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Adsorption and Prevention of Gastrointestinal Absorption of Nalidixic Acid by Activated Carbon Beads

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An activated carbon preparation suitable for oral administration as a gastrointestinal adsorbent was prepared by drying spherical beads in which 8% activated carbon powder was dispersed in 4% agar. The preparation, activated carbon beads containing about 67% activated carbon powder in agar matrices, consists of palatable fine granules with good flow properties and is free from many of the handling problems associated with activated carbon powder. In an adsorption test *in vitro* using nalidixic acid, no reduction of the adsorbing capacity of activated carbon powder was observed as a consequence of its incorporation into agar beads. Administration of 10 g of the beads 20 min after an oral dose of 500 mg of nalidixic acid effectively reduced intestinal absorption of the drug by about 53% ($p < 0.02$), based on the 24 h cumulative excretion of the drug in urine. These results indicate that the preparation is a promising candidate as a gastrointestinal adsorbent for the early treatment of possible intoxication by acidic drugs.

Keywords——activated carbon preparation; activated carbon; agar encapsulated activated carbon; activated carbon bead; nalidixic acid adsorption; gastrointestinal adsorbent

Activated carbon can adsorb a wide variety of substances *in vitro* and it has been shown to inhibit gastrointestinal absorption of various drugs and poisons in animals and humans.[1] However, the lack of suitable formulations of activated carbon for oral administration has prevented its wide use in many countries.[2]

Our approach was to encapsulate activated carbon powder in agar gel matrices, thereby overcoming many of the problems associated with the use of the fine powder, which is the most efficient form for adsorption. We have already reported the preparation of activated carbon beads as a palatable oral dosage form.[3] These beads were not only easy to handle but also were demonstrated to inhibit effectively the absorption of two neutral drugs, theophylline[4a] and phenytoin,[4b] and one basic drug, quinidine,[4c] from the gastrointestinal tract in human subjects. With theophylline, no significant difference in the degree of inhibition was observed between activated carbon powder and the beads ($p > 0.05$). The present work was performed to evaluate the effect of the activated carbon beads on absorption of nalidixic acid as a representative acidic drug.

Experimental

Materials——Activated carbon powder of Japanese pharmacopeial grade manufactured from wood and activated with steam was obtained from Inuhinode Pharmaceutical Co., Osaka. The powder was dried to constant weight before use. The activated carbon beads were prepared as described previously from the powder and agar (Wako Pure Chemical Industries, Osaka).[3] The final preparation, containing 67% of activated carbon in agar, was obtained by drying spherical beads of 28 to 48 mesh in which 8% activated carbon powder was dispersed in 4% agar. Nalidixic acid tablets (Wintomylon,® Daiichi Pharmaceutical Co., Tokyo) were commercially obtained. Authentic samples of nalidixic acid and 7-hydroxynalidixic acid were generous gifts from Daiichi Pharmaceutical Co., Tokyo.

***In Vitro* Experiments**——The adsorption studies were carried out at various activated carbon-to-drug ratios in the 1st (pH 1.2) and 2nd (pH 6.8) fluids of the disintegration test in the Japanese Pharmacopeia, 10th revision. After equilibration at 37 °C, the concentration of unadsorbed (*i.e.* free) drug was determined spectrophotometrically at the wavelengths of the maximum absorbance of the drug in each fluid. The amount of the drug adsorbed was calculated from the difference between the total drug added and unadsorbed drug.

***In Vitro* Experiments**——Three healthy male volunteers who had been fully informed about the objective and possible risks participated in the study. Nalidixic acid tablets (2 × 250 mg) were administered at 8 a.m. on an empty stomach 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. Urine was collected in fractions corresponding to 0—1, 1—2, 2—3, 3—4, 4—6, 6—8 8—10 and 10—24 h. After recording the volume of the urine, aliquots were stored at −20 °C until analyzed. Concentrations of nalidixic acid and a major metabolite, 7-hydroxynalidixic acid, in urine were measured by the high-performance liquid chromatography (HPLC) technique of Cuisinaud *et al*,[5] and the cumulative excretion of the drug in urine was calculated. Although another metabolite, the 7-carboxylic acid derivative, has also been found in urine, this metabolite was ignored since it accounted for only a small percentage of the dose administered.[6]

Results and Discussion

In Vitro Experiments

Figure 1 shows the adsorption of nalidixic acid on the activated carbon powder and the beads from the 1st (pH 1.2) and 2nd (pH 6.8) fluids of the disintegration test at 37 °C. These results indicated that the binding capacity of the powder for nalidixic acid was essentially retained in the beads, as was the case for other adsorbates, such as salicylate,[3] bile acids,[7]

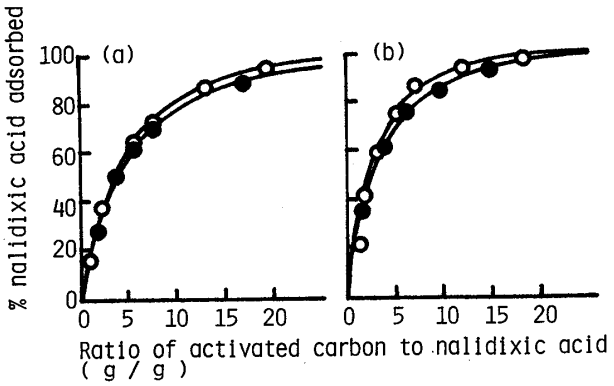

Fig. 1. Adsorption of Nalidixic Acid *in Vitro* at Various Activated Carbon-to-Nalidixic Acid Ratios in Disintegration Test Fluids at 37 °C

(a) 1st fluid, pH 1.2; (b) 2nd fluid, pH 6.8. ○, activated carbon powder; ●, activated carbon beads.

