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Activated charcoal for acute overdose: a reappraisal

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Sometimes mistakenly characterized as a 'universal antidote,' activated charcoal (AC) is the most frequently employed method of gastrointestinal decontamination in the developed world. Typically administered as a single dose (SDAC), its tremendous surface area permits the binding of many drugs and toxins in the gastrointestinal lumen, reducing their systemic absorption. Like other decontamination procedures, the utility of SDAC attenuates with time, and, although generally safe, it is not free of risk. A large body of evidence demonstrates that SDAC can reduce the absorption of drugs and xenobiotics but most such studies involve volunteers and have little generalizability to clinical practice. Few rigorous clinical trials of SDAC have been conducted, and none validate or refute its utility in those patients who are intuitively most likely to benefit. Over the past decade, a growing body of observational data have demonstrated that SDAC can elicit substantial reductions in drug absorption in acutely poisoned patients. The challenge for clinicians rests in differentiating those patients most likely to benefit from SDAC from those in whom meaningful improvement is doubtful. This is often a difficult determination not well suited to an algorithmic approach. The present narrative review summarizes the data supporting the benefits and harms of SDAC, and offers pragmatic suggestions for clinical practice.

Background

Charcoal for medicinal use is created by the controlled pyrolytic decomposition of carbon-based compounds, such as coconut shells or peat [1]. Thereafter, 'activation' with gases at high temperature removes previously adsorbed substances and further reduces particle size, resulting in an exceptionally porous final product [2]. Indeed, some 'superactivated' charcoal preparations have a surface area of up to 3500 m^2 g^{-1}, or about 175 000 m^2 per 50 g bottle [1]. (For perspective, the area of a large football pitch is about 10 000 m^2.) This allows the adsorption of drugs and toxins through weak intermolecular forces, with non-ionized, organic compounds binding more avidly than dissociated, inorganic ones [1].

The first reported use of charcoal as an antidote occurred in 1811, when the French chemist Michel Bertrand reportedly ingested charcoal with 5 g of arsenic trioxide [1, 3]. In 1852, Touéry showed no ill effects after consuming a large dose of strychnine with charcoal before sceptical colleagues of the French Academy of Medicine [4]. Dramatic anecdotes aside, SDAC was infrequently used in the management of acute poisoning until 1963, when a review article in the *Journal of Pediatrics* concluded that: 'This agent, presently somewhat neglected, has a wide spectrum of activity and when properly used is probably the most valuable single agent we possess' [5]. In the 1970s and 1980s, SDAC was a common element of gastrointestinal (GI) decontamination after acute poisoning, as were gastric emptying manoeuvres such as lavage and ipecac-induced emesis.

Unlike gastric lavage and ipecac, SDAC remains a common element of therapy for acutely poisoned patients, although its use has decreased substantially in recent years. For example, in 1999, poison centres in the United States recommended SDAC more than 136 000 times, compared to only about 50 000 times in 2013. The declining use of SDAC reflects an appreciation of its limitations and potential risks, along with waning enthusiasm for GI decontamination more generally.

It bears mention that decontamination with SDAC is conceptually different from the use of multiple-dose activated charcoal (MDAC), a less commonly deployed intervention involving the administration of multiple (typically, two to six) smaller doses of AC, with the goal of enhancing the total body clearance of a limited number of compounds such as dapsone [6], carbamazepine [7, 8],

phenobarbital [9, 10] and methylxanthines [11]. As such, the goal of MDAC is enhanced toxin elimination rather than reduced absorption per se. The balance of the present review focuses on the use of SDAC following acute overdose.

Effectiveness

Several lines of research demonstrate that SDAC effectively binds to a diverse range of toxins.

In vitro and animal studies

Dozens of *in vitro* simulations and animal studies convincingly show that SDAC binds to a wide range of drugs to varying degrees [1, 12]. Importantly, some compounds do not bind to SDAC, even under ideal conditions. Metals (notably including salts of iron and lithium), hydrocarbons and caustics are common exposures not suited to SDAC on this basis. Although toxic alcohols and cyanide are sometimes also listed as substances not adsorbed to AC, this is incorrect. Decker and colleagues [13] demonstrated that SDAC does indeed bind to both methanol and ethylene glycol; this is of little clinical utility, however, because the amounts of these typically ingested yield an unfavourable stoichiometric ratio of charcoal:toxin (discussed below). Also, although AC adsorbs cyanide less avidly than many drugs, the maximum binding ratio (35 mg of cyanide per gram of AC) [3] might have clinical utility if SDAC is given shortly after ingestion, as a standard 50 g dose of SDAC could theoretically bind more than a gram of cyanide. Indeed, in an animal model of massive cyanide poisoning, 14 of 26 rats given AC with potassium cyanide (35–40 mg kg^{-1}) displayed no signs of cyanide toxicity, whereas all rats not given AC died [14].

