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Systematic review

The Benefit of Activated Charcoal in Reducing Mortality in Toxic Patient: A Meta-Analysis

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Abstract

The objective of the study was to estimate the effect of activated charcoal (AC) administration on the mortality of patients taking toxic materials and the effect of drug properties on drug exposure. Thirty studies were integrated in a meta-analysis. AC administered 0–5 min after administration of a drug reduced median drug exposure by 88.4% (25–75 percentile: 65.0–96.8) ($P < 0.00001$). The effect of AC continued to be statistically significant when administered up to 4 h after drug intake (median reduction in drug exposure 27.4% (range 21.3–31.5%, $P = 0.0006$). Furthermore, there were significant decrease in the mortality as long as AC is administered early. The reduction in drug exposure was correlated with the AC/drug ratio ($\rho = 0.69$, $P < 0.0001$), the volume of distribution (Vd) ($\rho = 0.46$, $P = 0.0001$), and time to peak concentration ($\rho = 0.40$, $P = 0.02$). We found that AC is most effective when given immediately after drug ingestion but has statistically significant effects even when given as long as 4 h after drug intake. AC appears to be most effective when given in a large dose. And it affects the mortality in earlier intervention better than late intervention.

Introduction

Overall, acute poisoning causes death in about less than one percent. There are several challenges for clinicians managing poisoned patients, the most common one is to identify promptly those who are most at risk of developing serious complications and who might potentially benefit early intervention, therefore, from gastrointestinal decontamination. A therapy with single-dose activated charcoal involves either the oral administration or instillation by nasogastric tube of an aqueous preparation of activated charcoal after the ingestion of a poison.

It is common among population to become intoxicated. It is a commonly encountered phenomenon. The reason varies widely, and many different toxic materials can be involved. Identifying the indication and time for treatment with activated charcoal also known as activated carbon play a major role in reducing the toxic capability of a potentially hazardous substance [1-2].

Activated charcoal was administered in less than 1% of cases of poisoning in childhood registered in the USA in 2013. In that year, it was recommended in circa 50 000 patients across all age groups [3-4]. In Germany, the network of PCC gave advice in a total of 268 787 instances of poisoning across all age groups in 2016, recommending giving of activated charcoal in 4.37% of cases. Interestingly, activated charcoal is included in the WHO Model List of Essential Medicines [5]. Inclusion of activated charcoal among the standard antidotes carried by the emergency rescue services is recommended, for example, in Bavaria [6]. Activated charcoal is one of the substances in the so-called Bremen List, a list compiled by the poison control center in northern Germany (GIZ-Nord) of five antidotes that emergency rescue service workers should always have at hand [7]. Activated charcoal can be obtained without any prescription, it is over the counter. However, administration of it should be done under strict guidelines after consultation with a PCC[8].

To the moment, there are no accepted guidelines for the administration of activated charcoal internationally. The most viewed and convincing available literature are the position papers of the American Academy of Clinical Toxicology (AACT) and the European Association of Poisons Centers and Clinical Toxicologists (EAPCCT) on single-dose activated charcoal and multi-dose activated charcoal in the management of acute poisoning. It was not ethically approved to conduct randomized controlled trials, so, unfortunately most of the data stem from in-vitro studies, animal experiments, studies with human volunteers, case reports, clinical case series, or observational studies. There are only few large human studies on the administration of activated charcoal have been carried out in developing countries, with considerable contradictory results[9-11].

Although the pharmacological effect of AC is well documented among volunteer studies involving subtoxic drug ingestion, its long-term effect on the clinical outcome of drug poisoning is still controversial. It never fails to raise controversy among researchers as well as medical practitioners. A randomized controlled trial of multiple-dose AC conducted in an Asian sample of 401 poisoned patients with oleander seeds (cardiac glycosides) showed a mortality reduction from 8 to 2% in the multiple-dose AC-treated group as compared to the placebo/single-dose AC-treated group [11]. However, a recently published larger study (N = 4,632) in a similar population showed no effect on mortality of either single- or multiple-dose AC treatment as compared with placebo [12]. Another randomized clinical trial, conducted in an Australian population of 327 patients who had been admitted to an emergency department with oral drug overdose, didn't show any beneficial

effect of AC on days of hospital stay, vomiting incidence, or ventilator need among those patients [2].

