Opposite Effects of Metoclopramide and Propantheline on Intestinal Absorption of Imipramine in Rats

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Intraperitoneally administered metoclopramide (MCP) markedly increased the serum concentration of imipramine (IPM) soon after oral administration. In contrast, intraperitoneally administered propantheline (PPT) slightly decreased the serum concentration. The administration of these two drugs had no significant effect on the serum concentration of IPM after intravenous bolus administration. It was concluded from pharmacokinetic analyses and gastric emptying experiments that the administration of MCP markedly increased the rate of IPM absorption by counteracting the gastric emptying delayed by IPM, but that the administration of PPT slightly decreased the rate of IPM absorption by strengthening the gastric emptying also delayed by IPM.

Keywords — imipramine; intestinal absorption; metoclopramide; propantheline; gastric emptying; interaction mechanism

Introduction

Drugs are generally absorbed more readily from the small intestine than from the stomach. Thus gastric emptying is a major factor affecting drug absorption.1) Many drugs can alter gastric emptying and then influence the intestinal absorption of co-administered drugs.2-7) Metoclopramide (MCP) and propantheline (PPT) are typical drugs which cause such interactions. For example, MCP enhances acetaminophen absorption by accelerating gastric emptying, whereas PPT reduces the absorption of the drug by delaying gastric emptying.2)

Imipramine (IPM) is widely used in the treatment of endogenous depression and often administered in combination with various drugs. However, information concerning the interactions between IPM and other drugs having the ability to alter gastric emptying has been very limited. Since IPM is known to delay gastric emptying,8-10) the mechanism of interactions between IPM and other drugs having the ability to alter gastric emptying may be complicated. The present study was undertaken to elucidate the mechanism of the absorption interaction between IPM and MCP or IPM and PPT in rats.

Materials and Methods

Chemicals and Animals — IPM hydrochloride and desipramine hydrochloride were supplied by Yoshitomi Pharmaceutical Co. MCP dihydrochloride monohydrate was supplied by Fujisawa Pharmaceutical Co. PPT bromide was purchased from Sigma Chemical Co. All other chemicals were of reagent grade. Male Wistar rats (180-200 g) were fasted for 24-30 h before experiments, but had free access to water.

In Vivo Experiments — IPM at a dose of 30 mg/kg dissolved in 1.0 ml of distilled water and at a dose of 6 mg/kg dissolved in 0.4 ml of saline were administered orally and intravenously as a bolus, respectively, to rats. MCP at a dose of 10 mg/kg or PPT at a dose of 6 mg/kg dissolved in 0.4 ml of saline were administered intraperitoneally 0.5 h before administration of IPM. Blood samples were collected by cardiac puncture at appropriate times after oral or intravenous bolus administration of IPM. After standing for 1.0 h, the blood samples were centrifuged to obtain the serum for analysis.

Measurement of IPM and Desipramine Concentrations in Serum — The serum concentrations of IPM and desipramine were determined by a high-performance liquid chromatography (HPLC)11) with some modifications. Serum (1.0 ml) was transferred to a tube containing 0.5 ml
of saturated Na₂CO₃ solution. The samples were extracted with 5.0 ml of hexane and centrifuged at 3000 rpm for 5 min. The organic layer (4.0 ml) was evaporated in vacuo and the residue was dissolved in methanol (0.1 ml) and subjected to HPLC. Etillefrine hydrochloride was used as the internal standard. HPLC was carried out using a Waters model 510 HPLC apparatus equipped with a LiChrosorb Si-60 column (250 × 4 mm i.d.) and a JASCO UVIDEC-100V UV monitor (270 nm). Acetonitrile–methanol–triethanolamine (77:20:3, v/v/v) was employed as a mobile phase at a flow rate of 1.5 ml/min.

**Pharmacokinetic Analysis** — The serum concentration data of IPM were analyzed by statistical moment analysis¹²⁻¹⁴ to obtain values for the mean absorption time (MAT), total body clearance (Cltot), and steady-state volume of distribution (Vdss) of IPM according to the following equation:

\[
\text{MAT} = \frac{\text{MRT}_{\text{po}} - \text{MRT}_{\text{iv}}}{D/\text{AUC}_{\text{iv}}}
\]

\[
\text{Cltot} = \frac{D}{\text{AUC}_{\text{iv}}}
\]

\[
\text{Vd}_{\text{ss}} = \frac{D \cdot \text{MRT}_{\text{iv}}}{\text{AUC}_{\text{iv}}}
\]

where MRTpo and MRTiv are the mean residence time in oral and intravenous bolus routes of administration, respectively. D is the dose and AUCiv is the area under the serum concentration–time curve from zero to infinite time in intravenous bolus route of administration.

