PANIPENEM, A CARBAPENEM ANTIBIOTIC, ENHANCES THE GLUCURONIDATION OF INTRAVENOUSLY ADMINISTERED VALPROIC ACID IN RATS

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ABSTRACT:

Previously, a significant decrease in the trough plasma-concentration of valproic acid (VPA) owing to the concomitant administration of panipenem (PAPM)/betamipron, a carbapenem antibiotic, in epileptic patients was reported. To determine the site and mechanism of the drug interaction between VPA and PAPM, we performed in vivo and in vitro experiments using rats. A 30 mg/kg bolus dose of VPA was given i.v. to normal Sprague-Dawley rats, nephrectomized rats, and hepatectomized rats, with and without prior treatment of PAPM. PAPM treatment resulted in a significant reduction of biological half-life and a significant increase of total body clearance in normal rats. The effects of PAPM on the disposition kinetics of VPA were also observed in nephrectomized rats, whereas heptectomy abolished the interaction completely. Thus, the site of interaction was identified as the liver. At steady state, PAPM treatment significantly increased total body clearance, the biliary excretion rate of VPA glucuronide, and the apparent metabolic clearance of VPA by glucuronidation, but did not affect the biliary excretion clearance of VPA glucuronide. Initial uptake velocity of VPA into rat hepatocytes proportionally increased as a function of VPA concentration added and was not affected by PAPM. The plasma-unbound fraction of VPA in vitro was not altered by PAPM. These data demonstrate that PAPM does not affect the uptake of VPA into the liver, the plasma-unbound fraction, and the excretion process of VPA glucuronide. Consequently, PAPM appears to enhance the rate of metabolism of VPA to VPA glucuronide in the liver.

Valproic acid (VPA, Fig. 1) 1 , a simple, branched-chain fatty acid with a broad spectrum of anticonvulsant activity, is widely used for treatment of various forms of epilepsy (Rimmer and Richens, 1985). A major metabolic pathway of VPA is glucuronidation of the carboxylic acid. The other minor pathways are β-oxidation and α-hydroxylation at aliphatic hydrocarbon side chains (Eadie et al., 1988). Valproate glucuronide (VPA-Glu) metabolite is known to be excreted into urine of rat, dog, monkey, and human (Vree and Van der Kleijn, 1977; Dickinson et al., 1979).

The chemical structure of VPA differs very much from other antiepileptics, thus, VPA is often applied in combination with other anticonvulsant agents (Cloyd et al., 1985). Numerous types of drug-drug interactions between VPA and concomitantly administered drugs have been reported, e.g., reduction in the plasma concentration of VPA by phenytoin or phenobarbital due to induction of hepatic drug-metabolizing enzymes (Richens et al., 1975); enhanced VPA hepatotoxicity by phenytoin or carbamazepine due to the formation of 4-ene-VPA, a minor but toxic metabolite of VPA (Levy et al., 1990); and inhibition of plasma protein binding of VPA by salicylic acid (Feilman et al., 1980; Yu et al., 1989) or by endogenous free fatty acid (Bowlde et al., 1982). A clinically interesting drug interaction of VPA with Carbenin (panipenem (PAPM)/betamipron, Sankyo Co., Ltd., Tokyo, Japan), a carbapenem antibiotic, has been reported recently in three patients, who showed a reduction of trough plasma level of VPA during concomitant treatment with Carbenin (Nagai et al., 1997). A similar interaction was also found during concomitant therapy with VPA and meropenem, another carbapenem antibiotic. Carbapenem antibiotics have a broad spectrum of antibacterial activity that includes moderate activity against Gram-positive bacteria, excellent activity against Gram-negative aerobics and anaerobics (Shimada and Kawahara, 1994; Fish and Singletary, 1997), and are used frequently in treating various infections. These interactions resulted in the recurrence of epileptic seizures in patients and, therefore, prohibition of the concomitant use of carbapenem antibiotics with VPA was newly added to Information on Adverse Reactions to Drugs (Ministry of Health and Welfare, Japan, 1996).

