Effect of Gastric pH on the Bioavailability of Albendazole in Rabbits

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Abstract

The effect of gastric acidity on the bioavailability of albendazole, used for treating human echinococcosis, was evaluated using gastric-acidity-controlled rabbits in a crossover manner.

The normal gastric-acidity group, which had a gastric pH of around 1, showed threefold greater bioavailability than that of the low acidity group, which had a gastric pH of greater than 5. However, in solubility studies, albendazole showed a marked pH-dependent solubility, 900 μg mL⁻¹ at pH 1.2 and less than 10 μg mL⁻¹ at pH 6.8.

These results suggest that the absorption of albendazole is greatly influenced by gastric pH.

Materials and Methods

Human echinococcosis is caused by the larval forms of Echinococcus multilocularis, and the liver is the most affected organ (Lewis et al 1975). Patients with alveolar echinococcosis in the liver can be cured by complete excision of the lesions. However, it is not always completely resectable in advanced cases (Uchino et al 1993). Thus, effective chemotherapy is needed before or after surgery. Recent reports have shown albendazole to be effective for treating human echinococcosis (Wilson et al 1992; Wen et al 1994; Ishizu et al 1997). In clinical studies, there was a great inter-subject variability of bioavailability (Marriner et al 1986; Jung et al 1992; Sato et al 1994), and a significantly improved absorption was shown when the drug was taken with a fatty meal (Lange et al 1988; Awadzi et al 1994). This phenomenon may be due to the poor water solubility of this drug.

It has been shown that gastric acidity is an important factor in oral bioavailability of drugs. Bioavailability of thiamine disulphide, diazepam, metronidazole, indomethacin and dipyridamole solid preparations, which have pH-dependent dissolution rates and solubility, was significantly affected by the gastric acidity of the subjects (Ogata et al 1980, 1982, 1985; Aoyagi et al 1985; Kohri et al 1992). However, the effect of gastric acidity on bioavailability of albendazole has not been studied. In this study, we evaluated the bioavailability of albendazole in rabbits with low and high gastric acidity.

Solubility studies

The solubility of albendazole was determined over the pH range 1.2-7.3. An excess amount of albendazole sulphoxide was provided by Smith Kline Beecham (Madrid, Spain). Mebendazole was provided by Janssen Kyowa (Tokyo, Japan). Albendazole and phenacetin were purchased from Sigma Chemical Co. (St Louis, MO). Lansoprazole (Takepron) was obtained from Takeda Co., Ltd (Tokyo, Japan). All other chemicals were of the highest grade available and used without further purification.
carried out on a Hitachi L-6000 constant flow pump and a Hitachi L-4000 UV detector operating at 310 nm. Separations were performed on an ERC-ODS 1161 reversed-phase column (inner diam. 10 cm x 6 mm; particle size 3 μm; Erma Optical Works) warmed to 55°C. The mobile phase consisted of a phosphate buffer (pH 7.0) and acetonitrile (55:45), and pH was adjusted with phosphoric acid to 6.5. The flow rate was 1.0 mL min⁻¹ and the pressure was about 40 kg cm⁻².

Procedure for the preparation of low gastric-acidity rabbits and drug administration

Gastric-emptying-controlled rabbits were prepared by the method of Takahashi et al. (1985) to resemble human gastric emptying. White male rabbits, 2.5-3.5 kg, were used for the absorption study in a crossover manner with a 14-day washout period between dosing. To prepare the low gastric-acidity group, rabbits were fasted for one day before the absorption study but water was freely available. Hard gelatin capsules (Japanese Pharmacopoeia XIII, No. 3) containing 6 mg lansoprazole, H₂-pump inhibitor, were administered orally at 0900 and 2100 h. For the absorption study, 10 mL water was given orally through a plastic catheter at 0900 h on the next day, and gastric juice was withdrawn by suction. The pH of the gastric juice was determined in each rabbit using a pH test paper (Toyo Roshi Co., Tokyo). Hard gelatin capsules containing a physical mixture of albendazole and lactose (1:15) were administered orally at 0900 and 2100 h. For oral administration of lansoprazole or albendazole, each capsule was inserted into the stomach of the rabbit with a plastic catheter attached to a syringe. The plastic catheter was inserted through a hole in a wooden bar which held the mouth open so that the catheter passed through the oesophagus into the stomach. Capsules which had been fixed to the inserted end of the plastic catheter were pushed out with 10 mL water into the stomach interior. For the intravenous administration, a dimethylsulphoxide solution of albendazole sulphoxide (5 mg mL⁻¹), an active metabolite of albendazole, was injected through the ear marginal vein (1 mg kg⁻¹). For both intravenous and oral administrations, no water was given for the first 4 h and no food was allowed until the study was over. Plasma samples were collected from the marginal ear vein with a heparinized syringe at predetermined intervals.

