Prevention of Gastrointestinal Absorption of Phenobarbital by Activated Carbon Beads as an Oral Adsorbent

Yoshiteru HONDA, Masahiro NAKANO,* and Naomi I. NAKANO**

Department of Pharmacy, Kumamoto University Hospital, *1-1-1 Honjo, Kumamoto, 860, Japan and Ginkyo College of Medical Science, **819 Ohkubo, Shimizu-machi, Kumamoto, 860, Japan
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The in vitro adsorption characteristics of activated carbon beads suitable for oral administration and the original fine powder were examined, using phenobarbital as the test drug. The extent and rate of drug adsorption on carbon in the beads were almost equal to those on the powder. In three healthy volunteers, 10 g of activated carbon beads administered orally 20 min after 120 mg of phenobarbital, reduced the total bioavailability by 57% (p<0.005), based on the salivary AUC-value during 96 h and the achieved peak concentration of the drug in saliva by 51%. These results demonstrated the potency of activated carbon beads as a gastrointestinal adsorbent in acute intoxications from phenobarbital.

Keywords — activated carbon preparation; activated carbon; activated carbon beads; activated charcoal; phenobarbital adsorption; gastrointestinal adsorbent

Introduction

Intoxication with phenobarbital is a common occurrence on account of its narrow therapeutic plasma concentration range. Because phenobarbital has a long half-life, approximately 110 h, i.e. it is eliminated very slowly, patients who take an overdose of this drug in the accidental or intentional intoxications may enter a coma and unconsciousness may persist for many days.

Activated carbon is an old medicine but a recently rediscovered agent. Many recent researches and clinical experiences indicate that it can effectively remove most, but not all, drugs and poisons from the body by preventing absorption and enhancing elimination. However, activated carbon powder is difficult to handle and its slurry has many palatability problems.

We have, thus, prepared activated carbon beads for oral administration by drying spherical agar beads in which activated carbon powder is finely dispersed. The beads were not only easy to handle and swallow but were also demonstrated to inhibit effectively absorption of theophylline, phentoyin, quinidine and nalidixic acid from the gastrointestinal tract in human subjects. With theophylline, no significant difference in inhibitory effects in vivo was observed between activated carbon powder and the beads (p<0.05).

The purpose of this study was to examine in vitro and in vivo adsorption of phenobarbital by activated carbon beads and hence assess its potential value in the treatment of phenobarbital intoxication.

Materials and Methods

Materials — Activated carbon powder of Japanese Pharmacopeial grade manufactured from wood and activated with steam was obtained from Inuhinode Pharmaceutical Co., Osaka, Japan. Activated carbon beads, 2/3 parts of which consist of activated carbon, were prepared as described previously by drying spherical beads prepared by dispersing 8% activated carbon powder in 4% agar. The beads were passed through sieves of mesh sizes 28 (590 μm), 48 (297 μm), 80 (177 μm) and 250 (62 μm), and the fractions 28/48, 48/80 and 80/250 were employed for in vitro adsorption studies. The beads of mesh sizes 28/48, which were the main fractions prepared and roughly corresponded to granula in JP XI, were used for an in vivo study. Phenobarbital (JP XI grade) was purchased from Marushi Pharmaceutical Co., Osaka, Japan and phenobarbital tablets were purchased from Fujinaga Pharmaceutical Co., Tokyo, Japan. All other chemicals used were of the highest purity commercially available.
Adsorption Studies — Accurately weighed amounts of either activated carbon powder (about 10 mg) or activated carbon beads (about 15 mg) were placed in 100 ml Erlenmeyer flasks. Drug solutions of known concentrations (100—500 μg/ml) in the 1st (pH 1.2) and 2nd (pH 6.8) fluids of the disintegration test in JP XI (50 ml), were placed in each of the flasks. After equilibration by mixing in a water bath at 37°C, the concentration of unadsorbed (i.e. free) drug was determined spectrophotometrically at 220 nm on a Shimadzu model UV-240 double beam spectrophotometer. The amount of the drug adsorbed was calculated from the difference between the total amount of the drug added and the amount of the unadsorbed drug. The adsorption data were treated according to the Langmuir equation.  

The time course of adsorption was also studied in the 1st fluid of JP XI. The same procedure was employed as for the determination of equilibrium amounts of the drug adsorbed, with the exception that mixing was stopped at predetermined times before equilibration. Separate flasks were prepared for each predetermined time and the content of each flask was filtered through a membrane filter (Millex® -HA, 0.45 μm) immediately after the end of mixing.

In Vivo Study — Three healthy volunteers, two males and one female, aged 24 to 36 years, weighing 48 to 68 kg, who had been fully informed about the objective and possible risks participated in the study. To evaluate body fluid level profiles of phenobarbital in volunteers, salivary levels were measured, since a good correlation of plasma and salivary phenobarbital concentrations has been reported.  

