Valproic Acid Plasma Concentration Decreases in a Dose-Independent Manner Following Administration of Meropenem: A Retrospective Study

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Several case reports indicate that carbapenem antibiotics, especially meropenem, may decrease the plasma concentrations of valproic acid (VPA), thus decreasing its therapeutic activity. To investigate the onset, severity, and dose dependency of the interaction between meropenem and VPA, the authors carried out a retrospective evaluation of data collected during 24 months from patients hospitalized in a tertiary medical center. The analysis included 36 patients. VPA mean ± SEM plasma concentration decreased from of 50.8 ± 4.5 μg/mL to 9.9 ± 2.1 μg/mL (P < .001) following meropenem administration. After discontinuation of meropenem, VPA plasma concentrations remained low for 7 days and then gradually increased after 8 to 14 days, reaching values comparable to those before meropenem initiation. Different daily VPA doses showed a similar pattern of decreased VPA concentrations. The mean decrease in individual plasma VPA concentration was 82.1% ± 2.7%. The mean VPA plasma concentration of patients in whom samples were drawn within 24 hours of meropenem initiation was 9.9 ± 3.2 μg/mL. In conclusion, the interaction between meropenem and VPA causes a significant decrease in VPA plasma concentration, apparently within 24 hours. As the therapeutic effects of VPA are plasma concentration dependent, the data suggest that these drugs should not be administered concomitantly.

Keywords: *Meropenem; valproic acid; drug-drug interaction; epilepsy; pharmacokinetics*

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After the discovery of its antiepileptic activity by Meunier in 1963, valproic acid (VPA) has been extensively used for treatment of different forms of epilepsy,[1] peripheral neuropathic pain,[2] migraine prophylaxis,[3-5] bipolar disorder, and other psychiatric conditions.[6]

For the treatment of simple or complex seizures, VPA is usually initiated at doses of 10 to 15 mg/kg/d and may be gradually increased to achieve optimal clinical response up to a maximal dose of 60 mg/kg/d. The dose for prophylaxis of migraine might be somewhat lower than the antiepileptic dose, as several studies showed efficacy at doses of 500 to 1500 mg/d.[5] The target plasma concentrations of VPA for the treatment of epilepsy are 50 to 100 μg/mL, whereas lower plasma concentration increases the risk of breakthrough seizures.[7] Although not well defined, several studies suggest that the target concentration for indications other than epilepsy is approximately within the same range.[8]

Meropenem is a broad-spectrum, central nervous system (CNS)–penetrating carbapenem antibiotic used for the treatment of infections by gram-positive, gram-negative, and anaerobic infections. Meropenem

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is given intravenously in daily doses of 3000 mg for non-CNS infections or 6000 mg for CNS infections, with reduction of dose in patients with impaired renal function. During the study period, meropenem was the drug of choice for the empiric treatment of hospital-acquired meningitis in our institution, due to high prevalence of resistant species of *Acinetobacter baumannii*. Imipenem, another CNS-penetrating carbapenem, is usually not used for treating meningitis, as the reported incidence of carbapenem-induced seizures appears to be higher with imipenem than with meropenem.[9] For the same reason, meropenem is also the drug of choice for patients in whom carbapenem antibiotics are indicated but who have an active seizure disorder or are at high risk of developing seizures (eg, neurosurgical patients, patients with head trauma or history of epilepsy). Several case reports have been published lately indicating that carbapenem antibiotics, especially meropenem, may decrease the plasma concentrations of VPA, thus decreasing its therapeutic activity.[10-16]