Assay of albendazole sulphoxide in plasma

Plasma (600 μL) was mixed with 3 mL 0.1 M Na₂B₄O₇ solution containing phenacetin as an internal standard for HPLC and extracted with 6 mL chloroform. The organic layer (5 mL) was evaporated and reconstituted with 0.1 mL of the mobile phase. The resulting solution was used for HPLC injection. HPLC was performed according to the methods used in in-vitro solubility studies. The mobile phase consisted of a 0.05 M phosphate buffer and acetonitrile (75:25).

Pharmacokinetic analysis of plasma data

The parameters of the appropriate pharmacokinetic model were estimated using the MULTI program (Yamaoka et al. 1981). The area under the plasma concentration–time curve from 0 to 24 h (AUC₀-2₄h) was calculated according to the linear trapezoidal rule. Albendazole was completely metabolized to albendazole sulphoxide in rabbits. Therefore, bioavailability of albendazole was calculated according to the following equation: bioavailability = (AUC₀-2₄h albendazole sulphoxide p.o./dose p.o.)/(AUC₀-2₄h albendazole sulphoxide i.v./dose i.v.), after oral administration of albendazole and intravenous administration of albendazole sulphoxide.

Statistical differences between high and low gastric-acidity groups were assessed using Student's t-test.

Results and Discussion

Figure 1 shows that albendazole solubility decreased dramatically as the pH increased. The pKₐ₁ and pKₐ₂ values of albendazole are 2.68 and 11.83, respectively. For the cationic form at pH 1.2, the solubility of albendazole was 900 μg mL⁻¹, while an extremely low solubility (less than 1 μg mL⁻¹) was observed in the un-ionized form at pH above 5.

Figure 1. Solubility profile of albendazole in various pH solutions at 37°C.
Table 1. Pharmacokinetic parameters after administration of albendazole to rabbits in a crossover study.

<table>
<thead>
<tr>
<th>Group</th>
<th>Dose (mg kg⁻¹)</th>
<th>Cmax (µg mL⁻¹)</th>
<th>Tmax (h)</th>
<th>AUC₀₋₂₄h (µg h mL⁻¹)</th>
<th>Bioavailability (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal gastric-acidity</td>
<td>1 (i.v.)</td>
<td>2.1±0.8</td>
<td>4.0±0.8</td>
<td>6.9±1.3</td>
<td>67.6±17.9</td>
</tr>
<tr>
<td></td>
<td>5 (p.o.)</td>
<td>0.5±0.2</td>
<td>6.3±1.6</td>
<td>6.4±2.6</td>
<td>21.3±9.9</td>
</tr>
<tr>
<td>Low gastric-acidity</td>
<td>1 (i.v.)</td>
<td>6.3±0.5</td>
<td></td>
<td>6.3±0.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 (p.o.)</td>
<td>0.5±0.2*</td>
<td></td>
<td>6.4±2.6*</td>
<td>21.3±9.9*</td>
</tr>
</tbody>
</table>

Values represent mean±s.e.m. (n = 5). *P < 0.05 significantly different from normal gastric-acidity group.

It has been reported that gastric pH varies from about 1 to 7 depending on physiological conditions and food availability (Meldrum et al 1972; Mangelada et al 1976). Moreover, more than 50% of subjects, aged 50 to 59 years, showed low gastric acidity (Ogata et al 1984). Therefore, the variability of gastric pH may cause great differences in albendazole solubility and intestinal absorption. To examine the variability of bioavailability of albendazole, we prepared the gastric-acidity-controlled rabbits and investigated the relationship between gastric acidity and absorption. The gastric pH of lansoprazole-treated rabbits and untreated rabbits was around 1, respectively. Furthermore, the low gastric acidity of the former group was maintained for at least 4 h from the start of the absorption experiment.

When administered orally to rabbits, albendazole was rapidly metabolized to albendazole sulphoxide, a major metabolite, and there was almost no unchanged albendazole detected in the plasma, as is the case in man (Marriner et al 1986; Lange et al 1988). Therefore, the plasma levels of albendazole sulphoxide were determined to evaluate the absorption behaviour of albendazole. Figure 2 shows the mean plasma concentration–time profiles of albendazole sulphoxide after oral administration of albendazole to high and low gastric-acidity rabbits. The pharmacokinetic parameters are summarized in Table 1. Significantly higher bioavailability (3-2-fold) and Cmax (4-2-fold) were observed in the high gastric-acidity group compared with those in the low gastric-acidity group after oral administration of albendazole. No significant difference in AUC₀₋₂₄h was observed between the two groups after intravenous administration of albendazole sulphoxide. Moreover, unchanged albendazole was not detected in either group. These results indicate that the drug-metabolizing enzymes of albendazole were not affected by pretreatment with lansoprazole.

In conclusion, the solubility and bioavailability of albendazole may be significantly affected by the gastric pH.

References


