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Case Report

Interaction between valproic acid and carbapenems: Case series and literature review

Ming-Chia Lee [a], Yi-Hsuan Sun [a], Chih-Hsin Lee [b,c,d], An-Jan Wu [a], Ta-Wei Wu [a,*]

[a] Department of Pharmacy, Buddhist Tzu Chi General Hospital, Taipei Branch, New Taipei City, Taiwan
[b] Graduate Institute of Biomedical Electronics and Bioinformatics, National Taiwan University, Taipei, Taiwan
[c] Department of Internal Medicine, Buddhist Tzu Chi General Hospital, Taipei Branch, New Taipei City, Taiwan
[d] School of Medicine, Tzu Chi University, Hualien, Taiwan

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ABSTRACT

Several case reports and retrospective studies have indicated that carbapenems decrease the serum concentration of valproic acid (VPA), thus decreasing its therapeutic activity. This study evaluates a potential drug interaction between VPA and carbapenems in a regional hospital. This retrospective observational study was performed over a 14-month period from January 2010 to February 2011. Patients concurrently receiving VPA and carbapenems who had at least two serially measured concentrations of serum VPA prior to, during, or after this combined treatment were included. Patients whose serum samples for VPA were drawn within 2 hours after VPA administration who had severe liver impairment or who received other drugs that could potentially interact with VPA were excluded from the study. The serum levels and therapeutic activities of VPA during coadministration of carbapenems were recorded and evaluated. Nine VPA-treated patients were identified who concomitantly received meropenem ($n = 5$), ertapenem ($n = 3$), or imipenem ($n = 1$). Mean serum VPA trough levels during combined treatment decreased by 76.3% (from 55.6 ± 22.9 μg/mL to 13.2 ± 6.1 μg/mL) from values before carbapenem treatment. However, only one patient experienced seizures after a combination of VPA and carbapenems. The coadministration of VPA and carbapenems resulted in decreased trough concentrations of VPA. Clinicians should be aware of this potential interaction and closely monitor serum VPA levels and possible failure to control seizures with the concomitant use of carbapenems.

1. Introduction

Valproic acid (VPA) is widely used in the treatment of epileptic seizures and status epilepticus. A VPA serum concentration of 50–150 mg/L has been reported to be acceptable for therapeutic effects [1]. Several case reports and retrospective studies have reported an interaction between VPA and carbapenem antibiotics [2–19] leading to a rapid decline in the serum VPA concentration and, in some cases, myoclonia or seizures (Table 1) [2–15,18,19]. We report a possible interaction between VPA and carbapenem antibiotics resulting in reduced serum VPA concentrations in nine patients.

2. Case report

We performed this retrospective observational study over a 14-month period from January 2010 to February 2011 to assess potential drug interactions between VPA and carbapenem antibiotics including meropenem, ertapenem, and imipenem. Patients concurrently receiving VPA and carbapenems who had at least two serially measured concentrations of serum VPA prior to, during, or after this combined treatment were included. Patients whose serum samples for VPA were drawn within 2 hours after VPA administration, who had severe liver impairment, or who received other drugs that could potentially interact with VPA were excluded from this study. Drugs that could potentially interact with VPA included phenobarbital, phenytoin, carbamazepine, topiramate, acyclovir, rifampin, ritonavir, ethosuximide, isoniazide, and felbamate. The serum levels and therapeutic activities of VPA during coadministration of carbapenems were recorded and evaluated. The average drop in serum VPA levels before and during coadministration of carbapenems was tested using the Wilcoxon signed-rank test.

Conflict of interest: none.

* Corresponding author. Department of Pharmacy, Buddhist Tzu Chi General Hospital, Taipei Branch, 289, Jianguo Road, New Taipei City, Taiwan. Tel.: +886 2 6628 9779x8900; fax: +886 2 6628 5288.
E-mail address: p8561825@yahoo.com.tw (T.-W. Wu).

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Table 1
Overview of published case reports.