Blank salivary samples were collected a few minutes before drug administration. Phenobarbital tablets (4 × 30 mg) were administered at 8 a.m. on an empty stomach, after an overnight fast, with 200 ml of tap water. Activated carbon beads (10 g) suspended in 200 ml of water or water without the beads was taken 20 min after the drug administration. In the present study, 20 min was set as a delay between the ingestion of an overdose and initiation of the treatment. Timed salivary samples were collected at appropriate intervals up to 96 h. A small amount (about 10 mg) of citric acid, a salivary flow stimulant, was put on the tongue and held in the mouth for 1—2 min, then a 5-ml sample of the saliva was collected in a test tube and stored at −40 °C until analysis. No food was taken for 4 h postdose. This study consisting of two phases was conducted at an interval of one-month.

Analysis of Phenobarbital Levels in Saliva and Pharmacokinetic Calculations — Concentrations of phenobarbital in saliva were measured by the reverse-phase high performance liquid chromatography (HPLC) using hexobarbital as an internal standard. In short, a 3-ml portion of saliva was extracted with 10 ml of chloroform containing hexobarbital (1.0 μg/ml) after addition of 200 mg of ammonium sulfate. Separation was performed with a Shim-pack CLC-ODS column (6.0 mm i.d. × 15 cm, Shimadzu, Kyoto, Japan). The mobile phase consists of acetonitrile and water (30:70). At a flow rate of 1.5 ml/min, the eluate was monitored for absorbance at 220 nm. The area under the salivary phenobarbital concentration–time curve from 0 to 96 h (salivary AUC0−96 h) was chosen as the measure of the effectiveness of activated carbon beads and was calculated by the trapezoidal rule. The apparent elimination half-lives (t1/2) were based on salivary concentrations at 10, 24, 34, 48 and 96 h.

Results and Discussion

Adsorption Studies

Experimental results on adsorption of phenobarbital by activated carbon powder and the beads are shown in Fig. 1. The maximum binding capacities of the powder and the beads of mesh sizes 80/250, 48/80 and 28/48 for phenobarbital (mg per g of activated carbon), which were calculated according to the Langmuir equation, were 490.5, 481.7, 467.0 and 447.0 mg/g, respectively, in the 1st fluid (pH 1.2) and 357.8, 348.7, 345.5 and 331.6 mg/g, respectively, in the 2nd fluid (pH 6.8). These results indicated that the adsorption capacity of the powder for phenobarbital was essentially retained by more than 90% in the beads. As expected, ad-
Oral Activated Carbon Beads

Fig. 1. Adsorption Isotherms for Binding of Phenobarbital on Activated Carbon Powder and Beads at 37 °C
Key: (a) in the 1st fluid, pH 1.2; (b) in the 2nd fluid, pH 6.8. ●, activated carbon powder; ○, △ and □, activated carbon beads of mesh size 80/250, 48/80 and 28/48, respectively.

Adsorption of phenobarbital on carbon was also more pronounced in the acidic 1st fluid than in the 2nd fluid because more drug existed in the unionized, adsorbable form at pH 1.2 than at pH 6.8.

Figure 2 presents the adsorption rates of the drug. Adsorption by the powder was a fast process and equilibrium adsorption was attained within about 20 min, whereas that by the agar beads was somewhat reduced and the rate was inversely related to the size of the beads. However, its reduction was not serious as to make the beads impractical for oral use and fast attainment of equilibrium adsorption of phenobarbital by the powder seemed to be almost retained in the agar-encapsulated beads.

In Vivo Study

Phenobarbital, when administered alone in the fasting state, was rapidly absorbed, producing peak saliva concentrations of 1.10 ± 0.15 µg/ml (mean ± S.E.) at 1.33 ± 0.33 h (Fig. 3 and Table I). After the absorption phase, the phenobarbital concentrations decreased continuously very slowly at the apparent elimination half-life (t_{1/2}) of 116.3 ± 14.4 h.

During trials with the activated carbon beads, the rate of absorption of the drug appeared to

Fig. 2. Time Courses of Adsorption of Phenobarbital on Activated Carbon Powder and Beads in 1st Fluid, pH 1.2 at 37 °C
The values are the average of two determinations. Key: the same as in Fig. 1.