The mechanism of the interaction between VPA and meropenem has been studied in different animal models. Coadministration of meropenem was shown to significantly decrease plasma concentrations of VPA in a rabbit model.[17] The study showed that meropenem accelerated the glucuronidation of VPA to VPA glucuronide (VPA-G) and inhibited the hydrolysis (de-conjugation) of VPA-G back to the parent compound, thus increasing the clearance of VPA and VPA-G. The study showed no replacement of protein-bound VPA from its binding sites or increase in unbound VPA plasma fraction. Another study[18] clearly showed that panipenem, another carbapenem antibiotic, causes neither enzyme induction nor allosteric activation of UDP-glucuronosyltransferases (UGT), enzymes responsible for the glucuronidation of VPA. Further investigation of the interaction mechanism between carbapenem and VPA, using liver and kidney slices from monkeys and rats,[19] also showed an increase in VPA-G production. However, contrary to others,[18] this study did not show a significant increase in glucuronidation activity, thus explaining this interaction by inhibition of VPA-G de-conjugation. These results suggest that VPA-G undergoes de-conjugation by beta-glucuronidase to the parent compound VPA, and carbapenems increase the clearance of VPA by specifically inhibiting this step in hepatocyte cytosol.

Previously published case reports, indicating that interaction between VPA and meropenem occurs, led us to perform a retrospective inpatient data evaluation to estimate the incidence and severity of the pharmacokinetic interaction between meropenem and VPA in patients receiving the drug combination. Our secondary objectives were to discover whether the interaction is dose dependent and to determine the time course of plasma VPA decrease and recovery following meropenem treatment.

MATERIALS AND METHODS

Data Collection and Analysis

Data were collected from computerized charts of patients hospitalized in a tertiary 1800-bed medical center between January 2004 and January 2006, and these patients met the criteria of receiving therapy with VPA and meropenem during hospitalization. The study protocol was approved by the Institutional Review Board of Sheba Medical Center. Patients' demographic data, clinical records, comorbidities, concomitant medications, complete laboratory analyses data, and VPA plasma concentrations were obtained throughout the hospitalization period. The data were processed to discover the dose regimen, the duration of VPA and meropenem administration, and the overlapping period of treatment with both medicines.

To elucidate whether the interaction occurs at all dose regimens of VPA, we divided the patients into 4 subgroups for analysis, depending on VPA daily dose:

Group 1: daily dose <1000 mg
Group 2: 1000 mg ≤ daily dose < 2000 mg
Group 3: 2000 mg ≤ daily dose < 3000 mg
Group 4: daily dose ≥3000 mg

The patients in our study received different dosage forms of VPA: sodium valproate solution for injection (Orfiril, Desitin GmbH, Gronau, Germany), sodium valproate tablets or oral solution (Depalept, CTS Chemical Industries, Kiryat Malachi, Israel), or valproic acid tablets (Valporal, Teva Pharmaceutical Industries, Kfar Saba, Israel). The different dosage forms have previously been shown to vary in the rate of absorption of VPA but not in the extent absorbed due to the high (90%-95%) bioavailability of the drug.[1] Therefore, we calculated the daily dose of VPA regardless of the dosage form administered. We examined each dose group to find whether VPA plasma concentration decreased following administration of meropenem and to investigate the time course of VPA recovery after discontinuation of meropenem treatment. To examine the onset of the interaction, we

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separately looked at VPA concentration from samples that were obtained within 24 hours of meropenem initiation. In addition, to investigate whether the dose of meropenem influences the severity of the interaction, we compared the percentage of decrease in VPA concentration in patients who received high-dose meropenem for the treatment of CNS infections with patients who received low-dose meropenem for non-CNS infections.

Inclusion and Exclusion Criteria

Inclusion criteria were as follows: patients receiving VPA and meropenem during the hospitalization period between January 2004 and January 2006.

Exclusion criteria were as follows: patients in whom VPA therapy was discontinued before the initiation of meropenem; patients whose VPA plasma concentration data were lacking; patients whose plasma samples for VPA concentration measurement were drawn within 2 hours after VPA administration; patients with severe liver impairment, measured by an increase of the hepatocellular enzymes (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) more than 3-fold of their normal values (5-35 U/L and 8-36 U/L, respectively), which could be responsible for the increased VPA plasma concentration; and patients who received drugs potentially interacting with VPA (phenobarbital, phenytoin, carbamazepine,[20,21] topiramate,[20] acyclovir,[22] mefloquine, rifampin, ritonavir, ethosuximide, isoniazid, felbamate, imipenem, and ertapenem[19]) in a way that could affect VPA plasma concentrations relevant for data analysis.

