

Ertapenem-Induced Reduction in Valproate Levels: Case Report and Review of the Literature

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INTRODUCTION

The concomitant use of carbapenems and valproate is not recommended because carbapenems may decrease serum concentrations of valproate.^{1,2} Increasing the dose of valproate may not compensate for the reduction, which puts the patient at risk for recurrent seizures. Therefore, close monitoring of valproate levels is necessary when initiating a carbapenem antibiotic in patients whose condition has been stabilized with valproate therapy.

Several case reports of significant reductions in serum valproate concentrations following initiation of carbapenem antibiotics have been published. To the authors' knowledge, however, there has been no published systematic review of the carbapenem–valproate interaction. We report a case of ertapenem-induced reduction in valproate concentration and describe the extent, clinical relevance, potential mechanisms, and therapeutic options for management of the carbapenem–valproate interaction.

CASE REPORT

A 58-year-old woman was admitted to hospital with a 7-day history of malaise, low-back pain, and confusion.* Pertinent aspects of the medical history included multiple sclerosis, seizure disorder, and recurrent urinary tract infections. Medications before admission included calcium carbonate 500 mg twice daily, vitamin D 1000 IU daily, alendronate 70 mg weekly, amitriptyline 10 mg at bedtime, baclofen 10 mg twice daily, furosemide 20 mg daily, potassium chloride 40 mmol twice daily, lansoprazole 15 mg daily, brimonidine 0.2% one drop into each eye twice daily, timolol 0.5% one drop into each eye twice daily, and latanoprost 50 µg/mL one drop into each eye daily at bedtime. The patient was also taking valproate 250 mg 3 times daily.

The patient's seizure condition had been stabilized by the valproate therapy, and there had been no change in the dose over the previous 3 years. The patient's most recent seizure had occurred 7 months before the admission. Seven weeks before admission, a valproate trough of 556 µmol/L (normal range 350–700 µmol/L) was measured in a blood sample drawn before the morning dose. A urine sample obtained for culture 10 days before admission grew a multidrug-resistant strain of *Escherichia coli* (more than 1×10^8 colony-forming units per litre), and a 14-day course of nitrofurantoin 50 mg 4 times daily was initiated. The patient had reported allergies (in the form of a rash) to cephalosporins and phenytoin.

The patient was bedridden and had a permanent indwelling Foley catheter. She was alert and oriented. A neurological examination showed diffuse generalized weakness and delayed speech. An abdominal examination revealed mild tenderness on palpation. The results of head and neck, cardiovascular, respiratory, and musculoskeletal examinations were unremarkable. The patient was hemodynamically stable and afebrile. The white blood cell and neutrophil counts were normal at the time of admission. Serum creatinine was 55 µmol/L (normal range 35–100 µmol/L), with an estimated creatinine clearance of 82 mL/min. A sample for determination of valproate level was not drawn at the time of admission. Urinalysis showed that the urine was cloudy, with a pH of 6 (normal range 5–8.5), was negative for nitrites, and had a white blood cell count above 30 per high-power field (normal range 0–5 per high-power field). The results of urine culture were positive for *Candida albicans*, with a colony count of 1×10^7 to 1×10^8 colony-forming units per litre. The results of blood culture were negative.

Acute pyelonephritis was diagnosed. The nitrofurantoin was discontinued, and all other preadmission medications were continued. The patient was given a single dose of ceftriaxone 1 g in the emergency department with no adverse reaction. On day 2 of the admission, after review of the results of earlier urine

*The patient gave verbal consent for publication of this case report.

cultures, the patient was switched to amikacin 320 mg (4.3 mg/kg) IV every 8 h. On day 3, the infectious diseases service was consulted. At that point, the amikacin was discontinued because of the potential risk of ototoxicity. The patient had received a 10-day course of gentamicin 4 weeks before admission for *Providencia stuartii* infection of the urinary tract. Ertapenem 1 g IV daily was initiated, but no therapy was recommended for the *Candida albicans* infection, as this infection was thought to be due to colonization. The Foley catheter was removed, and intermittent catheterization (every 8 h) was initiated.