Many animal studies generally corroborate the findings of *in vitro* studies but they cannot be freely generalized to humans because of interspecies differences in GI morphology, function and other aspects involving pharmacokinetics [12].

Studies in human volunteers

The most recent iteration of the American Academy of Clinical Toxicology (AACT)/European Association of Poison Centres and Clinical Toxicologists (EAPCCT) joint position paper on SDAC observed that 46 drugs have been the subject of 122 evaluations of the effect of SDAC in healthy volunteers [12]. Most of these are small crossover studies examining the extent to which SDAC influences the area under the curve (AUC) of drug concentration *vs*. time.

These studies employed varying doses of SDAC (0.5–100 g) at intervals of up to 6 h following ingestion of paracetamol [15–17], acetylsalicylic acid and other anti-inflammatory agents [18–21], valproate [22] and calcium channel blockers [23–26], among others. Of 122 total comparisons, 84 (69%) involved the administration of SDAC within 5 min of drug ingestion, demonstrating a mean reduction in absorption of 74%. Among studies in which the dose of AC was at least 50 g, the average reduction in systemic drug absorption was 47.3% at 30 min, 40.1% at 60 min and 16.5% at 120 min [12].

In addition to recruiting medically well subjects, an important limitation of volunteer studies is that they involve subtoxic drug exposures. Although ethically inescapable, this seriously undermines their applicability to acutely poisoned patients who ingest much larger doses, often of multiple drugs, and who present with complications that might unfavourably influence the safety of charcoal, including altered mental status and airway compromise.

Studies in poisoned patients

Only two randomized trials have directly examined the efficacy of AC in acutely poisoned patients, demonstrating no clear benefit from the intervention. In a single-centre study, Cooper *et al*. randomized 327 acutely poisoned patients to receive either 50 g of SDAC or no decontamination within 12 h of ingestion [27]. In the primary analysis, they found no difference in the length of hospital stay between the SDAC and control arms (6.8 h *vs*. 5.5 h, respectively; $P = 0.11$), even in the subset of patients treated within 2 h of ingestion. However, the ability of this study to detect a benefit of SDAC might have been limited by the enrolment of patients destined to do well without AC (benzodiazepines and paracetamol represented more than half of all poisonings), and by the exclusion of a small number of patients presenting within 1 h of a potentially life-threatening ingestion. The latter group represents those most likely to benefit from the intervention.

In the largest study to date, Eddleston and colleagues randomized 4632 patients at three Sri Lankan hospitals to one of three treatment arms: SDAC (50 g) once; every 4 h for six doses; or no charcoal [28]. In the primary analysis, no mortality difference was evident among groups, and secondary analyses revealed no differences in the need for intubation or the risk of seizures. Limitations of this study include a median delay from ingestion to treatment of more than 4 h in all groups and uncertain generalizability to prescription drugs, as fully half of study subjects ingested pesticides, and more than a third ingested yellow oleander.

Although a major advance over previous decontamination trials, the studies of Cooper *et al*. and Eddleston *et al*. should not be overinterpreted. In spite of their negative findings, it must be emphasized that no randomized controlled trial has evaluated the efficacy of SDAC when given promptly (within 1–2 h) following ingestions likely to result in serious toxicity or death. Such a trial is impracticable, however, given the lack of equipoise in such subjects and the associated ethical barriers to a control group. Put differently, we should not anticipate that randomized trials will ever definitively address the utility of SDAC in those poisoned patients most likely to benefit from it.

The effect of SDAC following overdose has recently been the subject of several population pharmacokinetic and pharmacodynamic modelling studies. This is a promising avenue of research because it leverages detailed, prospectively collected data derived from 'real-world' overdose patients. Moreover, it accounts for important uncertainties (amount ingested, co-ingestants, timing, etc.) frequently encountered in clinical practice. Friberg and colleagues [29] evaluated 63 instances of citalopram overdose in 53 patients [median dose 270 (range 20–1700) mg], including 16 instances in which SDAC (50 g) was administered within 4 h of ingestion. The authors estimated that SDAC reduced citalopram bioavailability by 22% and increased total body clearance by 72%. Comparable studies estimate that early administration of SDAC following overdose reduces the absorption of quetiapine by 35% [30], sertraline by 27% [31], escitalopram by 31% [32] and venlafaxine by 29% [33]. It is not difficult to envision scenarios in which effects of this magnitude could favourably influence clinically important outcomes, perhaps even mortality.

