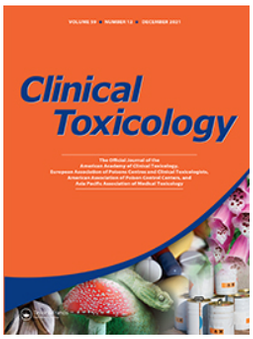

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REVIEW

Systematic review on the use of activated charcoal for gastrointestinal decontamination following acute oral overdose

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ABSTRACT

Introduction: The use of activated charcoal in poisoning remains both a pillar of modern toxicology and a source of debate. Following the publication of the joint position statements on the use of single-dose and multiple-dose activated charcoal by the American Academy of Clinical Toxicology and the European Association of Poison Centres and Clinical Toxicologists, the routine use of activated charcoal declined. Over subsequent years, many new pharmaceuticals became available in modified or alternative-release formulations and additional data on gastric emptying time in poisoning was published, challenging previous assumptions about absorption kinetics. The American Academy of Clinical Toxicology, the European Association of Poison Centres and Clinical Toxicologists and the Asia Pacific Association of Medical Toxicology founded the Clinical Toxicology Recommendations Collaborative to create a framework for evidence-based recommendations for the management of poisoned patients. The activated charcoal workgroup of the Clinical Toxicology Recommendations Collaborative was tasked with reviewing systematically the evidence pertaining to the use of activated charcoal in poisoning in order to update the previous recommendations.

Objectives: The main objective was: Does oral activated charcoal given to adults or children prevent toxicity or improve clinical outcome and survival of poisoned patients compared to those who do not receive charcoal? Secondary objectives were to evaluate pharmacokinetic outcomes, the role of cathartics, and adverse events to charcoal administration. This systematic review summarizes the available evidence on the efficacy of activated charcoal.

Methods: A medical librarian created a systematic search strategy for Medline (Ovid), subsequently translated for Embase (*via* Ovid), CINAHL (*via* EBSCO), BIOSIS Previews (*via* Ovid), Web of Science, Scopus, and the Cochrane Library/DARE. All databases were searched from inception to December 31, 2019. There were no language limitations. One author screened all citations identified in the search based on predefined inclusion/exclusion criteria. Excluded citations were confirmed by an additional author and remaining articles were obtained in full text and evaluated by at least two authors for inclusion. All authors cross-referenced full-text articles to identify articles missed in the searches. Data from included articles were extracted by the authors on a standardized spreadsheet and two authors used the GRADE methodology to independently assess the quality and risk of bias of each included study.

Results: From 22,950 titles originally identified, the final data set consisted of 296 human studies, 118 animal studies, and 145 *in vitro* studies. Also included were 71 human and two animal studies that reported adverse events. The quality was judged to have a Low or Very Low GRADE in 469 (83%) of the studies. Ninety studies were judged to be of Moderate or High GRADE. The higher GRADE studies reported on the following drugs: paracetamol (acetaminophen), phenobarbital, carbamazepine, cardiac glycosides (digoxin and oleander), ethanol, iron, salicylates, theophylline, tricyclic antidepressants, and valproate. Data on newer pharmaceuticals not reviewed in the previous American Academy of Clinical Toxicology/European Association of Poison Centres and Clinical Toxicologists statements such as quetiapine, olanzapine, citalopram, and Factor Xa inhibitors were included. No studies on the optimal dosing for either single-dose or multiple-dose activated charcoal were found. In the reviewed clinical data, the time of administration of the first dose of charcoal was beyond one hour in 97% ($n = 1006$ individuals), beyond two hours in 36% ($n = 491$ individuals), and beyond 12 h in 4% ($n = 43$

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Supplemental data for this article can be accessed here.

individuals) whereas the timing of the first dose in controlled studies was within one hour of ingestion in 48% ($n = 2359$ individuals) and beyond two hours in 36% ($n = 484$) of individuals.
Conclusions: This systematic review found heterogenous data. The higher GRADE data was focused on a few select poisonings, while studies that addressed patients with unknown and or mixed ingestions were hampered by low rates of clinically meaningful toxicity or death. Despite these limitations, they reported a benefit of activated charcoal beyond one hour in many clinical scenarios.

Introduction

The use of oral adsorbents to prevent or mitigate poisoning dates back to antiquity. Activated charcoal (AC), the modern adsorbent, was credited with preventing toxicity when two of its earliest proponents, Bertrand (1813) and Tourey (1831), publicly ingested arsenic and strychnine, respectively, with AC and survived [1]. Subsequent pioneers in clinical toxicology demonstrated *in vitro* adsorption of AC to a wide array of toxins including morphine, barbiturates, salicylates, ethanol and strychnine [2,3]. Several animal and human volunteer studies followed, demonstrating not only reduction in systemic absorption but also enhanced elimination of toxins with the use of AC [4–11]. Based on these data, the use of AC was administered to nearly 10,000 patients (4% of all exposures) reported to American Poison Centers in 1982 [12]. Because the safety and efficacy of gastric emptying (ipecac-induced emesis and gastric lavage) were called into question in subsequent decades, AC remained the only intervention that could address both goals of reduced absorption and enhanced elimination. With improvements in supportive care and the observed reduction in inpatient mortality from poisoning, clinicians began to reevaluate the risk/benefit ratio for decontamination. This philosophical shift in thinking became most apparent in the late 1990s when the American Academy of Clinical Toxicology (AACT) and the European Association of Poison Centres and Clinical Toxicologists (EAPCCT) published joint position papers calling into question the routine use of single-dose AC (SDAC) and multiple-dose AC (MDAC) [13,14].

Although the routine use of AC declined, many new drugs were subsequently marketed in sustained-, alternative-, or modified-release formulations, challenging previous assumptions about absorption kinetics with and the time of AC administration. Moreover, additional data on gastric emptying-time in poisoned patients was published [15–19], evidence-based medicine developed and matured while technological advances facilitate critical review of a large body of previously published literature, and technological advances allowed for the creation of Bayesian analyses to complex toxicological problems. With all of these advancements the clinical toxicology societies resolved to update the AC position papers.

The AACT, EAPCCT, and the Asia Pacific Association of Medical Toxicology (APAMT) founded the Clinical Toxicology Recommendations Collaborative (CTRC) in 2016. The purpose of the CTRC was to develop a framework to create evidenced-based recommendations for the management of poisoned patients.

The Activated Charcoal in Clinical Toxicology Workgroup (AC Workgroup), a subgroup of the CTRC, is comprised of experts in clinical toxicology, internal medicine, anesthesiology, emergency medicine, critical care, safety, and basic/clinical pharmacology, supported by medical librarians, statisticians, and methodologists. This workgroup was tasked with reviewing the evidence pertaining to the use of oral AC in toxicology to update the previous recommendations.

The ultimate objective of the AC Workgroup was to provide evidence-based recommendations on the use of AC in human poisoning, according to Institute of Medicine standards [20]. A subgroup of the AC Workgroup performed the systematic review. This article summarizes the available evidence on the clinical efficacy of oral AC to reduce systemic absorption of poisons, the efficacy of AC based on pharmacokinetic parameters, and the theoretical efficacy of AC measured by *in vitro* maximal adsorptive capacity (MAC) of poisons to AC. The clinical recommendations of the AC Workgroup, based on this systematic review, will be the focus of a subsequent publication.

Objectives

The main objective was: Does AC given to adults or children prevent toxicity or improve clinical outcome and survival of potentially poisoned patients compared to those who do not receive AC? Secondary objectives were to evaluate pharmacokinetic outcomes, the role of cathartics, and adverse events.

Methods

Literature search

A medical librarian created a systematic search strategy for Medline (Ovid), which is provided in the Appendix. The search strategy comprised a combination of Medical Subject Headings (MeSH), title/abstract keywords, truncations, and Boolean operators (Appendix 1). It was subsequently translated for Embase (*via* Ovid), CINAHL (*via* EBSCO), BIOSIS Previews (*via* Ovid), Web of Science, Scopus, and the Cochrane Library/DARE. All databases were originally searched from inception to December 31, 2015 supplemented with three rounds of updated searches on January 1, 2017, December 31, 2018, and March 1, 2020 using the same strategy to ultimately include in the final data set: all publications indexed in these databases through December 31, 2019. Identified articles were triaged into subgroups: Single-dose activated charcoal (SDAC) human; multiple-dose activated charcoal (MDAC) human; SDAC animal; MDAC animal;

experimental/*in vitro*; adverse events. Articles relating to additional doses of activated charcoal (ADAC) were included with the SDAC studies. There were no language limitations. Initial screening was performed with online translation services to English when feasible. When online translations were inadequate and for all full-text reviews, articles were translated by native speaking clinicians largely provided by the EAPCCT and APAMT. Group members performed cross-referencing of full-text articles to identify articles that were not captured with the search strategy.

Definitions and terminology

The international nature of the workgroup required standardized terminology to ensure clarity. The terminology used is included in Appendix 2.

Inclusion criteria

The decision was made *a priori* to include randomized controlled trials (humans), randomized controlled studies (animals), meta-analyses, observational studies, case series, case reports, and experimental/*in vitro* studies with reference to the adsorption of poisons in the setting of acute oral poisoning. The types of participants were as follows: subjects (humans or animals) at risk of developing toxic symptoms from poisoning, as defined below, by enteral route, who were dosed with oral AC (SDAC or MDAC) instituted for the purpose of treating poisoning; human volunteer studies in which the pharmacokinetics of a xenobiotic were studied in the setting of AC (SDAC or MDAC) administration compared to no AC; animal studies evaluating the pharmacokinetics of a poison and/or mortality. There was no limit to the age of subjects. All poisons were included and grouped depending on their use (medication) or origin (chemicals and natural substances like plants and mushrooms). Studies or reports on complications or adverse events related to the use of AC were also included.

Exclusion criteria were: subjects (humans or animals) at risk of developing toxic symptoms from poisoning or overdose by routes other than enteral; and *in vitro* studies with reference to the adsorption of drugs and toxins in non-poisoning settings, e.g., air- and water- filtration, sewage treatment, drinking water purification, and pathogen and toxin reduction in animal food.

Screening and study selection

One author (LH) screened all citations identified in the search based on the inclusion/exclusion criteria. Included and excluded citations were reviewed by at least two other authors to confirm correct categorization. Full text articles were reviewed for included citations and relevant data extracted by the systematic review subgroup who collectively made the final decision for inclusion based on the available data. Toxicokinetic data in animal poisonings were included if the results could be extrapolated to humans. This approach is consistent with well-recognized, US federal frameworks for incorporating animal data in clinical, occupational, environmental, and forensic toxicology settings. Although reliable human data are preferred to animal data, when not available, animal data can be used [21–24].

Data extraction and quality assessment

The subset of data to extract was decided *a priori* in consultation with the entire AC workgroup to capture the essential information for clinical decision making. A standardized spreadsheet was created. A smaller subgroup of members, (the authors) collectively extracted data from the included articles. Details of incomplete data for included studies were obtained, if possible, by consulting the corresponding authors. The following data were extracted: study design; patient characteristics; poison; ingestion details; vital signs and clinical findings on admission; AC administration – type, time and dose; cathartics; other treatment received – and time; and clinical data; signs and symptoms, treatment, extent of toxicity; and pharmacokinetic data such as concentration of the poison(s) in biological samples (e.g., blood, urine, gastric lavage fluid); primary outcome of survival; or survival with sequelae. Complications and/or adverse events were also keywords for inclusion. Extracted data from experimental and *in vitro* studies were: groups compared; poison investigated; activated charcoal type; medium type; quantitative poison concentration analysis; MAC; and interpretation to clinical settings.

Two authors (SG, RSH) used the GRADE methodology to independently assess the quality and risk of bias for each included study. After consultation with GRADE expert methodologists, a survey method was specifically designed for assessing indirectness in the context of poisoning. Studies in patients with drug overdoses were defined as a population of interest. Human volunteer studies lost one point for indirectness. The entire workgroup was polled to decide which drug concentrations were good surrogates of the severity of the poisoning. Drug concentrations were deemed adequate surrogate outcomes for select drug overdoses if the workgroup determined that there was a direct relationship between drug concentrations and clinical effects. Drug concentrations in human volunteer studies lost points for indirectness, if they were not representative of drug concentrations in overdose for either clinical or toxicokinetic outcomes [25–30]. Differences in rating were resolved by discussion and consensus.

Results

Included studies

The flow diagram of the search results after initial screening and study selection is presented in Figure 1 [2–11, 32–589].