References	Age, (year)	Daily VPA dose	Type of carbapenem	Effect on VPA concentration, (%)	Seizure attack after combination
Nagai (1997) [2]	10	8.3 mg/kg tid	panipenem	↓93.5	yes, on day 13
	8	500 mg	panipenem	↓95	no
De Turck (1998) [3]	65	1200 mg	meropenem	↓63.6	yes, on day 2
	57	unknown	meropenem	↓88.6	no
Yamagata (1998) [4]	3	35 mg/kg/day	panipenem	↓65	yes, on day 3
	22	32 mg/kg/day	panipenem	↓76	yes, on day 2
	4	25 mg/kg/day	panipenem	↓58.5	no
Llinares (2003) [5]	28	1600 mg	imipenem	↓70	no
	71	1500 mg	meropenem	↓75	yes, on day 9
	24	1600 mg	meropenem	unknown	no
Nacarkucuk (2004) [6]	14	50 mg/kg/day	meropenem	↓47.5	no
	7 month	75 mg/kg/day	meropenem	↓75.5	no
	14 month	75 mg/kg/day	meropenem	↓84.7	no
Clause (2005) [7]	30	3600 mg/day	meropenem	↓72	no
	77	24 mg/kg/day	meropenem	unknown	no
Coves-Orts (2005) [8]	21	1000 mg	meropenem	↓20.1	yes, on day 2
Santucci (2005) [9]	9.5	600 mg	meropenem	↓64	yes, on day 5
Cabanes (2006) [10]	80	1100 mg	ertapenem	↓49	no
Fudio (2006) [11]	55	1500 mg	meropenem	↓85	yes, on day 5
Spriet (2007) [12]	60	32 mg/kg/day	meropenem	↓68	no
	54	28 mg/kg/day	meropenem	↓56	no
Lunde (2007) [13]	41	2000 mg/day	ertapenem	↓84.7	yes, on day 7
Lee (2007) [14]	57	900 mg/day	panipenem	↓74	yes, on day 9
	56	900 mg/day	meropenem	↓91	no
	65	1200 mg/day	Imipenem	↓70	no
	79	1200 mg/day	meropenem	↓88	no
	80	1080 mg/day	meropenem	↓88	no
	51	1000 mg/day	imipenem	↓29	no
	28	1200 mg/day	imipenem	↓34	no
		1200 mg/day	meropenem	↓89	no
Gu (2009) [15]	85	800 mg	meropenem	↓72	no
				↓74	yes, on day 10
Liao (2010) [18]	47	24 mg/kg/day	ertapenem	unknown	no
	72	25 mg/kg/day	ertapenem	↓32.1	yes, on day 7
Hellwig (2011) [19]	54	750 mg	doripenem	↓62	unknown
	54	3750 mg	doripenem	↓69	unknown

Over the 14-month period of this study, 80 patients who received VPA and carbapenem antibiotics including meropenem, ertapenem, and imipenem were identified by a computerized file system. Patients who did not have measurements of the serum VPA concentration before the combined treatment (n = 56), and those who were receiving medications which could potentially interact with VPA (n = 15) were excluded. Only nine VPA-treated patients who concomitantly received meropenem (n = 5), ertapenem (n = 3), or imipenem (n = 1) met the inclusion criteria (Table 2). The ratio of men to women was 4:5, and the mean age was 73.0 ± 14.6 years. VPA was given for treatment of seizures (n = 8) and bipolar disorder (n = 1). The mean daily VPA dose was 1.04 ± 0.34 g. Fig. 1 summarizes the data on the mean trough VPA concentrations of all patients before, during, and after discontinuing of carbapenems. The mean serum concentration of VPA was 55.6 ± 22.9 μg/mL (range 29.8–98.6 μg/mL) before carbapenem treatment and 13.2 ± 6.1 μg/mL (range <3–22.41 μg/mL) during carbapenem treatment, representing an average drop of 76.3% (p = 0.008). However, only one patient experienced seizures during or after the combined treatment. During VPA and carbapenem treatment, one patient received 0.8 g as an emergency loading dose. The VPA doses for two patients were adjusted from 1.2 g to 1.8 g and 0.8 g to 1.2 g; however, this did not increase their serum VPA concentrations. The serum VPA concentration was obtained on the first day of combined treatment in one patient, and 4 to 9 days after the beginning of treatment in the other patients. Unfortunately, serum VPA concentrations were not obtained for all patients after discontinuation of carbapenems. After discontinuing carbapenem treatment, the serum VPA concentration increased from 11.6 mg/dL to 62.1 mg/dL on day 8 in one patient, and from 18.2 mg/dL to 49 mg/dL on day 12 in another patient.

Table 2
Demographic characteristics of our nine patients.

Patient	Age, y	Sex	Daily VPA Dose	Type of Carbapenem	Duration of concurrent use, days	Effect on VPA concentration, %	Outcome
1	88	F	800	meropenem	6	↓79	No acute seizure
2	87	M	1600	meropenem	6	↓68	No acute seizure
3	69	M	1200	meropenem	3	↓88	Seizure on day 4
4	54	M	1000	meropenem	9	↓90	No acute seizure
5	75	F	1200	meropenem	8	↓67	No acute seizure
6	47	F	1200	ertapenem	7	↓81	No acute seizure
7	85	M	1200	ertapenem	13	↓64	No acute seizure
8	82	F	800	ertapenem	12	↓85	No acute seizure
9	70	F	400	imipenem	4	↓49	Bipolar well-controlled

VPA = Valproic acid.