Fig. 3. Mean Salivary Concentration–Time Curves for Phenobarbital Alone (●) and Phenobarbital with Activated Carbon Beads Administered at 20 min (□)
Each point represents the mean ± S.E. of three subjects. Degree of significance: a) p < 0.005, b) p < 0.01, c) p < 0.05.
TABLE I. Effect of Activated Carbon Beads on Absorption of Phenobarbital, Assessed by Bioavailability Parameters

<table>
<thead>
<tr>
<th></th>
<th>Phenobarbital alone (control)</th>
<th>With activated carbon beads</th>
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</thead>
<tbody>
<tr>
<td>Peak concentration, $C_{\text{max}}$ $(\mu g/ml)$</td>
<td>$1.10 \pm 0.15$</td>
<td>$0.54 \pm 0.03$</td>
</tr>
<tr>
<td>% of control</td>
<td>100</td>
<td>50.1 $\pm 4.0^a$</td>
</tr>
<tr>
<td>Peak time, $t_{\text{max}}$ $(h)$</td>
<td>$1.33 \pm 0.33$</td>
<td>$3.00 \pm 1.00$</td>
</tr>
<tr>
<td>Elimination half-life, $t_{1/2}$ $(h)$</td>
<td>$116.3 \pm 14.4$</td>
<td>$83.9 \pm 7.3$</td>
</tr>
<tr>
<td>% of control</td>
<td>100</td>
<td>72.8 $\pm 2.8^d$</td>
</tr>
<tr>
<td>Bioavailability, salivary $AUC_{0-96\ h}$ $(\mu g\cdot h/ml)$</td>
<td>$68.7 \pm 2.3$</td>
<td>$29.4 \pm 5.5^d$</td>
</tr>
<tr>
<td>% of control</td>
<td>100</td>
<td>42.8 $\pm 8.1^d$</td>
</tr>
</tbody>
</table>

Each value represents the mean $\pm$ S. E. of three subjects. Degree of significance: $a) p<0.005$, $b) p<0.01$, $c) p<0.05$.

be virtually identical to the control for the first 20 min and absorption then stopped abruptly following administration of the beads. As a result, activated carbon beads inhibited the total bioavailability of phenobarbital by 57%, based on the salivary $AUC$-value during 96 h. $C_{\text{max}}$ was also reduced by about a half to 0.54 $\pm 0.03 \mu g/ml$.

On the other hand, the elimination rate constant of the drug was somewhat greater after a single dose of the beads, an apparent elimination half-life (83.9 $\pm 7.3$ h) being shortened by 27% from the control experiment.

**General Discussion**

Orally-administered activated carbon is a safe, effective and inexpensive alternative to more invasive treatments such as hemodialysis or peritoneal dialysis for some cases of drug overdoses and poisoning. However, there is a major limiting barrier before the full benefits of this black, messy powder can be realized. A major criticism of activated carbon is its poor palatability and patient acceptance, and thus the lack of suitable formulations of activated carbon for oral administration has prevented its wide use in many countries.

Agar-encapsulated activated carbon beads are fine granules with good flow properties and are free from many of the handling problems associated with activated carbon powder. In the present work, the extent and rate of drug adsorption on the beads were almost equal to those on the original fine powder. Although the adsorption characteristics for the beads were prone to be dependent on the size; the larger the size of the beads, the somewhat smaller the capacity and rate of drug adsorption, it seems that its reduction by incorporation of the powder into an agar matrix is scarcely a consideration unless the size of the beads is too large. It was also shown in this investigation that activated carbon beads administered 20 min after an oral dose of phenobarbital drastically reduced absorption of the drug. This demonstrates the potency of the beads as a gastrointestinal adsorbent for phenobarbital.

The present observation that apparent elimination rate constants were greater in the presence of the beads than in the control may be rationalized by possible accelerated elimination of the absorbed drug due to adsorption of the drug transported from the blood to the intestinal lumen.

Recently, it has been appreciated that the repeated doses of activated carbon can markedly enhance the clearance of various drugs that have already been absorbed and are in the systemic circulation, and this has been called gastrointestinal dialysis. Although we have no experience in trying out repeated doses of activated carbon beads for the purpose of gastrointestinal dialysis in the drug intoxications, our
previous studies\textsuperscript{11a,b} with the stimulating effect of
these beads on the fecal excretion of
2,3,4,7,8-pentachlorodibenzo furan, one of the
most important causal agents of Yusho\textsuperscript{12} which
accumulate in the body, seem to support the
expectation that the beads can exhibit the gastroin-
testinal dialysis effect in most intoxications by
drugs and poisons.

Because activated carbon beads are better
tolerated and are more convenient for patients
to take, the beads seems to be a promising can-
didate as a gastrointestinal adsorbent and also
may discover new applications in the field of
medicine. There is a good possibility that the
beads described here will be useful not only in
the treatment of drug intoxications but also as
a hypocholesterolemic agent\textsuperscript{13} and as a sup-
porting measure in patients who are under
hemodialysis.\textsuperscript{14}

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