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Letter to the Editor

Meropenem-induced low valproate levels in a cerebral palsy child



Dear Editor,

Valproate (VPA) is commonly prescribed as first-line agent to control seizure disorders.¹ Concomitant use of cytochrome P450 (CYP) inducers or inhibitors can result in altered VPA absorption or elimination rates. While CYP-based drug interactions are well described, non-CYP interactions are increasingly becoming visible in literature. The importance of non-CYP interaction is exemplified by a case of meropenem-induced VPA serum level reduction in a child with poor neurological prognosis.

A 3-year old boy was admitted to the hospital to investigate a genetic disorder and progressive uncontrolled convulsions. Since 11-months old, when the child was diagnosed with hypotonic cerebral palsy (CP), recurrent episodes of hospitalizations due to bronchiolitis and bronchopneumonia have occurred. On day 1, meropenem and vancomycin were started due to ventilator-associated pneumonia and VPA was progressively escalated from 40 to 70 mg/kg/day, due to uncontrolled convulsions and low VPA serum levels (<2.8 mcg/mL) on day 3. Concomitant drugs included phenobarbital, topiramate and clobazam. When meropenem was switched to piperacillin-tazobactam, VPA levels started to increase (10 mcg/mL) and, two weeks later, achieved 18.6 mcg/mL. The drug interaction was classified² as probable (score 6), according to Drug Interaction Probability scale due to well documented evidence on adults³ and a single study in children.⁴ Carbapenems can irreversibly inhibit acylpeptide hydrolase, an enzyme that deconjugates valproate-glucuronide complex and reduces urinary elimination of VPA.⁵ The abrupt onset³⁻⁵ (<24 h), the slow³⁻⁵ (7–20 days) time to return to therapeutic levels, and the risks associated with uncontrolled convulsions suggest to consider, when feasible, non-carbapenemic antibiotics in CP children on VPA.

REFERENCES

1. Putignano D, Clavenna A, Campi R, et al. Antiepileptic drug use in Italian children over a decade. *Eur J Clin Pharmacol*. 2017;73:241–8, <http://dx.doi.org/10.1007/s00228-016-2168-0>.
2. Horn JR, Hansten PD, Chan LN. Proposal for a new tool to evaluate drug interaction cases. *Ann Pharmacother*. 2007;41:674–80.
3. Wu CC, Pai TY, Hsiao FY, Shen LJ, Wu FL. The effect of different carbapenem antibiotics (ertapenem, imipenem/cilastatin, and meropenem) on serum valproic acid concentrations. *Ther Drug Monit*. 2016;38:587–92.
4. Miranda Herrero MC, Alcaraz Romero AJ, Escudero Vilaplana V, et al. Pharmacological interaction between valproic acid and carbapenem: what about levels in pediatrics? *Eur J Paediatr Neurol*. 2015;19:155–61.
5. Suzuki E, Nakai D, Yamamura N, Kobayashi N, Okazaki O, Izumi T. Inhibition mechanism of carbapenem antibiotics on acylpeptide hydrolase, a key enzyme in the interaction with valproic acid. *Xenobiotica*. 2011;41:958–63.

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Conflicts of interest

The authors declare no conflicts of interest.