

# Reduced Valproic Acid Serum Concentrations Due to Drug Interactions With Carbapenem Antibiotics: Overview of 6 Cases

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**Background:** The plasma concentrations of valproic acid (VPA) are known to decrease during the concomitant administration of carbapenem antibiotics, such as meropenem, imipenem, and ertapenem. This study summarizes 6 cases of drug–drug interactions between VPA and carbapenem antibiotics.

**Methods:** To investigate the onset and severity of the reductions in the concentration of VPA in patients with or without the coadministration of carbapenem antibiotics, the authors performed a retrospective evaluation of therapeutic drug monitoring (TDM) reports that described a decrease in the serum concentrations of VPA during the concomitant use of carbapenem antibiotics from January 2008 to December 2010 in the Seoul National University Hospital. The evaluated TDM reports included 6 cases. The decrement ratio of the VPA serum concentration was calculated from the TDM reports, and the change in the half-life of the VPA was also estimated.

**Results:** Six cases presented with changes in the VPA serum concentration before and after the administration of carbapenem antibiotics. (Three cases were treated with meropenem, 2 were treated with ertapenem, and 1 was treated with imipenem.) The VPA concentrations reduced by (mean  $\pm$  SD) 88.7  $\pm$  5.3% (3 cases of meropenem), 74.0  $\pm$  9.8% (2 cases of ertapenem), and 73.3% (1 case of imipenem), respectively, and the half-life of VPA reduced by 80.1  $\pm$  9.0%, 64.4  $\pm$  24.2%, and 50.6%, respectively.

**Conclusion:** The interaction between VPA and carbapenem antibiotics caused decreases in the VPA serum concentrations; the extent of this decrease was greater in the meropenem-treated patients than in the imipenem-treated or ertapenem-treated cases. Because the therapeutic effect of VPA depends on its serum concentration, it should be recognized that there may be a loss of seizure control in patients using VPA with carbapenem antibiotics.

**Key Words:** valproic acid, carbapenem antibiotics, drug–drug interaction, therapeutic drug monitoring

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## INTRODUCTION

Valproic acid (VPA) is widely used as a first-line treatment for various types of epilepsy. Since Meunier first described the antiepileptic effects of VPA in 1963,<sup>1</sup> it has been established as a broad-spectrum antiepileptic drug. A plasma VPA concentration of 50–100 mcg/mL is recommended for the treatment of epilepsy, and there is an increased risk for seizures when the maintenance concentration is less than the recommended concentration.<sup>2</sup> VPA has a bioavailability of more than 80% and mostly metabolized via glucuronidation. VPA is also partly metabolized by mitochondrial  $\beta$ -oxidation and microsomal  $\omega$ -hydroxylation. Less than 3% of VPA is excreted in the urine.<sup>1</sup>

Antibiotics in the carbapenem class of drugs exhibit the broadest spectrum of antibacterial activity of the  $\beta$ -lactam antibiotics. Furthermore, these drugs are active against gram-negative, gram-positive, aerobic, and anaerobic bacteria and resistant to  $\beta$ -lactamase activity.<sup>3,4</sup> Because carbapenem antibiotics also have a high tissue permeability, they are readily dispersed into body fluids, including cerebrospinal fluid.<sup>4</sup> As such, these antibiotics are widely used to treat infections of the central nervous system.

VPA interacts with antiepileptic drugs and other medications, and its interactions with carbapenem antibiotics are well known. Nagai et al<sup>5</sup> was the first to report a decrease in the serum VPA concentration in patients receiving both panipenem and VPA. Subsequently, De Turck et al<sup>6</sup> reported decreases in the VPA concentration (from 50–100 to near 0 mcg/mL) after meropenem coadministration. Llinares et al<sup>7</sup> also reported 3 cases of drug–drug interactions between VPA and imipenem or meropenem. Since publication of these reports, similar cases exhibiting a decrease in the serum VPA concentration due to carbapenem antibiotics have been reported.

This study analyzed patients who received both carbapenem antibiotics and VPA and admitted into the Seoul National University Hospital between January 2008 and December 2010. The VPA measurements were monitored through therapeutic drug monitoring (TDM) service and the

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**TABLE 1.** Summary of Patient Information and the Administration of the Concomitant Drugs

Case no.	Sex	Age	VPA Dose (mg/day)	Administration Route of VPA	Carbapenem (mg/day)	Administration Route of Carbapenem	Duration of the Concomitant Therapy (D)	Clinical Outcome (Seizures)
1	M	58	1200	PO	Meropenem, 2000	IV	6	No
2	M	19	1800	PO	Meropenem, 9000 for 1 day → 6000 for 3 days*	IV	4	No
3	F	15	900	PO	Meropenem, 6000	IV	6	No
4	F	50	1680	PO	Ertapenem, 1000	IV	7	No
5	M	69	1980 for 4 days* → 1800 for 9 days → 2400 for 3 days → 3200 for 5 days	PO IV IV IV	Ertapenem, 1000	IV	20	Yes
6	F	56	720	PO	Imipenem, 4000	IV	25	No

\*Change of dosing regimen (amount administered per day).

