JPP Journal of Pharmacy and Pharmacology

JPP 2001, 53: 823–829

Received October 25, 2000
Accepted February 16, 2001
ISSN 0022-3573

Inhibition by carbapenem antibiotic imipenem of intestinal absorption of valproic acid in rats

Mayumi Torii, Yoshiharu Takiguchi, Fumiko Saito, Miyako Izumi and Masayuki Yokota

Abstract

The concomitant use of carbapenem antibiotics with valproic acid has been prohibited because panipenem induced a decrease in plasma concentration of valproic acid in epileptic patients during valproic acid therapy. To clarify the possible mechanism of the carbapenem–valproic acid interaction, we investigated the effect of imipenem on the pharmacokinetic behaviour of valproic acid in rats. Co-administration of imipenem (30 mg kg^{-1}, i.v.) induced a decrease in the peak plasma concentration of valproic acid after oral administration. However, the imipenem-induced decrease in plasma concentrations of valproic acid was not observed within 60 min after intravenous injection of valproic acid. By utilizing in-situ vascular and luminal perfused small intestine, it was confirmed that absorption of valproic acid from the luminal to the vascular perfusate was decreased in the presence of imipenem (0.5 mM) in the vascular perfusate. The everted gut sac method was used to determine the effect of imipenem on active transport of valproic acid. The accumulation of valproic acid on the serosal side of the intestinal sac against the concentration gradient was reduced by lactic acid that inhibits the carrier-mediated transport of valproic acid across the intestinal brush-border membrane. However, imipenem did not affect the active transport of valproic acid. Therefore, the inhibition by imipenem of valproic acid absorption may be caused by a mechanism different from that of lactic acid. In conclusion, imipenem inhibits the intestinal absorption of valproic acid, which contributes to the decrease in plasma concentration of valproic acid after oral administration.

Department of Clinical Pharmacology, Graduate School of Pharmaceutical Sciences, The University of Tokushima, Tokushima 770-8505, Japan

Mayumi Torii, Yoshiharu Takiguchi, Fumiko Saito, Miyako Izumi, Masayuki Yokota

Correspondence: Y. Takiguchi, Department of Clinical Pharmacology, Graduate School of Pharmaceutical Sciences, The University of Tokushima, 1-78 Sho-machi, Tokushima 770-8505, Japan. E-mail: takiguti@ph2.tokushima-u.ac.jp

Introduction

Valproic acid, an anticonvulsant drug, is widely used for treatment of various forms of epilepsy (Rimmer & Richens 1985). It is rapidly and almost completely absorbed through the gastrointestinal tract, extensively metabolized in the liver and primarily excreted into the bile in a glucuronide conjugate form (Dickinson et al 1979). In pharmacotherapy with valproic acid it is important to maintain plasma concentrations in the therapeutic range of 50–150 μg mL^{-1} (Vajda et al 1978; Covain et al 1982). However, valproic acid is known to interact with concomitantly administered drugs. For example, other antiepileptic drugs, such as phenytoin, carbamazepine and phenobarbital, induce hepatic enzymes for metabolizing valproic acid (Bowdle et al 1979; Sackellares et al 1981) and salicylic acid replaces valproic acid at plasma protein-binding sites (Yu et al 1990), which induce a decrease in the plasma

concentration of valproic acid. Therefore, monitoring of valproic acid concentration in plasma is recommended.

Carbapenem antibiotics have a broad spectrum of antibacterial activity against both Gram-positive and Gram-negative bacteria (Birnbaum et al 1985), and are used frequently in treating various infections. Recently, it has been reported that co-administration of panipenem induced a reduction of plasma concentration of valproic acid in epileptic patients undergoing valproic acid therapy, resulting in the recurrence of epileptic seizures (Nagai et al 1997). Therefore, the concomitant use of carbapenems with valproic acid has been prohibited (Ministry of Health and Welfare, Japan 1996). A similar pharmacokinetic interaction was also found during concomitant therapy with valproic acid and meropenem (De Turck et al 1998). However, the mechanism of the carbapenem–valproic acid interaction is as yet uncertain.

Experimental studies using rats showed that panipenem increased the hepatic clearance of valproic acid (Yamamura et al 1999) and suppressed its enterohepatic recirculation (Kojima et al 1998), which are regarded as possible mechanisms of the drug–drug interaction. Valproic acid was intravenously administered in these studies, whereas it is given orally in patients. Therefore, this study was undertaken to examine the effect of a different carbapenem antibiotic, imipenem, on the plasma concentrations of valproic acid after oral administration of valproic acid, and to determine the possible mechanism of the carbapenem–valproic acid interaction in rats.