More recently, it was established that PAPM (Fig. 1), a pharmacologically active constituent of Carbenin, affects the pharmacokinetics of VPA also in cynomolagus monkey (Ministry of Health and Welfare, Japan, 1996). We previously reported that the VPA-PAPM interaction also occurred in Beagle dog and was related to the glucuronidation of VPA (Yamamura et al., 1998). The details of the interaction mechanism, however, have not yet been clarified.

In this report we examined the effect of PAPM on the hepatobiliary excretion of VPA-Glu in rat. Additionally, we investigated whether PAPM alters VPA uptake by rat hepatocytes and plasma-protein binding of VPA.

1 Abbreviations used are: VPA, valproic acid; VPA-Glu, valproate glucuronide; PAPM, panipenem; CLtot, total body clearance; CLmet, apparent metabolic clearance of VPA by glucuronidation; CLbile, biliary excretion clearance of VPA-Glu; C(VPA)plasma, plasma concentration of VPA at steady-state; C(VPA)LIVER, hepatic concentration of VPA-Glu at steady-state; Vbile, biliary excretion rate of VPA-Glu; UDPGA, UDP-glucuronic acid; SD, Sprague-Dawley; 14C-VPA, 14C-labeled sodium valproate; 3H-VPA, 3H-labeled sodium valproate; TLC, thin-layer chromatography.
proate (3 H-VPA, specific activity: 15 Ci/mmol, chemical purity: 99%) were given VPA and PAPM as described above and blood samples were collected from the jugular vein. In control animals, PAPM treatment was replaced by saline at 10 μl/min. After a stabilization period of 30 min, bile was collected at 15-min intervals for 45 min. Blood samples were collected simultaneously from the jugular vein before each collection of bile and centrifuged to separate plasma samples. In typical experiments, the plasma concentrations at 15, 30, and 45 min postdose were 86.1, 85.8 μg/ml, and 89.0 μg/ml, demonstrating the steady state has been achieved. After the final collection of bile, the liver was quickly removed and weighed. A small portion of liver was weighed and solubilized with NCS Tissue Solubilizer (DuPont-NEN Research Products, Boston, MA) to determine total radioactivity. Another portion of excised liver was homogenized with ethanol containing 1% acetic acid to extract VPA, VPA-Glu, and other metabolites. After centrifugation at 900g for 20 min at 4°C, the supernatant was evaporated to dryness. The extract was analyzed by TLC to determine VPA, VPA-Glu, and other metabolites. After centrifugation at 900g, the supernatant was evaporated to dryness. The extract was analyzed by TLC to determine VPA, VPA-Glu, and other metabolites.

Materials. Male, Sprague-Dawley (SD) rats (Charles River, Ibaragi, Japan) were housed in a well ventilated room maintained at 24°C and were allowed free access to food and water. The body weight of the rats used for the experiments ranged from 200 to 350 g. Rats were fasted for 12 h before use. Sodium valproate and β-glucuronidase were purchased from Sigma Chemical Co. (St. Louis, MO). 14C-Labeled sodium valproate (14C-VPA, specific activity: 55 mCi/mmol, chemical purity: 99%) and 3H-labeled sodium valproate (3H-VPA, specific activity: 15 Ci/mmol, chemical purity: 99%) were obtained from American Radiolabeled Chemicals Inc. (St. Louis, MO). PAPM was synthesized in our laboratories (Miyadera et al., 1991). Silica gel plates (Art. 5715) for thin-layer chromatography (TLC) were purchased from E. Merck (Darmstadt, Germany). Other chemicals used were commercially available, reagent grade products.

