DOSE-DEPENDENT KINETICS OF METHYLPHENIDATE ENANTIOMERS AFTER ORAL ADMINISTRATION OF RACEMIC METHYLPHENIDATE TO RATS

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The plasma concentration of methylphenidate (MPD) enantiomers after i.v. and oral administration of 0.5-5 mg/kg dose of racemic MPD was compared in rats. In i.v. administration, there was no dose dependence in the pharmacokinetic parameters of both enantiomers in this dose range. In oral administration, although the elimination rate constant of both enantiomers was relatively constant, the total body clearance of both MPD enantiomers decreased remarkably with increasing dose. The relationship between oral dose and the area under the concentration-time curve (AUC) of the individual MPD enantiomers showed a non-linearity. That is, the AUC of both enantiomers increased dramatically with increasing dose more than 2 mg/kg. The recovery (MPD + the metabolite) in urine for 24 h was 16-18% in the range of the oral doses. These results suggest that the dose-dependent characteristics of the MPD enantiomers may be due to the saturation in the presystemic elimination of the drug.

KEYWORDS——methylphenidate enantiomers; oral administration; intravenous administration; plasma concentration; dose-dependent kinetics; rat

INTRODUCTION

Methylphenidate [MPD; threo- (+)/(−)-methyl-α-phenyl-α-(2-piperidyl)acetate], a central stimulant, is of great clinical importance in the treatment of attention-deficit disorder and narcolepsy.1,2) Clinically, racemic MPD HCl is commonly used with the dose of 20-60 mg or 0.3-1 mg/kg. However, it is always necessary to control carefully the dose and schedule of administration of MPD, because of the appearance of severe side effects.2) Many pharmacokinetic studies of racemic MPD have
been performed in both animals and humans.\textsuperscript{3-6}) It has been demonstrated that MPD was almost completely absorbed from the intestinal tract and metabolized to various products rapidly and extensively in rat. One of these major metabolites was the deesterified product, known as ritalinic acid (RA). Wargin et al.\textsuperscript{6}) reported that the absolute bioavailability of racemic MPD was extremely low in rats and monkeys, suggesting that racemic MPD may be subject to substantial presystemic elimination. Recently, enantioselective analytical methods were developed for the quantitation of (+)-MPD (more active pharmacologically than the (−)-isomer), and (−)-MPD in biological fluids.\textsuperscript{7-9}) However, there has been no report on the pharmacokinetics of MPD enantiomers after administration of MPD to animals. In addition, concerning the presystemic elimination, only one as above\textsuperscript{6}) is available.

To clarify the effect of dose on the presystemic elimination of MPD, we have investigated the individual MPD enantiomer concentrations in plasma after oral and intravenous (i.v.) administration of four different doses of racemic MPD to rats.

**MATERIALS AND METHODS**

Chemicals——Racemic mixtures of threeo-form MPD HCl, and threeo-form RA HCl as a metabolite were a gift from Ciba-Geigy (Takarazuka, Japan).

Animals and Sample Collection——Male Wistar rats, weighing 250-320 g, were used in this investigation. Each rat was fasted overnight before use. Rats were anesthetized lightly with ether, and an indwelling cannula (polyethylene tubing) was inserted into the femoral vein and the femoral artery. Racemic MPD HCl was dissolved in physiological saline. A dose of 0.5, 2, 3.5 or 5 mg/kg of racemic MPD HCl was given intravenously through the venous cannula, or the same dose of the drug was given orally (dosing volume; 1 ml). Blood samples (ca. 0.3 ml) were withdrawn in heparinized tubes cooled on ice through the artery cannula at 2, 5, 15 and 30 min, 1, 2, 3 and 4.5 h after administration. Plasma (0.1 ml) was separated by centrifugation at 1620 g for 10 min at approximately 0°C. Urine was collected for 24 h in both cases. All samples were
immediately frozen at -80 °C until analyzed. After each blood sampling, an equivalent volume of blood withdrawn from other rats was transfused through the venous cannula.

Assay of Enantiomers——Concentrations of MPD enantiomers and its metabolite, RA, enantiomers in plasma and urine were determined by a gas chromatographic-mass spectrometric method described in the previous paper.8,9)

Pharmacokinetic Analysis——The plasma data after i.v. administration were fitted to the equation, Ct = Ae^{-\alpha t} + Be^{-\beta t} for the plasma concentration Ct at time t by nonlinear least-squares regression.10) Pharmacokinetic constants were determined from the biexponential equation constant, i.e., A, \alpha, B and \beta, using conventional equations.11) The area under the plasma concentration-time curve (AUC) was calculated by the trapezoidal method and extrapolated to infinity. The total body clearance (CL) were determined as dose/AUC. The bioavailability of MPD enantiomers was calculated from comparison of the AUC after oral and i.v. administration of an equal dose.

