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MINIREVIEW

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The effect of activated charcoal on drug exposure following intravenous administration: A meta-analysis

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Abstract

Activated charcoal both reduces primary drug absorption and enhances drug elimination. However, the two mechanisms of action overlap and are indistinguishable from each other. In order to estimate the extend of enhanced elimination, we summarized the effect of activated charcoal on intravenously administered drugs, where reduced drug exposure can be attributed to enhanced elimination. We performed a meta-analysis of randomized controlled studies evaluating the effect of orally administered activated charcoal on the systemic exposure of intravenously administered drugs. We searched the bibliographic databases PubMed, Embase and Cochrane. Meta-regression analyses of selected physiochemical drug properties on the effect sizes of activated charcoal were performed. All but one of 21 included studies used multiple-dose activated charcoal (MDAC). MDAC reduced the median half-life of the intravenously administered study drugs by 45.7% (interquartile range: 15.3%-51.3%) and area under the concentration time curve by 47.0% (interquartile range: 36.4%-50.2%). MDAC significantly improved drug elimination across nine different intravenously administered drugs, but we were unable to identify factors allowing extrapolation to other drugs. The results offer a possible and plausible rationale for the previously observed effects of single-dose activated charcoal beyond the timeframe where ingested drug is present in the gastro-intestinal tract.

KEYWORDS

activated charcoal, drug elimination, drug poisoning, intravenous administration, meta-analysis, systematic review

1 | INTRODUCTION AND BACKGROUND

Activated charcoal (AC) is cheap, safe and readily available and has been used for treatment of drug poisonings for decades.[1] It is well documented that AC reduces systemic drug exposure.[2] However, AC has not been consistently shown to affect clinical endpoints like mortality and morbidity. Thus, AC treatment is based on the theoretical assumption that reduced drug exposure translates into improved clinical outcome. Accordingly, current international guidelines from AACT/EAPCCT (American Academy of Clinical Toxicology and European Association of Poisons Centres and Clinical Toxicologists) are based primarily on studies of reduced drug exposure in healthy volunteers and expert consensus.[3,4]

AC reduces drug exposure via two distinct mechanisms. It diminishes primary drug absorption by binding drug in the gastrointestinal tract. It also enhances drug elimination by interrupting enterohepatic circulation or by binding drugs that have been reintroduced into the gastrointestinal tract, by passive or active transport (enteroenteric circulation).[5] Since the two mechanisms overlap, they are difficult to distinguish from each other.

In clinical settings, single-dose activated charcoal (SDAC) is predominantly used with intent to reduce drug absorption from the gastrointestinal tract. This effect declines as the drug is absorbed and becomes unavailable for gastrointestinal decontamination.[2,3] In their position statement on SDAC, the AACT/EAPCCT found mean reductions of drug exposure (measured as AUC, or percentage or amount of drug excreted in the urine) between 38.14% and 51.70% when administered within 1 hour of oral drug administration. When given 2 to 4 hours post-ingestion, reductions between 21.13% and 34.54% were found, and a 14% reduction was observed when used 6 hours after ingestion.[3] Accordingly, a meta-analysis found that at least 25% of the included study populations had a 31.5% reduction in drug exposure, when SDAC was administered 4 hours after drug ingestion, while at least 25% of the included study populations had a 14.6% reduction when SDAC was administered 6 hours after drug ingestion.[2] It could be speculated whether increased elimination contributes to these late effects.

The administration of multiple-dose activated charcoal (MDAC) is primarily used with intent to enhance drug elimination. The AACT/EAPCCT guidelines on MDAC recommend treatment with MDAC only for patients, who have ingested a life-threatening dose of carbamazepine, dapsone, phenobarbital, quinine or theophylline.[4]

The degree to which enhanced elimination contributes to the overall effect of both SDAC and MDAC is poorly understood. In order to examine to which extent SDAC and MDAC enhance drug elimination, we performed meta-analyses of studies of the effect of oral AC on intravenously administered drugs. Intravenous drug administration circumvents primary drug absorption. Thus, the effect of AC on drug exposure following intravenous administration can solely be attributed to enhanced drug elimination. Secondly, we intended to explore whether selected physiochemical properties were associated with enhanced drug elimination in order to predict which drugs are more prone to enhanced elimination with the administration of AC.

2 | METHODS

A protocol for internal use was written prior to data extraction, but neither published nor registered. The analyses described below are in accordance with the protocol. Results are reported according to the PRISMA guidelines.[6]

2.1 | Information sources

A systematic literature search of the bibliographic databases PubMed, Embase and Cochrane was performed until July 2020. Reference lists of included studies were hand-searched for additional records.

