Istanbul J Pharm 53 (1): 92-94
DOI: 10.26650/IstanbulJPharm.2023.1202590
Case Report

A clinical pharmacist's intervention on interaction between meropenem and valproic acid in paediatric inpatient clinic: A case report

Ahmet Cakir[1], Hasan Memis[1], Nesligul Ozdemir[2], Zeynep Ulkü Gün[1]

[1]Inonu University, Faculty of Pharmacy, Department of Clinical Pharmacy, Malatya, Turkiye
[2]Hacettepe University, Faculty of Pharmacy, Department of Clinical Pharmacy, Ankara, Turkiye

ORCID IDs of the authors: A.Ç. 0000-0003-1590-585X; H.M. 0000-0001-7158-1795; N.Ö. 0000-0003-2551-9549; Z.Ü.G. 0000-0002-7131-6585

Cite this article as: Cakir, A., Memis, H., Ozdemir, N., & Gun, N.U.(2023). A clinical pharmacist's intervention on interaction between meropenem and valproic acid in paediatric inpatient clinic: A case report. *Istanbul Journal of Pharmacy, 53(1), 92-94.* DOI: 10.26650/IstanbuJPharm.2023.1202590

ABSTRACT

Background and Aims: Drug-drug interactions cause many complex drug events, especially adverse drug effects. It is known that drug interactions occur when meropenem and valproic acid are used together. It was aimed to back up existing research on the interaction of valproic acid.
Methods: After an interaction had been suspected by the ward pharmacists, all of the patient's drugs were assessed via UpToDate® and Micromedex® databases and the interaction management was shared with the physician in charge.
Results: The patient's serum valproic acid through level was in therapeutic range before meropenem administration. After the administration of meropenem, the patient's number of seizures increased and the serum trough level of valproic acid decreased to 4.3 µg/ml. The valproic acid levels turned back to normal range after switching to a carbapenem antibiotic.
Conclusion: Drug interactions are often encountered in paediatric patients and it is of critical importance in terms of seizure control. Because of the drug interaction between valproic acid and meropenem, one should avoid using these medications concomitantly. If that is impossible, daily serum valproic acid levels should be monitored with caution. Clinical pharmacists could increase the clinicians' awareness about drug-drug interactions.

Keywords: Drug interactions, hospitalized child, meropenem, clinical pharmacists, valproic acid

INTRODUCTION

Valproic acid (VPA) is widely used as an antiepileptic drug among paediatric patients (Miranda Herrero et al., 2015). The therapeutic range for serum VPA levels is 50–100 µg/ml for seizures (Wu, Pai, Hsiao, Shen, & Wu, 2016).

As being wide-spectrum antibiotics, carbapenems are used to treat infections caused by Gram positive, Gram negative aerob and anaerobic microorganisms (Wu et al., 2016).

It is reported in case reports and retrospective studies that carbapenems decrease serum VPA levels (Park et al., 2012; Spriet et al., 2007). The interaction between carbapenems and VPA was reported firstly in Japanese literature in the late 1990s (Al-Quteimat & Laila, 2020). In animal studies, it is shown that carbapenems cause the formation of valproate glucuronide and a rise in uridine diphosphate levels (Yamamura, Imura-Miyoshi, & Naganuma, 2000). Also, carbapenems inhibit the activity of VPA-glucuronidase

Address for Correspondence:
Hasan MEMİŞ, e-mail: eczhasanmemis@gmail.com

Submitted: 11.11.2022
Revision Requested: 13.01.2023
Last Revision Received: 14.01.2023
Accepted: 17.02.2023
Published Online: 26.04.2023

in human liver cytosol (Nakamura, Nakahira, & Mizutani, 2008). Through these mechanisms, carbapenems can decrease VPA levels. The reduction in VPA levels rapidly happens in the first 24 hours of concomitant administration (Al-Quteimat & Laila, 2020). It is recommended to avoid the concomitant use of these two drugs (Spriet et al., 2007).

Here, we present a case regarding how the interaction happened and how clinical pharmacists can cope with that.

CASE PRESENTATION

A twelve-year-old female patient was admitted to an emergency department of a tertiary care hospital with complaints of fever, coughing, and breathing problems. Then, the patient was admitted to the general paediatric ward with pneumonia. The patient has cerebral palsy, epilepsy, and a gastrostomy feeding tube. The patient was receiving sodium valproate 400 mg q12h, zonisamide 100 mg q12h, ethosuximide 250 mg q8h and clobazam 15 mg q12h as epilepsy treatment via a gastrostomy feeding tube at home. The patient was experiencing seizure attacks up to four times daily which were lasting for about 20 seconds before admission.