In Vivo Study. Plasma concentration-time profile of VPA in normal SD rats, nephrectomized rats, and hepatocitzemized rats. The normal rats were lightly anesthetized with ether during the experiments and the femoral vein was cannulated with polyethylene tubing (PE-50, Becton Dickinson & Co., Sparks, MD). A loading dose of 10 mg/kg PAPM followed by a constant infusion of 1.43 mg/min/kg PAPM was administered through the femoral vein cannula using a constant rate infusion pump (pump 11, Harvard Apparatus, Sparks, MD). A loading dose of 16.8 mg/kg followed by a constant infusion of 24.6 mg/h/kg of 14C-VPA (specific activity: 2 μCi/mg) was administered through the femoral vein cannula. The maintenance dose of 14C-VPA was expected to produce a steady-state plasma level of about 75 μg/ml. In control animals, PAPM treatment was replaced by saline at 10 μl/min. After a stabilization period of 30 min, bile was collected at 15-min intervals for 45 min. Blood samples were collected simultaneously from the jugular vein before each collection of bile and centrifuged to separate plasma samples. In typical experiments, the plasma concentrations at 15, 30, and 45 min postdose were 86.1, 85.8 μg/ml, and 89.0 μg/ml, demonstrating the steady state has been achieved. After the final collection of bile, the liver was quickly removed and weighed. A small portion of liver was weighed and solubilized with NCS Tissue Solubilizer (DuPont-NEN Research Products, Boston, MA) to determine total radioactivity. Another portion of excised liver was homogenized with ethanol containing 1% acetic acid to extract VPA, VPA-Glu, and other metabolites. After centrifugation at 900g, the supernatant was evaporated to dryness. The extract was analyzed by TLC to determine VPA, VPA-Glu, and other metabolites.

In Vitro Study. Initial uptake of VPA into isolated rat hepatocytes. Rat hepatocytes were isolated with a slight modification of the method described by Moldeus et al. (1978). The viability of cells was assessed by the trypan blue exclusion method and cells with 90% or higher viability were used for the experiments. The initial rate of VPA uptake was measured by the method described by Schweng (1980). The hepatocytes were suspended in Krebs-Henseleit buffer at a final cell density of 2 x 10^6 cells/ml. 0.95 ml of this solution was preincubated at 37°C for 3 min before addition of 3H-VPA (0.05 μM). At 0.5 min after addition of the substrate, 0.2-ml aliquots were removed and centrifuged immediately through a silicone oil layer into 3 M KOH to separate the cells from the incubation medium. The radioactivity of the solubilized cells in the alkaline layer was determined in a liquid scintillation spectrophotometer. VPA uptake was calculated as an amount of VPA in pmol (the radioactivity in the pellet divided by the specific activity of 3H-VPA) incorporated in 10^6 cells in 30 s (pmol/10^6 cells/30 s).

Plasma unbound fraction of VPA. Animals were sacrificed by exsanguination from the abdominal aorta under light ether anesthesia. Blood samples collected in plastic tubes containing EDTA were immediately centrifuged to separate plasma samples. To determine the free fraction of VPA, with or without PAPM or salicylate, VPA (final concentration 50, 100, or 150 μg/ml) and PAPM (final concentration 50 μg/ml) or salicylate (final concentration 250 μg/ml) were added to plasma and, after incubation at 37°C for 15 min, centrifugal ultrafiltration of the plasma was carried out through an MPS-3 membrane (Amicon Division, W.R. Grace & Co., Beverly, MA) at 2500 rpm for 15 to 30 min. The concentration of VPA in plasma (Cp) and filtrate (Cu) was measured by fluorescence polarization immunoassay. The adsorption of VPA to MPS-3 membrane was negligible. The plasma unbound fraction was calculated as Cu/Cp.

Hepatic tissue unbound fraction of VPA. Animals were sacrificed by exsanguination from the abdominal aorta under light ether anesthesia. The liver was quickly isolated and homogenized with twofold volumes of 10 mM Tris-HCl (pH 7.4). Cytosol from 30% homogenate was prepared by centrifugation at 9,000g for 20 min at 4°C followed by ultracentrifugation (105,000g for 60 min at 4°C). To determine the free fraction of VPA (final concentration 25 μg/ml) in the presence of PAPM (final concentration 0, 20, or 200 μg/ml), VPA and PAPM were added to the cytosol and the mixture was treated in the same way as above for plasma protein binding.