2.2 | Search

A librarian assisted with the data search. The entry *activated charcoal* was combined with the entries *intravenous administration* and *infusions parenteral* to search the databases. The search was limited to human data. No language limitations were applied. Detailed search strategies for all databases are available in the Supplementary data file.

2.3 | Eligibility criteria

Studies were considered for inclusion if they fulfilled the following PICOs:

Types of studies. Original, randomized clinical trials, where the active intervention was controlled by placebo or no treatment.
Types of Participants. Studies of human patients or healthy volunteers.
Type of Intervention. Studies of AC to counteract intravenously administered drugs.
Types of Outcome. Studies of changes in elimination kinetics of the studied drugs.

Studies fulfilling the PICOs were included in the analyses if they also fulfilled the following inclusion criteria:

- Original clinical trials published in peer-reviewed journals.
- Trials must quantify elimination of the studied drug with pharmacokinetic data—half-life ($t_{½}$) or area under the concentration-time curve (AUC)—including a measure of variance (standard deviation, standard error or 95% confidence interval).

2.4 | Study selection

Two authors independently assessed articles for eligibility and quality. In case of uncertainties, articles were discussed and agreement reached between the authors.

2.5 | Data collection

Two authors extracted the following data from included studies:

1. Study design (number of participants; type, dose and timing of studied drug; dose and timing of AC in relation to study drug; trial duration).

2. Outcomes (mean differences in $t_{½}$ and AUC and measures of variance for both active treatment and controls).

2.6 | Risk of bias in individual and across studies

Risk of bias in individual studies was assessed using the Cochrane Collaboration tool for assessing risk of bias.[7] Specifically, studies were assessed for adequate random sequence generation, allocation concealment, blinding of participants and investigators and blinding of outcome data, attrition bias (incomplete outcome data) and selective reporting. Where individual risks of bias were different across studies, these were evaluated.

2.7 | Summary measures

Difference in $t_{½}$ and AUC of studied drug when AC was administered compared to a control group. We used standardized mean difference (SMD) to make comparisons between different drug regimens.

2.8 | Synthesis of results

Meta-analyses of the overall effects of AC were performed. Furthermore, sub-analyses of studies on SDAC and MDAC were planned.

The meta-analyses were done in Review Manager (version 5.3); The Cochrane Collaboration's software for preparing and maintaining Cochrane Reviews.[8]

If studies contained more than one AC intervention, only one was included in the meta-analysis. In case different dosing regimens were studied, results of the regimen with the most frequent AC dosages were used. Where different formulations of AC were compared, results from the study arm employing AC as a suspension without additives were preferred.

Where variance was given as standard error or 95% confidence intervals of the outcome measures, these were converted into standard deviations using the built-in calculator in Review Manager.

In order to interpret the SMD, mean reduction of drug exposure was calculated by dividing effect estimates of AC-treated groups with that of the controls for each outcome measure. Next, the overall medians of the means and interquartile range (IQR) were calculated.

2.9 | Additional analyses

Weighted least squares regression models were used to calculate linear regressions between SMDs of overall AC effects and selected physiochemical covariates, using the R statistical programming language (www.r-project.org). A statistician was consulted for assistance with the analyses. Physiochemical covariates were chosen based on their