The initial and subsequent searches included 22,950 results. The majority of the articles excluded during the initial screening process were not related to acute enteral poisonings in humans, but rather were on topics related to the removal of poisons in the environment or carbon monoxide poisoning. Articles excluded during the review process suffered from insufficient data and/or AC was administered as

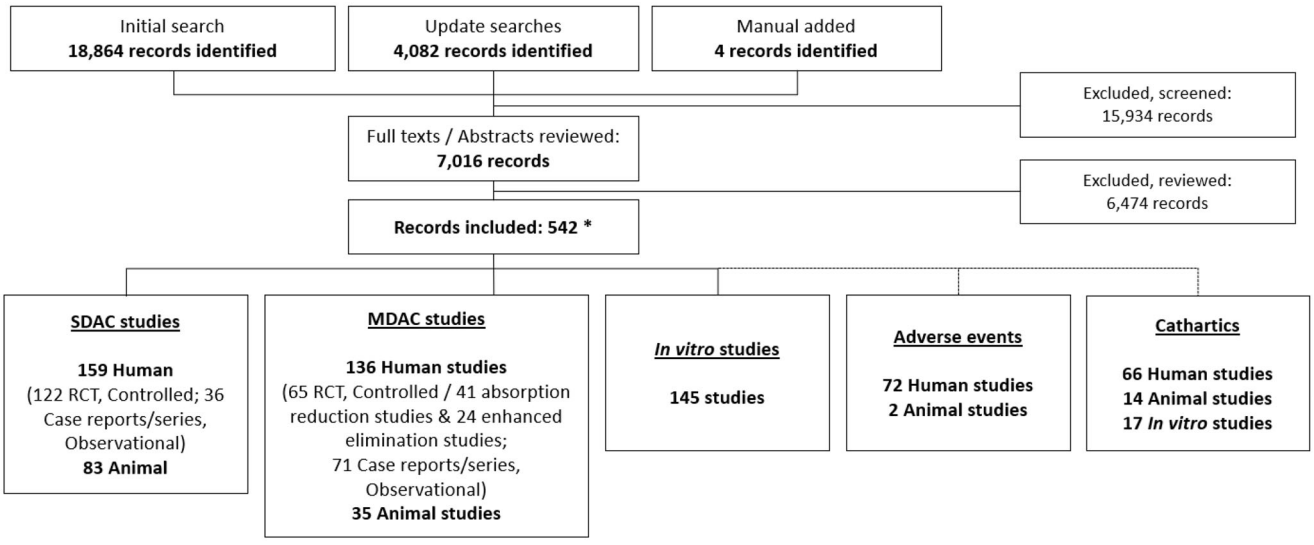


Figure 1. The studies included in the systematic review. * = Numbers in the individual subgroups do not add up as a number of studies are included in multiple subgroups.

part of a general treatment regimen, with no specific measure of effect. The final data set consisted of 296 human studies, 118 animal studies, and 145 *in vitro* studies. Also included were 72 human and 2 animal studies that reported adverse events of AC but, with the exception of one study, did not otherwise meet inclusion criteria for the clinical or pharmacokinetic effects of AC. Of note, some studies included combinations of either human and/or animal and/or SDAC and/or MDAC and/or *in vitro* experiments, so that the total number of articles and the total numbers in each category are not equal.

The publication dates of included studies are displayed in Figure 2. The earliest publication included in the systematic review dates to 1946 [2]. (Figure 2(D)) *In vitro* studies were relatively frequent from the beginning of the 1970s. No *in vitro* study was published in the last 5 years (Figure 2(D)). Human SDAC studies clustered between 1982 and 1991 and between 1997 and 2010. A similar pattern was noted for human MDAC studies around 1982 and 1996 (Figure 2(A,B)). Animal SDAC studies were unevenly distributed with the first included study dating back to 1951. The majority of animal MDAC studies were from 1983 to 1995 (Figure 2(C)).

Quality of evidence

The overall quality of available human evidence was Low to Very Low according to the GRADE criteria. Many well-designed studies were downgraded as a result of indirectness. Ultimately, only 90 studies were rated either Moderate or High GRADE (Supplementary material).

Substances

The tables summarizing the entire list of articles included in this systematic review are found in the Supplementary material. For the purposes of brevity, only poisons for which there is at least one paper with a Moderate or High level of evidence are discussed in the specific sections that follow. For each of these poisons, we present figures that demonstrate the timing of AC dosing for SDAC, and the timing of AC dosing and dosing intervals for MDAC. Studies that evaluated large groups of patients independent of any particular poison will be discussed as they have clinical relevance for patients with unknown ingestions. Following this section, we will present information on new methods of analysis and toxins that were not widely available at the time of the last update.

Paracetamol (acetaminophen)

In vitro studies. Numerous *in vitro* studies demonstrated that paracetamol was well adsorbed to AC [32–52]. When expressed as a maximal adsorptive capacity (MAC), values ranged from 122 mg/g-720 mg/g AC [44,46] and were somewhat dependent on the surface area of the AC studied. Expressed another way, when the ratio of AC:paracetamol dose was 5:1 or greater, nearly all of the paracetamol was adsorbed [32,33,35,36,40–42,48,52]. Unlike some other poisons there did not seem to be an effect of varying pH on paracetamol binding to AC [32,33,35,40–42,44,45,47,51].

Effect (clinical outcome): single-dose activated charcoal. Three studies met inclusion criteria for clinical outcomes of SDAC use in paracetamol poisoning. A 12-year retrospective observational study of nearly 40,000 poisoned patients who took paracetamol alone compared the effects of AC on clinical outcomes [53]. The 16,674 patients who were given AC with acetylcysteine had statistically significantly less elevation of aminotransferase activity, less severe coagulopathy and kidney injury, and there were fewer deaths when compared to the 23,199 patients who only received acetylcysteine. A similar effect was demonstrated in nearly 50,000 patients who ingested paracetamol with co-ingestants. Unfortunately, the delay between paracetamol ingestion and AC dose and number of AC doses was not specified.

A retrospective study compared the outcome of paracetamol poisoned patients who were given SDAC to those given no AC [54]. Among those patients who ingested 10 g or

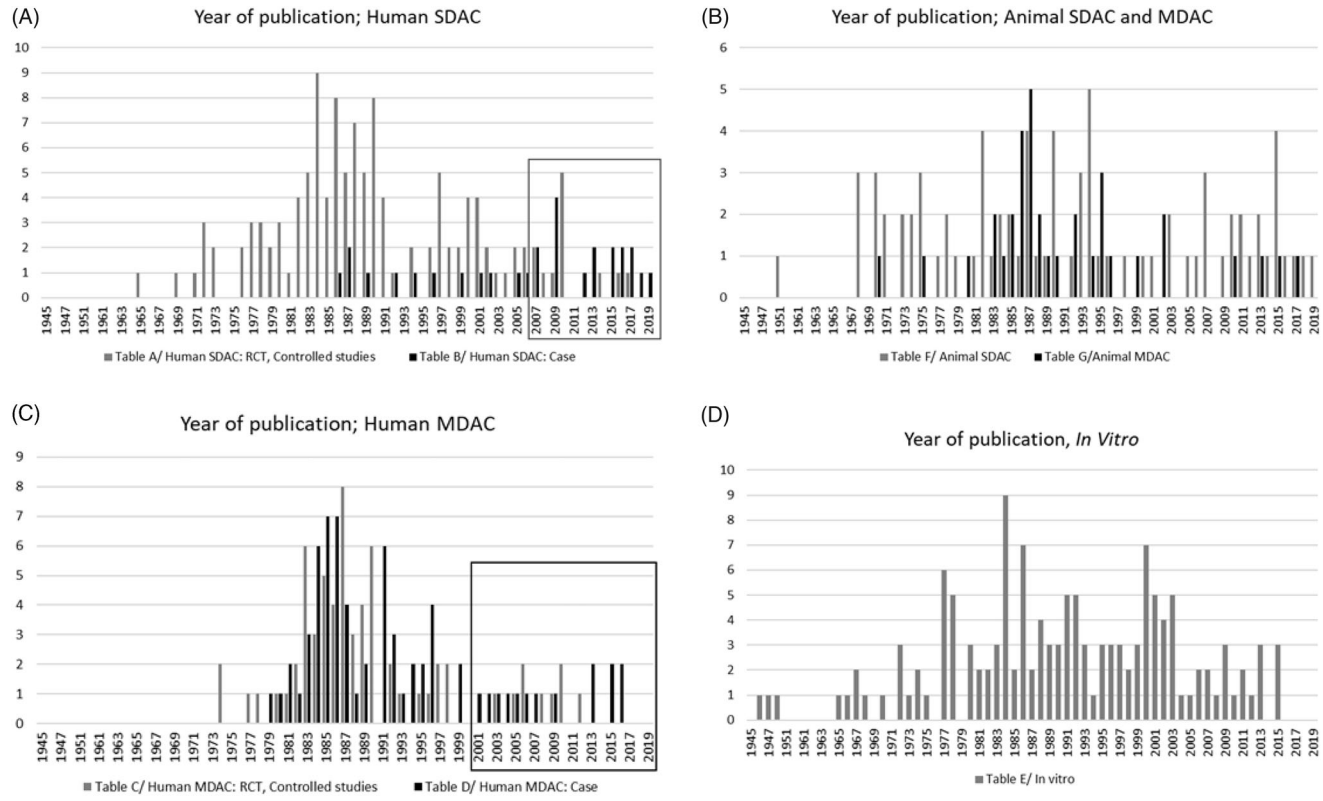


Figure 2. Year of publication of the included studies. The bars show the number of studies published each year. The boxes in panel A and B represent studies since the latest AACT and EAPCCT Position Statements on single-dose activated charcoal (SDAC) and multiple-dose activated charcoal (MDAC) respectively [14,31]. RCT: Randomized control trial. Table A–G refers to tables A–G in Supplemental material.

more of paracetamol 163 patients were given SDAC (1–2 g/kg) and 167 had no decontamination. Patients given AC were less likely to have subsequent paracetamol concentrations determined to be "high risk" (Odds ratio 0.36, 95% CI 0.23–0.58, $p < 0.0001$). The effect of AC was most notable within 2 h of ingestion, although the authors suggest an effect even up to 4 h post ingestion.

A prospective observational study enrolled 200 patients with massive paracetamol ingestions and evaluated the effect of SDAC [55]. The 36 patients who received AC within 4 h of ingestion had an unadjusted odds ratio of 0.12 for developing hepatotoxicity compared to those who did not receive AC. Additional toxicokinetic effects noted in this study are discussed in the next section.

Effect size (pharmacokinetic aspects): single-dose activated charcoal. Eighteen Moderate GRADE human volunteer studies [56–73] and two Moderate GRADE clinical studies [55,74] evaluated the effect of SDAC on paracetamol absorption. In the volunteer studies paracetamol doses ranged from 960 mg [58] to 80 mg/kg [68] and AC doses ranged from 5 g [63,75] to 70 g [70]. In most studies, the AC was given within 1 h although a few studies investigated dosing as late as 4 h post ingestion [66]. In one study of overdose patients, AC was given in a 10:1 ratio with the reported ingested dose of paracetamol [74].

In the other overdose study, most patients got a fixed dose of 50 g of AC although a few received 100 g (Chiew, 2017; personal communication with the author). Possibly as a result of the variable SDAC: paracetamol ratio, but also possibly relating to other experimental conditions, the reduction in paracetamol absorption in volunteer studies ranged from less than 30% [61,62,67,71] to over 60% [56,57,59, 63,68,69] when AC was given within 1 h of ingestion. All of the studies that compared AC administration at different times post ingestion demonstrated a rapid decline in its efficacy as the delay to AC administration increased [56,57,59,64,66,67,69,72]. Although several studies demonstrated efficacy at 2 h [64,66,69,70,72], only one was able to show an effect at 3 h post ingestion [70]. Several studies used high-surface area AC but only one [65] compared a high-surface area (2000 m^2/g) to a low-surface area AC (950 m^2/g). As expected, high-surface area AC outperformed low-surface area AC. Interestingly, one final study demonstrated that atropine-induced delayed gastric emptying improved the efficacy of AC [71].

In all these studies, the paracetamol was an immediate release formulation.

The first clinical study enrolled all patients who reportedly ingested 5 g or more of paracetamol within 4 h and randomized them to lavage, emesis, AC, or no decontamination [74]. Among patients who presented within 120 min of ingestion, those receiving AC had a significantly greater reduction in paracetamol concentrations than those receiving either emesis or lavage. The Control Group was terminated early because of rising concentrations while the concentrations in the other three groups all fell. In the second clinical study, patients who received AC within 4 h of a massive (≥40 g) paracetamol ingestion had a significantly lower ratio of their actual paracetamol concentration to the corresponding value on the Rumack-Matthew nomogram (paracetamol ratio) than those who did not receive AC: 1.4 versus 2.2 ($p < .0001$) [55].