**Gastric Emptying Experiments** — Gastric emptying was evaluated as the percentage of quinidine red remaining in the stomach 0.5 h after oral administration of quinidine red (0.005% (w/v)) solution according to the method of Tani et al.¹⁵

**In Situ Intestinal Absorption Experiments**¹⁶ — Rats were anaesthetized with pentobarbital sodium (33 mg/kg), and the small intestine was exposed by a midline abdominal incision. Each glass cannula was inserted into small slits at 10 and 50 cm above the end of the ileum. The cannulae were connected with polyethylene tubes to a flask containing 80 ml of drug solution prepared by dissolving IPM (75 µg/ml) and phenol red (indicator, 5 µg/ml) in 1/15 M isotonic phosphate buffer (pH 6.4). The drug solution was recirculated at 5 ml/min by a perfusion pump. The flask was kept in a water bath at 37 °C. The concentration of IPM in the perfusate was measured by HPLC described above. The concentration of phenol red in the perfusate was measured spectrophotometrically after alkalinization.

**In Vitro Metabolism Experiments** — Rats were sacrificed by decapitation. The liver was excised and homogenized with a Potter–Elvehjem homogenizer in 3 volumes of 0.01 M phosphate buffer (pH 7.4) containing 1.15% (w/v) KCl. The homogenate was centrifuged at 10000 g for 20 min and the resulting supernatant was used to assay for IPM-metabolizing enzyme activity. The activity was assayed in an incubation mixture containing IPM (0.1 mM), nicotinamide adenine dinucleotide phosphate (NADP) (0.4 mM), glucose-6-phosphate (7.0 mM), MgCl₂ (4.0 mM), glucose-6-phosphate dehydrogenase (0.5 units), the 10000 g supernatant and 0.1 M phosphate buffer (pH 7.4) in a final volume of 4.0 ml. After incubation at 37 °C for 10 min, the concentration of IPM remaining in the reaction mixture was measured by HPLC described.
above.

**Statistical Analysis** — The results were analyzed statistically with unpaired Student's t-test. A p value of 0.05 or less was considered to be significant.

**Results**

**Effects of MCP and PPT on Serum Concentration of IPM**

Figure 1 shows the effects of intraperitoneally administered MCP and PPT on the serum concentration of IPM after oral administration. The administration of MCP markedly increased the serum concentration of IPM 0.5 and 1.0 h after oral administration. On the other hand, the administration of PPT slightly but significantly decreased the serum concentration of IPM 0.5 h after oral administration. The administration of these two drugs had no significant effect on the serum concentration of IPM after intravenous bolus administration (Fig. 2). Table I summarizes the effects of MCP and PPT on the pharmacokinetic parameters of IPM. The administration of MCP decreased the MAT of IPM. Furthermore, the administration of MCP caused a significant increase in the $AUC_{po}$ ($AUC$ from zero to 6.0 h in oral route of administration) of IPM. The administration of PPT increased the MAT of IPM but had no sig-

**Table I. Effects of MCP and PPT on Pharmacokinetic Parameter of IPM**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>IPM alone</th>
<th>With MCP</th>
<th>With PPT</th>
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<tbody>
<tr>
<td>$AUC_{po}$ (μg·h/ml)</td>
<td>1.02 ± 0.13</td>
<td>2.10 ± 0.29&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.91 ± 0.13</td>
</tr>
<tr>
<td>MAT (h)</td>
<td>1.08 ± 0.02</td>
<td>0.45 ± 0.05&lt;sup&gt;b&lt;/sup&gt;</td>
<td>1.42 ± 0.08&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>$Cl_{int}$ (l/h/kg)</td>
<td>8.22 ± 0.80</td>
<td>8.08 ± 0.77</td>
<td>7.70 ± 0.92</td>
</tr>
<tr>
<td>$Vd_{a}$ (l/kg)</td>
<td>10.9 ± 0.8</td>
<td>11.3 ± 1.0</td>
<td>11.5 ± 1.5</td>
</tr>
</tbody>
</table>

Each value represents the mean ± S.E. of 3—5 rats. a, b) Significantly different from IPM alone (a) p < 0.05; b) p < 0.001).
significant effect on the $AUC_{po}$ of IPM. The administration of MCP or PPT, as expected from Fig. 2, did not affect the $Cl_{tot}$ and $Vd_{ss}$ of IPM.