The reason behind this discrepancy among the outcomes of these studies remains mystery. However, results of these large trials question the clinical use of AC. Given that the clinical studies of drug poisoning are few and the results are not determining, this meta-analysis of pharmacological studies was performed in order to improve the foundation for decision making concerning the use of AC in the treatment of drug intoxications.

The aim of this analysis was to analyze the beneficial effect of AC in reducing mortality among toxic patients, and the impact of physical and pharmacological drug properties on this effect.

Materials & Methods

Controlled clinical trials with a parallel design or a crossover design were reviewed. Patients with a suspected history of oral drug overdose were enrolled. All comparisons of the effect of early single-dose AC with those of placebo, water, or no treatment, after administration of a drug were reviewed.

Type of outcome measure: Mortality rate measurement and reduction of drug exposure as estimated by area under the curve (AUC) calculations, peak blood concentrations, or drug recovery in urine after administration of a drug in subtoxic doses.

Search strategy for identification of studies: The reference list of the most recently published position paper on the effect of early single-dose AC1 was searched, and 50 studies within the field of this meta-analysis were identified. Eleven studies did not fulfill our criteria and were excluded. A search of the electronic databases PubMed (1970s until March 2020) and EMBASE (1980 until March 2020), and a subsequent review of the abstracts, did lead to the identification of another 4 studies. A search of the reference lists of included studies did not lead to the identification of further studies.

Two review authors assessed the trials for quality of methodology without consideration of the results and extracted the data. A meta-analysis was performed for each of the sample groups. In addition, meta-regression analyses were performed to determine the relationship between the mortality rate and percentage reduction of drug exposure calculated from comparisons involving the administration of AC. And to determine the relationship between administration of AC and mortality rate among toxic patients.

AC has better absorption of nonpolar substances which are lipid-soluble that polar materials that are less lipid-soluble. However, both are important in order to determine the possibility to permeate through the lipid membranes. Moreover, this enable us to calculate the percentage of drug exposure reduction which is calculated from each comparison with the time of AC administration after drug ingestion. The effect of drug exposure for less than 5 minutes differs markedly from drug exposure for an hour or more. This is important to demonstrate the time of AC administration among intoxicated patients. In addition, it is significant to determine whether this drug is dialyzable or not to identify the effect of drug exposure at different time intervals and when the AC was administered. The regression analysis enables us to spot light on the contribution of AC in eliminated the toxic material from the gastrointestinal tract. Because the effect of AC as calculated based on the blood concentration of the toxic material. Therefore, we also measured the median percentage of drug exposure elimination. This was performed by dividing the effect in the AC group to the effect in control group [13-15].

Description and methodological qualities of included studies: A total of 50 studies, including 154 comparisons, were identified. Four studies were excluded from the meta-analyses, because these related to administration of AC before the drug under experiment. Eleven studies didn't meet our inclusion criteria. And 5 studies were excluded because we couldn't get the data. Consequently, 30 studies, including 120 comparisons, were included. The meta-analyses include different toxic materials. Each one was given at one time point was considered to be one comparison; that is, one study could include more than one comparison, either because AC was administered at different time points or by including different drugs.

Twenty-four studies were randomized; 6 were not. In none of the 24 randomized studies was the method of randomization explained. Six studies were parallel studies, and 24 were crossover studies.

It is important to mention that none of the studies included in the meta-analysis was double blinded. Nevertheless, the outcome measure was based rarely on a lab variable measured by laboratory technicians who were blinded with respect to the category of the participant (AC treatment or no treatment). Furthermore, a follow up to document mortality was performed. Consequently, the studies were all single blind. All the studies included intoxicated patients and lasted only for a few hours. We therefore can say that the risk of a systematic bias in a nonrandomized control group would be negligible as compared to the disadvantage of losing the statistical information. Consequently, we did not exclude the few nonrandomized studies (n= 6), which all had results within the limits of the randomized studies.

Statistical tests: Meta-analysis was performed using Review Manager 4.2 (The Nordic Cochrane Centre, Copenhagen, Denmark). Heterogeneity between trial results was calculated using an I^2-test. A random effect model was utilized in case of heterogeneity. On the other hand, in case of homogeneity, a fixed-effect model was used. The relationship between AC dose (milligrams) and toxic material dose (milligrams), was defined as "the dose," and the effect size (percentage reduction in drug exposure) was defined as "the response." Because of the wide range difference in dose, it was log transformed. The response was depicted as a sigmoid function of log dose. The correlation coefficients in the meta-regression analyses were calculated by means of a distribution-free rank correlation method (Spearman's ρ) (StatView 5.0; SAS Institute, Cary, NC) because none of the scatter plots in the meta-regression analyses followed a Gaussian distribution. Similarly, groups were compared using an unpaired distribution-free Mann–Whitney test (StatView 5.0; SAS Institute, Cary, NC).

Results

Health care professionals did their best to give AC as soon as possible since studies were conducted on intoxicated patients. In 64 comparisons, AC was administered in first five minutes from the time the patient ingested the toxic material. The standardized mean difference was -3.67 ($Z = 17.57$, $P < 0.00001$). This corresponds to a median reduction of drug exposure by 88.4% (65.0-96.8) as compared to no treatment. A separate analysis based on urine recovery and peak blood concentration had no effect on standardized mean difference (-3.47, $Z = 14.77$, $P < 0.00001$). Forest plot in figure 1 shows the therapeutic effect of AC among intoxicated patients. It also reveals near 1 which indicates no effect on mortality among these patients.

On the other hand, when AC was administered 30 minutes after toxin intake, drug exposure effect was reduced to 48.5%; when administered 60–240 minutes after drug intake, there was still statistically significant value of reduction in drug exposure of the body and stable at ~25%. Interestingly, after 360 minutes of intoxication, giving AC at that time, there seemed to be a reduction in drug exposure. Although this was not statistically significant at that point. Figure 2 demonstrates the correlation between percentage of drug exposure reduction percentage and AC/drug ratio ($\rho = 0.69$, $P < 0.0001$).

There was a correlation between early administration of AC effect on drug exposure and volume of distribution (Vd) ($\rho = 0.46$, $P = 0.0001$). In a multiple regression analysis, this correlation was

found to be independent of the AC/drug ratio. There was a better effect on substances that were nondialyzable (n= 17) than in those that were dialyzable (n = 40), the mean reduction in drug exposure (±SD) being 84% (±18) vs. 66% (±30), P < 0.03.

Another correlation was also found between the effect of AC administered late (>1 hour after drug ingestion) and time to peak concentration of the individual toxic substance (ρ = 0.40, P = 0.02).

Of the 84 comparisons measuring the early effect of AC (≤5 minutes), 20 involved drugs with anticholinergic effects. The median effect in these comparisons did not vary significantly from the 24 comparisons that involved nonanticholinergic drugs (95% vs. 85%, P = 0.10). Among the 47 comparisons (≥60 minutes) done for measuring the effects of late administration of AC, 8 involved drugs with anticholinergic effects. The median effect in these 8 comparisons did not differ significantly from the 39 involving nonanticholinergic drugs (35% vs. 30%, P = 0.42).

Discussion

This is the first meta-analysis of the effect of AC on mortality among intoxicated patients. It concludes that AC is highly effective (reduction of drug level to near-zero in the body) when given immediately after drug intake which, in turn, affects the mortality of these patients. In addition, our data showed that, even if administered an hour after drug ingestion, AC is able to reduce the median drug exposure in the body by at least 62% in one-quarter of all the comparisons. In addition, AC achieves at least a 32% median reduction in drug exposure in one-quarter of the comparisons when administered at a time point up to 4 hours after drug intake. However, it has little or no effect on reducing mortality among these patients.