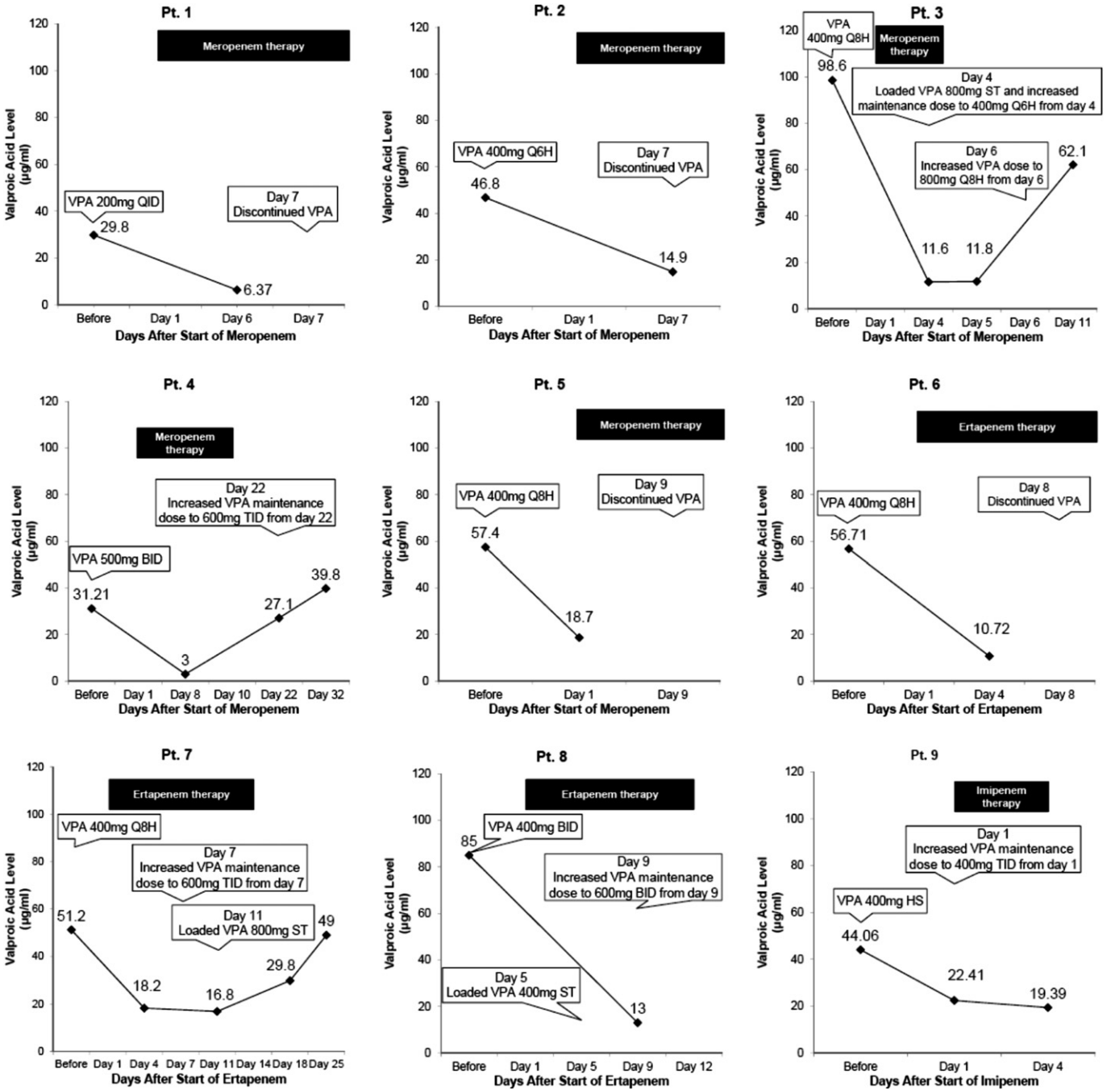

Fig. 1. The serum valproic acid (VPA) concentrations of 9 patients decreased after carbapenem was started. The serum VPA concentrations of patients 3, 4, and 7 increased after carbapenem was discontinued.

3. Discussion

Valproic acid, an anticonvulsant, is commonly used to treat various forms of epilepsy. The main metabolic pathways of VPA include N-glucuronidation, mitochondrial β-oxidation and cytochrome P-450 (CYP) microsomal oxidation [20]. CYP isoenzyme-inducing drugs such as phenytoin, carbamazepine, and phenobarbital decrease serum VPA concentrations [21]. Since 1997, several case reports have been published indicating marked reductions in serum VPA concentrations and, in some cases, breakthrough seizures, during concomitant VPA and carbapenem treatment (Table 1) [2–17,19]. In these reports, VPA concentrations fell within about 1 to 7 days of initiation of carbapenem therapy and recovered completely within 3 days to 2 weeks after discontinuation of carbapenem. Additionally, results of a retrospective study of 36 patients revealed that the mean serum VPA concentration decreased from 50.8 ± 4.5 μg/mL to 9.9 ± 2.1 μg/mL following meropenem administration, remained low for 7 days, and then gradually increased 8 to 14 days after discontinuation of meropenem, reaching values comparable to those before initiation of meropenem [16]. The pattern of a reduced VPA concentration during concomitant carbapenem treatment was similar between our patients and previous reports, suggesting that the interaction between VPA and carbapenem antibiotics is a class effect.