On the 16th day of hospitalization, the patient's serum VPA through level (C0) was 62.5 µg/ml. On the 17th day, a sputum culture test was done and resulted in *Pseudomonas aeruginosa* and on the 23rd day of hospitalization, intravenous 1-gram meropenem q8h therapy was started.

On the 29th day, clinical pharmacists had suspected that a drug interaction might occur between meropenem and VPA, and questioned the patient's caregiver about the seizure status. Upon learning that the patient's number of seizure count had increased to twenty-five per day, the clinical pharmacists assessed all the patient's drugs via the UpToDate® and Micromedex® databases. The clinical pharmacists recommended measuring the serum VPA C0 to the physician in charge. On the 30th day, it was seen that the blood C0 of VPA had decreased to 4.3 µg/ml. Although the VPA had been transitioned from oral to intravenous form on the same day, the patient's number of seizure count had not decreased on the first day of intravenous VPA therapy. The patient's meropenem therapy had switched to intravenous piperacillin-tazobactam 320 mg q8h on the patient's 31st day of hospitalization.

On the patient's 32nd and 38th day of hospitalization, the serum VPA C0 increased to 19.2 µg/ml and 40.9 µg/ml, respectively. Alongside an increase in VPA trough concentrations, the patient's seizure frequency had decreased and on the 48th day, the patient was discharged. The interaction was assessed according to Naranjo Adverse Drug Reaction Probability Scale (Naranjo et al., 1981). The interaction could be classified as "probable" as it gets 7 scores according to the Naranjo Scale.

DISCUSSION

In a study, a 21-year-old female patient was admitted to an emergency department with seizure. Then, VPA 1000 mg over 24-hour infusion therapy was started. On the 13th day of hospitalization, an intravenous meropenem 1-gram q8h therapy was started. On the 15th day, the patient experienced seizure episodes. Despite increasing the VPA dose to 3600 mg, the serum level of VPA remained smaller than 10 µg/ml. On the 19th day, an interaction was suspected between meropenem and VPA and upon that, meropenem therapy was suspended. On the 27th day, the patient's level of VPA was 52.4 µg/ml. The Naranjo Probability Scale indicated that there could be a possible relationship between meropenem-VPA interaction and acute seizures (Coves-Orts, Borras-Blasco, Navarro-Ruiz, Murcia-Lopez, & Palacios-Ortega, 2005).

In another study, a 3-year-old boy was admitted to hospital and on the first day of hospitalization, meropenem therapy was started to treat pneumonia. On his 3rd day, because of his uncontrolled seizures and low serum VPA levels, his VPA dose was gradually increased. When meropenem therapy was switched, the VPA level reached 18.6 µg/ml (Okumura, Andreolio, Di Giorgio, Carvalho, & Piva, 2017).

In another study, a 5-year-old female patient was admitted to a hospital with severe respiratory failure. On her 10th day of hospitalization, meropenem therapy was started because of hemodynamic deterioration. Five days after the meropenem therapy was started, the serum VPA level was found to be smaller than 3 µg/ml and due to that, the meropenem therapy was suspended. After the dose of VPA was increased, the VPA concentration was found to be 55 µg/ml. Eventually, the patient died because of refractory hypoxemic failure (González & Villena, 2012).

Although it is recommended that if using these two drugs concomitantly is inevitable, another drug that belongs to a different antiepileptic drug class should be added to the patient's drug regimen temporarily; that is however, not always the case. In this case report, the concomitant use of more than one drug belonging to different antiepileptic classes was of no benefit because of the patient's resistant seizures.

In our study, it has been shown that converting the oral form of VPA to the intravenous form has failed to prevent this interaction to happen. However, our study has some limitations: the daily serum VPA levels were not determined, so it is unclear when the interaction started or whether the VPA levels reached the therapeutic range after the antibiotic treatment was switched.

CONCLUSION

In conclusion, drug interactions are often encountered in paediatric patients and it is of critical importance in terms of seizure control. Because of the drug interaction between VPA and meropenem, one should avoid using these medications concomitantly. If that is impossible, daily serum VPA levels should be monitored with caution.

