Reversible Adsorption (Desorption) of Aspirin From Activated Charcoal

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• The potential desorption of aspirin from activated charcoal was investigated in eight patients in a randomized crossover study. Despite prebinding of aspirin, systemic absorption did occur. Desorption from activated charcoal was characterized by a peak salicylate concentration that was 16% of control and a time to peak salicylate concentration that was delayed in the study group. Bioavailability of aspirin from activated charcoal described by area under the curve was 19% of control. Elimination half-lives were similar in both groups until 12 hours after ingestion, but after 12 hours the half-life of the study group was prolonged while salicylate concentrations were undetectable in the control group. Fifteen percent to 20% of aspirin prebound to charcoal may desorb leading to systemic absorption. Furthermore, release from activated charcoal is initially delayed then sustained through 30 hours.
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Absorption of potentially toxic substances can be inhibited by removal from the stomach through emesis or gastric lavage and/or by sequestration of the substance in the gastrointestinal tract with activated charcoal.[1,2] The ability of activated charcoal to adsorb drugs and other toxins has made administration of this compound one of the most effective methods of treating poisoned patients.

While in vitro and in vivo studies have demonstrated the ability of activated charcoal to bind and inhibit the absorption of many drugs and chemicals,[2-10] the precise mechanism and dynamics of this process have not been well defined. The assumption has been that activated charcoal provides an extensive surface area for noncovalent binding of substances, thus preventing absorption from the gastrointestinal tract. Originally, activated charcoal was thought to bind these drugs in an irreversible manner[2,6]; recently, however, this concept has been disputed.[3,5] In fact, to our knowledge, the question of whether the charcoal-drug complex remains intact throughout its transit of the gastrointestinal tract or is displaced (desorbed) has not been answered.[6,11,12]

The purpose of this investigation was to examine the potential reversibility of binding (desorption) of aspirin from the aspirin–activated charcoal complex. Furthermore, it was the intent of this study to quantify the potential desorption of aspirin from activated charcoal.

PATIENTS AND METHODS

Informed consent, as required by the Clinical Investigation Committee at The Children's Hospital, Boston, was obtained from eight adult subjects. Subjects were excluded if they had any medical contraindications to aspirin or activated charcoal use or had taken any medication within seven days prior to the study. Subjects were requested to refrain from taking any medications during the study period and to fast for 12 hours prior to and four hours after the initiation of each trial.

All subjects participated in a randomized crossover trial in which aspirin (Bayer) alone or as a slurry with activated charcoal (Instachar) was administered. For the control trial, each subject received 1 g of aspirin that was crushed and mixed with 50 mL of water 15 minutes prior to ingestion. For the study trial, each subject received a slurry of 1 g of aspirin (similarly crushed) with 10 g of activated charcoal in a total of 50 mL of fluid. To assure that aspirin was bound to activated charcoal when administered, this slurry was also prepared 15 minutes prior to ingestion. An additional 180 mL (6 oz) of water was used to remove any residual aspirin or activated charcoal from the cup to assure ingestion of the total preparation. At least one week separated each trial.

Whole blood samples were obtained immediately prior to ingestion of the experimental preparation and at 0.5, 1, 2, 4, 6, 8, 10, 12, 24, and 30 hours following ingestion. Samples were drawn into heparinized specimen tubes from an indwelling venous catheter and immediately centrifuged. The plasma was recovered and assayed for salicylate using high-performance liquid chromatography with sensitivity limits of 0.5 mg/L.[13] In addition to the plasma samples, the aspirin–activated charcoal preparations were assayed to determine the concentration of salicylate in the preparations taken by the subjects.

Plasma salicylate concentration vs time curves for control and study groups were graphed and from these curves pharmacokinetic characteristics were defined. Salicylate absorption was characterized by four methods in this study: (1) by the peak

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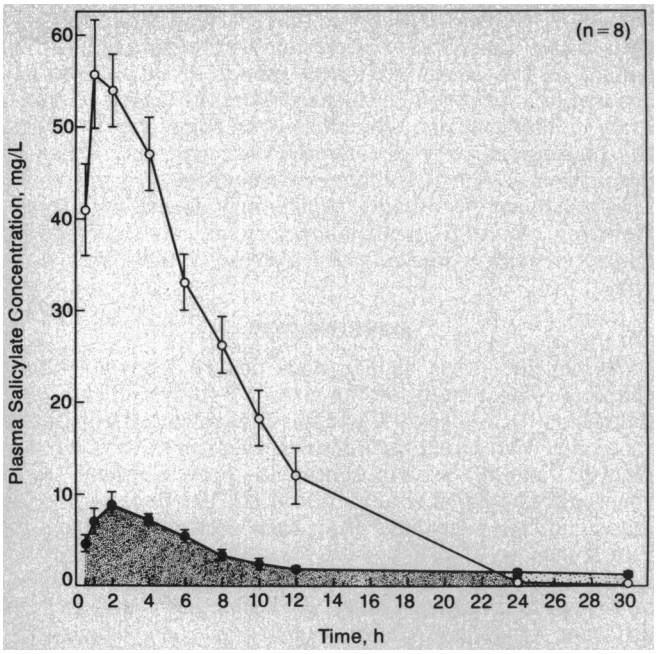