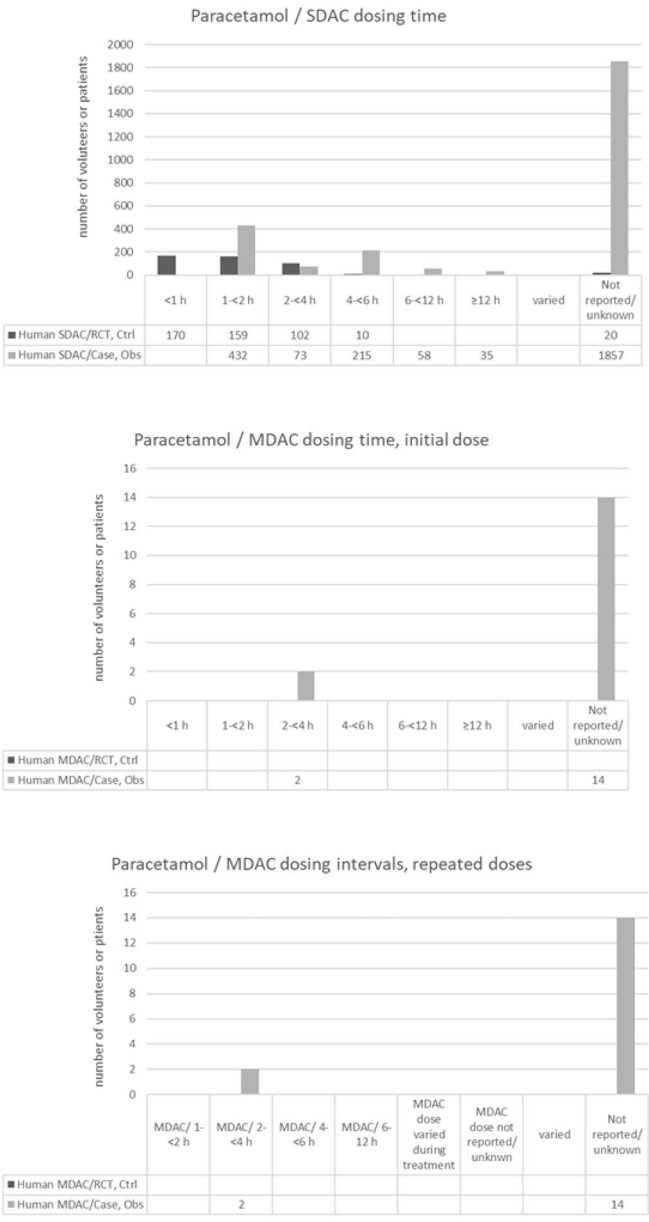


Figure 3. Activated charcoal dosing time and interval for SDAC and MDAC reported in studies for paracetamol included in the review. SDAC: Single-dose activated charcoal; MDAC: Multiple-dose activated charcoal; RCT: Randomized control trial; OBS: Observational study; CTRL: Controlled trial; h: hour(s). The nearly 40,000 patients from one paper [53] are not included because they cannot be displayed on the same scale with the other papers.

Effect size (pharmacokinetic aspects): multiple-dose activated charcoal. No human volunteer or clinical studies of Moderate or High GRADE tested the role of MDAC following paracetamol ingestion.

Figure 3 shows the initial dosing times and intervals for SDAC and MDAC reported in all studies included for paracetamol in the systematic review.

Antidepressants and antipsychotics: citalopram

In vivo: single-dose activated charcoal. In 16 patients (17 occasions) 50 g SDAC was administered following citalopram overdoses (80–1700 mg) at <1 h post-ingestion in one event, 1–2 h in nine events, or 2–4 h in seven events. Modelling predicted that AC administration resulted in a reduction of the QT interval prolongation following a 1200 mg citalopram overdose and reduced the probability of developing Torsade de Pointes. The relative decrease for Torsade de Pointes with SDAC was 60% for citalopram overdoses in the range of 600–1800 mg when AC was administered within 1 h of ingestion. Even if AC was administered as late as 4 h post ingestion, the model predicted a 20% reduction in the risk of Torsade de Pointes [76].

Antidepressants and antipsychotics: escitalopram

In 68 escitalopram overdose patients (78 occasions, 70–450 mg escitalopram) 50 g SDAC was administered within 1.8–2.5 h post-ingestion and resulted in a 31% reduction in fraction of escitalopram absorbed and a reduced risk of abnormal QT interval. Modelling predicted that one dose of 50 g SDAC decreased the risk for an abnormal QT interval by 35% for escitalopram overdoses higher than 200 mg [77].

Antidepressants and antipsychotics: quetiapine

In 54 distinct overdoses (in 42 patients), SDAC (50 g) was given to 19 patients a median of 3 h post-ingestion (range 0.5–6 h). A population pharmacokinetic model estimated that SDAC reduced the bioavailability of quetiapine by 35% [78]. In subsequent work using a similar approach in 286 overdose presentations, the same authors were able to estimate that if SDAC was given within 2 h of ingestion, the probability of endotracheal intubation was reduced by 7% [79].

Barbiturates: phenobarbital

In vitro studies. Numerous *in vitro* studies demonstrated excellent adsorption of phenobarbital to AC [2,42,80–90]. When reported, the range of MACs varied widely from 70 mg of phenobarbital/g AC [88] to 490 mg/g [85] but were mostly in the 200–400 mg/g range. Higher surface area adsorptive capacities (above 2000 m^2/g) had reported MACs near 1000 mg/g [80,82,83,89,90] and outperformed lower surface area adsorptive capacities (1000–1500 m^2/g) when directly compared. Several studies evaluated the effects of varied pH and the differences were small and often in conflict [80,84–86,88]. Many similar studies confirmed that various other barbiturates are well adsorbed to AC [2,7,33,80,84,88,89,91–95].

Effect (clinical outcome). No human studies using a clinical endpoint were of Moderate or High GRADE.

Effect size (pharmacokinetic aspects): single-dose activated charcoal. In three human volunteer studies, 120–200 mg of phenobarbital was administered orally, followed by SDAC (10–50 g) given 5–60 min after ingestion [85,96,97]. Immediate administration of AC significantly reduced phenobarbital absorption and shortened the elimination half-life compared to control. In one study, the effect was a nearly complete (97%) reduction in AUC when AC was

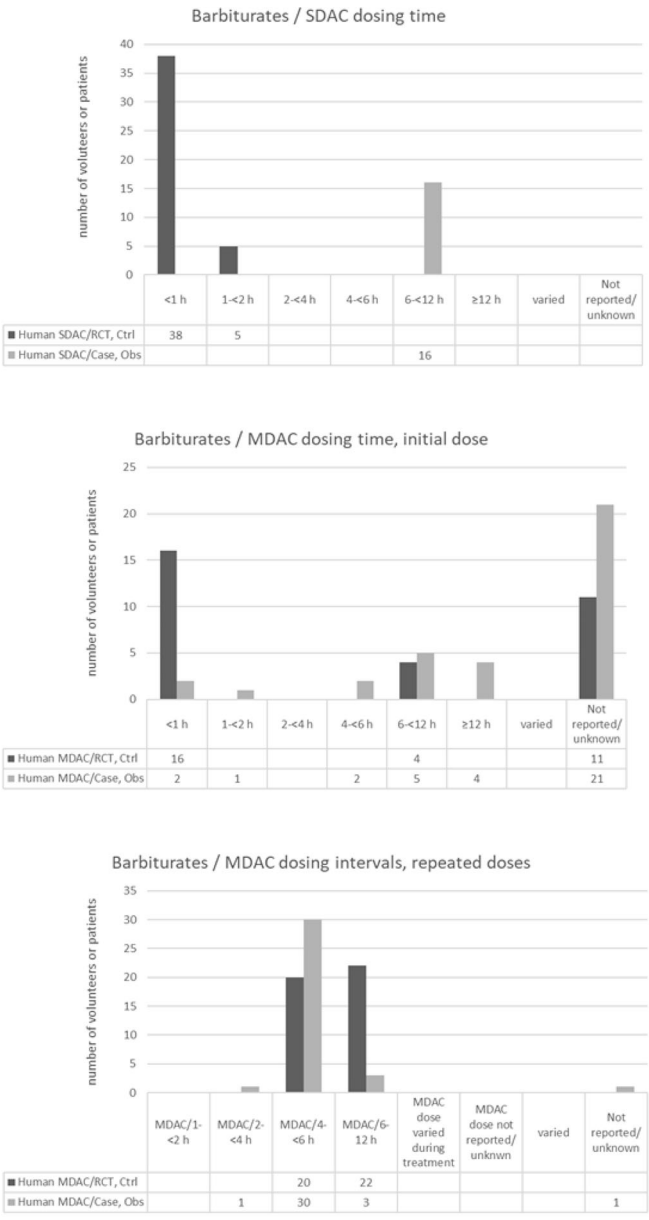


Figure 4. Activated charcoal dosing time and interval for SDAC and MDAC reported for phenobarbital in studies included in the review. SDAC: Single-dose activated charcoal; MDAC: Multiple-dose activated charcoal; RCT: Randomized control trial; OBS: Observational study; CTRL: Controlled trial; h: hour(s).

administered within 5 min which fell to a 57% reduction when the AC was delayed until 1 h after ingestion [97].

Effect size (pharmacokinetic aspects): multiple-dose activated charcoal. One clinical study of Moderate GRADE analyzed the effect of MDAC on patients with phenobarbital overdose [98]. Following gastric lavage, ten intubated patients were all given an initial AC dose of 50 g. The delay between ingestion and treatment was variable, and often unknown. The patients were subsequently randomized to receive no further AC or 17 g every 4 h until extubation. When pharmacokinetic parameters were compared between those who received MDAC ($n = 5$) and those who received SDAC ($n = 5$), the MDAC group had a significantly shorter mean half-life (36 ± 13 h vs 93 ± 52 h, $p < 0.01$) during AC administration. Importantly, after extubation when no AC was given to either group, both MDAC and SDAC patients had similar mean half-lives (93 ± 52 h vs 93 ± 7 h, $p > 0.05$).

Although the authors of this study intended to evaluate clinical outcomes such as Glasgow Coma Score (GCS) and duration of mechanical ventilation, methodological concerns resulted in downgrading this study to Low GRADE evidence for the clinical endpoints which is why it is not discussed in the above "Clinical Outcomes" section. Specifically, although the duration of mechanical ventilation would be an outcome of essential importance, patients were only extubated at a set time of the day for logistical purposes. Similar concerns arose over a lack of specified criteria to move patients out of the ICU or for discharge.

Four other studies evaluated the ability of MDAC to enhance phenobarbital elimination in human volunteers given intravenous (IV) doses of phenobarbital [99–102]. When IV phenobarbital (200 mg/70 kg) was administered in two human volunteer cross-over studies, MDAC (dose: 30 g, then 17 g every 6 h) removed 25–53% of the total phenobarbital dose, statistically significantly decreased the AUC by 13–52%, and shortened the half-life by 50% [100,101]. In another volunteer cross-over study of IV phenobarbital (200 mg/70 kg, $n = 6$), MDAC (dose: 40 g, then 20 g every 6 h) statistically significantly reduced phenobarbital half-life and increased total body clearance compared to no AC [99]. In a similar study using phenobarbital 5 mg/kg IV, MDAC (dose: 50 g, then 25 g every 4 h) significantly reduced the mean half-life (19 h vs. 148 h), and increased the total body clearance compared to no MDAC and was more efficacious than urinary alkalinization for both endpoints [102]. Figure 4 shows the initial dosing times and intervals for SDAC and MDAC reported in all studies included for barbiturates included in the systematic review.

Carbamazepine

In vitro study. One *in vitro* study using non-commercial very low surface area (267–447 m^2/g) AC demonstrated MACs of 4.46–14.5 mg/g of AC [103].

Effect (clinical outcome). No human studies using a clinical endpoint were of Moderate or High GRADE.

Effect size (pharmacokinetic aspects): single-dose activated charcoal. In three volunteer human studies a total of 20 subjects were given therapeutic doses of carbamazepine (200–400 mg orally) and 8–50 g of SDAC at 5 min or 1 h after ingestion. SDAC statistically significantly reduced serum carbamazepine AUC compared to no AC [97,104,105]. Interestingly, in one study when polyethylene glycol electrolyte lavage solution was added, AC was less effective (21% reduction in combination versus 38% reduction with AC alone; $p < 0.01$) [104].