Materials and Methods

Materials

Male Sprague-Dawley rats, 250–330 g (Japan SLC, Hamamatus, Japan), were used. The rats were housed under well-controlled conditions at 25°C and were allowed free access to a commercial food and water. The rats were fasted for 12 h before use. All experiments were conducted under the guidance of the Animal Care and Use Committee in the University of Tokushima.

Imipenem–cilastatin (Banyu, Tokyo, Japan) and panipenem–betamipron (Sankyo, Tokyo, Japan) were used in this study in the form of commercial preparations for injection. Valproic acid sodium salt, 2,4-dinitrophenol, dexamethasone and lactic acid were purchased from Sigma Chemicals (St Louis, MO). Horse serum was purchased from BioWhittaker (Walkersville, MD). Other chemicals used were commercially available reagent-grade products.

In-vivo study

Under light anaesthesia with ether, rats were cannulated with a polyethylene tube in the femoral vein for drug administration and in the femoral artery for blood sampling. Then, the rats were placed in Ballman cages and the experiments were started 90 min after awakening.

After 30 mg kg^{-1} imipenem or 125 mg kg^{-1} panipenem was intravenously injected, valproic acid at a dose of 100 mg kg^{-1} was orally administered. The control group was treated with saline in place of the carbapenem antibiotics. In another experiment, a bolus dose of 50 mg kg^{-1} valproic acid was intravenously injected after the treatment with the antibiotics. Blood samples of about 0.5 mL were collected at scheduled intervals after the administration of valproic acid and immediately centrifuged at 1400 *g* for 10 min to separate plasma samples.

The dose of each drug was selected to obtain the maximum drug concentration in plasma equivalent to that observed clinically.

In-situ absorption study

Simultaneous vascular and luminal perfusion of rat small intestine was performed, principally according to the method of Steel & Cousins (1985). Rats were anaesthetized with sodium pentobarbital (50 mg kg^{-1}, i.p.) and fixed on a heating-pad at 37°C.

To isolate blood supply to the small intestine, the blood vessels of the large intestine and pancreas were ligated. The inflow cannula was introduced into the superior mesenteric artery and then perfused with Krebs-Ringer bicarbonate buffer (composition in mM: 120 NaCl, 4.7 KCl, 2.5 $CaCl_2 \cdot 5H_2O$, 1.2 $MgSO_4 \cdot H_2O$, 25 $NaHCO_3$; pH 7.4) containing 5% horse serum, 4.7% high-molecular-weight dextran, 5.6 mM glucose and 600 mM dexamethasone. The portal vein was cannulated for collection of the effluent vascular perfusate. The flow rate of the vascular perfusate was adjusted with a peristaltic pump (SJ-1211, ATTO, Tokyo, Japan) to maintain arterial perfusion pressure at 100 mmHg. The arterial perfusion pressure was measured with a pressure transducer (DX-100 and AP621G, Nihon Kohden, Tokyo, Japan).

The inflow cannula for the intestine was inserted 15 cm distal to the pylorus, and the outflow cannula was placed 15 cm proximal to the ileal–caecal junction. The intestinal segment was then cleaned by perfusion of

25 mL of warm (37°C) luminal perfusate (composition in mM: 15 HEPES, 10 Tris, 5 $NaHCO_3$, 5.6 glucose; pH 7.4). Luminal perfusate containing 6 mM valproic acid was pumped at a rate of 0.5 mL min^{-1} by a second peristaltic pump.

The perfusates were maintained at 37°C and constantly gassed with a mixture of 95% O_2 and 5% CO_2. The intestine was covered with a gauze pad wetted with warm saline. After the experiment, the perfused intestinal segment was excised and the length was measured with a 2-g weight attached to one end. The length of the perfused segment was about 30 cm.