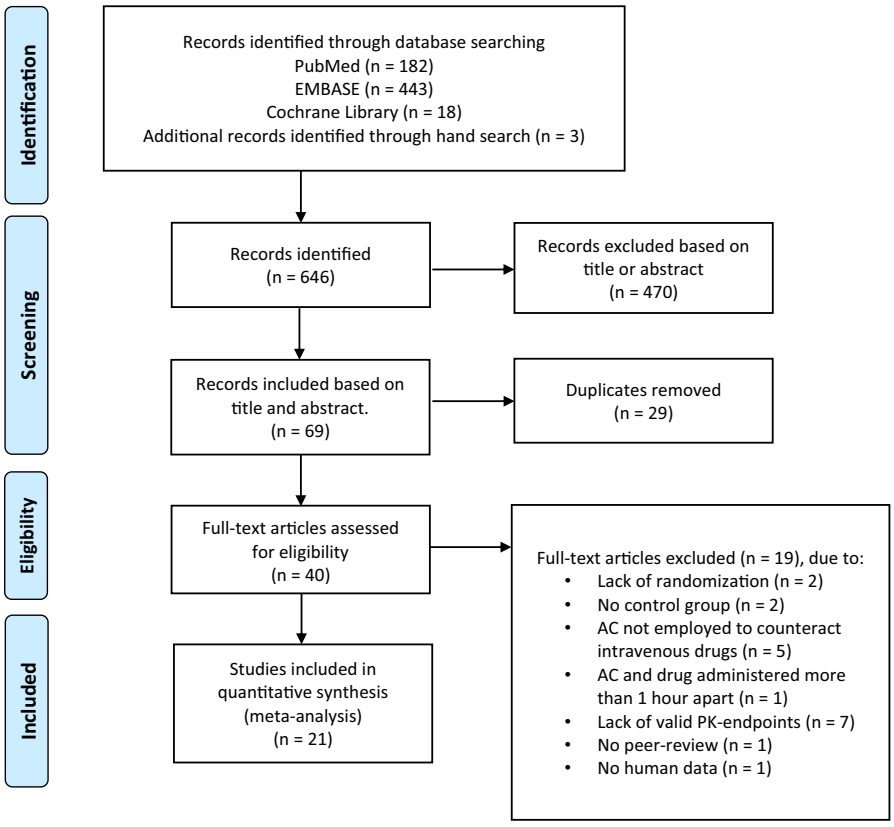

FIGURE 1 PRISMA flow diagram of the literature search. From: Moher et al.[51] For more information, visit www.prisma-statement.org

accessibility and influence on the permeability of drugs. We chose: Volume of distribution (V_d), molecular weight (MW), lipophilicity (measured as the logarithmic partition coefficient (Log*P*)) and predicted half-life ($t_{½pred}$.). Weight of the individual outcomes was calculated from the 95% CI's, using a T score of 1.96. To test for confounders, weighted least squares regressions towards cumulated AC dose and the AC/drug ratio were also calculated.

3 | RESULTS

3.1 | Study selection

A flow diagram of the literature search is shown in Figure 1. In total, 646 records were found in the primary literature search and another three studies were added from the reference lists of included articles. Forty full text articles were assessed for eligibility. Nineteen did not meet inclusion criteria and were excluded.

3.2 | Study characteristics

Baseline characteristics of the 21 included studies[9-29] are shown in Table 1. Twenty studies contained information on $t_{½}$ reduction and 9 on AUC reduction. All but one examined the effect of MDAC. All included studies, except the study by Radomski et al,[26] were conducted in healthy volunteers. Nine different drugs were studied: Digoxin, imipramine, moxifloxacin, phenytoin, phenobarbital, theophylline, aminophylline, tobramycin and vancomycin. All drugs were administered in non-toxic doses. Table 2 shows an overview of included drugs and their physiochemical properties.

3.3 | Risk of bias within and across studies

Risk of bias assessments is illustrated in Figure 2. All studies were scored as unclear risk of Random Sequence Generation, Allocation Concealment and Selective Reporting. In general, included studies were described as blinded and randomized without description of randomization or allocation method. As most studies were of older date, no protocols of included studies were available.

3.4 | Synthesis of results

Meta-analyses of studies on MDAC showed significantly enhanced elimination of nine intravenously administered drugs studied. SMD for $t_{½}$ was −1.24 [CI95%: −1.72, −0.76], and SMD of AUC was −1.72 [CI95%: −2.53, −0.92]. The reductions correspond to a 45.7% (IQR: 15.3%-51.3%) median reduction in $t_{½}$ and a 47.0% (IQR: 36.4%-50.2%) median reduction in AUC of the studied drugs. Figures 3 and 4 show the forest plots of MDAC studies for the $t_{½}$ and AUC outcome measures, respectively. Funnel plots of the analyses are available in the Supplementary Data File.

The one study on SDAC[12] found an SMD of −0.60 [CI95%: −1.36, 0.16]. This study did not contain data on the $t_{½}$ outcome.

3.5 | Additional analysis

Weighted least square meta-regression models between the SMDs of the primary outcome measures of AC effect and selected physiochemical drug properties failed to produce statistically significant results. Test for confounders did not reveal any associations with total dose of AC nor AC/drug ratio. Results of the meta-regressions are available in the Supplementary Data File.

4 | DISCUSSION

Our meta-analysis showed that MDAC substantially enhanced elimination and reduced drug exposure of the nine intravenously administered drugs studied. MDAC reduced median $t_{½}$ and median AUC by more than 45%, across included studies. We only identified one study of SDAC suitable for inclusion in the meta-analyses, rendering the planned subanalysis of SDAC studies meaningless. However, in the single study on SDAC,[12] the SMD of AUC reduction was −0.6 [−1.36, 0.16]. The 95% confidence interval of this study overlaps with the confidence interval of the overall effect estimate and with all but one of the included MDAC studies. Thus, the results of the SDAC study did not differ significantly from the MDAC studies. Since enhancement of elimination by SDAC and MDAC is not limited to intravenously administered drugs, we would expect similar effects on orally administered drugs.

We aimed to identify physiochemical drug properties associated with AC-induced enhancement of elimination. Identification of physiochemical drug properties governing enhanced drug elimination would allow to extrapolate existing data and approximate AC's efficacy on other drugs, and subsequently guide clinicians' decisions on AC use in specific clinical situations. In order to assess the physiochemical properties, we performed several meta-regressions. Relevant parameters were selected based on the properties of drugs that have been shown in studies to respond to the use of MDAC, that is carbamazepine, dapsone, phenobarbital, quinine and theophylline.[4] All exert properties that are associated with high cell permeability, such as high lipophilicity, long half-lives, low molecular weight and high volume of distribution.

TABLE 1 Characteristics of included studies

				Drug	
Study ID	**Ref #**	**Design**	**Population**	**Drug**	**Dose**
Belz '74 (Digoxin)	9	Randomized, cross-over design	6 healthy volunteers	Digoxin	1 mg
Berg '82 (Phenobarbital)	10	Randomized, cross-over design	6 Healthy volunteers	Phenobarbital	2.86 mg/kg
Berg '87 (Phenobarbital)	11	Randomized, cross-over design	6 Healthy volunteers	Phenobarbital	2.86 mg/kg
Berg '93 (Phenobarbital)[a]	12	Randomized, cross-over design	14 Healthy volunteers	Phenobarbital	200 mg
Berlinger (Theophylline)	13	Randomized, cross-over design	6 Healthy volunteers	Theophylline	6 mg/kg
Davis '87 (Vancomycin)	14	Randomized, cross-over design	6 Healthy volunteers	Vancomycin	1 g
Davis '88 (Tobramycin)	15	Randomized, cross-over design	6 Healthy volunteers	Tobramycin	2.5 mg/kg
Frenia (Phenobarbnital)	16	Randomized, cross-over design	10 Healthy volunteers	Phenobarbital	5 mg/kg
Goldberg '85 (Imipramine)	17	Randomized, cross-over design	4 Healthy volunteers	Imipramine	0.18 mg/kg
Ilkhanipour '92 (Aminophylline)[b]	18	Randomized, cross-over design	5 Healthy volunteers	Aminophylline	8 mg/kg
Ilkhanipour '93 (Theophylline)[a]	19	Randomized, cross-over design	5 Healthy volunteers	Theophylline	8 mg/kg
Lalonde (Digoxin)	20	Randomized, cross-over design	10 Healthy volunteers	Digoxin	10 µg
Mahutte (Aminophylline)	21	Randomized, cross-over design	8 Healthy volunteers	Aminophylline	8 mg/kg
Mauro (Phenytoin)	22	Randomized, cross-over design	8 Healthy volunteers	Phenytoin	15 mg/kg
McKinnon (Theophylline)	23	Randomized, cross-over design	6 Healthy volunteers	Theophylline	2.37 mg/kg
Park '83 (Aminophylline)[b]	24	Randomized, cross-over design	6 Healthy volunteers	Aminophylline	6 mg/kg
Park '85 (Digoxin)	25	Randomized, cross-over design	6 Healthy volunteers	Digoxin	10.7 µg/kg
Radomski (Aminophylline)	26	Randomized, cross-over design	6 patients with hepatic cirrohsis	Aminophylline	6 mg/kg
Rowden (Phenytoin)	27	Cross-over design	10 Healthy volunteers	Phenytoin	15 mg/kg
Sands (Thophylline)	28	Randomized, cross-over design	5 Healthy volunteers	Theophylline	6 mg/kg
Stass (Moxifloxacin)	29	Randomized, cross-over design	9 Healthy volunteers	Moxifloxacin	400 mg

[a]Comparison of different AC-formulations.

[b]Comparison of different AC dosing regimens.

Unfortunately, our meta-regressions did not reveal any associations between the effect measure of AC and Log$P$, V_d, molecular weight, nor the predicted half-life.

AC is generally considered to be a safe treatment although serious complications such as aspiration pneumonitis and gastrointestinal obstruction have occurred. Accordingly, AC is contraindicated if the patients cannot protect their airways or suffer from obstruction of or damage to the gastrointestinal tract. However, aspiration and obstruction in relation to AC are rare occurrences. In a retrospective analysis of 878 patients receiving MDAC, 5 (0.6%) patients had clinically significant pulmonary aspiration and none (0%) experienced gastrointestinal obstruction.[30] Another large retrospective analysis of more than 4,573 poisoned patients, 71 of which had aspiration pneumonitis, found that AC treatment was not among the risk factors for aspiration pneumonitis.[31]