On day 5 of the admission, the clinical pharmacist suggested that the trough valproate level be measured before the morning dose, because of the potential for an interaction between ertapenem and valproate. The trough level was 48 $\mu\text{mol/L}$ (Figure 1). The valproate dose was doubled, to 500 mg 3 times daily. On day 11, the serum valproate level before the morning dose was 88 $\mu\text{mol/L}$, and the patient was discharged back to the long-term care facility, where she received parenteral antibiotic therapy with ertapenem for an additional 7 days. Instructions were given to decrease the dose of valproate to 250 mg 3 times daily after completion of antibiotic therapy. However, this decrease was mistakenly implemented early, on day 16 after the admission (i.e., 5 days after discharge). On day 18 after the admission (i.e., 7 days after discharge), the ertapenem was discontinued; at that time, repeat testing revealed that the valproate level was 60 $\mu\text{mol/L}$.

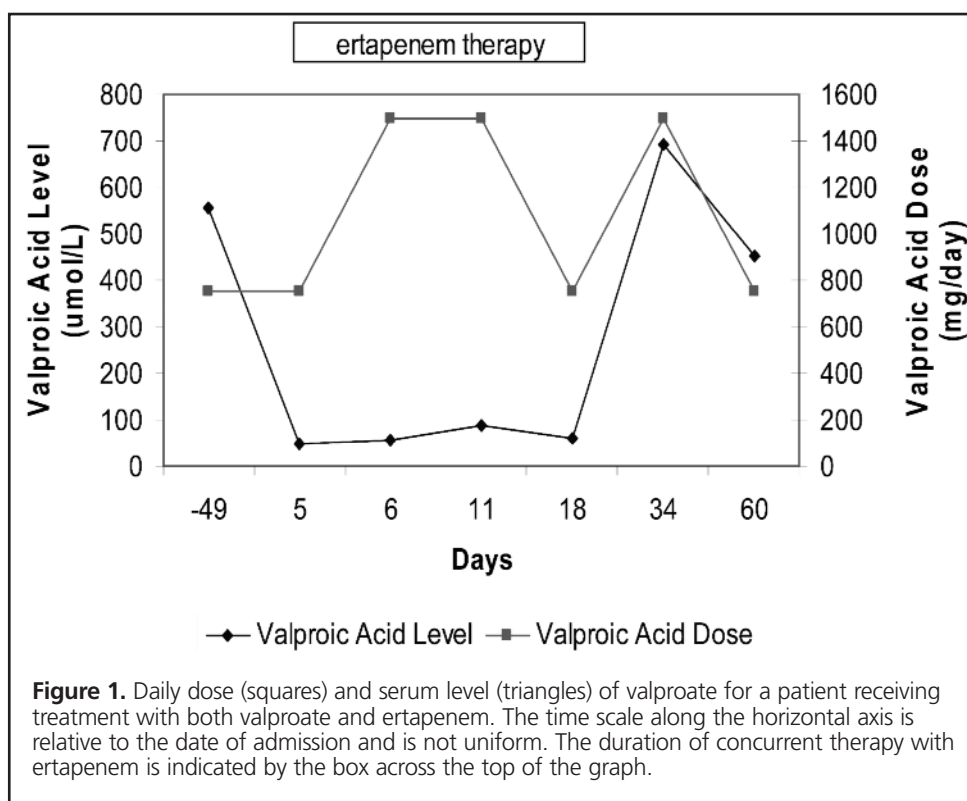
The dose was again increased to 500 mg 3 times daily. Despite prolonged subtherapeutic valproate, no seizure activity was observed. On day 34 after the admission, the valproate level was 692 $\mu\text{mol/L}$. On day 47, the dose of the drug was decreased to 250 mg 3 times daily, and at follow-up on day 60, the level was 392 $\mu\text{mol/L}$.

