDAC and no AC, although not significant.

Some authors have pointed to confounding in some aspects of the Eddleston landmark study. Such critiques included issues such as enhanced monitoring by the study team, the use of new protocols, and increased vigilance and expertise of treatment, all of which may have decreased mortality overall. Additionally, paraquat poisonings were excluded at the treating physician's discretion, also decreasing overall study mortality. However, the Eddleston study remains the single largest and best collection of AC data conducted in RPS that is currently available for analysis.

Adverse Events

AC has been reported to cause vomiting [31], aspiration [41], diarrhea [23], constipation [3], obstruction [42] electrolyte abnormalities [19] and corneal abrasion [43]. Aspiration pneumonitis, while extremely rare, is a life-threatening complication of AC administration and may further lead to such complications as bronchospasm [44] obstructive laryngitis [45], bronchiolitis obliterans [46], respiratory failure [41] and cardiopulmonary arrest [47].

Two large studies have directly addressed this risk. A recent study by Isbister and colleagues examined 4,562 toxic ingestions and found the risk of aspiration to be low at 1.6% [23]. AC did not increase the risk of aspiration although decreased GCS score, spontaneous emesis prior to AC, time to presentation >24 hours, TCA ingestion and seizure were statistically significant risk factors for aspiration [23]. Another retrospective study examined 878 patients who received MDAC, (0.6%) had aspiration pneumonitis all with no deaths or residual sequelae [19]. There were no reported bowel obstructions and the main adverse events were hypermagnesemia and hyponatremia with no apparent clinical sequelae.

In addition, secondary outcome analysis of the Eddleston (2008) study allows for estimation of the incidence of adverse events due to AC administration. Adverse events were extremely rare. Only two out of 2,957 patients treated with AC and atropine were referred for possible acute abdomen. No deaths were found to have charcoal aspiration at autopsy.

Conclusions

This review of the past two decades of literature found support for SDAC in undifferentiated overdose presenting in RPS. MDAC administration demonstrated great benefit for selected poisonings, likely due to enhanced elimination. Specific poisonings associated with the highest benefit from AC administration include cardiac glycosides and organophosphorus pesticides. In addition, adverse events associated with AC administration appear to be extremely rare. In summary, AC use is recommended in RPS as a safe, inexpensive first-line decontaminant which should be considered as early as possible in the course of poisoning management.

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This article was originally published in a special issue, **Epidemiology of Poisoning** handled by Editor(s). Dr. John F Gamble, Consultant, Somerset, New Jersey, USA; Dr. Monath Sanjaya Kuruppu, Monash University, Australia