Indeed, thematically similar studies suggest that SDAC can be associated not only with altered pharmacokinetics, but also with improvements in clinical outcomes. For example, in patients who have taken large overdoses of citalopram, SDAC reduced the chance of high-risk QT-RR combinations by approximately 60% [34], and, when given within 2 h of promethazine overdose, reduced the risk of delirium by more than half [35]. In another study involving paracetamol, SDAC reduced the likelihood of a concentration above the N-acetylcysteine treatment line on the Rumack–Matthew nomogram [36]. By design, these studies yield insights into the utility of SDAC in real-world practice not obtainable by other means. Despite their observational nature, they provide what is arguably the most clinically relevant evidence supporting the use of SDAC after acute overdose.

Harms

Although generally safe, SDAC is not free of risk [37]. The most widely cited concern associated with SDAC is pulmonary aspiration, although the risk of this complication is low. Indeed, in a cohort study of more than 4500 overdose patients, 71 (1.6%) developed aspiration pneumonitis. Emesis, seizure and altered mental status were among the independent predictors of aspiration but the administration of AC was not [38].

Nevertheless, aspiration following SDAC is well documented in isolated case reports, some of them dramatic [37, 39–41]. In one case, a young child died following aspiration of SDAC given to treat the ingestion of an unknown liquid from a chemistry set [37]. In another, a 34-year-old woman was given SDAC by nasogastric tube after a mixed drug overdose while intubated. The immediate appearance of AC in the endotracheal tube was followed by the development of acute respiratory distress syndrome and persistent parenchymal disease [41]. This case reflects suboptimal airway management but also illustrates the rare potential for harm resulting from aspiration of AC. Chronic lung disease [39], obstructive laryngitis with glottic oedema [42, 43], granulomatous lung mass [43], charcoal empyema [40] and bronchiolitis obliterans [44] have also been reported as pulmonary complications of SDAC.

GI complications represent another potential risk of SDAC administration. Published reports describe bowel obstruction [45, 46], bezoars [47, 48] and stercoliths [49] after SDAC use. Patients with pre-existing motility disorders, those receiving opioids or antimuscarinic drugs, and those treated with MDAC might be at greater risk but, on balance, the likelihood of GI complications following SDAC therapy is low.

Other considerations

Tolerability

Most patients tolerate SDAC well, in spite of its gritty, unpalatable taste. This can be a particular problem for children, for whom palatability can be improved by administration with cola or chocolate milk [50, 51]. In a substudy of the largest randomized trial to date, adults allocated to treatment with AC consumed 83% of their first dose, on average, and 27% subsequently vomited a portion of the dose [52]. This might partly reflect the emetogenic nature of the ingestions in that study as earlier studies suggested that the incidence of charcoal-associated emesis is considerably lower, on the order of 6–7% [53, 54].

Timing of SDAC

As with all decontamination methods, the balance of benefit *vs.* risk becomes less favourable with time. Figure 1 shows the reduction in AUC observed when SDAC was given at various lag times after ingestion in volunteer studies. The most recent AACT/EAPCCT position paper [12] states that: 'Although volunteer studies demonstrate that the reduction of drug absorption decreases to values of questionable clinical importance when charcoal is administered at times greater than 1 h, the potential for benefit after 1 h cannot be excluded'. This statement is problematic because volunteer studies permit no inferences regarding clinical importance, and the casual reader might conclude that SDAC has little utility more than 1 h after ingestion. Common sense and the population studies cited earlier suggest otherwise. Although most toxicologists recommend SDAC at 1 h following a significant ingestion [55, 56], in practice most acknowledge the potential benefits of later administration in certain settings.