Effect (pharmacokinetic aspects): multiple-dose activated charcoal. In a small randomized study of comatosed carbamazepine poisoned patients ($n = 12$) that compared SDAC (dose: 1 g/kg, $n = 6$) and MDAC (dose: 50 g every 6 h, $n = 6$),

MDAC significantly reduced the half-life (MDAC 12.6 h vs. SDAC 27.9 h, $p = 0.0004$) [106]. Although the authors of this study claim a clinical benefit of MDAC in terms of reduced duration of mechanical ventilation, coma, and length of stay, serious methodological concerns over randomization, blinding, and determination of endpoints resulted in rating this as Low GRADE for clinical evidence, which is why it is not discussed above.

Figure 5 shows the initial dosing times and intervals for SDAC and MDAC reported in all studies included for carbamazepine in the systematic review.

Cardiac glycosides: digoxin

In vitro study. One *in vitro* study demonstrated high adsorptive capacity of AC for digoxin [107].

Effect (clinical outcome). No human studies using a clinical endpoint were of Moderate or High GRADE.

Effect size (pharmacokinetic aspects): single-dose activated charcoal. In a randomized cross-over trial six healthy volunteers ingested 0.5 mg of digoxin either with water alone, or 50 g of AC within five minutes or 1 h of ingestion. Absorption was reduced by 98% when AC was given within 5 min, but only 40% when AC was delayed by 1 h ($p < 0.05$) [10]. In another randomized cross-over trial by the same authors six healthy volunteers ingested 0.25 mg of digoxin followed within five minutes by 8 g of AC. Similarly, AC reduced absorption by 96% ($p < 0.01$) [105].

Effect size (pharmacokinetic aspects): multiple-dose activated charcoal. The ability of MDAC to enhance the elimination of digoxin was examined by using IV digoxin in two studies. The first administered IV digoxin (0.75 mg/70 kg) or IV digitoxin (1 mg/70 kg) to six normal volunteers followed by MDAC (dose: 20 g immediately and then every 4 h for 36 h) or water in a randomized cross-over design. MDAC reduced the digoxin half-life by 26% and the digitoxin half-life by 54% ($p < 0.05$) [108]. The second study administered IV digoxin (10 mcg/kg) followed by MDAC (dose: 25 g immediately and repeated at 4, 8, 12, 16, 22, 28, 34 and 40 h) or water in a randomized cross-over design. MDAC increased digoxin clearance by 47% and decreased the half-life by 41% ($p < 0.05$) [109].

Figure 6 shows the initial dosing times and intervals for SDAC and MDAC reported in all studies included for digoxin in the systematic review.

Oleander

In vitro study. Significant *in vitro* binding of oleandrin and oleandrigenin to AC was demonstrated [110,111].

Effect (clinical outcome): single-dose and multiple-dose activated charcoal. The largest study of acute self-poisoning randomized patients to no AC, SDAC, or MDAC was performed in Sri Lanka [112]. Approximately one-third of the cohort ingested oleander seeds and they appear to be evenly distributed into the study groups. The mean time from ingestion to the first dose of activated charcoal was 4.2 h. There was no statistical difference in death, the use of digoxin-specific antibody fragments, or cardiac pacing among any of the groups. In contrast, another trial in patients who ingested oleander seeds compared placebo to MDAC after SDAC was given to both groups [113]. The mean time from ingestion to first dose of AC was 9.4 h. The MDAC patients had significantly less need for atropine, cardiac pacing, or digoxin-specific antibody fragments. In this trial, the number needed to treat with MDAC to save a life was 18. Methodological differences in patients receiving gastrointestinal decontamination prior to enrollment in the studies, the dose and duration of activated charcoal, compliance with AC dosing [114], availability of digoxin-specific antibody fragments, and other care received prevent direct comparison of the results of these two studies.

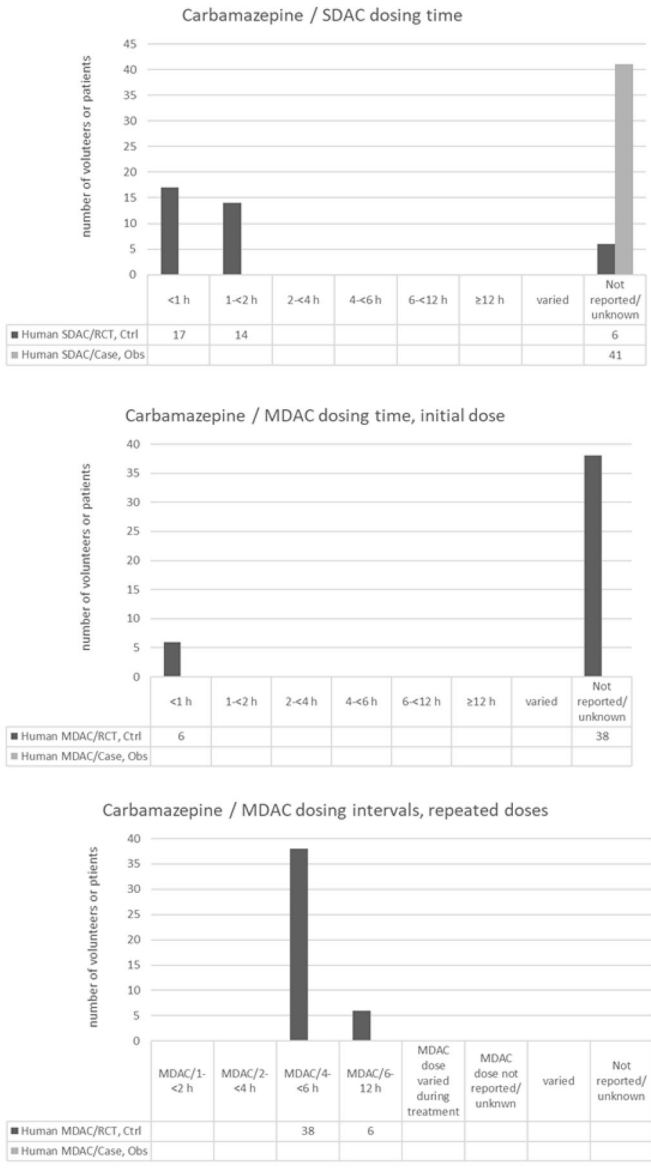
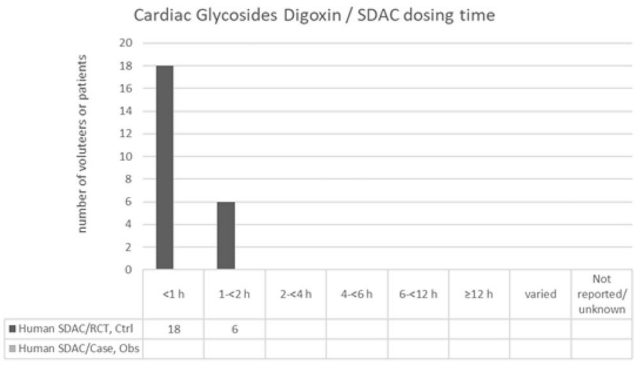
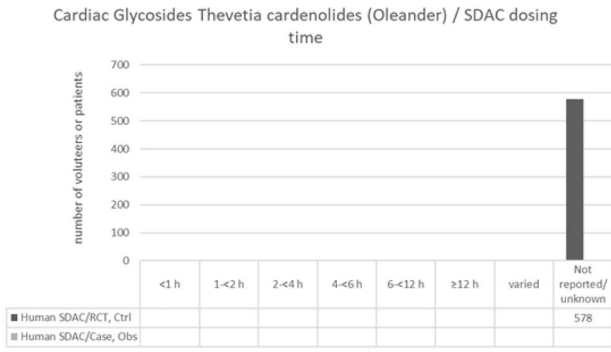
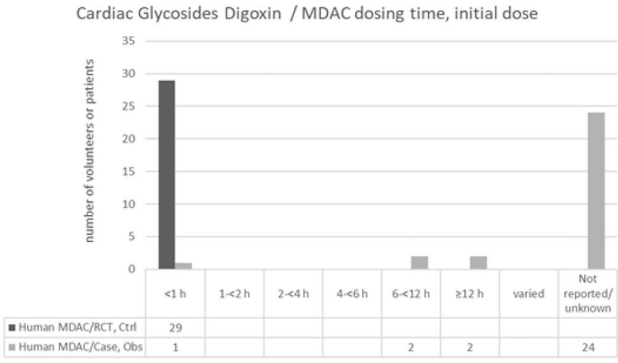
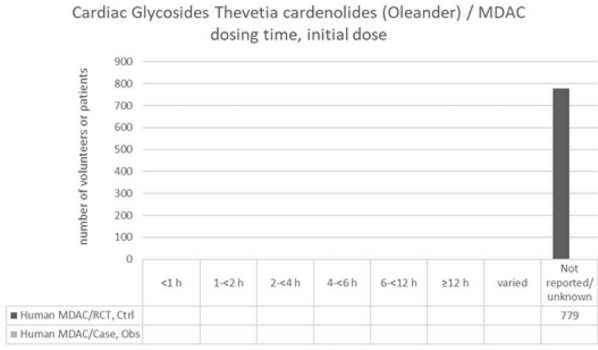


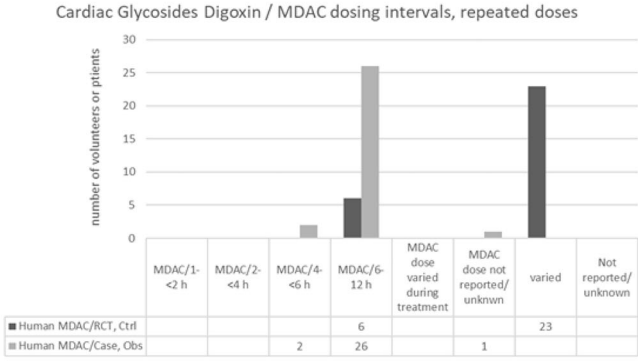
Figure 5. Activated charcoal dosing time and interval for SDAC and MDAC reported for carbamazepine in studies included in the review. SDAC: Single-dose activated charcoal; MDAC: Multiple-dose activated charcoal; RCT: Randomized control trial; OBS: Observational study; CTRL: Controlled trial; h: hour(s).











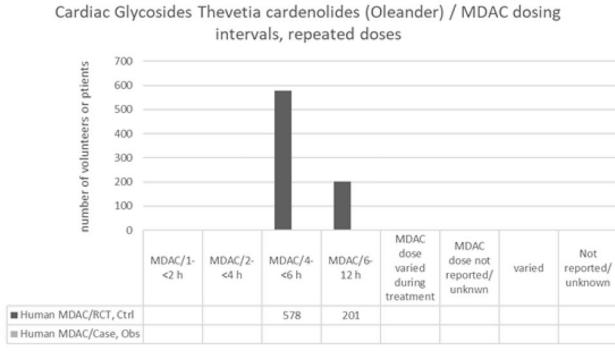


Figure 6. Activated charcoal dosing time and interval for SDAC and MDAC reported in studies for digoxin included in the review. SDAC: Single-dose activated charcoal; MDAC: Multiple-dose activated charcoal; RCT: Randomized control trial; OBS: Observational study; CTRL: Controlled trial; h: hour(s).

Figure 7. Activated charcoal dosing time and interval for SDAC and MDAC reported in studies for Oleander included in the review. SDAC: Single-dose activated charcoal; MDAC: Multiple-dose activated charcoal; RCT: Randomized control trial; OBS: Observational study; CTRL: Controlled trial; h: hour(s).

Effect size (pharmacokinetic aspects): single-dose and multiple-dose activated charcoal. The pharmacokinetic effects of AC were reported in a sub-study of 104 patients who were enrolled in the 2008 trial discussed above [115]. The patients in the no AC, SDAC, and MDAC groups presented to care an average of 6.5 h, 5.5 h and 5.0 h post ingestion, respectively. Although not significantly different from each other, both the SDAC and MDAC groups demonstrated a significant reduction in terminal elimination half-life and mean residence time when compared to the no AC group. Figure 7 shows the initial dosing times and intervals for SDAC and MDAC reported in all studies included for oleander in the systematic review.

Direct oral anticoagulants: apixaban

In vivo studies: single-dose activated charcoal. Eighteen human volunteers participated in a cross-over study in which they received a single dose of 50 g AC either 2 h or 6 h after a therapeutic dose of apixaban and pharmacokinetic parameters were determined compared to no AC (control) [116]. Both the AUC and elimination half-life were reduced with both the 2 h and 6 h AC dosing (AUC reductions of 51% and 28%, 90 % CIs 0.450–0.547 and CI 0.661–0.792, respectively; half-life reductions by 60% and 63%).