**Fig. 1.** Chemical structures of PAPM and VPA.
β-Glucuronidase activity in the liver toward VPA-Glu. Three rats were sacrificed by exsanguination under ether anesthesia and the livers were quickly isolated and homogenized in 3-fold volumes of 20 mM potassium bicarbonate buffer (pH 6.8). This homogenate was used as the enzyme source of β-glucuronidase. Because VPA-Glu was the major metabolite in the bile after i.v. administration of 14C-VPA to the rats above in in vivo study, the bile samples collected over a period of 2 h after administration of VPA (30 mg/kg) to three rats were combined and used as VPA-Glu. To measure the concentration of VPA-Glu in the pooled bile sample, the bile was hydrolyzed under alkaline condition as follows. A 0.2-ml aliquot of the bile was added with 0.1 ml of 5 N NaOH and incubated at room temperature for 2 h. The reaction was stopped by the addition of 0.1 ml 5 N HCl and the pH of the sample was adjusted to approximately 7 with 0.2 ml 1 M potassium bicarbonate buffer (pH 7.4). Then, the sample was applied to the TDX/TLX system to measure the concentration of VPA.

A 0.1-ml aliquot of the bile was added with 0.25 ml of the liver homogenate or 20 mM potassium bicarbonate buffer (pH 6.8) and the mixture was incubated at 37°C. For the time course study at 15, 30, and 60 min after starting the incubation, 0.07-ml aliquots were removed and added to 0.02 ml of 1 M citric acid to stop the reaction. The pH of the sample was adjusted to approximately 7 with 0.06 ml of 1 M potassium bicarbonate buffer (pH 7.0) and centrifuged by an Eppendorf centrifuge. The supernatant was measured for the concentration of VPA. For the inhibition by PAPM, 0.02 ml of the bile was added with 0.05 ml of the liver homogenate and 0.01 ml of PAPM (final concentration 0, 50, or 500 μg/ml). The mixture was incubated at 37°C for 1 h and treated in the same manner as above.

Pharmacokinetic Analysis. For individual rats, model-independent pharmacokinetic parameters, i.e., area under the plasma concentration-time curve (AUC,inf), biological half-life (T1/2), and distribution volume (Vd) were calculated using WinNONLIN (Scientific Consulting, Inc., Cary, NC) software.

Total body clearance of VPA (CLtot), the apparent metabolic clearance of VPA by glucuronidation (CLm(glu)), and the biliary excretion clearance of VPA-Glu [CLbile(glu)] were calculated as follows:

\[
CL_{tot} = \frac{\text{Dose/AUC}_{inf}}{V_d}
\]

\[
CL_{m(glu)} = \frac{V_{bile(glu)}}{CSS,\text{liver(glu)}}
\]

\[
CL_{bile(glu)} = \frac{V_{bile(glu)}}{CSS,\text{liver(glu)}}
\]

where \(CSS,\text{plasma(vpa)}\) is the plasma concentration of VPA at steady state, \(CSS,\text{liver(glu)}\) is the concentration of VPA-Glu in the liver at steady state, and \(V_{bile(glu)}\) is the biliary excretion rate of VPA-Glu.

Statistical Method. All results are shown as means ± S.D. Statistical differences in pharmacokinetic parameters between VPA alone and PAPM-treated groups were tested by Student’s \(t\) test. The criterion for statistical significance was \(p < 0.05\).

