The Metabolism and Excretion of Trimethadione in Patients with Percutaneous Transhepatic Biliary Drainage and Renal Dysfunction

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(Received July 29, 1988)

The metabolism and excretion of trimethadione (TMO) following an oral dose of 4 mg/kg has been examined in patients with percutaneous transhepatic biliary drainage (PTBD) and renal dysfunction.

Biliary excretion as the total amount of TMO and its metabolite, dimethadione (DMO) was 2.0% of the dose during 0 to 48 h after TMO administration in patients with PTBD. Total urinary excretion (0—48 h) was 2.8% and 3.0% of the dose in healthy volunteers and patients with renal dysfunction, respectively. The serum DMO/TMO ratio at 4 h after oral dosing in patients of PTBD and renal dysfunction was not significantly changed in comparison with the ratio reported previously in healthy volunteers. The elimination half-life of TMO was also not altered in patients with PTBD in comparison with that reported previously in volunteers.

These results suggest that metabolism and urinary and biliary excretion of TMO are not changed in patients with PTBD and renal dysfunction.

Keywords — biliary excretion; urinary excretion; trimethadione; dimethadione; human

Introduction

We have shown that trimethadione (TMO) is a useful substrate to be used for investigating the factors which influence the activity of hepatic oxidative drug-metabolizing enzymes in rats1—6) and humans.7—10) However, there are few reports on biliary and urinary excretion of TMO and its only metabolite dimethadione (DMO) in rats and in humans.4,11) Metabolism of TMO in patients with biliary and renal dysfunction has not yet been studied.

The purpose of the present investigation was to examine the change of metabolism and excretion of TMO in patients with percutaneous transhepatic biliary drainage (PTBD) and renal dysfunction following an oral dose of 4 mg/kg.

Materials and Methods

Materials — TMO (Dainippon Pharmaceutical Co., Ltd., Osaka, Japan) was used as supplied. DMO was purchased from Tokyo Kasei Kogyo Co., Ltd. (Tokyo, Japan). All other reagents were commercial products of analytical grade.

Clinical Study — (1) Biliary Excretion: Five patients with PTBD (two males, three females: mean age 65 years, range 57—70) were studied after obtaining informed consent. Bile samples were collected from these individuals at 0—2, 2—4, 4—8, 8—24 and 24—48 h and blood samples (0.5 ml) for estimation of serum TMO and DMO were collected at 0, 2, 4, 8, 12 and 24 h after oral administration of 4 mg/kg TMO.

(2) Urinary Excretion: Ten healthy male volunteers (mean age 27 years, range 22—42) were studied after obtaining informed consent. Five renal patients (4 males, 1 female: mean age 52 years, range 48—62) with varying degrees of renal dysfunction (creatinine clearance: mean 32 ml/min, range 26—42) were enrolled in the study. Urine samples were collected at 0—24 and 24—48 h after oral administration of 4 mg/kg TMO and blood samples were collected periodically at appropriate times.8)

Assay Study — Serum and bile levels of TMO and DMO were determined by gas liquid chromatography using maleinimide as an internal standard.12)

Data Analysis — Concentration—time curves of TMO and DMO were drawn on semi-
logarithmic scales. The half-life ($T_{1/2}$) and the elimination rate constant ($K_{el}$) were calculated from the linear portion of the curve obtained by means of linear regression analysis. The apparent volume of distribution ($V_d$) was calculated from the rate of the dose to the serum concentration extrapolated to the time zero. $K_{el}$ was calculated from the equation:

$$K_{el} = 0.693 / T_{1/2}$$

Metabolic clearance (Cl) was calculated according to the following equation:

$$Cl = V_d \cdot K_{el}$$

Statistical analyses were performed using an analysis of variance followed by Dunnett's multiple comparison test with the significance levels set at $p < 0.05$.

### Results

Tables I and II list information about metabolism and disposition of TMO and DMO in patients with PTBD after oral TMO administration. Total amounts (mg) of biliary excretion of TMO and DMO in these patients were 2.0% of the dose during 0 to 48 h; the serum DMO/TMO ratios at 4 h were 0.44 ± 0.07 (mean ± S.D.). This value was not significantly different from the serum DMO/TMO ratio obtained in age matched healthy volunteers (0.42 ± 0.11; $n = 5$) in our previous study.\(^{13}\) Total amounts of biliary excretion (0–48 h) of TMO and DMO correlated with bile flow rates (ml/min) with a correlation coefficient $r = 0.941$ ($p < 0.01$) in the patients.

### Table I. Metabolism and Disposition of TMO and DMO after Oral Administration of 4 mg/kg TMO in Patients with Percutaneous Transhepatic Biliary Drainage

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Patient</th>
<th>Mean</th>
<th>Normal</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>$T_{1/2}$ (h)</td>
<td>15.9</td>
<td>9.6</td>
<td>14.4</td>
</tr>
<tr>
<td>$V_d$ (l)</td>
<td>43.1</td>
<td>45.7</td>
<td>43.4</td>
</tr>
<tr>
<td>Cl (l/h)</td>
<td>1.89</td>
<td>3.31</td>
<td>2.10</td>
</tr>
<tr>
<td>Biliary clearance (ml/h)</td>
<td>13.0</td>
<td>19.6</td>
<td>20.1</td>
</tr>
<tr>
<td>Total biliary excretion $^{a}$</td>
<td>2.0 $^{b}$</td>
<td>2.8 $^{b}$</td>
<td>2.4 $^{b}$</td>
</tr>
<tr>
<td>Bilirubin concentration (mg/dl) $^{c}$</td>
<td>2.4</td>
<td>6.4</td>
<td>1.4</td>
</tr>
</tbody>
</table>

$^{a}$ Up to 48 h. $^{b}$ % of dose (TMO plus DMO). $^{c}$ Total bilirubin. $^{d}$ Age matched values appearing in our previous study.\(^{13}\) $^{c}$ Laboratory values.