DISCUSSION

A systematic review of the literature was conducted to identify publications describing the interaction between carbapenems and valproate. The search terms “meropenem”, “imipenem”, “ertapenem”, “doripenem”, “valproic acid”, and “valproate” were used to search PubMed, Ovid, EMBASE, International Pharmaceutical Abstracts, and Reactions Weekly (for January 1950 to September 2009). A total of 23 individual case reports and 3 case series (with a total of 147 patients) were identified. Two case reports were excluded from the analysis, one because valproic acid levels were not reported³ and the other because the report was in Korean and translation was not possible.⁴

Case Reports

Twenty-one cases of an interaction between a carbapenem and valproate were reviewed. Valproate was used for seizure prophylaxis (4 cases),^{5,6} acute symptomatic seizures (5 cases),⁷⁻¹⁰ and treatment of epilepsy (12 cases)¹¹⁻¹⁹ (Table 1). An average of



3.2 days of concurrent therapy resulted in reduction of valproate levels by an average of 73% (range 41%–100%). A median increase in the valproate dose of 850 mg/day (interquartile range [IQR] 728–1238 mg/day) did not result in achievement of therapeutic serum concentration of valproate for any patient (median valproate level 104 $\mu\text{mol/L}$ [IQR 68–132 $\mu\text{mol/L}$]). In 7 patients the carbapenem was changed to an alternative antibiotic, and a period of 1 to 20 days was required for serum valproate levels to return to the therapeutic range.^{6,8,10–14,18} In 4 patients the valproate was discontinued, and an alternative antiseizure medication was prescribed.^{5,9,17,18} Two patients required adjunctive seizure therapy.⁸ Two patients were rechallenged with meropenem, and experienced recurrent drops in valproate levels, which resulted in seizures.^{13,16} The limitations of these case reports included a lack of information about the patient's medical history, concomitant drug therapy, laboratory data (specifically creatinine clearance), and time at which samples were drawn for determining valproate levels.

Another report described a 10-year-old girl who was being treated for seizures with valproate 5 mg/kg every 12 h (usual maintenance dose 30–60 mg/kg per day) and carbamazepine.²⁰ The dose of carbamazepine and the baseline valproate level were not reported. After 2 days of treatment with panipenem–betamipron, the frequency of seizures increased (serum concentration of valproate 184 $\mu\text{mol/L}$). The carbamazepine level was 38 $\mu\text{mol/L}$ before and 39 $\mu\text{mol/L}$ during the panipenem–betamipron therapy (normal range 20–50 $\mu\text{mol/L}$). Phenobarbital was substituted for the valproate, which led to control of the seizures. The panipenem–betamipron was continued for 53 days for treatment of pleural empyema.

Case Series

Spriet and others²¹ conducted the most comprehensive review of the meropenem–valproate interaction published to date. They reviewed 39 patient charts. Valproate was used for treatment of acute seizures ($n = 24$), treatment of epilepsy ($n = 12$), prophylaxis of seizure ($n = 2$), and treatment of mood disorder ($n = 1$). The mean daily valproate dose (\pm standard deviation) was 1.6 \pm 0.68 g (range 0.4–4 g). The mean daily meropenem dose was 2.67 \pm 1.4 g (range 0.5–6 g). The mean creatinine clearance was 65.73 \pm 32 mL/min (range 12.3–112 mL/min).

Twenty-nine of the 39 patients received meropenem after initiation of valproate. The mean baseline valproate level was 446 \pm 146 $\mu\text{mol/L}$ (range 277–770 $\mu\text{mol/L}$). During concomitant meropenem therapy, the mean valproate level fell to 156 \pm 83 $\mu\text{mol/L}$ (range < 21 to 298 $\mu\text{mol/L}$), which represents an average drop of 66% \pm 17% (range 34%–92%). Nineteen patients experienced a reduction in valproate level within 24 h. No known proconvulsive drugs had been added to the patients' regimens.