Plasma salicylate concentrations over time in subjects given aspirin alone (open circles) and aspirin with activated charcoal (solid circles). Six of eight subjects had no measurable salicylate concentrations at 24 hours (open circle) and eight of eight subjects at 30 hours (open circle) after ingestion in aspirin alone group. All eight subjects had measurable salicylate concentrations at 24 and 30 hours (solid circles) after ingestion in aspirin–activated charcoal group.

salicylate concentration (Cmax), (2) by the time to reach peak concentration (Tmax), (3) by the area under the plasma concentration vs time curve (AUC) that was calculated using the trapezoidal rule, and (4) by elimination half-lives ($t_{1/2}$) that were defined by determining the elimination rate constant (k) from the terminal linear phase of the log plasma concentration vs time curve by the method of least mean squares and then calculating the $t_{1/2}$ as defined by the following: $t_{1/2} = 0.693/k$. Statistical differences between the two trials were established using Student's independent *t* test.

RESULTS

Eight subjects (four men and four women) between the ages of 22 and 38 years participated in the study. The mean plasma salicylate concentration vs time curves for the eight subjects are shown in the Figure. The salicylate concentration in the effluent of the aspirin–activated charcoal slurry was undetectable, indicating that all salicylate was bound to the activated charcoal prior to administration. These data indicate that the administration of either aspirin alone (control group) or aspirin–activated charcoal slurry (study group) resulted in measurable plasma salicylate concentrations. The quantitative differences between the control and study groups as defined by Cmax, Tmax, AUC, and $t_{1/2}$ are seen in the Table. The Cmax in the study group was 16% of that found in the control group ($P<.0001$), while the Tmax was delayed by 75% in the study group ($P<.05$). The bioavailability of salicylate from activated charcoal, as indicated by the AUC, was 19% of the control group ($P<.0001$). The elimination $t_{1/2}$ of the two groups were not significantly different between four and 12 hours after ingestion (see Table). However, the elimination $t_{1/2}$ between 12 and 30 hours was 21.6 hours in the study group, while six of eight subjects had no detectable plasma salicylate concentrations at 24 hours after ingestion in the control group. Mean salicylate concentrations were significantly greater in the control group from time zero to 12 hours, but the study group concentrations were significantly greater at 24 and 30 hours following ingestion ($P<.001$).

Pharmacokinetic Characteristic Differences Between the Aspirin and Aspirin–Activated Charcoal Groups*

	Aspirin (Control) (N=8)	Aspirin/Activated Charcoal (Study) (N=8)	Significance†
Cmax, mg/L	59.4±4.6	9.4±1.2	$P<.0001$
Tmax, h	1.6±0.4	2.8±0.5	$P<.05$
AUC, mg/L*h	475.6±54	88.5±6	$P<.0001$
$t_{1/2}$, h			
4-12	4.6±0.5	4.1±0.5	NS
12-30	...	21.8±2.2	...

*All values expressed as mean ± SEM. Cmax indicates the peak salicylate concentration; Tmax, the time to reach peak concentration; AUC, the area under the plasma concentration vs time curve; and $t_{1/2}$, half-life.

†Significance was established using Student's *t* test. NS indicates not significant.

COMMENT

Activated charcoal has played an increasingly important role in the management of the poisoned patient. Despite its increased use, however, the action of activated charcoal is not fully understood. One important question concerns the "irreversibility" of activated charcoal's binding. Aspirin was selected for this investigation since it represented a relatively common overdose treated with activated charcoal and since there were reports in the literature that reviewed the binding of aspirin to activated charcoal in vivo[8,14,15] as well as in vitro.[8,14] There were only four studies, however, that attempted to further investigate the irreversibility of aspirin's binding to activated charcoal,[2,3,5,6] and none of these studies was designed to examine this phenomenon specifically.

Decker et al[2] and Picchioni[6] concluded from their studies that desorption did not occur. Decker and associates administered 300 mg of aspirin alone or followed 30 minutes later by 30 g of activated charcoal. Serum salicylate concentrations between four and 24 hours suggested relatively consistent prevention of absorption of aspirin, although no concentrations were determined after 24 hours. This was an important interval in our study that demonstrated the presence of measurable salicylate concentrations and a prolonged elimination $t_{1/2}$, indicating desorption from the activated charcoal. Picchioni used data from studies in rats given chloroquine or pentobarbital with and without activated charcoal to support the theory of irreversible binding of drugs to activated charcoal. However, neither of these studies was designed to evaluate desorption and therefore could only speculate as to the irreversibility of aspirin's binding to activated charcoal.