### Table II. Changes of Biliary Excretion of TMO and DMO Expressed as Percentage of Dose in Patients with Percutaneous Transhepatic Biliary Drainage after Oral Administration of 4 mg/kg TMO

<table>
<thead>
<tr>
<th>Patient</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TMO</td>
<td>DMO</td>
<td>TMO</td>
<td>DMO</td>
<td>TMO</td>
<td>DMO</td>
</tr>
<tr>
<td>0–2 h</td>
<td>0.04</td>
<td>0.004</td>
<td>0.04</td>
<td>0.02</td>
<td>0.06</td>
<td>0.02</td>
</tr>
<tr>
<td>2–4</td>
<td>0.04</td>
<td>0.01</td>
<td>0.07</td>
<td>0.03</td>
<td>0.10</td>
<td>0.02</td>
</tr>
<tr>
<td>4–8</td>
<td>0.05</td>
<td>0.03</td>
<td>0.14</td>
<td>0.09</td>
<td>0.14</td>
<td>0.05</td>
</tr>
<tr>
<td>8–24</td>
<td>0.19</td>
<td>0.37</td>
<td>0.29</td>
<td>0.86</td>
<td>0.42</td>
<td>0.44</td>
</tr>
<tr>
<td>24–48</td>
<td>0.14</td>
<td>1.11</td>
<td>0.11</td>
<td>1.19</td>
<td>0.27</td>
<td>0.88</td>
</tr>
<tr>
<td>Total $^{a}$</td>
<td>0.46</td>
<td>1.524</td>
<td>0.65</td>
<td>2.19</td>
<td>0.99</td>
<td>1.41</td>
</tr>
</tbody>
</table>

$^{a}$ Up to 48 h, % of dose.
TABLE III. Changes of Urinary Excretion of TMO and DMO Expressed as Percentage of Dose in Healthy Volunteers and Patients with Renal Dysfunction after Oral Administration of 4 mg/kg TMO

<table>
<thead>
<tr>
<th></th>
<th>Volunteer</th>
<th>Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TMO</td>
<td>DMO</td>
</tr>
<tr>
<td>0—24 h</td>
<td>0.63±0.11</td>
<td>0.83±0.22</td>
</tr>
<tr>
<td>24—48</td>
<td>0.20±0.08</td>
<td>1.11±0.36</td>
</tr>
<tr>
<td>Total</td>
<td>0.84±0.09</td>
<td>1.94±0.25</td>
</tr>
</tbody>
</table>

Each value is the mean ± S.D.  

a) Up to 48 h.

Urinary excretion of TMO and DMO was studied in healthy volunteers and patients with renal dysfunction as shown in Table III. The amount of TMO plus DMO excreted in the urine was 2.8% and 3.0% of the dose during 0 to 48 h in the volunteers and patients, respectively. There was no significant difference between the two groups.

In the patients, the serum DMO/TMO ratio at 4 h after oral dosing was 0.52±0.09. The value was not significantly different from the serum DMO/TMO ratio obtained in healthy volunteers (0.54±0.12) in our previous study.13)

Discussion

Urinary and biliary excretion of a drug greatly alters the pharmacokinetic behavior of the drug. We showed that the serum concentration ratio of DMO to TMO measured at 4 h after oral administration of TMO correlated well with the hepatic microsomal drug-oxidizing capacity in humans.8–10) In the present study, we investigated urinary and biliary excretion of TMO and its metabolite DMO in patients with PTBD and renal dysfunction.

Total amounts of TMO plus DMO excreted in the bile during 0 to 48 h after oral dosing was 2.0% of the dose in patients with PTBD (Tables I and II). Biliary excretion of both TMO and DMO was thus minimal as urinary excretion and their biliary excretion had no effect on serum DMO/TMO ratio in the blood samples collected shortly after administration at 4 h.

We have already reported that urinary TMO and DMO excretions in rats were proportional to the administered dose levels (25—300 mg/kg), and DMO excretion in 10% NaHCO₃ (2 ml/kg for 2 d, p.o.) treated rats was increased to about 1.5-fold as compared with controls.41 Very slow urinary excretion of DMO in humans was also reported previously.11) Waddell and Butler14) ascribed this slowness to the weakly acidic property of DMO: this weak acid may be readsobered from renal tubules, delaying its urinary excretion. In dogs and humans, daily urinary excretion of DMO is about 6% of the dosed amount of TMO, and affected by pH of the urine.15,16) Japanese volunteers also excreted very small amounts of TMO and DMO in the urine within the day of administration (Table III). However, the excretion was about one half of the values reported by Waddell and Butler.14) This difference seemed to be due to environmental or therapeutic factors including food habit or dose rather than genetic factors including racial difference.

Urinary excretion of TMO and DMO as well as their biliary excretion was thus small. Consequently, the serum DMO/TMO ratios in the blood collected from patients with PTBD and renal dysfunction at 4 h after oral dosing were not significantly different in those estimated in healthy volunteers.

The present results suggest that metabolism, and urinary and biliary excretion of TMO after oral administration are not changed in patients with PTBD and renal dysfunction.

References


2) E. Tanaka, H. Kinoshita, T. Yoshida and Y. Kuroiwa:


