ACCELERATED CLEARANCE OF INTRAVENOUSLY ADMINISTERED THEOPHYLLINE AND PHENOBARBITAL BY ORAL DOSES OF ACTIVATED CHARCOAL IN RATS. A POSSIBILITY OF THE INTESTINAL DIALYSIS

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The effect of oral administration of activated charcoal on the clearance of theophylline and phenobarbital following their intravenous administration was studied in rats. Oral administration of multiple doses of activated charcoal significantly decreased the serum half-life and AUC (area under the curve) and increased the total body clearance of both theophylline and phenobarbital as compared with their respective controls. The volume of distribution was not significantly different between treatments. A single dose of activated charcoal showed only a slight enhancement of clearance of theophylline. Accelerated clearance of both drugs by oral activated charcoal was rationalized in terms of adsorption of exsorbed drugs and inhibition of their reabsorption by activated charcoal in the gastrointestinal tract.

Keywords — activated charcoal; theophylline; phenobarbital; intravenous administration; serum concentration; total body clearance; serum half-life; gastrointestinal tract; AUC; intestinal dialysis

INTRODUCTION

Activated charcoal has been widely used as an antidote for acute drug intoxication. It prevents the systemic absorption of a wide variety of drugs from the gastrointestinal tract by adsorbing the drugs onto its surface. For example, gastrointestinal absorption of theophylline and phenobarbital was suppressed by oral administration of activated charcoal or its beads. Neuvonen and Elonen demonstrated in normal volunteers that repeated oral doses of activated charcoal increased the rate of elimination of phenobarbital, carbamazepine and phenylbutazone. True et al. also showed that oral activated charcoal, administered to patients with theophylline toxicity, rapidly reduced the serum theophylline concentrations. Other reports also showed that the clearance of intravenously administered drugs was increased by orally administered activated charcoal. Since the mechanism of the accelerated elimination of intravenously administered drugs by orally administered activated charcoal has not been studied, we have examined in rats the relative importance of transmucosal transport (exsorption) and biliary excretion of the drugs. We have demonstrated that intravenously administered theophylline and phenobarbital were transported into the small intestinal lumen to a significant extent and into the bile juice to a small extent in rats. The present study, therefore, was designed to evaluate whether exsorbed drugs can be removed by adsorption to orally administered activated charcoal and consequently the clearance of the drugs administered intravenously to rats can be accelerated according to our earlier observations.

MATERIALS AND METHODS

Materials — Aminophylline (Neophylline) was purchased from Eisai Co., Tokyo. Phenobarbital sodium (Linasen) was obtained from Daiichi Seiyaku Co., Tokyo. Activated charcoal was obtained from Inuhiode Seiyaku Co., Osaka and the particle size used in this study was less than 62 μm (250 mesh).

Animal Treatment — Wistar strain male rats, weighing 200—380 g, were fasted overnight with free access to water. Each experiment was carried out by a crossover design, and an interval of more than two weeks was allowed prior to the next experiment. Aminophylline (10 mg/kg) or phenobarbital sodium (10 mg/kg) was administered intravenously via the caudal vein in about 2 min. In the case of the treatment with activated charcoal, the activated charcoal suspended in water (150 mg/ml) was administered orally with a single dose of 300 mg at time zero, with an initial dose of 300 mg at time zero and additional
doses of 150 mg each at 1, 2, 3, and 4 h after the intravenous administration of theophylline, or was administered orally with the initial dose of 300 mg at time zero and additional doses of 150 mg each at 1, 2, 3, 4, and 6 h after the intravenous administration of phenobarbital. No suspending agent was employed and the suspension was administered soon after shaking. In the case of the control treatment, no charcoal was administered at any time but only 2 ml water at time zero. Blood samples (200 μl) were collected periodically from the tail.

Analytical Methods — The concentrations of theophylline and phenobarbital in the serum were measured by a homogeneous immunoassay technique (Ames TDA, Ames Co.) as described in the previous paper. 10)

Pharmacokinetic Analysis — The one-compartment model was used for pharmacokinetic analysis. The total body clearance (Cl), the serum half-life (t_{1/2}), and the area under the serum concentration-time curve extrapolated to time infinity (AUC) were calculated by means of the following equations:

\[ V_d = D/C_0 \]

\[ t_{1/2} = 0.693/k_{el} \]

\[ Cl = k_{el}V_d = D/AUC \]

\[ AUC = C_0/k_{el} \]

where D is the dose, \( V_d \) is the apparent volume of distribution, \( C_0 \) is the extrapolated initial serum concentration at the end of the infusion, and \( k_{el} \) is the elimination rate constant. The paired \( t \) test was used to assess the effect of charcoal treatment on the pharmacokinetic parameters.