	AC					
Relative dose size	**Dose**	**Number of doses**	**Total dose (g)**	**Time from drug till 1st dose (min)**	**Timing of subsequent doses (h)**	**Study duration (h)**
Supratherapeutic	2 g t.i.d.	6	12	−10	8,16,24,32,40	48
Subtherapeutic	40 g at time zero 20 g thereafter	8	180	0	6,12,18,24,30,42,66	90
Subtherapeutic	30 g at time zero 15 g thereafter	6	75	0	6,12,18,24,36	492
Subtherapeutic	30 g	1	30	0	-	504
Therapeutic	40 g at time zero 20 g thereafter	6	140	0	2,4,6,9,12	24
Therapeutic	50 g at time zero 15 g thereafter	5	110	0	2,4,6,8	24
Subtherapeutic	50 g at time zero 15 g thereafter	4	95	0	2, 4, 6	8
Therapeutic	50 g at time zero 25 g thereafter	6	175	30	4,8,12,16,20	24
Subtherapeutic	20 g	9	180	0	2,4,6,9,12,16,20,24	48
Therapeutic	50 g at time zero 12.5 g thereafter	8	150	60	2,3,4,5,6,7,8,9	12
Therapeutic	50 g	3	150	60	4,8	12
Subtherapeutic	25 g	9	175	0	4,8,12,16,22,28,34,40	48
Therapeutic	30 g	4	120	0	2,4,6	8
Supratherapeutic	60 g at time zero 30 g thereafter	8	300	0	2,4,8,12,24,30,36,48	72
Subtherapeutic	40 g at time zero 20 g thereafter	4	100	0	2,4,6	8
Therapeutic	10 g	12	120	0	1,2,3,4,5,6,7,8,9,10,11	24
Supratherapeutic	20 g	11	220	0	4,8,12,16,20,24,28,32,36,48	96
Therapeutic	40 g at time zero 20 g thereafter	6	140	0	2,4,6,9,12	24
Supratherapeutic	40 g at time zero 20 g thereafter	5	140	0	2,4,6,8,10	72
Therapeutic	40 g at time zero 20 g thereafter	6	140	0	2,4,6,10,12	24
Therapeutic	5 g before and after infusion 10 g thereafter	3	40	±5	2,4,8	96

Recommendations for the use of SDAC and MDAC are primarily based on findings of reduced drug exposure in healthy volunteers, clinical case series or reports and expert consensus.[3,4] Only few studies have examined the effect of AC on clinical outcome in poisoned patients and their results are not consistent. One randomized, controlled trial found that MDAC reduced mortality after poisoning with yellow oleander seeds, while another did not find significant reduction of mortality.[32,33] An observational study found that SDAC significantly lowered concentrations and half-life of paracetamol when given within 4 hours of massive paracetamol overdoses, and found a probable, lowered rate of hepatotoxicity, but no effect on overall survival.[34] Another randomized, controlled trial found no effect of SDAC on length of stay, nor on mortality, or the risk of aspiration, vomiting or need for external ventilation compared

TABLE 2 Physiochemical properties of included drugs

Drug	V_d[45] (L/kg)	MW[46] (g/mol)	Log P[45]	P-gp[45]	Entero-hepatic recirculation	Entero-enteric recirculation	Water solubility[45] (mg/mL)	$t½_{pred}$[46] (h) Mean	Range
Digoxin	6	780.9	1.26	S	Y[47]	Ukn	0.127	39	34-44
Phenobarbital	0.7	232.2	1.47	S	Ukn	Y[48]	0.276	79	53-118
Theophylline	0.45	180.2	−0.02	NS	Ukn	Y[49]	22.9	8	7-9
Aminophylline	0.5	420.4	−3.03	S	Ukn	Ukn	200.000	8	7-9
Vancomycin	0.6	1449.3	−3.1	S	Ukn	Ukn	0.225	6	4-11
Tobramycin	0.25	467.5	−5.8	S	Ukn	Ukn	53.7	2	
Imipramine	15	280.4	4.8	S	Y[50]	Ukn	0.0664	12	
Phenytoin	0.8	252.3	2.47	NS	Y[47]	Ukn	0.0711	22	7-42
Moxifloxacin	2.6	401.4	2.9	S	Ukn	Ukn	0.168	12	
Mean	2.99	496.0	0.11				22 231		
Median	0.7	401.4	1.26				0.225		

Abbreviations: S, substrate; NS, non-substrate; Y, yes; N, no; Ukn, unknown (no literature found on recirculation of the drug).