In-vitro absorption study

The everted intestinal sac was prepared according to the modified method described by Binks & Dobrota (1990). After anaesthesia with sodium pentobarbital, the blood supply to the small intestine was ligated. A reproducible region of the small intestine (15 cm distal to the pylorus) was rapidly excised and placed in ice-cold buffer (composition in mM: 145 NaCl, 4.56 KCl, 1.25 $CaCl_2 \cdot 2H_2O$, 5 $NaHPO_4$, 10 glucose; pH 7.4) gassed continuously with a mixture of 95% O_2 and 5% CO_2. The intestine was washed gently and cut into 2-cm lengths. Each segment was gently everted and one end of the segment was tied with a thread ligature. The whole length of the segment was filled with the pre-oxygenated buffer at 37°C containing 1 mM valproic acid (serosal fluid; about 1.2 mL) and then the other end was tied with the second ligature. The everted sacs were immersed in 50 mL of the oxygenated buffer (pH 6.4) at 37°C containing 1 mM valproic acid (mucosal fluid), and incubated for 60 min. Test drugs were included in both mucosal and serosal fluids. After incubation, the mucosal and serosal fluids were collected.

Drug analysis

The concentration of valproic acid was measured by the fluorescence polarization immunoassay method using the TDx/TDxFLx system (Abbott Laboratories, North Chicago, IL). Plasma concentrations of valproic acid were fitted to a bi-exponential equation and pharmacokinetic parameters (i.e. the area under the plasma concentration–time curve (AUC), maximum drug concentration in plasma (C_{max}), half-life ($t_{\frac{1}{2}}$) and total clearance (CL)) were calculated using Phaconet 1 (System Wave, Tokyo, Japan) software.

The glucose concentration was measured by the *o*-toluidine–boric acid method using a glucose assay kit (Wako Co. Ltd., Osaka, Japan).

Statistical analysis

All results are shown as mean ± s.d. Data from the everted sac experiment were statistically analysed by a one-way analysis of variance followed by Scheffe's multiple range test. Comparison between control and the carbapenem-treated groups in pharmacokinetic parameters and the in-situ absorption study was performed by Student's *t*-test. Results were considered significantly different if $P < 0.05$.

Results

In-vivo study

The time-course of the plasma concentration of valproic acid after oral administration in rats is shown in Figure 1. The plasma concentrations were decreased when 30 mg kg^{-1} imipenem was injected just before the valproic acid administration. The pharmacokinetic parameters of valproic acid are listed in Table 1. C_{max} was lower in rats treated with imipenem than in control rats, although it was achieved within 15 min after administration in both groups. A significant decrease in AUC was observed in the imipenem-treated group. The pretreatment with imipenem tended to decrease $t_{\frac{1}{2}}$ and

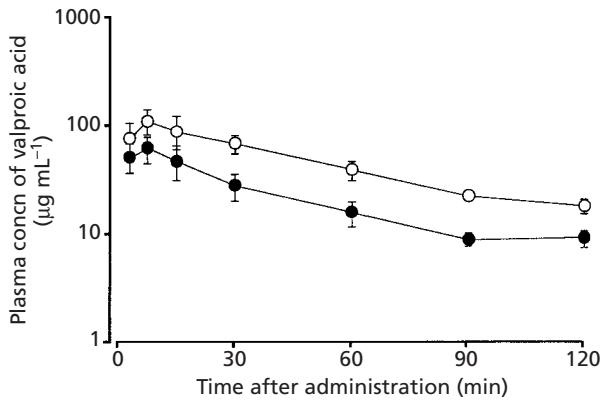

Figure 1 The plasma concentration–time course of valproic acid after oral administration in rats with (●) or without (○) imipenem treatment. Imipenem (30 mg kg^{-1}) was intravenously injected just before the administration of 100 mg kg^{-1} valproic acid. Each point represents the mean ± s.d. of results from 3 rats.

Table 1 Pharmacokinetic parameters of valproic acid after oral administration to rats with or without imipenem treatment.

	C_{max} (μg mL^{-1})	AUC (μg h mL^{-1})	$t_{\frac{1}{2}}$ (h)	CL (L h^{-1})
Control	93.4±9.0	96.2±6.8	0.61±0.03	0.31±0.05
Imipenem	55.2±30.8	41.6±16.4**	0.49±0.12	0.79±0.35

Each value represents the mean±s.d. of results from 3 rats; $^{**}P <$ 0.01 vs control.

