Effects of Codeine on the Agitating Force and Gastrointestinal Transit Time in Dogs, for Use in Drug Absorption Studies

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Drug absorption studies using dogs have been difficult because of different gastrointestinal (GI) conditions between dogs and humans, including dogs’ shorter intestinal transit time and strong agitation force in the GI tract. We attempted to modify the agitation force and GI transit time in dogs using codeine. The agitation force was examined based on the in vitro/in vivo correlation for a CR tablet of acetaminophen showing agitation-dependent release. Codeine improved the GI condition better than atropine or loperamide, employed previously.

Key words codeine; acetaminophen; drug absorption; hydrodynamic flow; gastrointestinal (GI) transit time; in vitro/in vivo relationship

In drug absorption studies using dogs, we encounter difficulties because of the difference in the environment of the gastrointestinal (GI) tract between humans and dogs. Highly variable gastric pH, vigorous agitation in GI tract and shorter small intestinal residence time in dogs results in a disagreement between humans and dogs concerning drug release/absorption properties. In our previous study, treatment using atropine (an acetylcholine blocker) and loperamide (an anti-diarrheal drug) was attempted in order to improve GI agitation and intestinal transit time in dogs. These treatments partially improved the adversity, but not to satisfaction.

In the present study, we attempted to modify the agitation force and GI transit time in dogs using codeine, because it has been reported that codeine delays oro-caecal transit and reduces the motility of the colon without modifying gastric emptying time. The GI agitation force was examined based on the in vitro/in vivo correlation for acetaminophen (paracetamol) controlled-release (CR) formulations showing the agitation-dependent release rates used in our previous studies.

MATERIALS AND METHODS

Dosage Forms We used CR acetaminophen (100 mg) tablets which showed agitation speed-dependent (50—100 rpm) release; they were labeled tablet A in our previous reports. Tablet A’s components and dissolution properties have already been reported.

Dog Study Three male beagle dogs, weighing 9.4—13.3 kg, received a CR tablet and a solution containing acetaminophen under a fasting condition. Codeine phosphate (0.05 mg/kg) was intravenously administered 15 min before dosing of the acetaminophen formulations. Two of these dogs were also used for a study involving 0.1 mg/kg codeine phosphate treatments, and one of them was used for the 1.0 mg/kg treatment. Treatments were carried out with a 7-d washout period.

The sampling procedure, determination of drugs in plasma and measurement of GI transit times were carried out in the same way as reported previously.

Data Analysis The amount of acetaminophen absorbed following oral administration was calculated by the pointarea deconvolution method modified by Iga et al. Weight functions of deconvolution were determined using the pharma-

macokinetic model parameters estimated from the i.v. administration data. The cumulative amount absorbed was normalized for the absolute bioavailability of the p.o. solution.

To test the significance of difference between two means, an unpaired Student’s t-test (one-side) was used. When the homogeneity of variance was not significant, the Welch test was used.

RESULTS

GI Agitation Force The in vivo absorption properties of acetaminophen in dogs treated with codeine phosphate were compared with those of the control dogs in Fig.1, also and are compared with an in vitro dissolution of acetaminophen by the paddle method. The drug amount released from a CR tablet in 0.5 mg/kg codeine-pretreated dogs was significantly lower than that from the control dogs. Comparison of the in vitro and in vivo dissolution profiles indicated that the codeine treatment reduced the dogs’ GI agitation force from about 100 to 50 rpm paddle speed. The difference in absorption profiles among the different codeine doses was not large (Fig. 1).

GI Transit Time Variations in GI transit time are shown in Table 1. There was no significant difference in GI transit time between the control and codeine-treated dogs. The codeine treatment did not prolong the oro-caecal transit time of salicylazosulfapyridine (SASP), and the gastric emptying rate of the acetaminophen solution was also unchanged by codeine pretreatment. However, codeine treatment prolonged the duration of absorption from the CR tablet. The absorption profile of the control dog showed that the drug absorption almost stopped at about 3 h (Fig. 2). In the case of the codeine-treated dogs, the profile showed that drug absorption continued until 4 h.

DISCUSSION

Several attempts have been made to improve the dog GI environment by treatment with such drugs as ACh blockers (atropine), gastric acid stimulators (pentagastrin and antidiarrheal drugs (loperamide). In our previous study, atropine and loperamide were used to prolong a dog’s GI transit time and to weaken the GI agitation force. In the present study, codeine was used for the same purposes. The re-

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result was that codeine did not prolong the GI transit time in dogs, however, it prolonged the drug absorption-time and reduced the agitation force in the GI tract. Accordingly, codeine brought the dogs' GI condition close to that of humans. Comparison of codeine with the other two drugs we used in a previous study are shown in Figs. 2 and 3. Codeine and atropine significantly reduced the in vivo agitation force and prolonged the duration of drug absorption; but loperamide did not (Fig. 2). Atropine treatment extraordinarily decreased the gastric emptying rate, whereas codeine and loperamide did not (Fig. 3). The gastric emptying rates in humans and dogs under a fasting condition are almost the same; therefore, such a prolongation of gastric emptying time by atropine is unfavorable. Additionally, no unfavorable side-effect occurred in the codeine study. In conclusion, among the three drug treatments, codeine treatment is most

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Table 1. Effect of Codeine Treatment on GI Transit Time in Dogs

<table>
<thead>
<tr>
<th>Codeine (mg/kg)</th>
<th>Reaching time to colon (h)</th>
<th>Gastric emptying (min)a)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>mean ± S.D.</td>
</tr>
<tr>
<td>Control</td>
<td>4</td>
<td>4.50 ± 1.00</td>
</tr>
<tr>
<td>0.1</td>
<td>2</td>
<td>5.00 ± 1.41</td>
</tr>
<tr>
<td>0.5</td>
<td>6</td>
<td>4.00 ± 2.28</td>
</tr>
<tr>
<td>1.0</td>
<td>1</td>
<td>6.00</td>
</tr>
</tbody>
</table>

a) Elimination half life of liquid from stomach. b) Not significantly different from the control.
suitable for drug absorption study in dogs, considering the similarity to humans it creates.

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REFERENCES