to no decontamination in 327 patients presenting at a hospital with a drug overdose.[35] Finally, an observational study found that SDAC significantly reduced drug exposure and the risk of QT prolongation following citalopram overdose.[36] The inconsistent results could be due to the inherent challenges associated with conducting trials in drug-poisoned patients, complicating inclusion and assessment of the patients. Uncertainties regarding ingested drug(s), doses and co-intoxication with alcohol and/or illicit drugs complicate the practical feasibility of well-designed, randomized clinical trials. Furthermore, the relatively low mortality in drug-poisoned patients (approximately 3%) complicates its measurement as a clinical outcome, partly because large numbers of patients are required, but also because the most severely poisoned patients are underrepresented in clinical trials. Therefore, extrapolation of pharmacokinetic data from healthy volunteers is necessary and important. However, the uncertainties regarding the effect of AC on clinical outcomes of drug-poisoned patients leave room for discussion as to whom should be treated. Still, in light of the fact that AC is a safe and cheap treatment and treatment options in some cases of poisoning is limited, AC should not be withheld patients suffering from severe drug poisonings.

The AACT/EAPCCT- guidelines on SDAC recommend that treatment with SDAC should be limited to within one hour of drug ingestion.[3] However, according to data from the American Association of Poison Control Centers, only 16% of patients presenting with an acute overdose arrived at a treatment facility within 60 minutes of drug ingestion.[37] More recent data show that AC was administered to only 1.8% of the more than 2 000 000 exposures reported in American patients. These exposures contain both pharmaceuticals and non-pharmaceuticals, as well as overdosed and non-overdosed patients.[38]

A previous meta-analysis of SDAC found reduced systemic drug exposure (standardized mean differences of different outcome measures of elimination) by 88% when given within 5 minutes of drug ingestion.[2] The reduction fell to 38% and 25% when AC was administered 1 and 4 hours after drug exposure, respectively. Low statistical power due to few included studies rendered the effects of AC beyond 4 hours after drug exposure statistically non-significant.[2] Examining the studies of SDAC administered with a lag time ≥2 hours reveals not only reduced areas under the concentration-time curve (AUC) or peak concentrations (C_{max}), but also reduced half-lives ($t½$).[39-41] The reduced half-lives support the assumption that SDAC not only reduces absorption, but also increases drug elimination. Our results, showing that MDAC substantially enhances drug elimination, offer a possible mechanism for these later effects of SDAC. This could extend the timeframe for SDAC beyond drug absorption. In the severely poisoned patients, presenting later than one hour after drug ingestion, administration of AC could therefore still be feasible.

There are several limitations to the analyses.

Comparing different drugs inevitably leads to heterogeneity of included studies. Furthermore, differences in doses and pharmacokinetics of the studied drugs, dose of AC, number and timing of AC doses, AC/drug ratio, and duration of follow-up contributed to the overall heterogeneity. The heterogenic nature of included studies is, however, also a precondition for meaningful evaluation of physiochemical properties associated with enhanced drug elimination and gives a good impression of the expected variability of the effect under real clinical conditions.

In 17 studies, the first dose of AC was given immediately within 5 minutes of drug infusion. In the study by Belz, AC was given 10 minutes before infusion,[9] and in the study by Frenia et al[16] and the two studies by Ilkhanipour et al,[18,19]