The interaction probability was estimated using the Drug Interaction Probability Scale (DIPS),[23] previously used to estimate the interaction between VPA and meropenem.[24] We defined the interaction "event" as a drop in VPA plasma concentration of more than 50%. When no plasma VPA concentration was available before meropenem initiation at the current hospitalization but the patient had prior documented 50- to 100-mcg/mL VPA plasma concentration, the "event" was defined as VPA concentration below the lower threshold of the therapeutic window after administration of meropenem. To eliminate insignificant changes, we defined this lower threshold as 40 μg/mL instead of 50 μg/mL, which is accepted in the literature. When the patient received one of the drugs that could be responsible for low VPA plasma concentration (as used in exclusion criteria), we graded (–1) on the "reasonable alternative causes for the event" question, even when the affecting drug was administered chronically with no dose changes during the treatment period.

Statistics

All results are presented as mean ± SEM. One-way analysis of variance (ANOVA) method was used to compare among the groups, and intergroup significance was tested using the Tukey multiple-comparisons test. The Instat (GraphPad Software, San Diego, California) program was used to calculate the intergroup statistical differences and the P values. The differences were considered significant at $P < .05$.

RESULTS

Study Population

Over a 24-month period of the study, 68 patients who received both VPA and meropenem during the hospitalization period were identified by a computerized file system. Thirty-two patients met the exclusion criteria and therefore were not included in the analysis. Thirty-six patients met the inclusion criteria. Their mean age was 58.7 ± 3.1, and mean weight was 78.3 ± 4.3 kg (29 men and 7 women). Twenty-two patients were hospitalized in the neurosurgery department, 7 patients in internal medicine departments, 3 patients in the neurology department, 3 patients in the surgical department, and 1 patient in the hematology department. The mean daily dose of VPA was 2.04 ± 0.07 g. The mean daily dose of meropenem was 4.88 ± 0.25 g. Twenty-four patients received high-dose meropenem for CNS infections, and 12 patients received low-dose meropenem for non-CNS infections. As a rule, the blood samples for VPA concentration measurement were obtained in the morning, prior to the first morning VPA administration. Two patients had significantly increased ALT/AST levels, as determined by exclusion criteria, at 1 occurrence each. Both of them were under combined meropenem and VPA treatment at that point. The VPA concentrations were very low: 1.5 mcg/mL for 1 patient and 2.9 mcg/mL for the other patient. As the patients were under meropenem treatment at that point and because hepatic failure may cause an increase and not a decrease in VPA plasma concentration, those 2 patients were not excluded from the analysis because they did not have increased VPA concentration due to severe liver failure.

Figure 1 summarizes the data on the mean trough VPA concentration in all patients before initiation of

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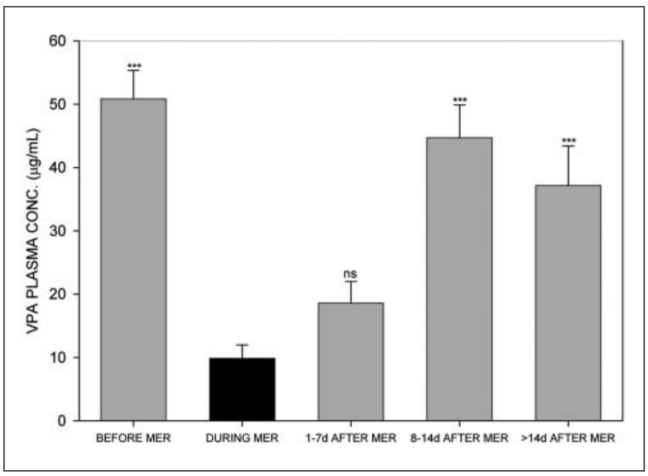