Direct oral anticoagulants: rivaroxaban

Similarly, 12 volunteers received a single dose of AC (dose not specified) at either 2 h, 5 h, or 8 h after a therapeutic dose of rivaroxaban [117]. Using population pharmacokinetic modeling the authors demonstrated reductions in AUC for all intervals (43%, 31%, and 29% at 2 h, 5 h, and 8 h, respectively).

Ethanol

In vitro study. The MAC of ethanol to AC is reported to range from 300 mg ethanol/g AC [2] to 460 mg ethanol/g AC [91].

Effect (clinical outcome). No human studies using a clinical endpoint were of Moderate or High GRADE.

Effect size (pharmacokinetic aspects): single-dose activated charcoal. In a randomized cross-over study eight healthy men ingested 88 g of ethanol followed in 30 min with either 20 g of SDAC in water or the same volume of water. There were no significant differences in peak ethanol concentration, elimination rate or AUC [118]. Figure 8 shows the initial dosing times and intervals for SDAC reported in all studies included for ethanol in the systematic review.

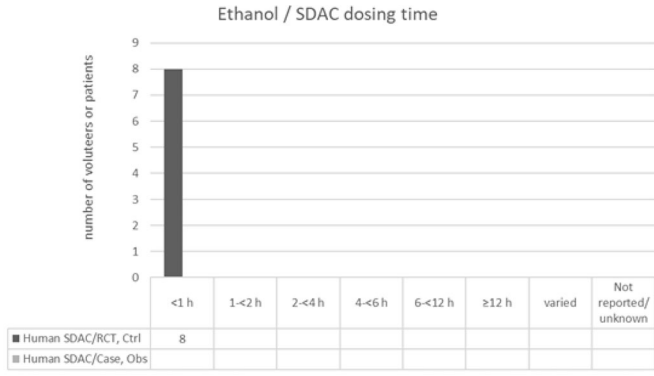


Figure 8. Activated charcoal dosing time and interval for SDAC reported in studies for ethanol included in the review. SDAC: Single-dose activated charcoal; RCT: Randomized control trial; OBS: Observational study; CTRL: Controlled trial; h: hour(s).

Iron

In vitro study. The MAC of iron to AC was 100–103 mg iron/g AC at a fluid pH 4.5–7.5 [119]. At gastric pH the MAC of iron to AC was 33 mg iron/g AC [91].

Effect (clinical outcome). No human studies using a clinical endpoint were of Moderate or High GRADE.

Effect size (pharmacokinetic aspects): single-dose activated charcoal. One cross-over human volunteer study gave 11 subjects 5 mg/kg elemental iron either alone or pre-mixed with 25 g of SDAC. Following AC there were no significant changes in AUC, C_{max} or T_{max} [120].

Figure 9 shows the initial dosing times and intervals for SDAC reported in all studies included for iron in the systematic review.

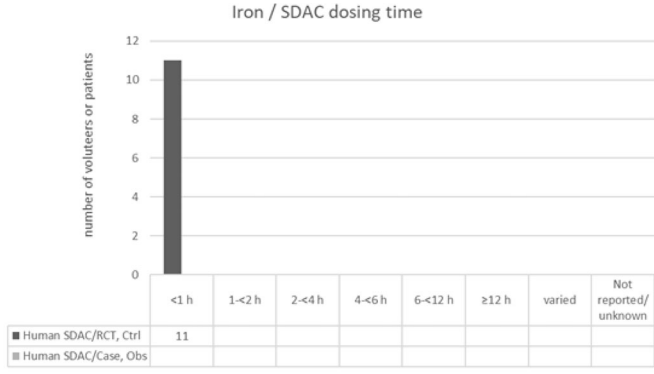


Figure 9. Activated charcoal dosing time and interval for SDAC reported in studies for iron included in the review. SDAC = Single-dose activated charcoal; AC = Activated charcoal; RCT = Randomized control trial; OBS = Observational study; CTRL = Controlled trial; h = hour(s).

Salicylates

In vitro studies. The *in vitro* study of salicylate adsorption to AC includes nearly 60 years of research beginning with one of the first systematic investigations of AC adsorption [2,33,41,42,84,88,91–93,121–132]. In a classic work, Andersen [2] reported the MAC of AC for salicylic acid as 550 mg/g. Subsequent studies showed excellent adsorption with variability based on experimental conditions [33,42,84,88,91,92,122,123,126,127,129–131,133]. The most significant variable was solution pH, with the highest adsorptive capacities in acidic pHs. For example, in one study the MAC was 464 mg/g AC in acidic conditions vs 176 mg/g AC in alkaline conditions [91].

Effect (clinical outcome). No human studies using a clinical endpoint were of Moderate or High GRADE.

Effect size (pharmacokinetic aspects): single-dose activated charcoal. Twenty-eight human volunteer studies compared the ability of SDAC to reduce the absorption of ingested salicylate to control without SDAC [4,10,122,125–128,134–154]. Ingested doses range from 30 mg [4] to almost 3 g [145,150]. The AC doses ranged from 2.5 g [128] to 50 g [143,146,147,150,153] producing large variations in the AC:salicylate ratio. Possibly as a result of the variable AC:salicylate ratio, but also potentially relating to other experimental conditions, the reduction in salicylate absorption ranged from 20% or less [139,147,149,151] to over 75% [10,127,144]. Only two studies directly compared administration of AC at different time points [10,142]. Delaying AC by 1 h significantly reduced the efficacy of AC. Several studies evaluated the use of high surface area ACs. When directly compared in the same study, higher surface area ACs (3000 m^2/g) always outperformed intermediate (1500 m^2/g) and lower surface area (950 m^2/g) preparations [145,149,151]. The effect was often more than a doubling in adsorption.

Effect size (pharmacokinetic aspects): multiple-dose activated charcoal. Six controlled trials examined the role of MDAC in human volunteer models of salicylate ingestion [143,146,155–158]. Single salicylate doses range from 1300 mg [155] to 2800 mg [157]; one regimen gave 7800 mg over 48 h [158]. The MDAC regimens ranged between doses of 25 g every 4 h for a total of 150 g [158] or doses of 50 g each for a total of 150 g [143,146] with the first dose given within 1 h [143,146] to 4 h after the ingestion.[156,157] The effect size of MDAC ranged from no significant difference

from control (no AC) [155,157,158], no significant difference from SDAC treatment [143], a significant benefit for three AC doses over either one or two doses [146], and 9% reduction in AUC with AC with water compared to water alone [156].

Figure 10 shows the initial dosing times and intervals for SDAC and MDAC reported in all studies included for salicylates in the systematic review.

Theophylline/aminophylline

In vitro studies. Adsorption of theophylline to various types of AC was demonstrated [35,42,83,159–161]. The MACs were in the range of 203–282 mg theophylline/g AC.

Effect (clinical outcome). No human studies using a clinical endpoint were of Moderate or High GRADE.

Effect size (pharmacokinetic aspects): single-dose activated charcoal. Four human volunteer studies showed a statistically significant decrease in absorption of theophylline following SDAC compared to no AC [104,159,162,163]. When SDAC was given 30–60 min post ingestion, the AUC was reduced from 51% [159] to 75% [104] of control. Similarly, when reported, reductions in C_{max} were from 36% [163] to 66% [104].

Effect size (pharmacokinetic aspects): multiple-dose activated charcoal. Thirteen human volunteer studies showed a statistically significant decrease in pharmacokinetic parameters such as AUC, C_{max}, T_{max}, $T_{1/2}$, and an increase in clearance of theophylline or aminophylline when MDAC was compared to SDAC or no AC [159,162,164–174]. The latest time of administration of the first dose of AC as part of MDAC that showed a benefit was 6 h [172]. For all human volunteer studies included, the doses of theophylline/aminophylline varied widely as did the doses and intervals for AC. Additionally, the surface areas of the ACs used were not universally reported.

Figure 11 shows the initial dosing times and intervals for SDAC and MDAC reported in all studies included for theophylline in the systematic review.

Tricyclic antidepressants

In vitro studies. Several studies demonstrated adsorption of tricyclic antidepressants to AC. Many studies highlighted pH dependency with the highest adsorptive capacities occurring in alkaline pHs [33,35,46,51,88,127,175–178]. The MACs in commercially available brands of AC were: amitriptyline 490–700 mg/g [51], nortriptyline 318 mg/g [175], and imipramine 372–610 mg/g [178].

Effect (clinical outcome): single-dose activated charcoal. Following gastric lavage, 77 patients with known tricyclic antidepressant overdose were randomized to receive either 20 g of AC ($n = 34$) or no AC ($n = 43$). The time between ingestion and AC administration was not reported. There was no statistical difference between the two groups in terms of toxic signs and symptoms, patients needing greater than 48 h in ICU, and admission to hospital for greater than three days [179].

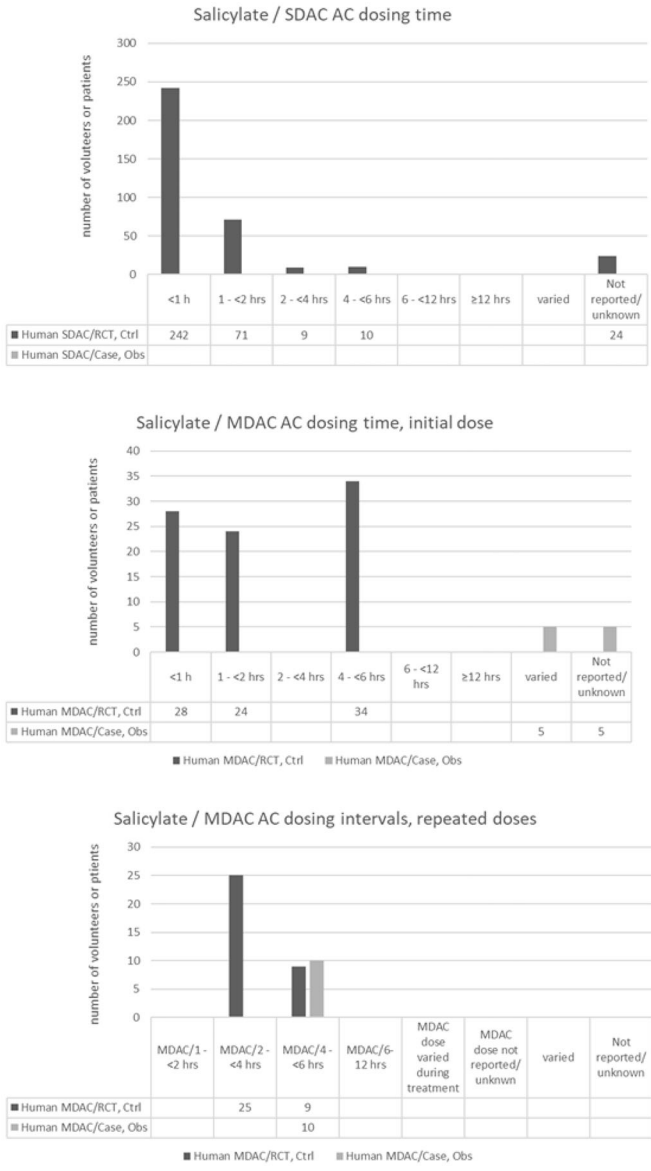


Figure 10. Activated charcoal dosing time and interval for SDAC and MDAC reported in studies for salicylates included in the review. SDAC: Single-dose activated charcoal; MDAC: Multiple-dose activated charcoal; RCT: Randomized control trial; OBS: Observational study; CTRL: Controlled trial; h: hour(s).

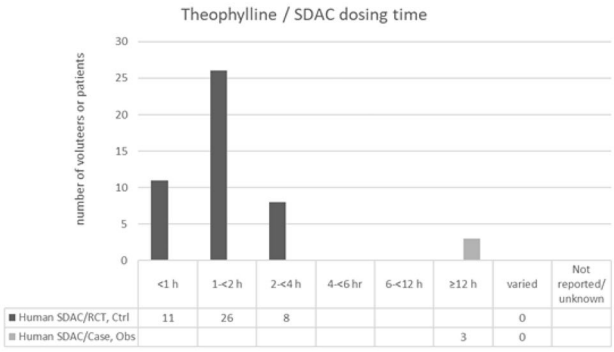
Effect size (pharmacokinetic aspects): single-dose activated charcoal. In the clinical study mentioned above there were no differences between the two groups with regard to the following pharmacokinetic parameters: AUC, peak concentration (C_{max}) or half-life [179].