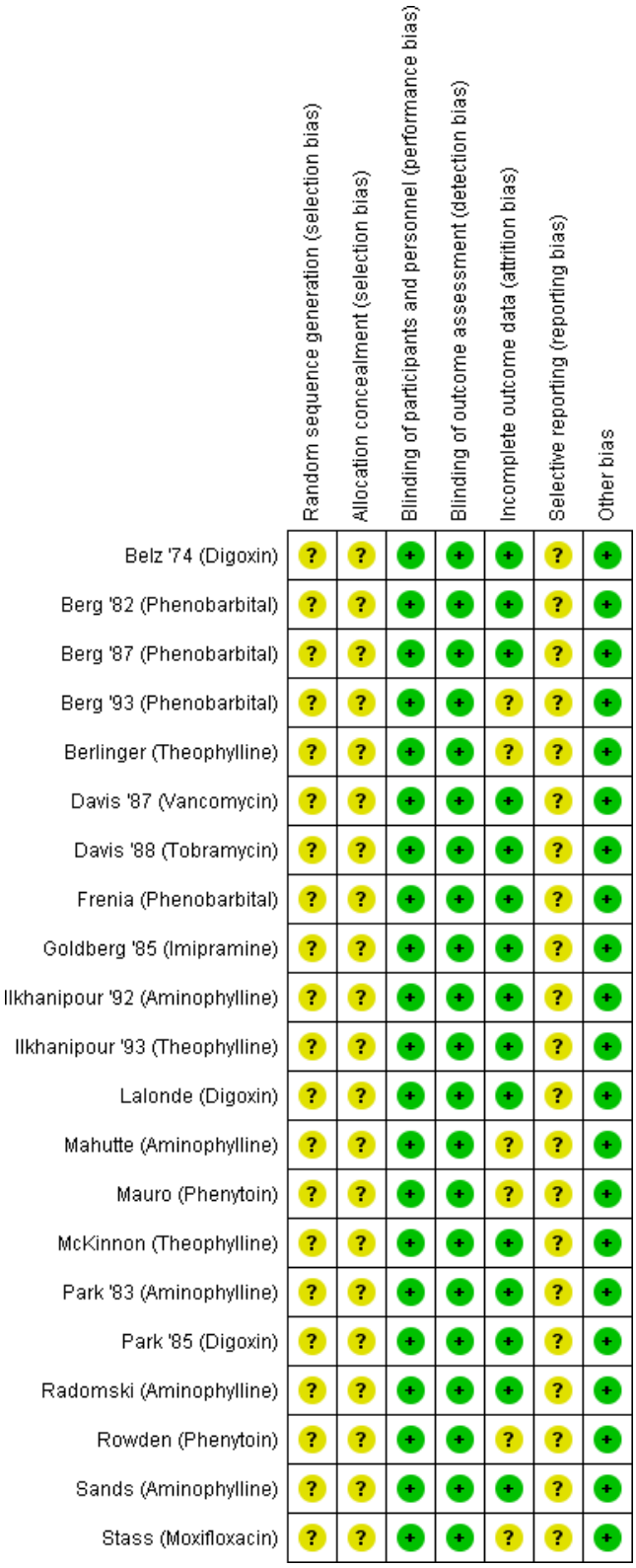

FIGURE 2 Risk of bias summary. Review authors' judgements about each risk of bias item for each included study

AC was administered 30 and 60 minutes after infusion, respectively. Except from the SDAC study by Berg et al,[12] all included studies examined the effect of MDAC. The last dose of AC was administered 0.46 to 3.00 predicted half-lives after drug administration. The rate of AC administration was between 2.08 to 20 g per hour, except in the studies by Berg et al[12] and Belz.[9] Differences in AC regimen could have affected the pharmacokinetic outcome measures and contributed to the variability observed.

Only nine different drugs were included in this meta-analysis. The low number of drugs might reflect selection or publication bias across studies. Selection of specific drugs to study might have been made in anticipation of showing relevant differences, and studies showing relevant differences might become published more easily. If the studied drugs all exhibit similar physiochemical properties, for instance all have similar volumes of distribution, it might confound the identification of predictors associated with the effect of AC. For instance, all studied drugs have moderate to large volumes of distribution (17.5 to 1050 L), and relatively low molecular weight (180.2 to 1449.3 g/mol), but relatively well-distributed Log*P* values (−5.8 to 4.8). Thus, the lack of association found in our analyses must be interpreted with caution.

All studies were conducted in a small number of participants (N = 4-14) and thus suffered from "small study effects."

Differences in drug dose might affect the pharmacokinetic outcomes due to differences in concentration gradients, amount of drug available for transportation, etc. Of the included studies, 10 utilized a dose within normal therapeutic range, whereas 7 studies employed subtherapeutic and 4 supratherapeutic doses. None were administered in toxic doses.

Risk of bias was found to be low or unclear for all domains in the risk of bias assessment. All domains for selection bias (random sequence generation and allocation concealment) were scored as unclear risk of bias and all blinding domains as low risk of bias. All included studies employed study designs using healthy volunteers in a cross-over design with pharmacokinetic outcome measures. It is unlikely that selection or blinding biases would influence the pharmacokinetics outcomes of the studied drugs. No protocols of included studies were available. However, no signs selective reporting bias were found either.

All but one of the included studies used healthy volunteers and all were conducted in highly standardized settings. Extrapolation of pharmacokinetic results from these to clinical setting may be difficult. In the clinical setting, and especially in the case of self-inflicted drug poisoning, multiple medications in supratherapeutic doses, as well as co-intoxication with alcohol or illicit drugs might be involved.[42,43] Furthermore, severe drug poisoning is associated with impaired clearance due to changes in protein binding, renal and hepatic blood flow, and delayed gastric emptying.[44] Thus, the effect of AC in real-life poisoned patients might be greater than in healthy volunteers. Direct extrapolation might be