The other 10 patients received valproate after initiation

of meropenem. Plasma valproate concentrations remained subtherapeutic, despite IV administration of an adequate loading dose (mean 21 mg/kg) and maintenance dose (mean 31.5 mg/kg daily). The mean plasma concentration of valproate during concomitant use of valproate and meropenem was 82 \pm 69 $\mu\text{mol/L}$ (range < 21 to 257 $\mu\text{mol/L}$).

Nine of the 39 patients had an extra valproate loading dose (mean 944 mg). For 19 patients, the maintenance dose of valproate was increased while they were receiving the combination of meropenem and valproate (mean increase 146%). For 8 patients, increasing the valproate dose did not result in elevation of plasma concentrations of the drug. In one patient, the maintenance dose of valproate was increased to 12 g/day (usual maintenance dose 10–60 mg/kg daily). This was the only patient for whom plasma concentrations of valproate reached therapeutic levels during the course of concomitant therapy (361 $\mu\text{mol/L}$). After discontinuation of the meropenem, it took an average of 8 days for valproate levels to return to the therapeutic range. Mean plasma concentration of valproate after the combination therapy was 385 $\mu\text{mol/L}$.

Spriet and others²¹ reported that lack of documentation in 19 cases prevented determination of the clinical impact of the drug interaction. Twenty-five of the 39 patients died during the hospital stay. The interaction might have contributed to an increase in seizure activity ($n = 3$), a change in electroencephalography recordings ($n = 2$), or both ($n = 5$). For 5 patients, the valproate was discontinued and replaced with alternative antiepileptic drug therapy; 2 patients required adjunctive antiepileptic medications.

Haroutiunian and others²² conducted a chart review of 36 adult patients (29 men, 7 women; mean age 59 years) who had received concomitant therapy with valproate and meropenem. The mean daily doses were valproate 2.04 \pm 0.07 g and meropenem 4.88 \pm 0.25 g. The mean plasma concentration of valproate decreased from 352 \pm 31 $\mu\text{mol/L}$ to 68.6 \pm 15 $\mu\text{mol/L}$ during concomitant therapy. Five patients had samples drawn for valproate measurement within 24 h after initiation of meropenem, and the mean plasma valproate concentration for these patients was 68.6 \pm 22.2 $\mu\text{mol/L}$. Haroutiunian and others²² also reported the reduction in valproate concentration in relation to the dose of meropenem. The mean decrease in valproate concentration was 83.4% for patients receiving high-dose meropenem (6 g/day) and 81.0% for patients receiving standard-dose meropenem (< 3 g/day). Different daily doses of valproate were associated with a similar reduction in concentration of valproic acid. Valproate levels remained low for 7 days after discontinuation of meropenem and gradually increased from 8 to 14 days to levels comparable to those before initiation of meropenem.

Table 1. Summary of Case Reports of Concurrent Therapy with Valproic Acid and Carbapenem