*Figure 1. Mean valproic acid (VPA) plasma concentrations before (n = 49), during (n = 41), and at 3 periods after meropenem (MER) treatment in all patients. The 3 periods are 1 to 7 days after meropenem discontinuation (post-MER) (n = 29), 8 to 14 days post-MER (n = 19), and more than 14 days post-MER (n = 22). The bars indicate the SEM. ***P < .001. ns, no significant difference (P > .05). n, number of VPA samples.*

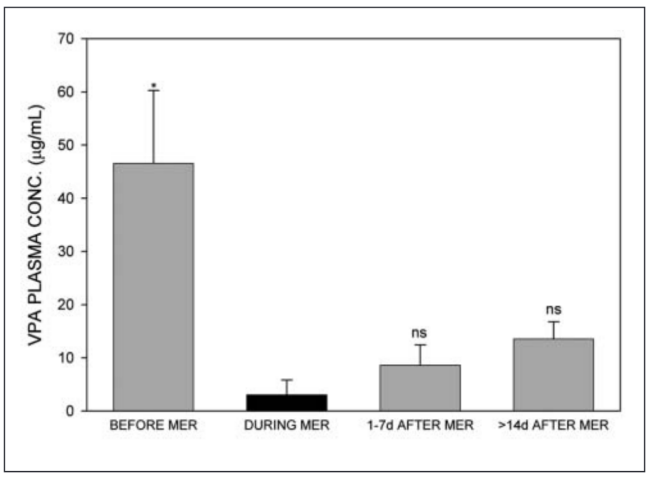

*Figure 2. Mean valproic acid (VPA) plasma concentrations before (n = 4), during (n = 4), and at 2 periods after meropenem (MER) treatment in patients receiving up to 1000 mg VPA/d. The 2 periods are 1 to 7 days after meropenem discontinuation (post-MER) (n = 5) and more than 14 days post-MER (n = 4). The bars indicate the SEM. *P < .05. ns, no significant difference (P > .05). n, number of VPA samples.*

meropenem, during meropenem treatment, and at 3 time periods after discontinuation of meropenem, regardless of VPA daily dose. These time periods were chosen as 1 to 7 days, 8 to 14 days, and more than 14 days after meropenem discontinuation. This division was chosen as some data show that VPA concentrations recover within an average of 8 days,[24] whereas other data indicate that the influence of meropenem on VPA levels can last more than 2 weeks.[16] The mean trough VPA plasma concentrations decreased from 50.8 ± 4.5 µg/mL to 9.9 ± 2.1 µg/mL ($P < .001$) following administration of meropenem. During 1 to 7 days after meropenem discontinuation, the concentrations remained low (18.6 ± 3.4 µg/mL, $P > .05$). Eight to 14 days after discontinuation of meropenem, the VPA plasma concentrations reached a level comparable to the pretreatment values (44.7 ± 5.2 µg/mL; $P > .05$) and were higher than during the 1- to 7-day period ($P < .001$). The VPA concentrations measured >14 days after meropenem discontinuation did not differ from the pretreatment group or 8- to 14-day group ($P > .05$).

Figures 2 to 4 summarize the data on mean VPA concentrations measured following administration of up to 1000 mg (Figure 2), 1000 to 2000 mg (Figure 3), and 2000 to 3000 mg (Figure 4) daily VPA doses, along the same time periods. Figure 2 compares only 4 time periods because VPA plasma concentrations were not measured at 8 to 14 days after meropenem discontinuation in group 1. A significant decrease in VPA plasma concentration is shown in all dose groups as a result of meropenem administration. In the first period of less than 8 days after meropenem discontinuation, all groups showed a small and insignificant increase in VPA concentration compared with the concentrations measured under meropenem therapy. After 8 or more days following meropenem discontinuation, VPA plasma levels in all groups were not different from VPA concentrations before meropenem initiation. They were significantly higher than the concentrations under meropenem treatment, except in group 1, where after more than 14 days, a 4-fold numerical but statistically insignificant increase in VPA concentration was observed. VPA concentration in the 1000- to 2000-mg and 2000- to 3000-mg groups recovered within 8 to 14 days of meropenem discontinuation.