Although neither study was designed specifically to evaluate release of drug bound to activated charcoal, reports by Neuvonen et al[3] and Levy and Tschiva[5] suggested reversible binding. Neuvonen and associates administered activated charcoal five minutes after ingestion of aspirin tablets and found that serum concentrations were higher in the aspirin–activated charcoal group than in the aspirin-alone group from 24 to 96 hours after ingestion. This suggests either a delayed absorption or continued desorption from activated charcoal. In this study, however, aspirin was not premixed with activated charcoal; therefore desorption cannot be determined with certainty. Levy and Tschiva gave activated charcoal premixed with aspirin solution in ratios calculated (but not assayed) to adsorb

either 50% or more than 99% of the drug and found recovery in the urine to be 87.4% and 60.6%, respectively, of total aspirin administered. While this also suggests partial reversibility of adsorption of aspirin to activated charcoal in vivo, lack of assay for free salicylate prior to administration prevents being able to say that aspirin was completely bound to the activated charcoal.

The present investigation is the first of its kind, to our knowledge, in which the desorption of drug from activated charcoal has been described and quantified. In this investigation, the single most important fact was that aspirin was premixed with activated charcoal and assayed to assure that complete binding of aspirin to activated charcoal had occurred. From this study, there are four major areas that will help in understanding the nature of desorption from activated charcoal: Cmax, Tmax, AUC, and $t_{1/2}$.

The Cmax is an indicator of the initial impact of a drug exposure and is often used to determine the severity of a poisoning exposure. The findings of this study indicate that 15% to 16% of aspirin bound to activated charcoal is initially displaced. If this relationship were to hold with larger doses of aspirin, then desorption could contribute to the measured peak plasma concentration. Furthermore, the Tmax determined from our aspirin–activated charcoal group indicates that the most significant desorption of aspirin occurs early, ie, within 2.8 hours of ingestion. However, this peak occurs statistically significantly later than aspirin alone, suggesting that desorption from activated charcoal may not occur instantaneously but may be delayed. The AUC reflects the total extent of absorption of aspirin, ie, its bioavailability. If the release from activated charcoal were the same as that reflected by Cmax, then we would expect a 15% to 16% difference between the two groups. In fact, we see a 19% difference, which suggests additional delayed release and subsequent absorption.

Finally, initial elimination of salicylate occurred in both the study and control groups in a similar fashion, with $t_{1/2}$ of 4.1 and 4.6 hours, respectively. However, elimination after 12 hours was different between the two groups. While the plasma salicylate concentration in the control group fell to undetectable levels after 12 hours, the $t_{1/2}$ in the study group was prolonged during this time period. These data suggest that there is an initial release of aspirin from activated charcoal and then a subsequent period after 12 hours in which aspirin is again released (or in a greater quantity) from its binding sites.

This investigation was not designed to study the mechanism of desorption but rather the occurrence of desorption. Several theories may be postulated to explain this phenomenon. Neuvonen[8] proposed that the adsorption of drugs to activated charcoal is a reversible equilibrium process in which, as the concentration of free drug decreases (ie, absorption), drug will be released from the activated charcoal. In addition, pH, which has been suggested to affect the binding capacity of activated charcoal, may enhance desorption as the pH changes throughout the gastrointestinal tract.[14] And finally, aspirin may desorb with time. However, results from our laboratory indicate that over 30 hours, no aspirin was released from activated charcoal in vitro.

CONCLUSIONS

We conclude that aspirin does desorb from activated charcoal. The results of the present study indicate the following: (1) 15% to 20% of aspirin is released from activated charcoal, (2) the time course of aspirin release may be delayed, and (3) aspirin continues to be released from charcoal 24 hours after administration. The findings of this study indicate that desorption from activated charcoal is real, but more work is needed to establish how desorption occurs, what factors may increase or decrease this phenomenon, and how the extent of desorption is affected by different drugs and different doses of these drugs. Although the results of this investigation can only directly apply to the factors used in these experiments, the clinical value of these observations may be more far reaching.

The clinician needs to recognize that binding of drugs or chemicals to activated charcoal is a complex and poorly understood process. We have described a process (desorption) that could lead to changes in the way we manage overdosed patients in several important ways. First, with drugs or chemicals that show a tendency to desorb from activated charcoal, we may see an increased benefit from repetitive charcoal, ie, as the drug desorbs more charcoal is available to bind it. Second, cathartics may become more important since desorption may result from increased residence time of the drug in the gastrointestinal tract. Third, that desorption occurs may lead to the development of other substances, ie, resins and other binding agents that may be more effective for drugs that desorb from activated charcoal. Whatever is the final outcome, binding to activated charcoal is not an irreversible process, and maneuvers that involve the gastrointestinal tract, ie, dilution, altering intestinal pH, or changing gastrointestinal tract motility time may influence the availability of drug for absorption.

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