Examining the literature, it is found that there is not as much research in Türkiye compared to studies around the world on clinical pharmacists' detection and the management of drug interactions in paediatric clinics.

Peer-review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- Z.Ü.G., N.Ö.; Data Acquisition- A.Ç., H.M.; Data Analysis/Interpretation- H.M., A.Ç., N.Ö., Z.Ü.G.; Drafting Manuscript- H.M., A.Ç.; Critical Revision of Manuscript- N.Ö., Z.Ü.G.; Final Approval and Accountability- H.M., A.Ç., N.Ö., Z.Ü.G.

Conflict of Interest: The authors have no conflict of interest to declare

Financial Disclosure: Authors declared no financial support.

REFERENCES

- Al-Quteimat, O., & Laila, A. (2020). Valproate Interaction With Carbapenems: Review and Recommendations. *Hospital Pharmacy, 55*(3), 181-187. doi:10.1177/0018578719831974
- Coves-Orts, F. J., Borras-Blasco, J., Navarro-Ruiz, A., Murcia-Lopez, A., & Palacios-Ortega, F. (2005). Acute seizures due to a probable interaction between valproic acid and meropenem. *Annals of Pharmacotherapy, 39*(3), 533-537. doi:10.1345/aph.1E358
- González, C., & Villena, R. (2012). Interacción entre meropenem y ácido valproico: A propósito de dos casos pediátricos. *Revista chilena de infectología, 29*, 353-355. Retrieved from http://www.scielo.cl/scielo.php?script=sci_arttext&pid=S0716-10182012000300018&nrm=iso
- Miranda Herrero, M. C., Alcaraz Romero, A. J., Escudero Vilaplana, V., Fernandez Lafever, S. N., Fernandez-Llamazares, C. M., Barredo Valderrama, E., . . . de Castro, P. (2015). Pharmacological interaction between valproic acid and carbapenem: what about levels in pediatrics? *European Journal of Paediatric Neurology, 19*(2), 155-161. doi:10.1016/j.ejpn.2014.12.010
- Nakamura, Y., Nakahira, K., & Mizutani, T. (2008). Decreased valproate level caused by VPA-glucuronidase inhibition by carbapenem antibiotics. *Drug Metabolism Letters, 2*(4), 280-285. doi:10.2174/187231208786734049
- Naranjo, C. A., Busto, U., Sellers, E. M., Sandor, P., Ruiz, I., Roberts, E. A., . . . Greenblatt, D. J. (1981). A method for estimating the probability of adverse drug reactions. *Clinical Pharmacology & Therapeutics, 30*(2), 239-245. doi:10.1038/clpt.1981.154
- Okumura, L. M., Andreolio, C., Di Giorgio, C., Carvalho, P. R. A., & Piva, J. P. (2017). Meropenem-induced low valproate levels in a cerebral palsy child. *The Brazilian Journal of Infectious Diseases, 21*(4), 491. doi:10.1016/j.bjid.2017.01.010
- Park, M. K., Lim, K. S., Kim, T. E., Han, H. K., Yi, S. J., Shin, K. H., . . . Yu, K. S. (2012). Reduced valproic acid serum concentrations due to drug interactions with carbapenem antibiotics: overview of 6 cases. *Therapeutic Drug Monitoring, 34*(5), 599-603. doi:10.1097/FTD.0b013e318260f7b3
- Spriet, I., Goyens, J., Meersseman, W., Wilmer, A., Willems, L., & Van Paesschen, W. (2007). Interaction between valproate and meropenem: a retrospective study. *Annals of Pharmacotherapy, 41*(7), 1130-1136. doi:10.1345/aph.1K079
- Wu, C. C., Pai, T. Y., Hsiao, F. Y., Shen, L. J., & Wu, F. L. (2016). The Effect of Different Carbapenem Antibiotics (Ertapenem, Imipenem/Cilastatin, and Meropenem) on Serum Valproic Acid Concentrations. *Therapeutic Drug Monitoring, 38*(5), 587-592. doi:10.1097/FTD.0000000000000316
- Yamamura, N., Imura-Miyoshi, K., & Naganuma, H. (2000). Panipenum, a carbapenem antibiotic, increases the level of hepatic UDP-glucuronic acid in rats. *Drug Metabolism and Disposition, 28*(12), 1484-1486. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/11095587