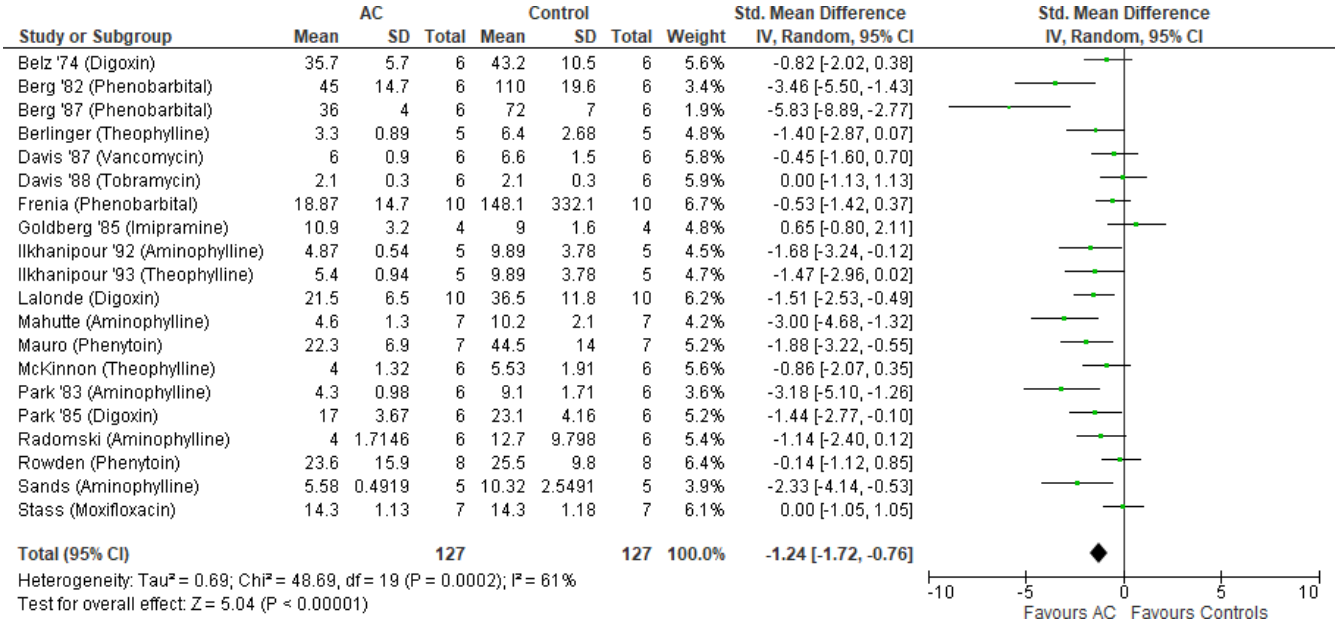

FIGURE 3 Forest plots for *t½* reduction following multiple-dose activated charcoal

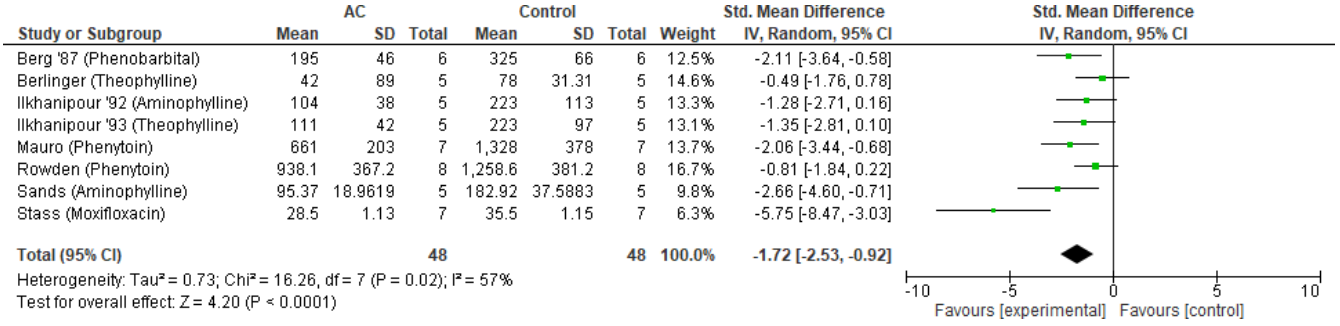

FIGURE 4 Forest plots for AUC reduction following multiple-dose activated charcoal

confounded, but our results are indicative of and support later administration (>1 hour after drug intake) of AC in severely poisoned patients.

In conclusion, we found that MDAC significantly improved drug elimination across nine different intravenously administered drugs. We were unable to identify factors allowing extrapolation from the nine included drugs to other drugs. Furthermore, our results offer a possible and plausible rationale for the previously observed effects of SDAC beyond the timeframe where ingested drug is present in the gastrointestinal tract.

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CONFLICT OF INTEREST

The authors report no conflict of interest.

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SUPPORTING INFORMATION

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