**Effects of MCP and PPT on Gastric Emptying**

Figure 3 shows the effects of intraperitoneally administered MCP and PPT on the percentage of quinaldine red remaining in the stomach 0.5 h after oral administration of quinaldine red solution containing IPM. The administration of MCP significantly reduced the percentage of quinaldine red remaining in the stomach, as compared with single administration of IPM. This implies that gastric emptying during oral administration of IPM was accelerated by the co-administration of MCP. In contrast, the administration of PPT significantly enhanced the percentage, indicating that gastric emptying during oral administration of IPM was further delayed.

**Effects of MCP and PPT on the in Situ Intestinal Absorption of IPM**

The effects of intraperitoneally administered MCP and PPT on the intestinal absorption of IPM were examined by using an in situ recirculation technique. As shown in Fig. 4, the administration of MCP did not affect the percentage of IPM remaining in the intestinal lumen. The administration of PPT also gave a similar result.

**Effects of MCP and PPT on the in Vitro Metabolism of IPM**

Figure 5 shows the effects of MCP and PPT on the metabolism of IPM in the 10000 $g$ supernatant fraction of liver homogenate. Each bar represents the mean ± S.E. of 4 rats. Control shows the activity of IPM-metabolizing enzyme in the absence of MCP or PPT (IPM concentration; 0.1 mm). *a* Significantly different from control ($p<0.01$).

**Discussion**

In this study, we examined the interaction of IPM with MCP or IPM with PPT in rats. Intraperitoneally administered MCP and PPT caused a marked increase and a slight decrease, respectively, in the serum concentration of IPM soon after oral administration. Since the administration of these two drugs did not affect the serum concentration of IPM after intravenous bolus administration, the interaction of IPM
with MCP or IPM with PPT is considered to occur in the intestinal absorption process.

In order to elucidate the mechanism of interaction of IPM with MCP, pharmacokinetic parameters of IPM were derived from the serum concentration data. The administration of MCP decreased the MAT of IPM. This suggests that the administration of MCP increased the rate of IPM absorption. IPM is known to delay gastric emptying and a similar result has been observed in our gastric emptying experiments. In addition, intraperitoneally administered MCP accelerated gastric emptying during oral administration of IPM. Therefore, it is possible to assume that the administration of MCP markedly increases the rate of IPM absorption by counteracting the gastric emptying delayed by IPM. This is supported from the fact that the administration of MCP had little effect on the in situ intestinal absorption of IPM.

Tricyclic antidepressants with anticholinergic activity delay gastric emptying and are presumably absorbed slowly when given alone. MCP can cause marked increases in the absorption rate of tricyclic antidepressants, by antagonizing the pharmacological action. The interaction of IPM with MCP during intestinal absorption described above provides such a good example.

On the other hand, the administration of PPT increased the MAT of IPM, suggesting that the rate of IPM absorption was decreased by the coadministration of PPT. It is concluded that the administration of PPT caused a decrease in the rate of IPM absorption by strengthening the gastric emptying delayed by IPM.

Several investigators have reported that change in gastric emptying has no significant effect on drug bioavailability. Nevertheless, the administration of MCP significantly increased the bioavailability (AUC) of IPM. Cimetidine has been demonstrated to increase the bioavailability of IPM from 40 to 75% by inhibiting its metabolizing enzyme. However, the possibility that MCP exhibits inhibitory effect for IPM-metabolizing enzyme is unlikely because MCP at all concentrations tested had no significant effect on the in vitro metabolism of IPM.

The increase in the bioavailability of IPM by the co-administration of MCP may be because the first-pass metabolism of IPM is saturable. In fact, the administration of MCP was found to decrease the desipramine/IPM ratio from 1.94 ± 0.09 to 1.07 ± 0.07 (mean ± S.E., n = 4 or 5, p < 0.001, concentration ratio), in serum 0.5 h after oral administration of IPM; IPM is mainly metabolized to desipramine in rats.

On the basis of only this finding, however, we cannot fully explain the reason why the administration of MCP caused the increase in the bioavailability of IPM. Additional studies including the oral administration of IPM at different doses should be conducted.

References

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Intestinal Absorption of Imipramine