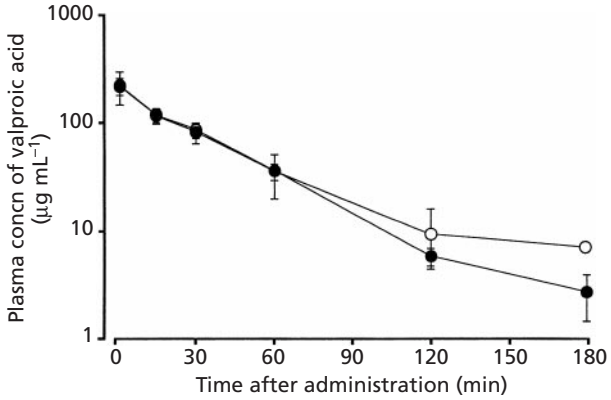

Figure 2 The plasma concentration–time course of valproic acid after intravenous administration in rats with (●) or without (○) imipenem treatment. Imipenem (30 mg kg^{-1}) was intravenously injected just before the administration of 50 mg kg^{-1} valproic acid. Each point represents the mean±s.d. of results from 3 rats.

Table 2 Pharmacokinetic parameters of valproic acid after intravenous administration to rats with or without imipenem treatment.

	AUC (μg h mL^{-1})	$t_{\frac{1}{2}}$ (h)	CL (L h^{-1})
Control	120.6±19.2	0.52±0.12	0.14±0.019
Imipenem	115.4±20.6	0.46±0.03	0.15±0.014

Each value represents the mean±s.d. of results from 3 rats.

increase CL of valproic acid. In contrast, imipenem did not affect the pharmacokinetic behaviour of valproic acid after intravenous injection, except for the plasma concentration after 180 min being lowered (Figure 2 and Table 2).

Pretreatment with panipenem (125 mg kg^{-1}, i.v.) induced a decrease in the plasma concentrations of valproic acid when valproic acid was orally, but not intravenously, administered (Figure 3).

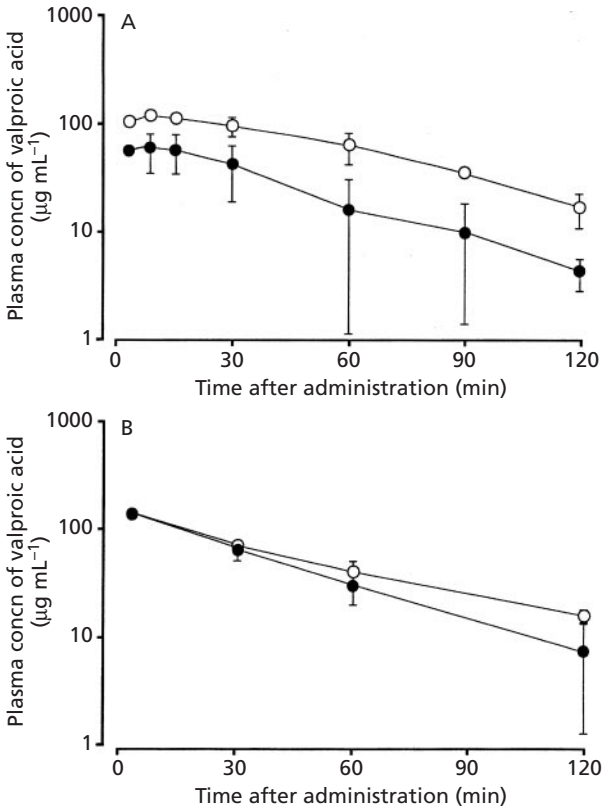

Figure 3 The plasma concentration–time courses of valproic acid after oral (A) and intravenous (B) administration in rats with (●) or without (○) panipenem treatment. Panipenem (125 mg kg^{-1}) was intravenously injected just before the administration of valproic acid (100 mg kg^{-1}, p.o.; 50 mg kg^{-1}, i.v.). Each point represents the mean±s.d. of results from 3 rats.

In-situ absorption study

The absorption of valproic acid from the luminal to the vascular perfusate is shown in Figure 4. The luminal perfusion was initiated at 0 min, and the entire intestine was filled with the perfusate within 2 min. The amount of absorbed valproic acid was decreased throughout the perfusion period in the presence of 0.5 mM imipenem in the vascular perfusate. The total amount of valproic acid absorbed over 40 min was decreased by 42% in the presence of imipenem (15.9±6.6 μg cm^{-1}, n = 6, P = 0.08) as compared with the amount absorbed in the absence of imipenem (27.8±14.0 μg cm^{-1}, n = 6).