Figure 5 compares plasma VPA concentration during treatment and 1 to 7 days after discontinuation of meropenem therapy in patients who received daily doses of 3000 mg VPA or more. There are no data on VPA plasma concentrations before meropenem initiation in this group, as no patient needed such high doses to achieve therapeutic levels of VPA. No difference was observed between the mean plasma VPA concentration of 10.4 ± 5.3 µg/mL

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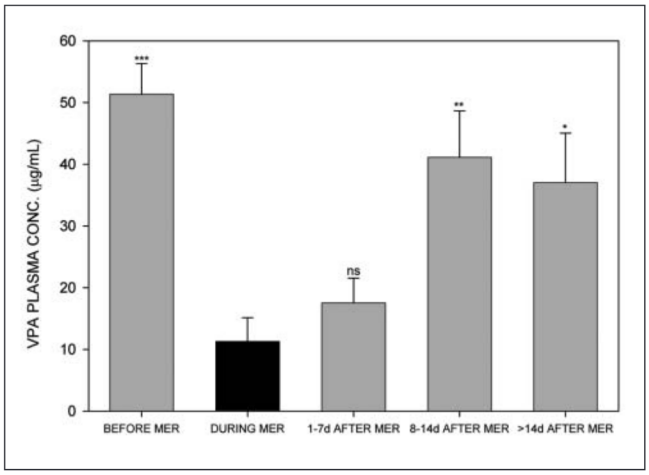

*Figure 3. Mean valproic acid (VPA) plasma concentrations before (n = 36), during (n = 19), and at 3 periods after meropenem (MER) treatment in patients receiving 1000 to 2000 mg VPA/d. The 3 periods are 1 to 7 days after meropenem discontinuation (post-MER) (n = 13), 8 to 14 days post-MER (n = 9), and more than 14 days post-MER (n = 12). The bars indicate the SEM. *P < .05. **P < .01. ***P < .001. ns, no significant difference (P > .05). n, number of VPA samples.*

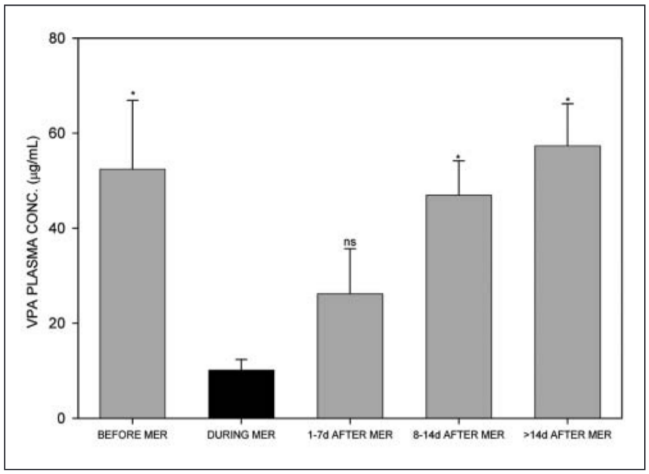

*Figure 4. Mean valproic acid (VPA) plasma concentrations before (n = 10), during (n = 13), and at 3 periods after meropenem (MER) treatment in patients receiving 2000 to 3000 mg VPA/d. The 3 periods are 1 to 7 days after meropenem discontinuation (post-MER) (n = 8), 8 to 14 days post-MER (n = 10), and more than 14 days post-MER (n = 7). The bars indicate the SEM. *P < .05. ns, no significant difference (P > .05). n, number of VPA samples.*

achieved by administration of these VPA daily doses during meropenem therapy and 13.5 ± 3.3 µg/mL ($P > .05$) achieved within 1 to 7 days after discontinuation of meropenem.