Reference	Sex	Age (years)*	Valproic Acid at Baseline			Carbapenem Drug and Dosage	Duration of Concurrent Therapy (days)	Valproic Acid (Subsequent)			Clinical Outcome: Seizures
			Dosage (mg/day)*	Serum Level (µmol/L)	Repeat Serum Level (µmol/L)			Adjusted Dose (mg/day)*	Repeat Serum Level (µmol/L)†		
Adults											
Eimil-Ortiz et al. ¹¹	F	25	1000	NR‡	meropenem 1g tid	1.5	Undetectable	2200	69.3	Yes	
Coves-Orts et al. ⁷	F	21	1920	364	meropenem 1g tid	4	48.5	3600	69.3	Yes	
Fudio et al. ¹²	F	50	1500	NR‡	meropenem 500 mg bid	5	143.5	2750	44.4	Yes	
Lunde et al. ¹⁴	M	41	2000	901.4	ertapenem 1g qd	6	485.4	2750	74.2	Yes	
Cabanes Mariscal et al. ¹⁵	F	80	1100	499.2	ertapenem 1g qd	4	252.4	2000	7.2	No	
De Turck et al. ⁵	F	65	1600	402.2	meropenem 1g tid	1	159.5	2000	104	No	
Spriet et al. ⁸	F	57	NR	305.1	meropenem§	1	34.7	NR	Not repeated	No	
	F	60	1600	360.6	meropenem 1g tid	2	69.3	2400	221.9	Yes	
Clause et al. ⁶	M	54	2000	492.3	meropenem 1g bid	2	215	2200	152.5	Yes	
	M	30	3600	423	meropenem 2 g q6h	1.5	119.3	Dose not increased	Level undetectable after 5 days concurrent therapy	No	
Gu et al. ¹⁶	M	77	3120	374.4	meropenem 2 g q8h	1	221.9	3840	201	No	
	M	85	800	332.8	meropenem 500 mg q8h	1	94.5	No change	63.2	No	
Perea Falomir et al. ¹⁰	F	46	1200	NA¶	imipenem§	4	106.1	4800	338.4	Yes	

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Table 1. Summary of Case Reports of Concurrent Therapy with Valproic Acid and Carbapenem (continued)

Reference	Sex	Age (years)*	Valproic Acid at Baseline			Carbapenem Drug and Dosage	Duration of Concurrent Therapy (days)	Valproic Acid (Subsequent)			Clinical Outcome: Seizures
			Dosage (mg/day)*	Serum Level (µmol/L)	Repeat Serum Level (µmol/L)			Adjusted Dose (mg/day)*	Repeat Serum Level (µmol/L)†		
Pediatric patients											
Salo Piñol et al. ¹⁸	F	12	130 mg/kg daily	471.5	meropenem 60 mg/kg daily	3	194.2	170 mg/kg daily	124.8		Yes
	M	4	30 mg/kg daily	561.7	meropenem 120 mg/kg daily	8	117.9	110 mg/kg daily	110.9		Yes
Nacarkucuk et al. ¹⁹	M	14	50 mg/kg daily	513.1	meropenem§	6	145.6	200 mg/kg daily	104		No
	F	7 months	75 mg/kg daily	624.1	meropenem§	4	152.5	130 mg/kg daily	124.8		No
	M	14 months	75 mg/kg daily	589.4	meropenem§	3	90.1	150 mg/kg daily	Not repeated		No
Santucci et al. ¹³	F	9.5	600	322.4	meropenem 600 mg tid	5	69.3	750	Not repeated		Yes
San Antonio Arce et al. ¹⁷	F	2 months	50 mg/kg daily	326	meropenem§	2	4.85	Dose not increased	Not repeated		Yes
Pérez Plasencia et al. ⁹	F	15	1600	374.4	meropenem§	2	76.3	Dose not increased	Not repeated		Yes

NA = not applicable, NR = not reported.

*Unless indicated otherwise.

†With increased dose.

‡Authors stated that baseline valproic acid level was within the therapeutic range.

§Dose not reported.

¶Imipenem started before valproic acid.

Borobia and others²³ reviewed the concomitant use of meropenem and valproate for patients seen over a 5-year period. A total of 72 patients (63 adults and 9 children; 40 males and 32 females) received both drugs simultaneously. The median age was 47.5 years (range 9 months to 86 years). Samples for determination of valproate levels were drawn for 19 patients. The average reduction in valproate level was 74% (range 34%–98%). Four of the patients had seizures, but no further information about these patients was provided.