Results

In Vivo Study. Effects of PAPM on plasma concentration-time profiles of VPA in normal SD rats, nephrectomized rats, and hepatectomized rats. The time courses of the plasma concentration of VPA, with or without PAPM treatment, in normal SD rats and in nephrectomized rats are shown in Fig. 2 and Fig. 3, respectively. VPA rapidly disappeared from plasma in both groups of rats with PAPM treatment. Significant increases in the CLtot as well as a significant reduction in the disappeared from plasma in both groups of rats with PAPM treatment. CLtot and CLm(glu) were 1.4-fold higher respectively, in the PAPM-treated rats than in the control rats. CLbile(glu) was also 1.8-fold higher in the PAPM-treated rats than in the control rats. CLm(glu) values were nearly identical in the PAPM-treated and the control rats. In addition, the contribution of the clearance parameters other than
CL\textsubscript{m(glu)} to \(\text{CL}_{\text{tot}}\) (\(\text{CL}_{\text{tot}}\) minus \(\text{CL}_{\text{m(glu)}}\)), namely the clearance due to other elimination pathways, was not affected by the PAPM treatment. Thus, the increase in \(\text{CL}_{\text{m(glu)}}\) by the PAPM treatment was concluded to be the major reason for the increased \(\text{CL}_{\text{tot}}\) in the PAPM-treated rats.

**In Vitro Study. Effects of PAPM on initial uptake of VPA by rat hepatocytes.** The initial velocity of VPA uptake by rat hepatocytes was linear over a concentration range from 1 to 200 \(\mu\text{M}\) and independent of temperature (Fig. 6). Addition of PAPM at 50 or 200 \(\mu\text{M}\) did not affect the initial uptake.

**Effects of PAPM on plasma unbound fraction of VPA.** As shown in Fig. 7, there was no significant difference in the plasma-unbound fractions of VPA determined in vitro at 50, 100, or 150 \(\mu\text{g/ml}\) between plasma containing PAPM (50 \(\mu\text{g/ml}\)) and the control plasma. In contrast, a clear increase in the plasma-unbound fraction of VPA was observed by addition of salicylic acid (final concentration 250 \(\mu\text{g/ml}\)), a known inhibitor of plasma protein binding of VPA.

**Effect of PAPM on hepatic tissue-unbound fraction of VPA.** As shown in Table 4, addition of PAPM (20 or 200 \(\mu\text{g/ml}\)) did not significantly affect the tissue-unbound fractions of VPA in hepatic cytosol determined in vitro at 25 \(\mu\text{g/ml}\).

**Effect of PAPM on hepatic \(\beta\)-glucuronidase activity toward VPA-Glu.** The concentration of VPA-Glu in the bile, which was used as the substrate solution in this experiment, was 0.415 \(\mu\text{mol/ml}\) (60 \(\mu\text{g/ml}\) as VPA). VPA produced from VPA-Glu by the action of \(\beta\)-glucuronidase in 25\% liver homogenate proportionally increased as a function of incubation time up to 60 min (result not shown). Therefore, the effect of PAPM on hepatic \(\beta\)-glucuronidase activity toward VPA-Glu was investigated after incubation for 60 min as shown in Table 5.

### TABLE 1
Pharmacokinetic parameters of VPA in normal rats, nephrectomized rats, and hepatectomized rats, with or without PAPM treatment