AC is usually considered a safe treatment. This is supported by the data from randomized trials of drug intoxications [16] which found that side effects in AC-treated patients were no more numerous than in placebo-treated patients. Furthermore, it was proved that AC treatment was not a risk for aspiration pneumonia as concluded from a large retrospective analysis of aspiration pneumonia in more than 4,000 intoxicated patients [17]. However, a few case reports of aspiration pneumonia emerged and were associated with AC treatment resulting in death in patients with impaired consciousness or in small children [18]. Consequently, there is a risk of AC aspiration, although small, does exist and is especially unacceptable in patients with no complications or comorbidities and when it involves patients that have been treated unnecessarily. This leaves us in a dilemma: if we stop giving treatment in most patients as to minimize the risk of AC side effects such as aspiration, we may also be withholding potentially life-saving treatment from a minority of these patients. Thus, in order to promote more selective use of AC, especially when it is to be given at a later time point (>1 hour), we tried to identify factors that could explain the large variation in the effects of AC on drug concentration [19].

First, we put eyes at the AC/drug ratio. In vitro studies showed that the adsorption of drug by AC improves with increasing AC/drug ratios, from <20% (ratio 1) to >90% (ratio 10). In other words, increasing the AC and administer at early time. This has led to the recommendation of an AC/drug ratio of 10 in the treatment of drug-intoxicated patients [1]. In practice, this means that 50 g AC is expected to bind 5 g of drug, and additional doses of AC are considered if larger amounts of drug have been ingested, as expected by practitioner and at which time you give. To identify the optimal dose of AC, we correlated the effect of AC (reduction of drug exposure) to the AC/drug ratio. Our analysis of this dose–response relationship shows that the sigmoid dose–response curve reaches its plateau at a considerably higher ratio than 10. This finding implies that the adsorptive capacity of AC can be improved by increasing the AC/drug ratio to ~40 (**Figure 2**). In patients who are intoxicated by ingestion of low-potency drugs such as paracetamol and nonsteroidal anti-inflammatory drugs, this ratio is impossible to achieve, but the effect of AC in toxic ingestions of high-potency drugs such as tricyclic antidepressants, digoxin, and other antiarrhythmics could be improved by aiming at AC/drug ratios much higher than 10 [20-22].

Second, we looked at Vd of the single drugs. Experimental studies showed that the binding capacity of AC is influenced by physicochemical drug properties. Vd is usually easily available and reflects a large number of drug properties. It is related to a decreased effect of other drug eliminating procedures, such as dialysis [23]. Our analysis showed a direct relationship between increase in Vd of the study drugs and the early effect of AC. It is interesting to see that the same drug property that limits dialysis clearance renders agents more likely to exhibit enhanced adsorption by AC. Therefore, these drug characteristics could be used to better identify which patients would benefit most from AC therapy. Although our data cannot distinguish between the mechanisms of absorption by AC and increased elimination, it is tempting to believe that elimination plays an increasing role as the time interval between drug intake and AC administration increases, and this may explain the apparent stabilization of the effect when AC is administered between 2 and 4 hours after drug ingestion (**Figure 1**).

Third, we looked for the time point at which the highest drug concentration occurs after oral administration (time to peak concentration), as an expression of a slow absorption and a larger amount of drug being present in the gut. As expected, this parameter correlated with the effect of later administered AC (>1 hour). A subsequent analysis of the influence of anticholinergic side effects (reduction of gut motility and increase in the gut transit time14) on the effect of early (within 5 minutes) or late (>1 hour) administration did not show an increased effect of AC. However, this could very well be a consequence of the often very low doses (always subtoxic and sometimes subtherapeutic) that were used in this population of healthy volunteers [24-25].