Doripenem is the newest carbapenem to be released in Canada. The literature search revealed no human cases of interaction between doripenem and valproate. The product monograph²⁴ states that the administration of 4 doses of doripenem (500 mg every 8 h) to 23 healthy male subjects who had been receiving valproate 500 mg every 12 h for 7 days resulted in a decrease in the mean minimum concentration (by 78%), maximum concentration (by 45%), and the area under the concentration–time curve (0 to τ , where τ is the dosing interval; by 63%) relative to valproic acid alone. A reduction in serum concentration of valproic acid was observed within 12 h after initiation of doripenem.

Pharmacokinetics of Valproate

A brief overview of the pharmacokinetics of valproic acid is necessary to identify the possible mechanisms of the valproate–carbapenem interaction.^{25–27} The bioavailability of valproate is 90%–100%, and the drug has a volume of distribution of 0.2 L/kg. Protein binding is substantial, with 90%–95% of administered valproate being bound to albumin, which is saturable. Valproate is eliminated by first-order kinetics and reportedly has an elimination half-life of 5–20 h (mean 10.6 h).

The hepatic metabolism of drugs depends on the flow of blood to the liver, the extent of protein binding, and the level and activity of drug-metabolizing enzymes. Valproate has a low hepatic extraction, and clearance is therefore independent of blood flow. Metabolism of valproate in the liver is extensive. The 3 main metabolic pathways, in order of importance, are glucuronidation catalyzed by uridinediphospho-glucuronyl transferase (UDPGT) (30%–60%), β -oxidation (more than 40%), and Ω -oxidation (up to 15%–20%).^{25–27} Up to 60% of the drug is excreted as glucuronide conjugates. The metabolites do not appear to have antiepileptic activity. There is minor cytochrome (CYP) P450 metabolism via the CYP2A6, CYP2C9, CYP2C19, and CYP2B6 isozymes.²⁶ Less than 7% of a dose is excreted unchanged in the urine.

Potential Mechanism of Interaction between Valproate and Carbapenem

Several animal studies have been carried out in attempts to determine the mechanism of the carbapenem–valproate

interaction. Some evidence suggests a decrease in valproate absorption. Carbapenems may inhibit the absorption of valproate at the basolateral membrane of the intestinal epithelial cells.^{28,29} Kojima and others³⁰ suggested that carbapenems decrease valproate levels through suppression of the enterohepatic circulation.

Increased uptake of valproate into erythrocytes during therapy with carbapenems has also been suggested.^{31,32} Omoda and others³¹ measured valproate levels in plasma, whole blood, and erythrocytes for 2 patients receiving imipenem 500 mg twice daily for 5 and 7 days. Baseline plasma valproate levels were 318 and 351 $\mu\text{mol/L}$. Treatment with imipenem decreased plasma valproate levels to 57% and 49% of the original levels, respectively. The concentration of valproate in erythrocytes was about 69.3 $\mu\text{mol/L}$ during treatment with imipenem and fell to undetectable levels within 13–35 days after discontinuation of the carbapenem.

The liver appears to be the key organ involved in the decrease of serum valproate concentrations during concurrent therapy with a carbapenem. Yamamura and others³³ studied the effects of valproate given intravenously to rats that had undergone nephrectomy or hepatectomy with and without prior treatment with panipenem. Pretreatment with panipenem enhanced the elimination of valproate in the nephrectomized rats but not the hepatectomized rats. Yamamura and others³³ concluded that panipenem enhanced the rate of metabolism of valproate to valproic acid glucuronide in the liver. Nakajima and others³⁴ studied the effects of panipenem, meropenem, and doripenem on valproate in monkeys and rats. They concluded that carbapenems increased production of valproic acid glucuronide, inhibited hydrolysis of valproic acid glucuronide in the liver, and increased clearance of valproic acid glucuronide by hepatocytes and the kidneys, which thereby decreased valproate levels. An *in vitro* study of pooled human liver microsomes preincubated with meropenem and biapenem showed a 35% increase in valproate glucuronidation.³² In the case reported by Nagi and others,²⁰ the fractional excretion of valproate (urinary valproate \times serum creatinine/serum valproate \times urinary creatinine \times 100) increased from 0.06% to 0.21% after 18 h of panipenem–betamipron therapy.