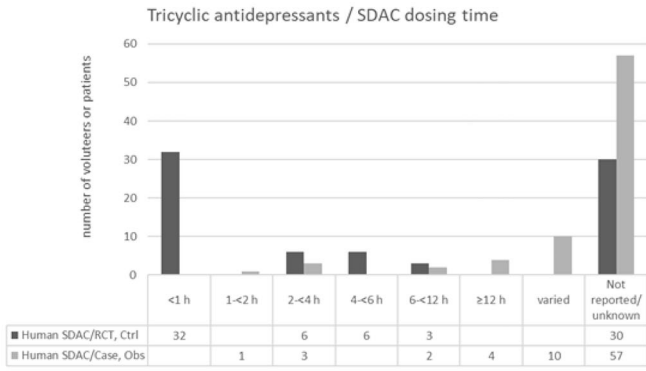
There were no other Moderate of High GRADE pharmacokinetic studies.

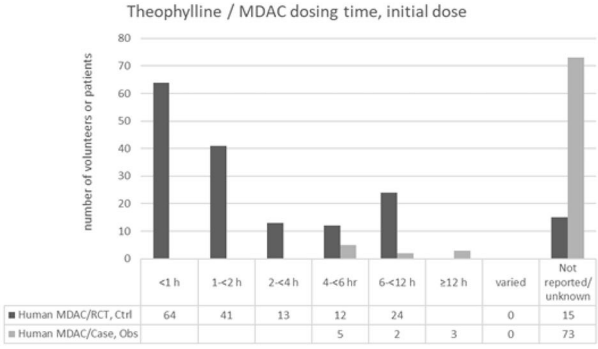
Figure 12 shows the initial dosing times and intervals for SDAC and MDAC reported in all studies included for tricyclic antidepressants included in the systematic review.

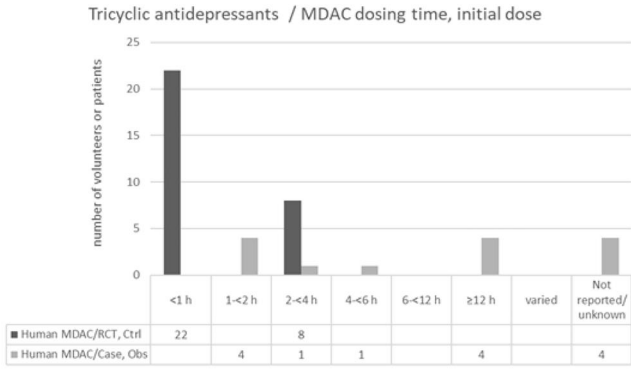
Valproic acid

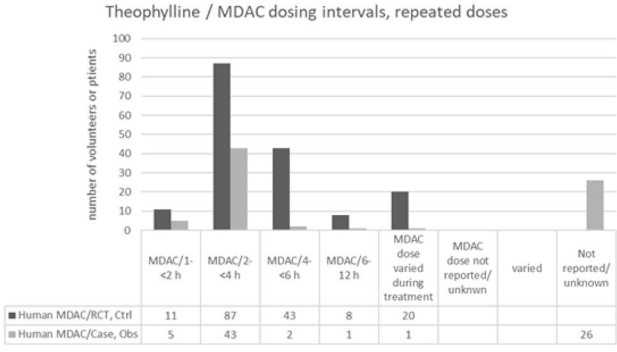
In vitro studies. There were no *in vitro* studies describing MAC of valproic acid to AC.











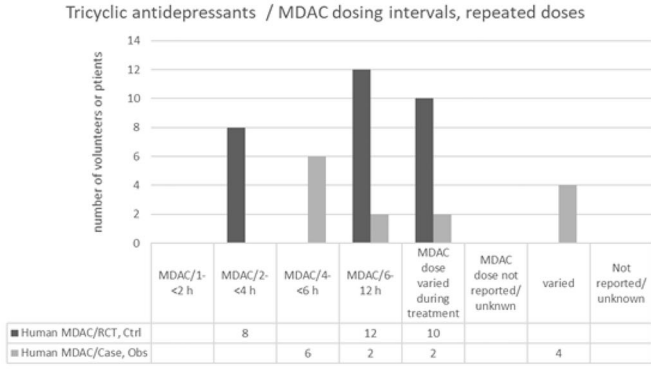


Figure 11. Activated charcoal dosing time and interval for SDAC and MDAC reported in studies for theophylline included in the review. SDAC: Single-dose activated charcoal; MDAC: Multiple-dose activated charcoal; RCT: Randomized control trial; OBS: Observational study; CTRL: Controlled trial; h: hour(s).

Figure 12. Activated charcoal dosing time and interval for SDAC and MDAC in reported in studies for tricyclic antidepressants included in the review. SDAC: Single-dose activated charcoal; MDAC: Multiple-dose activated charcoal; RCT: Randomized control trial; OBS: Observational study; CTRL: Controlled trial; h: hour(s).

Effect (clinical outcome). No human studies using a clinical endpoint were of Moderate or High GRADE.

Effect size (pharmacokinetic aspects): single-dose activated charcoal. A randomized cross-over study administered to six healthy volunteers 500 mg of sodium valproate, followed five minutes later by 50 g of SDAC or water control [180]. Activated charcoal produced a statistically significant reduction in peak concentration (35% of control) and AUC (37% of control).

Effect size (pharmacokinetic aspects): multiple-dose activated charcoal. The use of MDAC for valproic acid was addressed in a crossover study in which seven volunteers were provided 300 mg of valproic acid syrup and received MDAC 20 g of AC at 4 h, then 10 g at 8 h, 12 h, 24 h, and 32 h compared to no AC (control) [181]. No significant difference was observed for AUC, C_{max}, T_{max}, or $T_{1/2}$. between the two groups.

Figure 13 shows the initial dosing times and intervals for SDAC and MDAC reported in all studies for valproic acid included in the systematic review.

Clinical studies of mixed populations

A prospective, unblinded controlled trial randomized poisoned patients to SDAC (50 g) or no AC over a 16 month period was conducted at one institution [182]. A total of 327 presentations met final inclusion and exclusion criteria. Over 80% of patients presented within 4 h of ingestion and nearly 60% were within 2 h of ingestion. Benzodiazepines

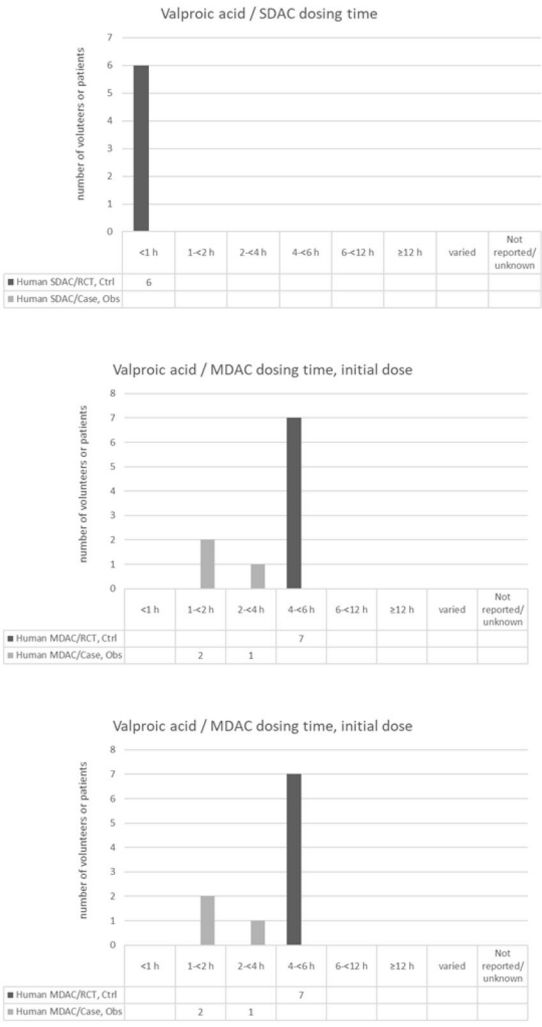


Figure 13. Activated charcoal dosing time and interval for SDAC and MDAC reported in studies for valproic acid included in the review. SDAC: Single-dose activated charcoal; MDAC: Multiple-dose activated charcoal; RCT: Randomized control trial; OBS: Observational study; CTRL: Controlled trial; h: hour(s).

composed 37% of the toxins ingested, followed by paracetamol 26–29%, and SSRIs 16–21%. The estimated dose ingested was not reported. When the two groups were compared there were no significant differences in length of stay or adverse events associated with AC administration. The authors commented that the study was underpowered to evaluate an effect in the small numbers of patients who presented within 1 h of ingestion.

The largest study of acute self-poisoning randomized over 4500 patients to no AC, SDAC (50 g), or MDAC (50 g every 4 h for 6 doses) [112]. The patients, who were enrolled from three hospitals, presented between 4–5 h post ingestion and over half in each group had another decontamination procedure (emesis or lavage) performed prior to enrollment. There were no significant differences in mortality between the three groups. An *a priori* sample size calculation was based on 80% power to detect an absolute difference of 3% in mortality (a decrease from 10% to 7%) with 95% certainty. A subgroup analysis was unable to detect differences with regard to time of presentation or in the two most common toxins (oleander, and organophosphorus and carbamate pesticides combined).

Advances since the last position statements

Several important developments have occurred since the last iterations of the AACT/EAPCCT single-dose and multiple-dose activated charcoal Position Statements in 2005 and 1999, respectively [14,31]. Some of this information is presented in the individual poison sections above and the summary tables. Some additional points deserve special recognition and are summarized here. Because this information is new, we chose to discuss all the evidence included regardless of GRADE classification. We hope that with time higher quality data will become available on these topics.

Time window to administer activated charcoal

The AACT/EAPCCT SDAC position statement relied heavily on volunteer data to create a one-hour time frame post ingestion to consider AC administration. A subsequent meta-analysis of all human volunteer studies found evidence to support the efficacy of AC up to 4 h post ingestion [590]. Two previously discussed paracetamol articles of Moderate GRADE reported a clinical benefit of AC administration as late as 4 h post ingestion [54,55]. An article of Low GRADE added clinical support for administration of AC to paracetamol poisoned patients beyond 4 h post ingestion [183]. However, in a prospective observational study of patients who ingested modified release paracetamol (median ingested dose 32 g) no benefit was found when SDAC was given at a median of 3.5 h post ingestion [184].

Further experimental support for delayed AC administration can be derived from studies of gastric emptying times in overdose patients. Using a radiolabeled tracer, a group of prospectively recruited overdose patients exhibited substantially prolonged gastric emptying times with 47 of 85 patients having emptying half-times greater than 120 min, 12 of whom were greater than 300 min [15]. More recently, another study reported on direct visualization of gastric contents by endoscopy. In this study, the majority of patients studied had visible tablets as the predominant finding up to 4 h post-ingestion. Tablets and soluble material combined were still present in the majority (62.5%) of patients' stomachs at 6 h to 12 h post ingestion [16]. This study confirmed the results of an earlier endoscopy study, which found significant persistent gastric tablet contents in overdose patients despite both delayed presentation (up to 4.5 h) and a gastric emptying procedure (ipecacuanha or gastric lavage) [19]. Similarly, of 19 patients who underwent gastroscopy 2.25–13 h after ingestion of a sustained release formulation of quetiapine, 9 had pharmacobezoars present [17].

Of the reviewed overdose case reports and case series, the time to administration of the first dose of AC was beyond 1 h in 97% ($n = 1006$ patients), beyond 2 h in 36% ($n = 491$ patients), and beyond 12 h in 4% ($n = 43$ patients). In contrast, the timing of the first dose in controlled studies was within 60 min of ingestion in 48% ($n = 2359$ patients) and beyond 2 h in 36% ($n = 484$) patients. These data are represented in Figure 14.