In-vitro absorption study

To determine the effect of imipenem on active transport of valproic acid in the rat small intestine, the everted intestinal sac experiment was conducted. The initial

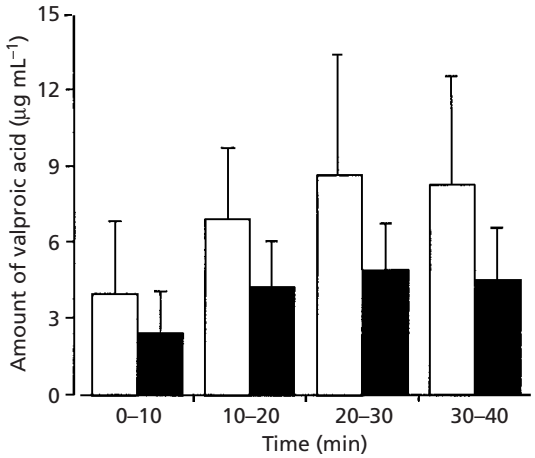

Figure 4 Effect of imipenem on absorption of valproic acid from the luminal to the vascular perfusate in perfused rat intestine. Valproic acid (6 mM) was perfused into the intestinal lumen for 40 min in the presence (■) or absence (□) of 0.5 mM imipenem in the vascular perfusate. Each column represents the mean ± s.d. of results from 6 rats.

Table 3 Effects of imipenem, lactic acid and 2,4-dinitrophenol on serosal-to-mucosal concentration (S/M) ratios for valproic acid and glucose in everted intestinal sacs from rats.

	S/M ratio	
	Valproic acid	**Glucose**
Control	2.03 ± 0.34	1.91 ± 0.20
Imipenem	2.31 ± 0.44	2.28 ± 0.32
Lactic acid	1.67 ± 0.35**	1.91 ± 0.23
2,4-Dinitrophenol	1.35 ± 0.30**	0.91 ± 0.11**

Rat everted intestinal sac was incubated for 60 min at 37°C in medium containing 1 mM valproic acid and 10 mM glucose in the presence of 0.5 mM imipenem (n = 11), 80 mM lactic acid (n = 11), 0.25 mM 2,4-dinitrophenol (n = 10) or saline (control; n = 16). Each column represents the mean ± s.d.; $^{**}P < 0.01$ vs control.

concentrations of valproic acid and glucose were the same on the serosal and mucosal sides of the intestinal sac. After the 60-min incubation period, the concentrations of valproic acid and glucose on the serosal side (S) were higher than those on the mucosal side (M) (i.e. the S/M ratio was greater than unity) (Table 3). The accumulation of valproic acid, as well as glucose, on the serosal side against the concentration gradient was inhibited by 0.25 mM 2,4-dinitrophenol, a metabolic inhibitor, indicating the existence of active transport. The active transport of glucose was used to assess viability of everted intestinal preparations. The S/M ratio of valproic acid was significantly reduced in the presence of 80 mM lactic acid, but it was not changed in the presence of 0.5 mM imipenem. Neither valproic acid nor lactic acid affected the S/M ratio of glucose.

Discussion

This study demonstrated that pretreatment with imipenem, as well as panipenem, induced a decrease in plasma concentrations of valproic acid after oral administration. This finding warns us that such a pharmacokinetic drug interaction can happen in epileptic patients undergoing valproic acid therapy if imipenem is given for treatment of complicated infection, like panipenem (Nagai et al 1997) and meropenem (De Turck et al 1998).

Treatment with a single injection of imipenem or panipenem just before the oral administration of valproic acid induced a decrease in C_{max} and AUC of valproic acid. Valproic acid was rapidly absorbed and C_{max} was achieved within 15 min of administration. On the other hand, when valproic acid was intravenously administered, the carbapenem-induced decrease in plasma concentration of valproic acid was not observed within 60 min of injection. The carbapenem antibiotics are distributed to the small intestine after intravenous injection (Hara et al 1985; Takahagi et al 1991). Therefore, it is considered that the carbapenems may interfere with the intestinal absorption of valproic acid. The in-situ absorption study provided us with supporting evidence that the absorption of valproic acid from the luminal to the vascular perfusate was decreased when imipenem was perfused in the vasculature. Valproic acid is highly excreted in the bile (about 50% of the administered dose) in a glucuronide conjugate form and undergoes enterohepatic recirculation (Dickinson et al 1979). Perhaps imipenem also inhibits the reabsorption of valproic acid, which may cause the decrease in plasma valproic acid concentrations at the late period after the injection of valproic acid. Panipenem was reported to suppress the enterohepatic recirculation of valproic acid (Kojima et al 1998). This effect of panipenem was proposed to be due to a decrease in the number of enteric bacteria that can deconjugate valproic acid glucuronide. However, such an antibacterial action in the intestine may be of little consequence because the biliary excretion of panipenem and imipenem is very limited (Drusano & Standiford 1985; Tanimura et al 1991).