In our opinion, data from our meta-analysis support the use of AC in drug-poisoned patients to prevent further complications, but not to reduce mortality. AC is an inexpensive treatment and does not usually require invasive procedures. It has the advantage that the effect is based primarily on the reduction of absorption, while other options to remove the drug from the body, such as hemodialysis, are based solely on increasing the elimination, which means that the drug has already been absorbed and has possibly done harm.

This means that AC should be given in situations of potentially dangerous drug intoxication, especially in patients in whom other treatment options, such as hemodialysis, are limited. AC/ drug ratios that are much higher than the usually recommended ratio of 10 can be used, especially in cases of poisoning with high-potency drugs.

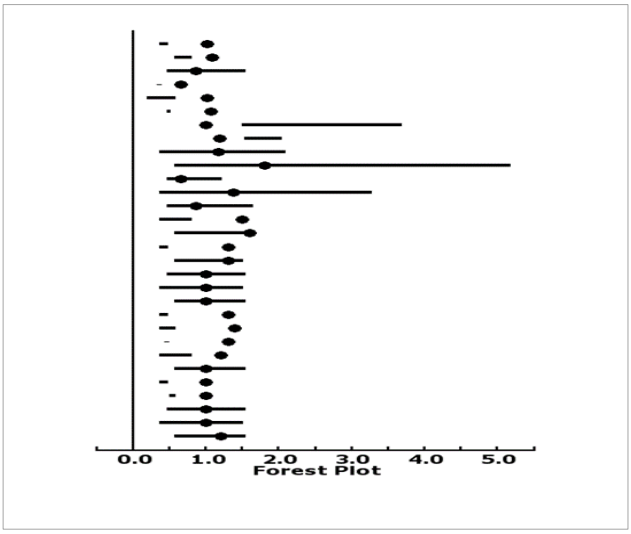

Figure 1: Forest plot shows the effect of AC among different articles included in the analysis.

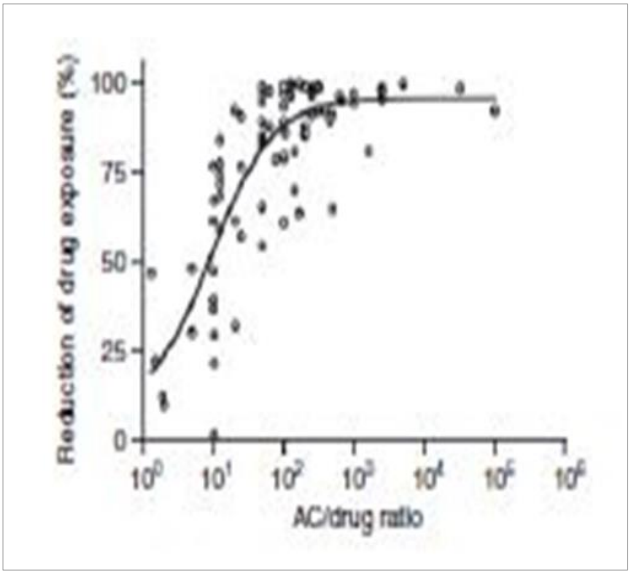

Figure 2: Effect of AC administration at 0-5 mins on reduction of drug exposure.

Conclusion

We reviewed the available literature systematically and found 40 studies dealing with the adsorption of toxic materials and the use of activated charcoal in management. Within our meta-analysis, we performed statistical tests (ANOVAs) and evaluated "Specific CBZBV20%" to check the results for significance.

We conclude that activated charcoal is indicated for primary elimination of the toxin in moderate to severe cases of poisoning. AC has a significant role in treating toxic patients, but has no statistically significant in reducing mortality. It should be given as soon as possible (generally within 30 to 60 min of ingestion), and the patient must be alert and cooperative. The most important contraindication is a not fully conscious patient with no swallowing reflex. Furthermore, the toxin must display adequate binding to activated charcoal, which is not the case for acids/bases, alcohols, glycols, organic solvents, or metals.

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Conflicts of Interest

None of the authors have any conflicts of interest

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