RESULTS AND DISCUSSION

Figure 1 shows the time course of the serum theophylline level after intravenous administration of aminophylline (10 mg/kg) to rats with or without activated charcoal treatment. Oral administration of multiple doses of activated charcoal considerably reduced the serum theophylline levels as compared with the control treatment. Its mean serum level at 6 h after i.v. aminophylline was significantly decreased from 8.43 to 4.67 μg/ml by multiple doses of activated charcoal. A single dose of charcoal, though not very marked, showed a similar tendency to that of multiple doses. Pharmacokinetic parameters are shown in Table I. Both the serum half-life and AUC of theophylline were decreased by the

![Graph showing serum theophylline levels over time.

FIG. 1. Serum Theophylline Levels after the Intravenous Administration of Aminophylline (10 mg/kg) to Rats with or without Treatment with Activated Charcoal

Each point represents the mean ± SE of 5 rats. a) \( p < 0.01 \) and b) \( p < 0.05 \) in (○) vs. (●) or (●) vs. (●).

Key: ○ no charcoal treatment, ● treatment with a single dose (300 mg) of charcoal, ● treatment with multiple doses (900 mg) of charcoal.

<table>
<thead>
<tr>
<th>Pharmacokinetic Parameters</th>
<th>No charcoal treatment</th>
<th>Treatment with a single dose (300 mg) of charcoal</th>
<th>Treatment with multiple doses (900 mg) of charcoal</th>
</tr>
</thead>
<tbody>
<tr>
<td>( t_{1/2} ) (h)</td>
<td>4.63 ± 0.49</td>
<td>3.35 ± 0.14 (^{a)})</td>
<td>2.84 ± 0.20 (^{a)})</td>
</tr>
<tr>
<td>( V_d ) (ml/kg)</td>
<td>421 ± 16.2</td>
<td>398 ± 26.9</td>
<td>404 ± 17.3</td>
</tr>
<tr>
<td>( Cl ) (ml/kg/h)</td>
<td>66.7 ± 9.03</td>
<td>82.8 ± 6.33</td>
<td>101.2 ± 9.77 (^{a)})</td>
</tr>
<tr>
<td>( AUC ) (μg·h/ml)</td>
<td>138.1 ± 17.5</td>
<td>105.7 ± 6.82</td>
<td>88.0 ± 8.39 (^{b)})</td>
</tr>
</tbody>
</table>

Each value represents the mean ± SE of 5 rats. a) \( p < 0.05 \), b) \( p < 0.02 \); compared with no charcoal treatment.
treatment with activated charcoal, especially in multiple doses. Oral administration of multiple doses of activated charcoal decreased the serum half-life by 61% and $AUC$ by 64%. The total body clearance showed an increase of 52% as compared with the control treatment. The volume of distribution was not significantly different between treatments. A significant difference between the treatment by a single dose of activated charcoal and the control treatment was observed only in the serum half-life. Hence, it was suggested that the administration of activated charcoal in multiple doses seems to be more effective than that in a single dose. These results show that the oral administration of activated charcoal not only inhibits absorption of orally administered theophylline\textsuperscript{21} in humans but also accelerates clearance of intravenously administered theophylline in rats as well as in humans.\textsuperscript{5–7}

Figure 2 shows the time course of the serum phenobarbital level after intravenous administration of phenobarbital sodium (10 mg/kg) to rats with or without treatment with multiple doses of oral activated charcoal. Oral administration of multiple doses of activated charcoal reduced the serum levels of phenobarbital. Its mean serum level at 24 h after \textit{i.v.} administration of phenobarbital was significantly decreased from 2.10 to 0.78 $\mu$g/ml by multiple doses of activated charcoal. Pharmacokinetic parameters following \textit{i.v.} administration of phenobarbital with or without activated charcoal are shown in Table II. Oral administration of multiple doses of activated charcoal decreased the serum half-life by 67% and $AUC$ by 64%. The total body clearance increased by 54% as compared with the control treatment. The volume of distribution was not significantly different between treatments. These results show that the oral administration of activated charcoal also enhanced the clearance of intravenously administered phenobarbital in the same way as that of theophylline in rats.