The results obtained from the in-vitro study using the

everted intestinal sac indicated the existence of an energy-dependent process in intestinal valproic acid absorption, which is consistent with the results of Cato et al (1995). Valproic acid is transported across the intestinal brush-border membrane via both proton-coupled monocarboxylic acid specific transport and anion antiport mechanisms (Tamai et al 1997). Recently, a monocarboxylic acid–proton co-transporter was identified in rat and human intestine (Takanaga et al 1995). Lactic acid is also transported by carrier-mediated mechanisms and competitively inhibits the active transport of monocarboxylic acids, including valproic acid (Tamai et al 1995, 1997). In the everted gut study, the accumulation of valproic acid on the serosal side of the intestinal sac against the concentration gradient was inhibited by lactic acid, probably due to the competitive inhibition of the carrier-mediated absorption at the mucosal surface. However, imipenem did not affect the active transport of valproic acid, although it inhibited in-situ valproic acid absorption at the same concentration. Therefore, imipenem seems to inhibit the intestinal absorption of valproic acid by a mechanism different from that of lactic acid. Although further studies are needed to clarify the mechanism for the inhibition by imipenem of intestinal valproic acid transport, the following actions can be considered: inhibition of uptake at the brush-border membrane from the inside of epithelial cells; inhibition of transport across the basolateral membrane into interstitial fluid; and inhibition of transport into blood at vascular endothelial cell. Imipenem is very slightly lipophilic and is hardly absorbed from the intestine (Drusano & Standiford 1985). Therefore, imipenem could not be delivered to intra-tissue and intra-cellular spaces in such an in-vitro condition, which may be a reason for the lack of the effect of imipenem in the everted gut sac study.

Recently, Yamamura et al (1999) reported that panipenem enhanced the glucuronidation of valproic acid in the liver, which is regarded as a possible mechanism for the interaction between valproic acid and panipenem. In their in-vivo study, the plasma concentrations of valproic acid after intravenous injection were significantly decreased throughout the experimental period during the continuous injection of panipenem from 30 min before the valproic acid injection. However, such a significant change in plasma valproic acid concentrations after injection was not found when panipenem was given as a single injection just before the valproic acid administration.

In conclusion, co-administration of imipenem decreased the plasma concentrations of valproic acid after oral administration of valproic acid, as well as panipenem, probably by inhibiting the intestinal absorption of valproic acid.

References

Binks, S. P., Dobrota, M. (1990) Kinetics and mechanism of uptake of platinum-based pharmaceuticals by the rat small intestine. *Biochem. Pharmacol.* **40**: 1329–1336

Birnbaum, J., Kahan, F. M., Kropp, H. (1985) Carbapenems, a new class of beta-lactam antibiotics: discovery and development of imipenem/cilastatin. *Am. J. Med.* **78** (Suppl. 6A): 3–21

Bowdle, T. A., Levy, R. H., Cutler, R. E. (1979) Effects of carbamazepine on valproic acid kinetics in normal subjects. *Clin. Pharmacol. Ther.* **26**: 629–634

Cato, A., Gary, M. P., Kim, L. R. B. (1995) Age-dependent intestinal absorption of valproic acid in the rat. *Pharm. Res.* **12**: 284–290

Covain, A., Gupta, A. K., Jeavons, P. M. (1982) Valproate: monotherapy and polytherapy. *Epilepsia* **23**: 693–720

De Turck, B. J. G., Diltoer, M. W., Cornelis, P. J. W. W., Maes, V., Spapen, H. D. M., Camu, F., Huyghens, L. P. (1998) Lowering of plasma during concomitant therapy with meropenem and amikacin. *J. Antimicrob. Chemother.* **42**: 563–564