RESULTS AND DISCUSSION

Plasma concentrations of (+)- and (-)-MPD declined biex-

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dose (mg/kg)</th>
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<tbody>
<tr>
<td></td>
<td>0.5 (+) (-)</td>
</tr>
<tr>
<td>A (ng/ml)</td>
<td>86.0 (23.7)</td>
</tr>
<tr>
<td>B (ng/ml)</td>
<td>24.5 (5.7)</td>
</tr>
<tr>
<td>\alpha (h^{-1})</td>
<td>5.97 (0.52)</td>
</tr>
<tr>
<td>\beta (h^{-1})</td>
<td>0.784 (0.164)</td>
</tr>
<tr>
<td>Vss (1/kg)</td>
<td>5.9 (0.3)</td>
</tr>
<tr>
<td>CL (1/h/kg)</td>
<td>5.6 (0.7)</td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate the standard deviation of three to four rats.
ponentially after i.v. administration at each dose of racemic MPD. The disposition of both enantiomers was best described by a two compartment open model. Table I summarizes the pharmacokinetic parameters of MPD enantiomers after i.v. administration. Although the parameters (β, Vss and CL) of the enantiomers fluctuated slightly with dose, there was no dose-dependence in these parameters in the dose range studied.

Fig. 1. Relationship between I.V. Dose (a) or Oral Dose (b) of Racemic MPD and the AUC of MPD Enantiomers (Mean ± S.D., n=3-4)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>0.5 (+)</th>
<th>0.5 (-)</th>
<th>2 (+)</th>
<th>2 (-)</th>
<th>3.5 (+)</th>
<th>3.5 (-)</th>
<th>5 (+)</th>
<th>5 (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tmax (min)</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
<td>15</td>
</tr>
<tr>
<td>Cmax (ng/ml)</td>
<td>2.1 (0.7)</td>
<td>1.8 (0.6)</td>
<td>35.7 (10.6)</td>
<td>19.8 (3.3)</td>
<td>62.5 (29.1)</td>
<td>58.2 (34.4)</td>
<td>258.8 (81.9)</td>
<td>172.4 (64.9)</td>
</tr>
<tr>
<td>β (h⁻¹)</td>
<td>0.541 (0.430)</td>
<td>1.018 (0.430)</td>
<td>0.583 (0.210)</td>
<td>1.347 (0.569)</td>
<td>1.654 (0.056)</td>
<td>0.737 (0.088)</td>
<td>0.477 (0.222)</td>
<td>0.992 (0.383)</td>
</tr>
<tr>
<td>CL (l/h/kg)</td>
<td>85.9 (36.4)</td>
<td>134.6 (47.7)</td>
<td>42.0 (23.9)</td>
<td>79.5 (32.8)</td>
<td>26.5 (9.7)</td>
<td>34.9 (16.2)</td>
<td>11.7 (2.6)</td>
<td>23.2 (10.4)</td>
</tr>
</tbody>
</table>

Numbers in parentheses indicate the standard deviation of three to four rats.
Figure 1 (a) shows the AUC plotted against dose. The AUC increased linearly with dose. The mean recoveries [(+)-MPD + (-)-MPD + (+)-RA + (-)-RA] in urine for 24 h were 19-22% in the range of the i.v. doses.

Table II summarizes the pharmacokinetic parameters of the individual MPD enantiomers after oral administration of racemic MPD. Both (+)- and (-)-MPD were found in the first sample at 2 min after oral administration of each dose. The maximum plasma concentration of the (+)- and (-)-isomers was detected at 15 min after administration. The mean peak concentrations of (+)- and (-)-MPD in 5 mg/kg were 123 and 96-fold those in 0.5 mg/kg, respectively. The β of (+)- and (-)-MPD was relatively constant at each dose, and these values were similar to those after i.v. administration. However, the CL of both (+)- and (-)-MPD decreased remarkably with dose (p<0.05). Similar to the results in the i.v. administration as above, the values of β and CL of (+)-MPD were smaller than those of (-)-isomer, respectively. This difference may be responsible for the difference of the metabolizing rate among the enantiomers. Figure 1 (b) shows the AUC of the individual MPD enantiomers plotted against the oral dose. The relationship between the AUC of both enantiomers and the dose showed a non-linearity, and the AUC of both (+)- and (-)-MPD increased dramatically with increasing dose more than 2 mg/kg. From the AUCs after oral and i.v. administration, the bioavailability of (+)- and (-)-MPD was estimated to be 0.07 and 0.06 in 0.5 mg/kg, 0.11 and 0.08 in 2 mg/kg, 0.16 and 0.16 in 3.5 mg/kg, and 0.36 and 0.27 in 5 mg/kg, respectively. On the other hand, the mean recoveries [(+)-MPD + (-)-MPD + (+)-RA + (-)-RA] in urine for 24 h were 16-18% in the range of the oral doses. This finding indicates that the change in the bioavailability with dose may not have resulted from the fluctuation of the absorption of racemic MPD.

These results suggest that the dose-dependent characteristics of the MPD enantiomers may be due to the saturation in the presystemic elimination of the drug. Further study will be necessary to elucidate this mechanism.
REFERENCES


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