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>S.D.</th>
<th>Nephrectomized</th>
<th>PAPM treatment</th>
<th>Hepatectomized</th>
<th>PAPM treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{CL}_{\text{tot}}) (ml/h/kg)</td>
<td>343.3 ± 62.0* &amp; 0.44 ± 0.09 &amp; 211.6 ± 13.2 &amp; 6</td>
<td>258.8 ± 43.9 &amp; 0.58 ± 0.07 &amp; 218.5 ± 51.4 &amp; 3</td>
<td>125.5 ± 39.5 &amp; 0.58 ± 0.01 &amp; 218.5 ± 51.4 &amp; 3</td>
<td>605.2 ± 62.0* &amp; 0.18 ± 0.01* &amp; 211.6 ± 17.4* &amp; 4</td>
<td>47.4* &amp; 0.07 &amp; 165.5 ± 50.2 &amp; 3</td>
<td>156.0 ± 46.0 &amp; 0.07 &amp; 265.9 ± 25.3 &amp; 3</td>
</tr>
<tr>
<td>(T_{1/2}) (h)</td>
<td>0.44 ± 0.09 &amp; 0.18 ± 0.01* &amp; 211.6 ± 13.2 &amp; 6</td>
<td>0.58 ± 0.07 &amp; 0.27 ± 0.06* &amp; 218.5 ± 51.4 &amp; 3</td>
<td>1.56 ± 0.46 &amp; 2.16 ± 0.70 &amp; 265.9 ± 25.3 &amp; 3</td>
<td>24.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(V_d) (ml/kg)</td>
<td>0.44 ± 0.09 &amp; 0.18 ± 0.01* &amp; 211.6 ± 13.2 &amp; 6</td>
<td>0.58 ± 0.07 &amp; 0.27 ± 0.06* &amp; 218.5 ± 51.4 &amp; 3</td>
<td>1.56 ± 0.46 &amp; 2.16 ± 0.70 &amp; 265.9 ± 25.3 &amp; 3</td>
<td>24.3</td>
<td></td>
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*Values are the mean ± S.D.

n, number of determinations.

* \(P < .01\) by Student’s t-test.

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**FIG. 4.** The plasma concentration-time course of VPA in hepatectomized rats with (C, n = 3) or without (○, n = 3) PAPM treatment.

Hepatectomized rats were prepared by ligating the hepatic artery and hepatic portal vein and VPA (30 mg/kg) was administered intravenously (see details in text).

**FIG. 5.** Typical chromatogram of bile after administration of \(^{14}\text{C}-\text{VPA}\) (A) and the plasma concentration-time course of VPA in rats with a bile duct fistula (B), with (○, n = 3) or without (●, n = 5) PAPM treatment.

Rats were prepared with a bile duct cannulated and collected bile after intravenous administration of \(^{14}\text{C}-\text{VPA}\) (30 mg/kg). Bile sample with ethanol was subjected to TLC with \(n\)-butanol:acetic acid:distilled water (4:1:1; see details in text).
Addition of PAPM (50 or 500 μg/ml) caused no effect on the VPA production from VPA-Glu by liver homogenate.

**Discussion**

The drug interaction between VPA and PAPM is due to the pharmacokinetic interaction, because the marked reduction of trough plasma level of VPA was recognized in every patient (Nagai et al., 1997). The mechanism of the interaction is noteworthy because the physiochemical and pharmacokinetic characteristics of VPA and PAPM are completely different.

**Table 2**

<table>
<thead>
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<th>Proportion of each metabolite in bile</th>
<th>Cumulative recovery</th>
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<tbody>
<tr>
<td>VPA alone</td>
<td>PAPM treatment</td>
</tr>
<tr>
<td>TLC %</td>
<td>% of Dose</td>
</tr>
<tr>
<td>VPA</td>
<td>2.7 ± 1.2a</td>
</tr>
<tr>
<td>BM-2</td>
<td>3.9 ± 0.6</td>
</tr>
<tr>
<td>BM-1</td>
<td>2.9 ± 0.8</td>
</tr>
<tr>
<td>BM-1</td>
<td>3</td>
</tr>
<tr>
<td>BM-2</td>
<td>5</td>
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*The batches of bile collected (90–120 min) were assayed.

**Table 3**

<table>
<thead>
<tr>
<th>Effect of panipenem on bilary excretion of VPA-Glu in rats under steady-state conditions, with or without PAPM treatment</th>
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<tbody>
<tr>
<td>VPA alone</td>
</tr>
<tr>
<td>Css, plasma (vpa) (μg/ml)</td>
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<tr>
<td>Css, liver (glu) (μg/g liver)</td>
</tr>
<tr>
<td>BER (glu) (μg/min/kg)</td>
</tr>
<tr>
<td>CL_{LVE} (ml/h/kg)</td>
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<td>CL_{LVE} (ml/h/kg)</td>
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<td>CL_{LVE} (ml/h/kg)</td>
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<td>CL_{LVE} (ml/h/kg)</td>
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*Values are the mean ± S.D., n = 3.