Management of Carbapenem–Valproate Interaction

Clinicians have few antibiotic options for the treatment of infections with multidrug-resistant gram-negative organisms. The carbapenems are considered the drugs of choice for treatment of infection with organisms that produce extended-spectrum β -lactamases (ESBLs), as these drugs are highly resistant to hydrolysis by such organisms and are distributed into the body tissues at high concentrations, and there is no inoculum effect.^{35–37} An alternative antibiotic regimen could be considered in the management of an interaction between carbapenem and valproate.

Tigecycline is one therapeutic option.^{38,39} Renal excretion is a minor route of elimination for this drug, but there are case reports of tigecycline having been used to treat urinary tract infections.⁴⁰⁻⁴⁶ Polymyxins have extensive coverage of gram-negative organisms, but their use has been limited by risks of nephrotoxicity (about 20% of cases) and neurotoxicity (7%–10% of cases).^{35,38,47} Furthermore, there is limited information on their pharmacokinetics, pharmacodynamics, standardization of dosing, and safety. Only colistin sulphomethate sodium is available as an IV formulation in Canada. Colistin has been used to treat urinary tract infections caused by multidrug-resistant organisms.⁴⁸⁻⁵⁰ Ertapenem was chosen for the patient described in the current case report because carbapenems are the drug of choice for treatment of infections with ESBL-producing organisms and would allow for once-daily administration at the patient's long-term care facility. The team did not have any experience with the management of a carbapenem–valproate interaction, and it was decided to follow the valproate levels and adjust the dose as necessary.

For a patient whose condition has been stabilized with an anticonvulsant regimen, the clinician might also consider use of an adjuvant seizure medication while the patient is receiving concurrent carbapenem and valproate therapy. This decision would be influenced by the duration of antibiotic therapy and the frequency of seizures. The choice of anticonvulsant would depend on the seizure type, potential adverse effects, interactions with other medications, and comorbid medical conditions. Previous authors have described the management of carbapenem–valproate interactions by switching the valproate to phenobarbital, phenytoin, or clobazam and oxcarbazine, whereas others have added levetiracetam, topiramate, phenytoin, or phenobarbital to the valproate therapy.^{5,8,9,17,18} Adjuvant therapy may be continued for up to 7 days after the carbapenem is discontinued, as it may take 7 days or more for the serum valproate concentration to return to baseline. The serum valproate level may be measured again 7 days after discontinuation of carbapenem.

For some low-risk patients with seizures (e.g., seizure-free for a number of years or requiring seizure prophylaxis after neurosurgery), it may be sufficient to follow the patient's clinical status and to monitor serum valproate levels. In the case reported here, the team chose not to alter the patient's antiepileptic therapy. This case confirmed previous literature reports that an increase in valproate dose does not compensate for the reduction in serum valproate concentration caused by a carbapenem.

CONCLUSIONS

The carbapenem–valproate interaction has been well documented among both pediatric and adult patients. The interaction does not appear to be influenced by the total daily dose of either valproate or carbapenem. Concurrent therapy may result in a 60% to 80% decrease in serum concentration

of valproate within the first few days. As a consequence, approximately 20% of patients had recurrent seizures. There are 4 options for management of this drug interaction. First, an alternative antibiotic could be used instead of carbapenem. If changing the antibiotic is not feasible, an additional anticonvulsant medication could be added to the patient's regimen or the valproate could be switched to another antiepileptic agent, since increasing the valproate dose does not compensate for the reduction in serum valproate levels caused by the carbapenem. In low-risk patients with seizures who are receiving a short course of carbapenem therapy, monitoring serum valproate concentrations may be adequate.

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