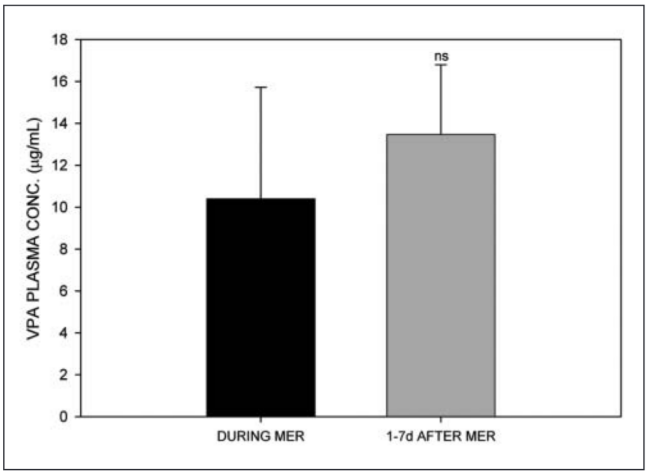

Figure 5. Mean valproic acid (VPA) plasma concentrations during (n = 6) and 1 to 7 days after (n = 4) meropenem (MER) treatment in patients receiving > 3000 mg VPA/d. The bars indicate the SEM. ns, no significant difference (P > .05). n, number of VPA samples.

We calculated the percentage of decrease in trough VPA concentration of individual patients following meropenem addition. The mean decrease was 82.1% ± 2.7% (range, 70.1%-91.5%). Five patients had VPA concentrations obtained within 24 hours of meropenem initiation. The VPA plasma samples were drawn 14.7 ± 2.2 hours after the first meropenem dose. The mean VPA dose of these patients was 1670 ± 220 mg, and the mean time these patients received the same dose of VPA prior to meropenem initiation was 4.6 ± 2.1 days. Their mean VPA plasma concentration was 9.9 ± 3.2 µg/mL. The mean decrease in VPA plasma concentration was 83.4% ± 3.8% in patients receiving high-dose meropenem for CNS infections and 81.0% ± 4.8% in patients receiving low-dose meropenem for non-CNS infections ($P > .05$).

Interaction Probability Evaluation

DIPS[23] was used to assess whether the decline of VPA plasma concentration is, in fact, due to an interaction with meropenem. The VPA-meropenem interaction "event" was recorded in 32 patients. The mean DIPS score for the interaction was 5.2, a value that is defined as "probable." Specifically, 1 patient was categorized as "highly probable" (DIPS score of 9-10 points), 17 patients as "probable" (5-8 points), and 14 patients as "possible" (2-4 points). No patient received a "doubtful" (less than 2) DIPS score.

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DISCUSSION

The results show that regardless of the daily dose, a meaningful decrease in trough VPA plasma concentration to subtherapeutic values occurred in all our patients due to administration of meropenem. The trough plasma concentration of VPA decreased at least by 70% following initiation of meropenem therapy. Increasing the daily dose of VPA to 3000 mg or more while under treatment with meropenem or 1 to 7 days after meropenem discontinuation did not raise the plasma concentration of VPA above 20 μg/mL. Because the optimal target VPA plasma concentration range is accepted to be 50 to 100 μg/mL,[25] we suggest that even tight monitoring of plasma VPA concentration throughout meropenem therapy, as previously proposed,[14] or even up to 7 days after its discontinuation might not succeed in maintaining therapeutic concentration of the drug.

Although one would have expected to have somewhat higher initial VPA concentrations in patients on a higher VPA dose, in fact, only insignificant differences between the different dose groups were observed. It can be explained by the significant interpatient variability and a poor correlation between the dose of VPA and its plasma concentration.[26,27] Because the dose of VPA is mainly guided by the plasma concentrations, we believe that similar initial VPA concentrations in the different dose groups were the result of plasma concentration-targeted individualization of the patient's VPA dose.