The mechanism of the interaction between carbapenems and VPA has been explored in several animal studies but has yet to be fully elucidated. Possible mechanisms include interference with VPA metabolism, alterations in the intestinal absorption of VPA, and a shift in the distribution of VPA (Table 3) [22]. From an enzymatic interference perspective, Yokogawa et al indicated that meropenem accelerated the glucuronidation of VPA to VPA glucuronide (VPA-G), and inhibited the hydrolysis (deconjugation) of VPA-G back to the parent compound, thus increasing the clearance of VPA and VPA-G [23]. Yamamura et al examined the interaction between panipenem and valproic acid in rats. They showed that panipenem significantly increased hepatic uridine diphosphate (UDP)-glucuronic acid levels by about 1.7-fold ($p < 0.05$) along with an increase in VPA-glucuronide formation. Furthermore, this study also indicated that panipenem does not cause enzyme induction or allosteric activation of UDP-glucuronosyltransferases, enzymes responsible for the glucuronidation of VPA, but most likely increases UDP-glucuronic acid levels [24]. However, Nakajima et al found no correlation between glucuronidation acceleration and the levels of UDP-glucuronic acid in monkeys and rats, and suggested that carbapenem antibiotics greatly inhibit the hydrolysis of valproic acid glucuronide to valproic acid in the liver, and increase the clearance of valproic acid glucuronide by hepatocytes and the kidneys [25].

Torii et al [26] conducted a study in rats to determine the effect of imipenem on serum VPA concentrations after administration of oral VPA. The area under the serum concentration-time curve of the orally administered VPA decreased by 57% ($p < 0.01$) after intravenous administration of imipenem. Utilizing *in situ* vascular and luminal perfused small intestine, they found the absorption of VPA from the luminal to the vascular perfusate was decreased in the presence of imipenem. However, it is possible that imipenem also inhibits the reabsorption of valproic acid during enterohepatic recirculation. Torii et al [27] also reported that carbapenems may inhibit valproic acid transport in Caco-2 cell monolayers. Valproic acid absorption at the basolateral membrane of intestinal epithelial cells was inhibited by carbapenems, resulting in a decrease in serum VPA concentration after oral administration.

It has been suggested that the decrease in serum VPA concentrations with concomitant carbapenem treatment may be partly due to an increase in erythrocyte distribution of valproic acid in rats and humans [28]. Further, Ogawa et al [29] found that in the presence of carbapenems, the efflux of valproic acid from erythrocytes was inhibited by multidrug resistance-associated proteins in rats.

Our results revealed that the onset of the interaction can be rapid, as a significant decrease in the serum VPA concentration was observed within 1 to 9 days. This suggests that the mechanism of the interaction may involve enzyme inhibition rather than enzyme induction, because any enzymatic induction process usually takes days to weeks to occur. Similar to previously published results, our results revealed a slow recovery of serum VPA concentrations after discontinuation of carbapenems, which is longer than kinetically dictated by the carbapenem half-life. Although there are no *in vitro* data to support this hypothesis, we suggest that the inhibition of beta-glucuronidase by carbapenems could be irreversible; therefore, recovery of serum VPA concentrations is dependent on the rate of the enzyme turnover and not the carbapenem half-life.

Only one patient had seizures in this study. Possible reasons may be that VPA was used for seizure prophylaxis in patients with brain injuries, or that the patients were taking at least two antiepileptic drugs to control seizures.

The interaction between VPA and carbapenems resulted in decreased serum concentrations of VPA. The mechanism of this interaction is unclear, however the rapid onset suggests enzymatic inhibition is likely. Increasing the dose of VPA during concomitant carbapenem therapy did not elevate the serum concentrations of VPA. Clinicians should be aware of this potential interaction, and closely monitor serum VPA concentrations and possible failure to control seizures during the concomitant use of carbapenems.

Table 3
The possible mechanisms of the interaction between VPA and carbapenems.

Type	Mechanism
Absorption	The perfusion of VPA from the luminal to the vascular perfusate was decreased. [26] The absorption of VPA at the basolateral membrane of intestinal epithelial cells was inhibited. [27]
Distribution	Erythrocyte distribution of VPA was increased. [28] The efflux of VPA from erythrocytes was inhibited by multidrug resistant-associated proteins. [29]
Metabolism	The glucuronidation of VPA to VPA-G was accelerated and the hydrolysis of VPA glucuronide back to the parent compound was inhibited. [23]

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