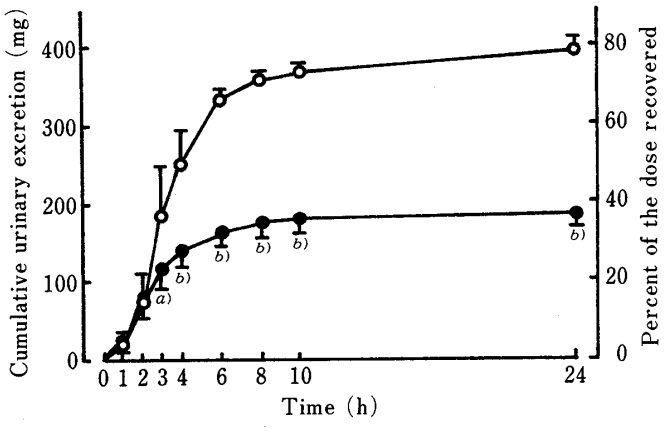

Fig. 2. Effect of Activated Carbon Beads on the Absorption of Nalidixic Acid, Based on the Excretion Pattern of Nalidixic Acid plus 7-Hydroxynalidixic Acid in Urine

Mean ± S.E.M. in three volunteers. Degree of significance: *a*) $p < 0.02$. *b*) $p < 0.05$. ○, without activated carbon beads; ●, with activated carbon beads.

TABLE I. Effect of Activated Carbon Powder or the Beads on the Gastrointestinal Absorption of Various Drugs in Humans

Drug (Molecular weight)	Period (h)	% inhibition		Reference
		Powder	Beads	
Theophylline[a] (180)	0→∞	54[b]	47[b]	7*a*
Phenytoin[a] (252)	0→48	—	40	7*b*
Quinidine[a] (325)	0→8	—	66	7*c*
Nalidixic acid[c] (232)	0→24	—	53	This work

a) Calculated on the basis of the area under the plasma or saliva concentration–time curve for the period indicated after administration of 200 mg of the drug alone and that for the same amount of drug followed by an adsorbent preparation equivalent to 6.7 g of activated carbon powder. *b*) No significance at $p=0.05$. *c*) Calculated on the basis of the cumulative urinary excretion of the drug and its major metabolite, 7-hydroxynalidixic acid. Other conditions were as for *a*).

theophylline,[4a] phenytoin[4b] and quinidine.[4c]

In Vivo Experiments

Cumulative excretion of nalidixic acid and 7-hydroxynalidixic acid into urine during the first 24 h after a single oral dose of 500 mg of nalidixic acid is presented in Fig. 2. A total of 395.4 ± 12.6 mg of nalidixic acid equivalent was recovered, corresponding to $79.1 \pm 2.5\%$ of the dose. Administration of 10 g of activated carbon beads 20 min after the drug intake inhibited absorption of the drug by about 53% ($p<0.02$), based on the 24 h cumulative excretion (Fig. 2).

Table I summarizes our data on the inhibitory effect of the beads on intestinal absorption of various types of drugs so far studied. These drugs do not vary greatly in molecular size. However, theophylline and phenytoin are essentially neutral molecules under physiological conditions, whereas quinidine and nalidixic acid are a cation and an anion, respectively. Although adsorption by activated carbon is generally more favorable for neutral molecules than ionic species, the *in vivo* data show that the extent of inhibition of the intestinal absorption of these drugs by the beads does not vary greatly.

Although the adsorption capacities of activated carbon powder are retained in the beads, the rate of adsorption is somewhat reduced, particularly as the size of the beads is increased.[7] This effect is, however, not so detrimental for oral use, since in the case of theophylline, which is the only drug for which both the powder and the beads have been compared *in vivo*, no significant difference ($p<0.05$) was observed between the beads and the powder in preventing the gastrointestinal absorption. In the present work on nalidixic acid adsorption, the 53% reduction in gastorointestinal drug absorption by the beads supports the view that the expected slight reduction in the rate of adsorption caused by incorporation of the powder into agar matrix is not a practical problem in *in vivo* adsorption.

Thus, the activated carbon beads are expected to be a useful oral sequestering preparation in cases of acute drug poisoning, particularly when the toxin can not be readily identified.

General Discussion

Activated carbon is probably the most effective single agent available as a gastrointes-

tinal adsorbent and seems to carry little risk of serious complications in the treatment of acute poisonings. Usually, activated carbon is given as an aqueous suspension in large doses (about 50 to 100 g to adults and proportionally less to children). However, activated carbon powder, which is the most efficient form for adsorption, is difficult to handle and its suspension has many palatability problems, such as a stickiness and gritty feeling in the mouth and throat, difficulty in swallowing, *etc.* In many countries the lack of appropriate activated carbon formulations has prevented its wide use and the development of oral formulations designed to overcome the aforementioned problems without a concomitant decrease in adsorbing capacity is desirable. Much effort has been devoted to developing palatable activated carbon formulations and the work has involved the use of excipients such as carboxymethylcellullose, bentonite, gelatin, ice cream, jam, milk and sorbitol, *etc.*[8] However, success has been only partial, because the excipients themselves can be adsorbed onto the carbon powder and thus tend to decrease its adsorbing capacity. 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. They can be reconstituted into a homogeneous and easily swallowable suspension after shaking for a minute or two with tap water. In addition, the beads may be effective in preventing constipation, which is the only side effect of activated carbon powder, because agar has a laxative action. Activated carbon beads should be a part of first-aid kits both at home and at work in order to avoid unnecessary delays in administration of adsorbents.

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