Dickinson, R. G., Harland, R. C., Llias, A. M., Rodgers, P. M., Kaufman, S. N., Lynn, R. K., Gerber, N. (1979) Disposition of valproic acid in the rat: dose-dependent metabolism, distribution, enterohepatic recirculation and choleretic effect. *J. Phamacol. Exp. Ther.* **211**: 583–595

Drusano, G. L., Standiford, H. C. (1985) Pharmacokinetic profile of imipenem/cilastatin in normal volunteers. *Am. J. Med.* **78** (Suppl. 6A): 47–53

Hara, K., Shibata, M., Kobayashi, H., Hamajima, K., Hayase, K. (1985) Physiological disposition of imipenem and cilastatin sodium in rats. *Chemotherapy* (*Tokyo*) **33** (Suppl. 4): 290–304

Kojima, S., Nadai, M., Kitaichi, K., Wang, L., Nabeshima, T., Hasegawa, T. (1998) Possible mechanism by which the carbapenem antibiotic panipenem decreases the concentration of valproic acid in plasma in rats. *Antimicrob. Agents Chemother.* **42**: 3136–3140

Ministry of Health and Welfare, Japan (1996) *Adverse Reactions of Drugs*. No. 137. Tokyo

Nagai, K., Shimizu, T., Togo, A., Takaya, M., Yokomizo, Y., Sakata, Y., Matsuishi, T., Kato, H., (1997) Decrease in serum levels of valproic acid during treatment with a new carbapenem, panipenem/betamipron. *J. Antimicrob. Chemother.* **39**: 295–296

Rimmer, E. M., Richens, A. (1985) An update on sodium valproate. *Pharmacotherapy*. **5**: 171–184

Sackellares, J. C., Sato, S., Dreifuss, F. E., Penry, J. K. (1981) Reduction of steady state valproate levels by other antiepileptic drugs. *Epilepsia* **22**: 437–441

Steel, L., Cousins, R. J. (1985) Kinetics of zinc absorption by luminally and vascularly perfused rat intestine. *Am. J. Physiol.* **248**: G46–G53

Takahagi, H., Matsushita, Y., Hiraota, T., Shigeta, M., Muramatsu, S., Nakajima, E., Kawahara, Y. (1991) Metabolic studies on panipenem/betamipron distribution, metabolism and excretion of panipenem/betamipron in rats and dogs. *Chemotherapy* (*Tokyo*) **39** (Suppl. 3): 197–225

Takanaga, H., Tamai, I., Inaba, S., Sai, Y., Higashida, H., Yamamoto, H., Tsuji, A. (1995) cDNA cloning and functional characterization of rat intestinal monocarboxylate transporter. *Biochem. Biophys. Res. Commun.* **217**: 370–377

Tamai, I., Takanaga, H., Maeda, H., Sai, Y., Ogihara, T., Higashida, H., Tsuji, A. (1995) Participation of a proton-cotransporter, MCT1, in the intestinal transport of monocarboxylic acids. *Biochem. Biophys. Res. Commun.* **214**: 482–489

Tamai, I., Takanaga, H., Maeda, H., Yabuuchi, H., Sai, Y., Suzuki, Y., Tsuji, A. (1997) Intestinal brush-border membrane transport of monocarboxylic acids mediated by proton-coupled transport and anion antiport mechanisms. *J. Pharm. Pharmacol.* **49**: 108–112

Tanimura, H., Ochiai, M., Sugimoto, T., Aoki, M., Nakamura, K., Nakatsuka, G., Kobayashi, Y. (1991) Tissue concentrations and clinical efficacy of panipenem/betamipron in surgical infections. *Chemotherapy* (*Tokyo*) **39** (Suppl. 3): 585–595

Vajda, F. J. E., Drummer, O. H., Morris, P. M., McNeil, J. J., Bladin, P. F. (1978) Gas chromatographic measurement of plasma levels of sodium valproate: tentative therapeutic range of a new anti-convulsant in the treatment of refractory epileptics. *Clin. Exp. Pharmacol. Physiol.* **5**: 67–73

Yamamura, N., Imura, K., Naganuma, H., Nishimura, K. (1999) Panipenem, a carbapenem antibiotic, enhances the glucuronidation of intravenously administered valproic acid in rats. *Drug Metab. Dispos.* **27**: 724–730

Yu, H.-Y., Shen, Y.-Z., Sugiyama, Y., Hanano, M. (1990) Effects of salicylate on pharmacokinetics of valproic acid in rats. *Drug Metab. Dispos.* **18**: 121–126