New toxins and population pharmacokinetics

Since the last AACT EAPCCT positions statement on AC decontamination in 2005, new pharmaceuticals (toxins) have become available (e.g., direct oral anticoagulants) and some

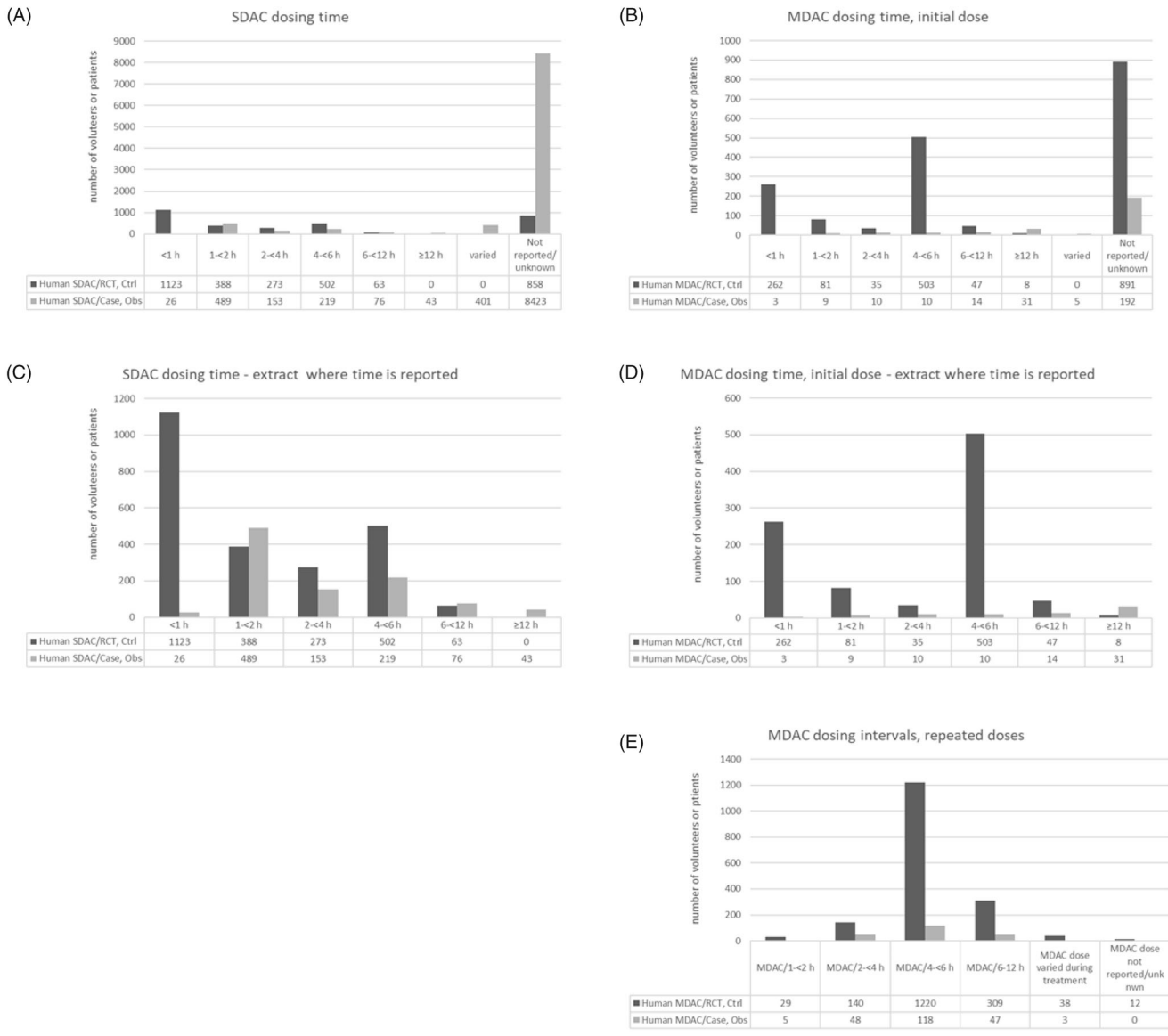


Figure 14. Time to single dose activated charcoal (A) and multiple-dose activated charcoal (C) dosing since time of ingestion, all substances. Panel B and D highlight activated charcoal dosing time by excluding reports in which the activated charcoal dosing time was not reported. SDAC: Single-dose activated charcoal; MDAC: Multiple-dose activated charcoal; RCT: Randomized control trial; OBS: Observational study; CTRL: Controlled trial; h: hour(s).

of these, as well as older ones, are formulated as modified release preparations. Bayesian population pharmacokinetics were also used to determine the clinical effects of SDAC on three drugs; citalopram, escitalopram and quetiapine, and the findings (summarized above) challenge the 'one hour' position statement dogma [76–79].

New formulations

In overdoses of pharmaceutical preparations, the active pharmaceutical ingredient (API) needs to be in solution before adsorption to AC is possible. The design of solid dosages forms has influence on this step, as disintegration and dissolution vary. Fast disintegration and dissolution are expected from immediate release preparations in therapeutic doses, but both parameters may be prolonged in overdose situations. The key concept in extended-release preparations and possibly in large doses of immediate release preparations is the slow release of the API and a prolonged absorption phase. Disintegration and dissolution depend on several factors including the tablet or capsule core and/or the tablet coating or capsule material. Several commercially available preparations attached to each other to form a firm and sticky mass *in vivo*, post-mortem and *in vitro* when the dose exceeds normal therapeutic amounts [17,185–188].

The precise thresholds for the formation of these pharmacobezoars have not yet been established. These values vary widely depending on the specific preparations and individual host factors such as the volume and types of fluid co-ingested. That being said, the concept of an extended time of release of the API beyond what is normally expected in therapeutic dosing might apply to the majority of the extended-release preparations.

Dose

The optimal dose of AC in poisoning was not reported in the majority of the articles in this systematic review. The

rationale behind the actual dose administered in volunteer studies or case reports was seldom described. Determination of the dose seems to have been based on a number of factors such as the patient's weight, the ingested dose, an arbitrary fixed dose, without considerations of the AC surface area, or the container size of the available activated charcoal preparation (see Figure 15).

Single-dose activated charcoal

The most frequent fixed SDAC dose used in controlled studies and case series was 50 g in adults. Lower doses ranging between 10 and 30 g originated from studies published before 2000. However, in the great majority of clinical cases, administration of SDAC is reported as part of the treatment, without a specific dose (Figure 15).

Studies on SDAC showed a gradual increase in dose with publication year. Doses of SDAC and the initial dose of MDAC increased over time, from 10–30 g to 50–60 g. The single-substance group volunteer studies, administering 10–30 g AC dose were from studies published between 1969 and 1998 [4,125,126,134,135,136,137,138,139,140,144,145,149,151,152,189]. Higher SDAC doses were first reported in the late 1980s, during which doses of 50 g [143,146–148,150,153] or 60 g [141] were used with salicylate.

Multiple-dose activated charcoal

Controlled MDAC studies reported predominantly an initial AC dose of 50 g (Figure 15). The repeated doses were also mainly reported as 25–50 g doses (Figure 15). Activated charcoal dosing based on the AC to poison ratio was infrequently reported in relation to SDAC dosing and not reported in the MDAC studies. Initial MDAC doses of 25 g [155–157] were studied during the same period as larger doses in MDAC studies in which initial doses were 50 g [143,146,158] or even 60–75 g [190,191].

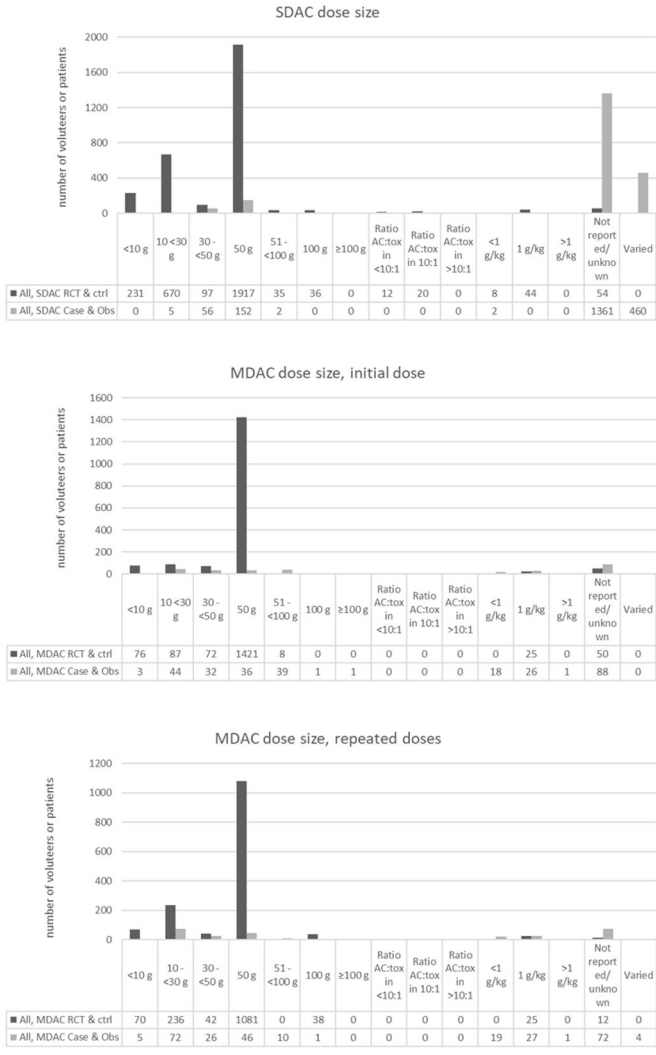


Figure 15. Summary of activated charcoal dosing included in SDAC and MDAC studies. SDAC: Single-dose activated charcoal; MDAC: Multiple-dose activated charcoal; RCT: Randomized control trial; OBS: Observational study; CTRL: Controlled trial; h: hour(s).

Addition of cathartics

The addition of cathartics to AC purportedly decreases intestinal transit time, which theoretically reduces the time of contact between poison and gut available for absorption. Data for the use of cathartics with AC are reported in the same method as above studies, with human studies only discussed in detail if they were of Moderate GRADE of evidence or greater. The summary of studies including cathartics during treatment is available in supplemental material Table J.

***In vitro* studies.** Cathartics had variable effects on the *in vitro* adsorption of poisons to activated charcoal.

Sorbitol produced a statistically significant reduction on the adsorption of tilidine [192] but had no statistically significant effect on the adsorption of AC to paracetamol [193] or phenazone [194]. One study compared the effect of sorbitol on the adsorption of pentobarbital to three different activated charcoals: Darco (G60), USP, and SuperChar. Sorbitol had no effect on either the low surface area (Darco, 650 m^2/g) or moderate surface area (USP, 1000 m^2/g) charcoal, but produced a statistically significant reduction in adsorption of pentobarbital to the high surface area (SuperChar, 2800–3500 m^2/g) charcoal [195].

Sodium sulfate had no statistically significant effect on the adsorption to AC of salicylate [133,196], chloroquine [197] or mefloquine [197]. In contrast, sodium citrate statistically significantly increased adsorption to AC of salicylate [196] and rifampicin [198] but decreased the adsorption of doxycycline [199].

Magnesium sulfate statistically significantly increased the adsorption of salicylate in one study [196], but not another [133]. Similarly, in one model magnesium sulfate statistically significantly increased adsorption of metronidazole [200] and quinine [201], statistically significantly decreased the adsorption of quinidine [201] and had no statistical effect on the adsorption of tinidazole [200]. Magnesium citrate statistically significantly increased adsorption of salicylate to AC in one study [196], statistically significantly decreased the adsorption of salicylate in another [133] and had no significant

effect on the adsorption of salicylate in a third study [202]. Magnesium citrate appeared to increase the adsorption of paraquat to AC, but statistical analysis was not performed [203].

Polyethylene glycol electrolyte lavage solution (PEG-ELS) produced a statistically significant reduction in adsorption to AC for salicylate [204], cocaine [205], and theophylline [206]. PEG-ELS also numerically reduced the adsorption of chlorpromazine but no statistical analyses were performed [207].

Sodium chloride had no statistically significant effect on the adsorption of salicylate [196] or rifampicin [198] but statistically increased the adsorption of doxycycline [199].

Animal studies. In dogs, the use of AC with sorbitol and mannitol combined statistically significantly decreased the reduction in peak paracetamol concentration produced by activated charcoal alone [208]. Castor oil had no statistically significant effect in this same model. The effect on AUC was not statistically significant. In a dog model of carprofen poisoning the addition of sorbitol to AC did not produce a statistically significant alteration in the pharmacokinetic benefits of AC [209]. In a rat model of pentobarbital poisoning sorbitol produced a statistically significant increase in the efficacy of Darco (G-60) and USP activated charcoal, but not that of SuperChar [95]. This is consistent with the *in vitro* study by the same authors above.

In a rat model the addition of sorbitol to AC did not interfere with pharmacokinetic benefits of AC to reduce the absorption of chlorpheniramine, chloroquine, pentobarbital, or salicylate [210]. In each case, sorbitol appeared to augment the effect of AC, but statistical comparisons were only made to control. None of the cathartics sorbitol, sodium sulfate, nor magnesium sulfate improved the efficacy of SuperChar in a lethality study of T-2 toxin in rats [211]. When AC with and without magnesium citrate were compared in a model of lethal paraquat poisoning in mice, only AC plus magnesium citrate produced a statistically significant improvement in lethality compared to control [203].

Human volunteer studies: sorbitol. Adult volunteers ingested salicylate 325 mg followed immediately by either water, activated charcoal, sorbitol, or activated charcoal plus sorbitol in a crossover design. Activated charcoal alone and AC plus sorbitol resulted in a statistically significant ($p < 0.001$) decrease in salicylate absorption compared to the water control. There was no statistically significant difference between the AC alone and AC plus sorbitol groups [135]. In a similar study, volunteers ingested salicylate followed immediately by either AC alone or AC plus one of two different sorbitol doses. There was no statistically significant difference between the ability of the three groups to reduce salicylate absorption [125]. In contrast, when volunteers ingested salicylate followed in 60 min by either AC alone or AC plus sorbitol using a crossover design, the addition of sorbitol to AC reduced salicylate absorption by 28% ($p < 0.05$) [212].