Arrow signifies order of changes of dosing regimen; F, female; IV, intravenous; M, male; PO, per oral.

changes in the patients' VPA concentrations and elimination half-lives ( $t_{1/2}$ ) were analyzed. In addition, possible mechanisms contributing to the reduction in VPA concentrations are discussed by comparing the present data with previous reports examining the drug interactions between carbapenem and VPA.

## MATERIALS AND METHODS

### Subjects

Patients who met the following criteria were included in the study: (1) patients who were admitted to the Seoul National University Hospital between January 1, 2008, and December 31, 2010; (2) patients who received VPA treatment to control or prevent seizures; (3) patients who were tested regularly to check their serum VPA concentrations using the TDM service; and (4) patients who received carbapenem antibiotic treatments to control their infections. Furthermore, of the patients who received VPA treatment, only those whose drug concentrations had already reached a steady state before carbapenem antibiotic treatment had commenced (as confirmed by the TDM) participated in the study. The following patients were excluded: (1) patients who stopped VPA treatment before receiving carbapenem antibiotics; (2) patients whose blood samples were not collected at the trough concentration (to measure valproate concentrations); (3) patients who concomitantly used drugs that are known to interact with VPA; and (4) patients who showed clinically significant increases in liver function tests.

### Data Collection and Analysis

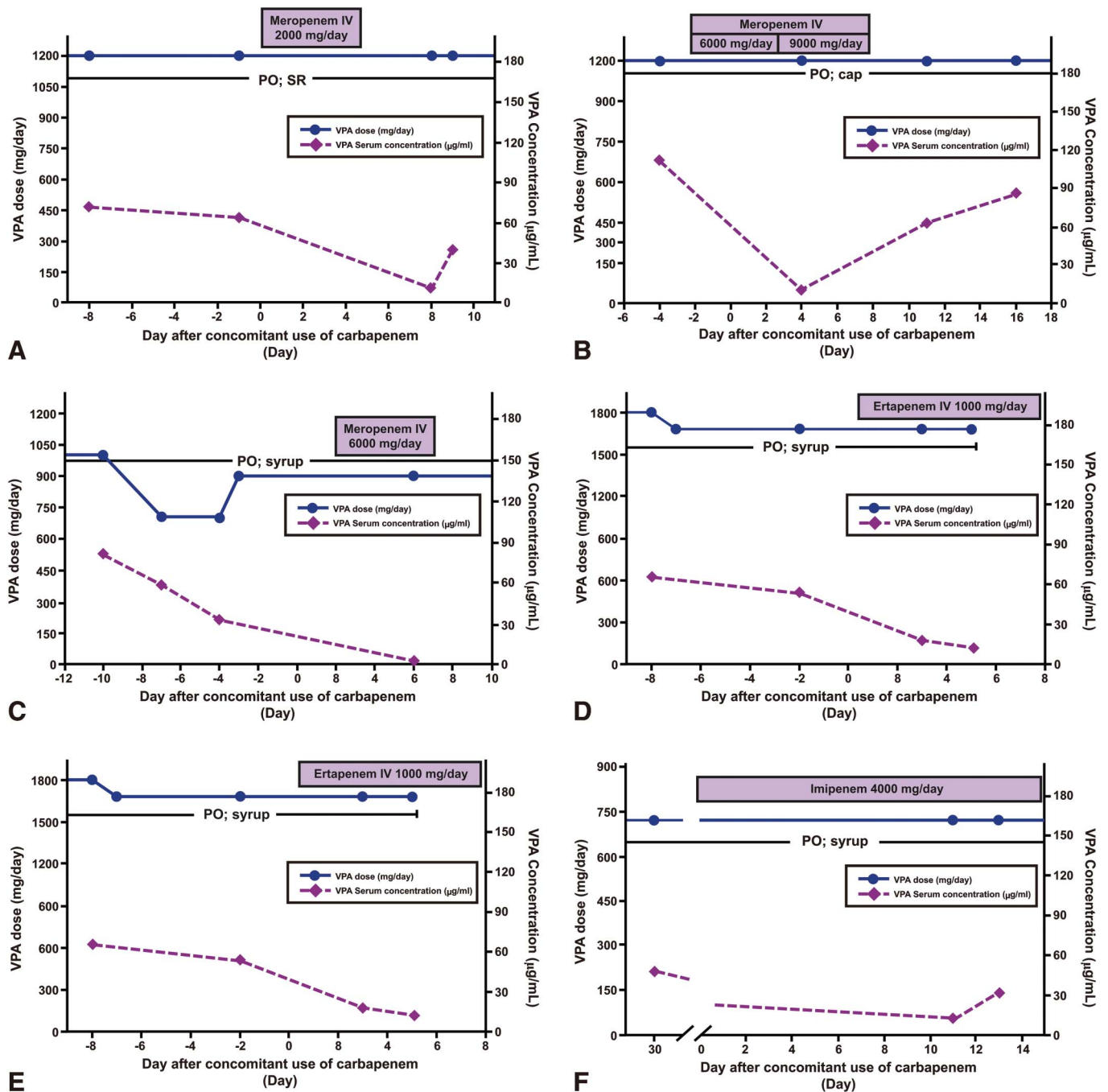
For the TDM service, blood samples were collected in serum-separating tubes at the trough concentration, and the serum concentration of VPA was measured using a fluorescence polarization immunoassay method with a Cobas Integra analyzer (Roche Diagnostics, Basel, Switzerland). Serum concentrations of VPA were recorded, and concentration changes were analyzed according to the TDM service in the electronic medical record system. All the medical information of the patients was collected during the entire period of admission, and the dose