Our results show that the onset of the interaction is rapid, as a significant decrease of VPA to subtherapeutic concentration was observed in all patients who had VPA concentration recorded within 24 hours of meropenem initiation. This result may suggest that the increase in clearance of VPA by meropenem does not involve enzyme induction but more probably enzyme inhibition, as discussed earlier. Our results, as well as previously published results, indicate slow recovery of VPA concentrations after administration of carbapenem antibiotics, which is longer than kinetically dictated by the carbapenem half-life. Although there are no in vitro data to support it, we think that the inhibition of beta-glucuronidase by meropenem is irreversible; therefore, recovery of VPA plasma levels is dependent on the rate of the enzyme turnover and not meropenem plasma half-life. Enzyme induction by carbapenem, though previously proposed,[28] does not seem to be a probable mechanism in this interaction because the enzyme induction process usually takes days to weeks to occur.[29] As meropenem increases the clearance of VPA and rapidly decreases its plasma concentration, we suggest it might be of value in the management of VPA overdose or toxicity, which is usually managed by extracorporeal therapies such as hemodialysis and hemoperfusion.

A retrospective study by Spriet et al[24] showed an interaction between meropenem and VPA, leading to a significant decrease in the plasma concentration of VPA that recovered within an average of 8 days. The results of our study similarly showed a decrease of VPA plasma levels following meropenem administration, with recovery occurring 8 to 14 days after meropenem discontinuation. Moreover, we performed a subgroup analysis of different VPA daily doses, which showed that the decrease and the subsequent increase in VPA plasma concentration followed similar behavior in all dose groups. The patients in group 1 (VPA dose <1000 mg/d) had a 4-fold numerical increase in VPA concentration more than 14 days after meropenem discontinuation, but the difference did not reach statistical significance, probably because of the small sample size in this group. We also assessed whether meropenem daily dose affected the decrease in VPA plasma and found no difference between the 3000-mg/d and 6000-mg/d groups, indicating that the decrease of VPA plasma concentration is significant and not affected by the meropenem dose administered. The pharmacokinetic interaction between VPA and meropenem is significant and has a rapid onset. As the therapeutic effect of VPA is considered concentration dependent, when meropenem treatment is essential, we recommend substituting VPA with another antiepileptic drug; otherwise, its therapeutic effect may be compromised.

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REFERENCES

1. Zaccara G, Messori A, Moroni F. Clinical pharmacokinetics of valproic acid—1988. *Clin Pharmacokinet.* 1988;15:367-389.

2. Kochar DK, Rawat N, Agrawal RP, et al. Sodium valproate for painful diabetic neuropathy: a randomized double-blind placebo-controlled study. *QJM.* 2004;97:33-38.

3. Kochar DK, Jain N, Agarwal RP, Srivastava T, Agarwal P, Gupta S. Sodium valproate in the management of painful neuropathy in type 2 diabetes: a randomized placebo controlled study. *Acta Neurol Scand.* 2002;106:248-252.

4. Yoon MS, Savidou I, Diener HC, Limmroth V. Evidence-based medicine in migraine prevention. *Expert Rev Neurother.* 2005;5:333-341.

5. D'Amico D. Antiepileptic drugs in the prophylaxis of migraine, chronic headache forms and cluster headache: a review of their efficacy and tolerability. *Neurol Sci.* 2007;28(suppl 2): S188-S197.

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6. Ehret MJ, Levin GM. Long-term use of atypical antipsychotics in bipolar disorder. *Pharmacotherapy*. 2006;26:1134-1147.

7. Dutta S, Faught E, Limdi NA. Valproate protein binding following rapid intravenous administration of high doses of valproic acid in patients with epilepsy. *J Clin Pharm Ther*. 2007; 32:365-371.

8. Fleming J, Chetty M. Therapeutic monitoring of valproate in psychiatry: how far have we progressed? *Clin Neuropharmacol*. 2006;29:350-360.

9. Klugman KP, Dagan R. Carbapenem treatment of meningitis. *Scand J Infect Dis Suppl*. 1995;96:45-48.

10. Santucci M, Parmeggiani A, Riva R. Seizure worsening caused by decreased serum valproate during meropenem therapy. *J Child Neurol*. 2005;20:456-457.