In a nonrandomized controlled trial, ten overdose patients were given 30 g of magnesium sulfate along with a single dose of AC at presentation (time 0). Fourteen overdose patients received 30 g of magnesium sulfate at time 0, 4 h and 8 h after presentation. Magnesium concentrations were measured prior to each magnesium dose and at 1 h and 4 h after the last dose of cathartic. Although in the single dose group, magnesium concentrations increased in 7/10 patients and two cases rose above the upper limit of normal, these changes were not statistically significant. In contrast, there was a statistically significant increase in magnesium concentrations in the multiple dose group, with one patient developing hypotension and oliguria [213]. None of the other studies with cathartics that were of Moderate or High GRADE of evidence addressed rates of adverse events.

A randomized crossover study assessed the effect of sorbitol in addition to AC on the absorption of paracetamol. One hour after ingesting paracetamol, volunteers either took AC alone, AC plus sorbitol, or nothing and had serial paracetamol concentrations determined. Both AC alone and AC plus sorbitol produced a statically significant reduction in the AUC compared to no treatment, but there was no difference between the treatment groups [61].

A randomized crossover study assessed the effect of sorbitol in addition to MDAC on pharmacokinetics of a modified release theophylline preparation. Volunteers were given either AC alone or AC plus sorbitol at 6 h, 7 h, 8 h, 10 h, and 12 h after ingestion and the AUCs were compared. The addition of sorbitol to the MDAC regimen produced a statistically significantly greater reduction in the AUC when compared to the MDAC regimen alone [167]. Another crossover study assessed the effect of sorbitol in addition to MDAC on pharmacokinetics of a modified release theophylline preparation. Volunteers were randomized to either water, AC alone, or AC plus sorbitol 2 h after ingestion and then again every 6 h for 3 more doses. The MDAC and MDAC plus sorbitol regimens both produced a statistically significantly greater reduction in the AUC, C_{max}, and T_{max} compared to water only. However, there were no statistically significant differences between the MDAC and MDAC plus sorbitol treatments [164].

In a randomized crossover study the effects of MDAC with or without sorbitol were compared for ingestion of sustained release theophylline in volunteers. The addition of sorbitol to AC given at 6 h, 10 h and 18 h after ingestion did not result in a statistically significant alteration in the ability of MDAC to limit theophylline bioavailability [172].

A randomized crossover study assessed the effect of sorbitol in addition to MDAC to enhance the elimination of intravenous phenobarbital. Volunteers were given either AC alone or AC plus sorbitol immediately and then again at 6 h, 12 h, 18 h, 24 h, and 36 h after the infusion vs no Intervention Group. Although both treatments produced a statistically significant increase in the clearance of phenobarbital, there was no difference between MDAC alone and MDAC plus sorbitol [101].

Human volunteer studies: sodium and magnesium sulfate. A randomized crossover study assessed the effect of sodium sulfate addition to AC on the absorption of paracetamol. Immediately after ingesting paracetamol, volunteers either

took water, AC alone, or AC plus sodium sulfate. Absorption was assessed by the analysis of paracetamol metabolites over 48 h. Although both treatments produced a statistically significant reduction in paracetamol absorption compared to water only, there was no difference between AC with and AC without sodium sulfate [60].

A randomized crossover study assessed the effect of sodium sulfate addition to AC on the absorption of salicylate. Thirty minutes after ingesting aspirin (acetyl salicylic acid) 975 mg, volunteers either took water, AC alone, or AC plus sodium sulfate. Venous blood samples and urine were collected over 48 h. When compared to control, administration of AC alone produced statistically significant reductions in C_{max}, AUC, and the percent of urine recovery, while reductions for AC plus sodium sulfate only reached statistical significance for C_{max} and percent of urine recovery. There were never statistically significant differences between AC and AC plus sodium sulfate for any of the parameters studied [140].

No human volunteer studies of Moderate or greater GRADE of evidence evaluated the use of magnesium sulfate with and without AC.

Human volunteer studies: sodium and magnesium citrate.

A randomized crossover study assessed the effect of magnesium citrate addition to AC on the absorption of salicylate. Immediately after ingesting aspirin (acetyl salicylic acid), volunteers either took water, AC alone, AC plus magnesium citrate, or AC followed in 30 min by magnesium citrate. Salicylate absorption was measured by urine collection over 48 h. When compared to control, administration of AC alone or AC plus either immediate or delayed magnesium citrate produced a statistically significant reduction in salicylate absorption. There was no statistically significant difference between administration of AC alone and either AC plus magnesium citrate treatments [139].

A single crossover study assessed the effect of magnesium citrate addition to AC on the absorption of salicylate, phenylpropanolamine, and atenolol. Only the salicylate data are of a Moderate GRADE of evidence. Five minutes after the ingestion of aspirin (acetyl salicylic acid) 1000 mg, volunteers either took water, AC alone, or AC plus magnesium citrate. Serial blood specimens were obtained over 24 h and urine was collected for 72 h. Activated charcoal alone statistically significantly reduced the bioavailability of salicylate compared to water.

There was no statistically significant difference in bioavailability between AC alone and AC plus magnesium citrate [214].

No human volunteer studies of Moderate or greater GRADE of evidence evaluated the use of sodium citrate with and without AC.

Adverse effects of activated charcoal

The most frequently reported adverse events following AC administration were gastrointestinal and included nausea, vomiting, diarrhea, and abdominal pain. However, deaths from pulmonary aspiration or gastrointestinal obstruction were also reported [215–223]. Understanding the incidence and risk factors for such events is crucial to clinical decision making for the use of AC in poisoned patients. No data were reported on the presence or absence of chronic sequelae.

Six comparative studies evaluated the adverse effects of AC in poisoned patients as primary or secondary endpoints [113,224–228]. In these studies, vomiting was the most common adverse event and occurred in 6–28% of patients. No deaths were reported. Comparisons of different types of AC did not result in significantly different rates of adverse events [224,225]. Two studies compared AC to no AC. In the first, vomiting occurred more frequently in patients that did not receive AC (28%) than in patients that did receive AC (20%) [228]. Likewise, another study reported that nausea occurred more frequently in patients that did not receive AC (13%) than in patients that did receive AC (8%) [227]. One clinical trial comparing SDAC and MDAC in yellow oleander ingestions reported that adverse GI effects (diarrhea and abdominal discomfort) only occurred in 13 of 201 patients that received MDAC [113].

Twelve observational studies and one volunteer study with no comparator groups reported adverse events associated with AC use [229–240]. In these studies, a total of 3086 patients were given AC and an adverse event occurred in 405 patients (13%); these included GI effects in 354 (11%) and aspiration in 52 (2%,) and no deaths were attributed to AC use. In the volunteer study, the duration of loose stool or diarrhea lasted on average 12 h [240]. An additional observational study found that administration of multiple doses of magnesium citrate along with AC was associated with increased serum magnesium concentrations well above the normal reference values [241].

The remaining articles included 56 cases of adverse events and 10 deaths that were associated with AC use (aspiration) [215, 216,218,219, 223, 231,242,243] or AC use as a possible cofactor [222]. The most frequently published adverse effects were categorized as respiratory complications ($n = 24$), gastrointestinal obstruction ($n = 16$) and electrolyte abnormalities ($n = 10$). In these reports, a number of themes regarding risk factors were observed. The most frequently published adverse events involved respiratory complications due aspiration of vomitus ($n = 15$) or errors in nasogastric tube placement ($n = 9$). Three reports of aspiration occurred in patients that had undergone bariatric surgery. Respiratory complications accounted for 8 of the reported deaths and 4 cases of long-term neurologic or pulmonary sequelae. Gastrointestinal obstruction secondary to AC administration occurred in 16 cases and was associated with two deaths. Seventy five percent of the cases with AC obstruction had received multiple doses of activated charcoal. Reports of electrolyte abnormalities were associated with excess use of magnesium cathartics ($n = 5$), polyethylene glycol ($n = 3$), and sorbitol ($n = 2$). Detailed information in studies reporting on adverse events are available in the supplemental material, Table H.

Limitations

As with any systematic review there is a publication bias. We cross-referenced articles but did not search non-peered

reviewed abstracts or case postings in the grey literature. It is possible, however unlikely that a High GRADE study would not have been found because the search strategy was intentionally very broad. While it is also possible that we excluded an article with relevant data, excluded articles were all reviewed by two panelists. Our graders decided GRADING criteria *a priori* with the assistance of the workgroup experts for determining indirectness of the surrogate outcomes. Another possible limitation exists in the GRADING of studies inasmuch as other methodologists might downgrade or upgrade studies differently or another group of experts might have come to different opinions on the role of certain drug concentrations for surrogacy. That being said, when there was a dispute in GRADE the default by design was always to the lower value.

Conclusions

Despite more than six decades of research on the use of activated charcoal in poisoning, this systematic review retrieved heterogeneous data, mostly consisting of case reports. Higher GRADE data was limited to a few select poisonings, such as paracetamol and oleander. Because studies that addressed patients with unknown and or mixed ingestions were limited by low reported rates of clinically meaningful outcomes of interest such as toxicity or death, they were unable to quantify precisely the potential benefit of AC. Evidence in support of the use of cathartics was also lacking. However, there was evidence that the activity of activated charcoal extended beyond the traditional "one hour" in certain clinical scenarios. The administration of activated charcoal to patients with unprotected airways or who are obtunded is not without significant risk, but as studies reporting adverse events are infrequent, the number needed to harm is impossible to calculate. As a result, recommendations on the use of SDAC and MDAC in poisoned patients require a sound, reproducible and transparent consensus methodology that balances benefits with adverse effects.

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Appendix 1

Publication selection

Medline (Ovid) search strategy for effect of activated charcoal.

1. "*** CONCEPT 1: Activated charcoal ***".sm.
2. exp Charcoal/
3. (charcoal or actidose* or (activated adj (carbon or coal)) or adsorba or "carbo activatus" or carbomix or charac or charbon or charcoaid or charcocaps or charcodote or formocarbine or instachar or kohle-compretten or kohle-hevert or kohle-pulvis or kohle-tabletten or liqui-char or norit or ultracarbon).mp.
4. (actidose-aqua or carbomix or "di-gon ii" or diarrest or donnagel* or ez?char or kao-con or kaodene or kaolinpec or kaope* or parepectolin).mp.
5. 16291-96-6.rn.
6. or/2-5
7. "*** CONCEPT 2: Toxicology/Poisoning ***".sm.
8. exp Poisoning/
9. exp Antidotes/
10. exp Drug Overdose/
11. exp Noxae/
12. exp Toxicity/
13. (overdos* or antidote*).tw.

14. (toxic* or pharmacotoxic* or intoxic* or poison* or noxious or noxa*).tw.
15. (po or to).fs.
16. or/8-15
17. 6 and 16

Appendix 2

Definitions and terminology

Activated charcoal (Activated carbon or Medicinal Carbon): A powdered or granular form of carbon used to reduce gastrointestinal absorption or enhance the elimination by adsorbing to poisons. Activated charcoal is made by carbonization of organic material followed by chemical or physical manipulation (activation) to increase surface area and meets international pharmacopeia standards for purity and adsorptive capacity [591]. While there is no set standard for surface area, most AC products used in acute poisoning have surface areas of 500–2500 m^2/g. In general three ranges of surface are charcoals are studied; high (>2500 m^2/g), intermediate (1500–2000 m^2/g), and low surface area (<1200 m^2/g).

Enteral dosing: Oral or rectal administration.

Multiple dose activated charcoal (MDAC): Doses, regardless of individual dose amounts, given repeatedly for the purpose of enhancing poison elimination.

Poison: A xenobiotic (drug or toxin – exogenous substance, including medications and naturally occurring substances in plants or animals) or an endogenously found chemical (e.g., elementals, or vitamins) with the potential to cause toxicity.

Poisoning: Exposure to a poison causing or capable of causing toxicity, regardless of intent.

Potentially poisoned: All information available at the time indicates the possibility of an ingestion of a toxic dose of a poison regardless of whether or not signs of toxicity are present at the time of the decision-making process.

Single dose activated charcoal (SDAC): Amount given in one single administration to humans or animals to prevent gastrointestinal absorption (usually 1 g/kg, 50–100 g).

Toxic symptoms: Undesirable effects caused by a poison's action on the body.