and duration of VPA administration and concomitant carbapenem use were analyzed. To evaluate whether the change in the VPA serum concentration was related to any changes in its pharmacokinetic profile, its half-life ( $t_{1/2}$ ) was calculated using the ABBOTTBASE pharmacokinetic system software (version 1.10/1995; Abbott Laboratories, Irving, TX), and the changes in the volume of distribution and clearance were assessed. To investigate the relationship between the VPA serum concentration and the type of carbapenem antibiotic used, the degree of the change in the VPA serum concentration was also analyzed depending on the drug type that was concomitantly administered with VPA.

## RESULTS

Of the patients who were treated with VPA during the surveyed 36-month period, 8 received carbapenem antibiotics and had their VPA concentrations continuously checked via TDM. Two patients were excluded because one patient received carbapenem antibiotics before VPA and the other patient had no VPA concentration before receiving the carbapenem antibiotics. Thus, the study involved 6 participants (3 males and 3 females) who were between 15 and 69 years of age. The patients received various types of carbapenem antibiotics, such as 3 patients received meropenem, 1 patient was treated with imipenem, and 2 others were treated with ertapenem. The patient information was analyzed during the study and is shown in Table 1.

The duration of the concomitant use of both drugs ranged from 4 days to 25 days. The lowest concentration of VPA occurred between day 4 and day 11 (Table 1; Fig. 1). The VPA concentrations in individual patients were reduced by 67.0% to 92.8%, and the average reductions according to the different carbapenem antibiotics were (mean  $\pm$  SD) 88.7  $\pm$  5.3% (the 3 cases of meropenem), 74.0  $\pm$  9.8% (the 2 cases of ertapenem), and 73.3% (the single case of imipenem). Overall, the VPA concentration decreased by an average of 81.2% compared with the concentration observed before the carbapenem antibiotic treatment (Fig. 1; Table 2). The changes in



**FIGURE 1.** The individual serum VPA concentration changes according to the drug regimen. VPA with meropenem (case 1) (A), VPA with meropenem (case 2) (B), VPA with meropenem (case 3) (C), VPA with ertapenem (case 4) (D), VPA with ertapenem (case 5) (E), and VPA with imipenem (case 6) (F). The time scale along the horizontal axis is relative to the duration of the concomitant VPA and carbapenem exposures.

the ratio of the body weight–corrected concentration of VPA to the dose of VPA are also presented in Table 2.

When a change in the VPA concentration was observed, the half-life of VPA was evaluated for each patient. The VPA half-life reduced by 47.3% to 90.2%, and the reduction for each carbapenem antibiotic was  $80.1 \pm 9.0\%$  (the 3 cases of meropenem),  $64.4 \pm 24.2\%$  (the 2 cases of ertapenem), and 50.6% (the

single case of imipenem). In each case, the half-life of VPA decreased with the use of the carbapenem antibiotics (Table 2).