11. Clause D, Decleire PY, Vanbinst R, Soyer A, Hantson P. Pharmacokinetic interaction between valproic acid and meropenem. *Intensive Care Med*. 2005;31:1293-1294.

12. Nacarkucuk E, Saglam H, Okan M. Meropenem decreases serum level of valproic acid. *Pediatr Neurol*. 2004;31:232-234.

13. De Turck BJ, Diltoer MW, Cornelis PJ, et al. Lowering of plasma valproic acid concentrations during concomitant therapy with meropenem and amikacin. *J Antimicrob Chemother*. 1998;42:563-564.

14. Coves-Orts FJ, Borras-Blasco J, Navarro-Ruiz A, Murcia-Lopez A, Palacios-Ortega F. Acute seizures due to a probable interaction between valproic acid and meropenem. *Ann Pharmacother*. 2005;39:533-537.

15. Fudio S, Carcas A, Pinana E, Ortega R. Epileptic seizures caused by low valproic acid levels from an interaction with meropenem. *J Clin Pharm Ther*. 2006;31:393-396.

16. Spriet I, Meersseman W, De Troy E, Wilmer A, Casteels M, Willems L. Meropenem-valproic acid interaction in patients with cefepime-associated status epilepticus. *Am J Health Syst Pharm*. 2007;64:54-58.

17. Yokogawa K, Iwashita S, Kubota A, et al. Effect of meropenem on disposition kinetics of valproate and its metabolites in rabbits. *Pharm Res*. 2001;18:1320-1326.

18. Yamamura N, Imura-Miyoshi K, Naganuma H. Panipenum, a carbapenem antibiotic, increases the level of hepatic UDP-glucuronic acid in rats. *Drug Metab Dispos*. 2000;28: 1484-1486.

19. Nakajima Y, Mizobuchi M, Nakamura M, et al. Mechanism of the drug interaction between valproic acid and carbapenem antibiotics in monkeys and rats. *Drug Metab Dispos*. 2004;32: 1383-1391.

20. Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: interactions between antiepileptic drugs and other drugs. *Lancet Neurol*. 2003;2:473-481.

21. Tanaka E. Clinically significant pharmacokinetic drug interactions between antiepileptic drugs. *J Clin Pharm Ther*.1999;24:87-92.

22. Parmeggiani A, Riva R, Posar A, Rossi PG. Possible interaction between acyclovir and antiepileptic treatment. *Ther Drug Monit*. 1995;17:312-315.

23. Horn JR, Hansten PD, Chan LN. Proposal for a new tool to evaluate drug interaction cases. *Ann Pharmacother*. 2007;41: 674-680.

24. Spriet I, Goyens J, Meersseman W, Wilmer A, Willems L, Van Paesschen W. Interaction between valproate and meropenem: a retrospective study. *Ann Pharmacother*. 2007;41:1130-1136.

25. Beydoun A, Sackellares JC, Shu V. Safety and efficacy of divalproex sodium monotherapy in partial epilepsy: a double-blind, concentration-response design clinical trial. Depakote Monotherapy for Partial Seizures Study Group. *Neurology*. 1997;48:182-188.

26. Blanco-Serrano B, Otero MJ, Santos-Buelga D, Garcia-Sanchez MJ, Serrano J, Dominguez-Gil A. Population estimation of valproic acid clearance in adult patients using routine clinical pharmacokinetic data. *Biopharm Drug Dispos*. 1999;20: 233-240.

27. Battino D, Estienne M, Avanzini G. Clinical pharmacokinetics of antiepileptic drugs in paediatric patients: Part I. Phenobarbital, primidone, valproic acid, ethosuximide and mesuximide. *Clin Pharmacokinet*. 1995;29:257-286.

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

29. Armstrong SC, Cozza KL, Sandson NB. Six patterns of drug-drug interactions. *Psychosomatics*. 2003;44:255-258.

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