**Table 4**

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<th>Effect of PAPM on unbound fraction of VPA in hepatic cytosol</th>
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<tbody>
<tr>
<td>Panipenem added</td>
</tr>
<tr>
<td>μg/ml</td>
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<tr>
<td>0</td>
</tr>
<tr>
<td>20</td>
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<tr>
<td>200</td>
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Cytosolic fraction was obtained from 33% rat liver homogenate. VPA was added at 25 μg/ml.

*Values are the mean ± S.D., n = 3.

**Table 5**

<table>
<thead>
<tr>
<th>Effect of PAPM on hydrolysis of VPA-Glu by liver β-glucuronidase</th>
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<tbody>
<tr>
<td>PAPM added</td>
</tr>
<tr>
<td>μg/ml</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>50</td>
</tr>
<tr>
<td>500</td>
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</table>

Bile collected after intravenous administration of VPA to rats was used as the substrate. VPA-Glu in the bile was finally at 0.416 mM and incubated for 60 min with 25% liver homogenate used as β-glucuronidase.

*Values are the mean ± S.D., n = 3.

In a series of in vivo studies, it was found that i.v. administration of PAPM significantly reduces \( T_{1/2} \), but did not alter the maximum plasma concentration \( (C_{max}) \) of VPA after oral administration of VPA to monkey and dog (Ministry of Health and Welfare, Japan, 1996; Nouda and Perez, 1997; Yamamura et al., 1998). In the present study, a similar result was obtained in rat with a significant reduction in AUCinf and a significant increase in CL_{tot} of VPA by PAPM cotreat-
The biochemical mechanism of the interaction between VPA and PAPM has not been elucidated yet, but the following factors are considered as possible reasons for the increased glucuronidation of VPA: 1) enzyme induction of UDP-glucuronosyltransferase (Fig. 8–5) and 2) increased cofactor availability [UDP-glucuronic acid (UDPGA), Fig. 8–5; Rowland and Tozer, 1980].

Repeated administration of anticonvulsant drugs such as carbamazepine is well known to cause the reduction of plasma level of VPA due to enzyme induction (Richens et al., 1976), which generally takes a relatively long time, whereas the reduction of the plasma VPA level due to interaction with PAPM is immediately observed after coadministration (Nagai et al., 1997). Therefore, it is unlikely that the induction of UDP-glucuronosyltransferase explains this drug interaction.

The cofactor availability is considered to be one of the most possible mechanisms for the drug interaction between VPA and PAPM (Fig. 8–5). Because the glucuronidation is a bimolecular...
reaction between the substrate and UDPGA. UDPGA is an essential determinant for the conjugation reaction. As an example of the availability of UDPGA being rate-limiting in glucuronidation, Braun et al. (1997) have demonstrated that pretreatment by GSH-depleting agents causes the enhancement of glycogenolysis, the increase of UDP-glucose, from which UDPGA is produced and the enhancement of ρ-nitrophenol glucuronidation in isolated murine hepatocytes.

In conclusion, the increase in CL_int of VPA by PAPM is mainly due to the increased hepatic intrinsic clearance, especially the enhanced glucuronidation of VPA.

References


Braun L, Kardon T, Puskas F, Csala M, Banhegyi G and Mandl J (1997) Regulation of -nitrophenol glucuronidation in isolated murine hepatocytes. glucose, from which UDPGA is produced and the enhancement of glucuronidation, especially the enhanced CL_int of VPA by PAPM is mainly due to the increased hepatic intrinsic clearance, especially the enhanced glucuronidation of VPA.