In the previous \textit{in situ} single-pass perfusion study, it was found that 12–14% of theophylline\textsuperscript{10} and 6% of phenobarbital\textsuperscript{11} were exsorbed into the intestinal lumen in 2 h, and only 0.2% of theophylline and 0.5% of phenobarbital were excreted into the bile juice in 2 h after intrave-

![Graph showing serum phenobarbital levels after intravenous administration of phenobarbital sodium (10 mg/kg) to rats with or without treatment with activated charcoal.](image)

**FIG. 2. Serum Phenobarbital Levels after the Intravenous Administration of Phenobarbital Sodium (10 mg/kg) to Rats with or without Treatment with Activated Charcoal**

*Each point represents the mean ± SE of 5 rats. a) $p < 0.01$ and b) $p < 0.02$ and c) $p < 0.05$ in (○) vs. (●).*

*Key: ○ no charcoal treatment, ● treatment with multiple doses (1050 mg) of charcoal.*

<table>
<thead>
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<th>Treatment with a multiple dose (1050 mg) of charcoal</th>
</tr>
</thead>
<tbody>
<tr>
<td>$t_{1/2}$ (h)</td>
<td>8.52 ± 0.62</td>
<td>5.71 ± 0.35\textsuperscript{a)}</td>
</tr>
<tr>
<td>$V_d$ (ml/kg)</td>
<td>609 ± 23.8</td>
<td>633 ± 31.3</td>
</tr>
<tr>
<td>$Cl$ (ml/kg/h)</td>
<td>50.2 ± 2.73</td>
<td>77.0 ± 1.21\textsuperscript{b)}</td>
</tr>
<tr>
<td>$AUC$ (μg·h/ml)</td>
<td>184.2 ± 9.56</td>
<td>118.7 ± 1.88\textsuperscript{b)}</td>
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</table>

*Each value represents the mean ± SE of 5 rats. a) $p < 0.05$, b) $p < 0.01$; compared with no charcoal treatment.*
nous administration of the drugs. Thus, theophylline and phenobarbital, exsorbed and/or excreted into the gastrointestinal tract, are expected to be adsorbed by activated charcoal. Consequently, activated charcoal may prevent reabsorption of these drugs due to little availability of free drug in the gastrointestinal tract. Furthermore, it may be expected that exsorption is accelerated due to a greater concentration gradient between blood and the fluids in the gut because concentration of absorbable (free) drug be kept low in the presence of activated charcoal in the gastrointestinal tract (Fig. 3). The results, as illustrated in Figs. 1 and 2, demonstrate that activated charcoal adsorbs theophylline and phenobarbital exsorbed and/or excreted into the gastrointestinal tract. The marked enhancement (increase of 86–130% in theophylline and 170% in phenobarbital) of the clearance by activated charcoal, as shown in human subjects, was not observed in the present study in rats. Moreover, a single dose of activated charcoal showed only a slight enhancement of theophylline clearance. The present finding may be explained by the quantitative differences in the rate of exsorption between the human and the rat. Activated charcoal adsorbs various substances including the drugs and the gastrointestinal contents for adsorption site. Levy and Tsuchiya showed that the effect of activated charcoal on the absorption of aspirin increased with increasing doses and decreased in the presence of food. They also found appreciable desorption of aspirin from charcoal in the gastrointestinal tract. Therefore, the administration of activated charcoal in multiple doses may be important to prevent desorption from the charcoal and subsequent reabsorption in the gastrointestinal tract.

In conclusion, it was confirmed that the oral administration of activated charcoal can enhance the clearance of the drug which has been parenterally administered or has already been absorbed into the systemic circulation from the gastrointestinal tract. It may be expected that oral administration of activated charcoal may serve as one of the hemo-purification methods such as hemodialysis, peritoneal dialysis, and hemoperfusion. Removal of toxic amounts of drugs and physiological metabolites in the blood by oral administration of adsorbents such as activated charcoal has been named gastrointestinal dialysis (Fig. 3B).

REFERENCES

Drug Clearance with Activated Charcoal