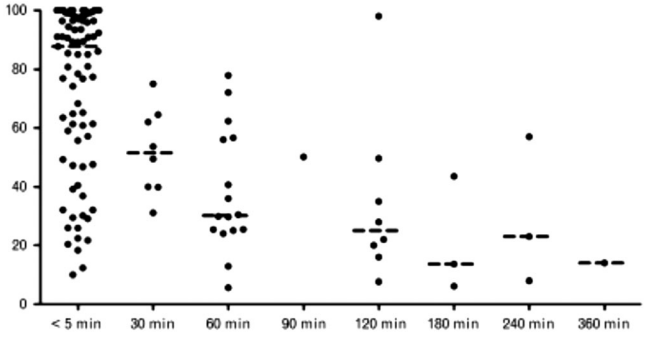

Figure 1

Summary of human volunteer studies of activated charcoal. Figure shows reduction in area under the curve (AUC) *vs.* time to single-dose activated charcoal. Included studies are those cited in the 2005 American Academy of Clinical Toxicology/European Association of Poison Centres and Clinical Toxicologists Position Statement. Reproduced from Isbister *et al.* [58] with permission

It is unsurprising that delays to administration render SDAC less effective, but factors other than timing must be taken into account. Chief among these are the expected toxicity of the ingestion and the availability of other specific therapies. For example, a large overdose of colchicine or cyclic antidepressant presents a very high risk of morbidity and mortality, with limited adjunctive therapies to offer. In such cases, there is little to be lost in the administration of SDAC up to 4 h following ingestion. By contrast, for a patient with a large opioid overdose, naloxone and ventilatory support make late administration of SDAC at 4 h less easy to justify.

Other factors to consider include the co-ingestion of drugs that slow gastric emptying, including antimuscarinics or opioids as well as the presence of food. A case can be made for administration of SDAC within 2 h (and perhaps longer) following ingestion, when the clinician has reason to believe that a clinically important amount of drug remains in the GI tract and that its adsorption to charcoal might favourably influence the patient's clinical course. Although it is not possible to specify with certainty when SDAC represents an appropriate intervention, Table 1 lists factors that cumulatively increase its appropriateness.

Stoichiometry

Because SDAC adsorbs drugs and other xenobiotics, it follows that a stoichiometric relationship must exist under which a higher ratio of charcoal:drug will more effectively inhibit systemic absorption. Put differently, one might expect that 50 g of AC would more effectively prevent the absorption of sixty 50 mg tablets of amitriptyline (3 g of drug) than of sixty 500 mg tablets of valproic acid (30 g of drug), all other factors being equal. Previous studies bear this out [57]. It is commonly taught that an AC:drug ratio of 10:1 is ideal but Olson suggests that a ratio of perhaps 40:1 might be superior [1].

Table 1

Factors that cumulatively increase the appropriateness of single-dose activated charcoal

– Serious toxicity anticipated
– Recent ingestion
– Alert, cooperative patient
– Intact airway
– Lack of a specific antidote
– Favourable stoichiometry (mass of charcoal:mass of drug >40:1)
– Ingestion of a modified-release product
– Substance known to adsorb to activated charcoal
– Absence of ileus or intestinal obstruction

Clearly, neither is possible in patients with 'high-mass ingestions' – i.e, those involving many tablets of valproic acid, acetylsalicylic acid, verapamil or metformin, for example. Common sense dictates that administering more than 50 g of AC might be worthwhile in such cases but this is speculative and often impractical.

Modified-release products

Many drugs exist as modified-release formulations in which the release of medication is retarded by, for example, an enteric coating, an osmotic pump delivery system or incorporation into a matrix. Examples frequently encountered in acute poisoning include acetylsalicylic acid, calcium channel blockers, methylxanthines, long-acting opioids, paracetamol and valproic acid. In such instances, clinical toxicity can be both delayed and sustained. It follows that these cases might be more amenable to treatment with SDAC, and also that administration of SDAC several hours after ingestion might be advisable when significant toxicity is anticipated. The potential benefit of delayed SDAC in a modified-release overdose was illustrated, for example, in a volunteer study in which SDAC given 4 h after ingestion of 2.9 g of enteric-coated acetylsalicylic acid reduced absorption by 57% [18].

Summary

In patients with acute overdose, SDAC remains an important therapeutic option, and recent studies involving real-world patients have reinforced the long-held belief that it can significantly reduce systemic drug absorption when given shortly after overdose. Although generally well tolerated, SDAC is rarely associated with significant complications, most notably pulmonary aspiration. The decision to use it is not well suited to an algorithmic approach but rather requires clinical judgement involving a global assessment of several patient-specific factors. As with all medical interventions, SDAC should be given only to patients in whom its use can reasonably

be expected to reduce morbidity (or perhaps even mortality) in a manner that exceeds its risks.

Competing Interests

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organisation for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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