### DISCUSSION

Regardless of the patients' sex or age, the major findings of the present study are that the VPA concentration

**TABLE 2.** Summary of Cases Undergoing Concurrent Therapy With VPA and Carbapenem

Case No.	Carbapenem	VPA Concentration Without Carbapenem (mcg/mL)*	VPA Concentration With Carbapenem (mcg/mL)†	Serum Concentration Change (%)	VPA Half-life Without Carbapenem (hr)	VPA Half-life With Carbapenem (hr)	Concentration: Dose Ratio of VPA Without Carbapenem (mcg/mL:mg/kg)	Concentration: Dose Ratio of VPA With Carbapenem (mcg/mL:mg/kg)
1	Meropenem	64.3	11.1	-82.7	11.6	2.6	3.4	0.6
2	Meropenem	112.0	10.7	-90.5	26.4	2.6	7.6	0.7
3	Meropenem	33.1	2.4	-92.8	9.5	2.6	2.0	0.1
4	Ertapenem	66	12.6	-80.9	9.2	1.7	2.1	0.4
5	Ertapenem	68.1	22.5	-67.0	7.4	3.9	2.5	0.9
6	Imipenem	47.2	12.6	-73.3	8.5	4.2	2.1	0.6

\*VPA concentration before administration of carbapenem.

†The minimum concentration of VPA after administration of carbapenem.

decreased by 67.0% to 92.8% compared with the baseline after treatment with carbapenem antibiotics and that these decreases occurred concomitantly with changes in the half-life of VPA, which involved changes in the clearance and volume of distribution. Of the 3 types of antibiotics examined in this study, meropenem was the most potent in reducing both the concentration and half-life of VPA. However, the individual effects of these carbapenems on VPA concentration must be interpreted with caution.

Numerous case studies have reported an exacerbation of seizures during the concomitant use of carbapenem and VPA. For example, Coves-Orts et al<sup>8</sup> reported that the VPA concentration decreased from 52.5 mcg/mL to 7.0 mcg/mL after meropenem administration and led to the development of seizures in adults.<sup>8</sup> In addition, Santucci et al<sup>9</sup> reported the worsening of seizures in a child who used concomitant meropenem and VPA. In the present study, 1 of the patients (case 5) experienced seizures, although the daily dose of VPA was increased nearly 2-fold because of decreased VPA concentrations; this result suggests that the decrease in the VPA concentration induced by carbapenem antibiotics may cause seizures. When no antibiotic options except for carbapenem are available for patients using VPA, a dosing adjustment and close monitoring are generally recommended.<sup>10</sup> However, the findings indicated that the adjusted dose of VPA was limited in its ability to control seizures.

Although decreases in the VPA serum concentration caused by the drug-drug interactions between VPA and panipenem,<sup>5</sup> meropenem,<sup>7</sup> and imipenem<sup>6</sup> have been reported, the exact pharmacological mechanism underlying these interactions remains unclear; 4 hypotheses have been proposed.<sup>11</sup> The first hypothesis concerns the mechanisms related to the absorption of VPA.

Carbapenem antibiotics seem to repress VPA absorption from the intestinal lumen by inhibiting the intestinal transporter of VPA.<sup>12</sup> In addition, the enterohepatic recirculation of VPA may be inhibited due to the activity of carbapenem antibiotics against  $\beta$ -glucuronidase, which is produced by normal gut flora and mediates the conversion of VPA-glucuronide to VPA.<sup>13,14</sup> Another mechanism is the enhanced metabolism of VPA after increased glucuronidation in the

liver by increasing uridine diphosphate glucuronic acid concentrations.<sup>15</sup> The final mechanism is the decrease in the VPA serum concentration due to the increased distribution of VPA into red blood cells (RBCs) after the use of carbapenem antibiotics.<sup>16</sup>

Although it is difficult to conclude the mechanism from the findings of the present study, the results suggest a causative mechanism. In case 1, the VPA concentration increased rapidly up to 4-fold 3 days after stopping meropenem administration. Previous reports have claimed that carbapenem administration may affect the normal gut flora,<sup>17</sup> which play significant roles in the enterohepatic recirculation of VPA. However, the observed recovery time after stopping imipenem coadministration was too short to allow a reversion of the changes in the normal gut flora. Thus, it seems unlikely that enterohepatic recirculation was reduced in this case. In case 5, a reduction in VPA concentration was observed even when it was administered intravenously. Therefore, it is unlikely that the carbapenem antibiotics directly restricted VPA absorption. Hence, we conclude that an increase in the clearance of VPA or an increased distribution of VPA into RBCs contributed to the results of this study. The above deductions are also applicable to the changes in the half-life of VPA. These findings imply that carbapenem may increase the elimination of VPA or the distribution of VPA into RBCs. However, given the limitations of this study, it is difficult to confirm which mechanism was involved in the observed effects because the VPA concentration was measured only in the serum, which could allow for a measured reduction in the serum concentration even when the total amount of the drug remained unchanged.

## CONCLUSIONS

In conclusion, a decrease in the VPA serum concentration due to drug interaction with carbapenem antibiotics was observed. Notably, decreases in the VPA serum concentration caused by carbapenem antibiotics can result in the failure of seizure control. Therefore, the concomitant administration of VPA and carbapenems should be avoided because dosing adjustments have limited efficacy for seizure control.



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