**Case Report**

**Drug Interaction between Valproic Acid and Meropenem: A Case Report**

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Valproic acid and meropenem is commonly co-administrated in neurosurgical patients. Meropenem potentially decreases the valproic acid level, which may cause perioperative seizure. There has been no previous report of drug interaction between valproic acid and meropenem in Thailand. The authors report a patient who faced uncontrolled seizure after co-administrated valproic acid and meropenem. The level of valproic acid was assessed in different times after the administration of meropenem. Rapid decrease of valproic level was detected. However, due to the administration of other antiepileptic agents, seizure did not develop. It is important for the physicians to recognize drug interaction between valproic acid and meropenem. Avoiding co-administration of both agents, valproic acid level monitoring and additive of other antiepileptic agents seem to be the appropriate solution.

**Keywords:** Drug interaction, Valproic acid, Meropenem

*Nosocomial central nervous system infection from multi-drug resistant bacteria is one of the major problems in neurosurgery units, especially in tertiary care or referral hospitals.*

**Case Report**

A 77-year-old male patient who had had a ventriculo-peritoneal shunt implanted after removal of a sellar meningioma was admitted due to seizure. He also had hypertension and end-stage renal disease for which he required intermittent hemodialysis. Oral valproic acid (2,400 mg per day) and topiramate (100 mg per day) were used to control the seizures. The serum level of valproic acid was 66.51 μg/ml after 61 days of receiving these drugs. He developed fever with alteration of consciousness and was empirically treated with 1 gm of meropenem, followed by 500 mg intravenous injections every 12 hours. Twenty-four hours after the meropenem was begun, the valproic acid serum level was 18.96 μg/ml. Due to the unresolved seizure the valproic acid was continued at 2,400 mg per day but changed to an intravenous injection form, with an increased dose of topiramate to 225 mg per day. Six days after beginning the meropenem, the valproic acid level was 6.26 mg/ml. At this time, the valproic acid was stopped, while the topiramate was continued to control his seizures.

**Discussion**

Meropenem, one of the antibiotics which
belong to the carbapenem group, is used in the empirical treatment of nosocomial infections due to its broad-spectrum action against both gram positive and gram negative bacteria\(^2\). Among the available carbapenem antibiotics, meropenem is also commonly administered in neurosurgical units because of the absence of cilastatin that potentially causes seizure\(^2\).

Valproic acid is an antiepileptic agent commonly used to control seizure, partial seizures, generalized seizure and status epilepticus\(^3\). Due to its broad-spectrum epileptic control, valproic acid is widely used for prophylaxis against seizures in brain injuries and neurosurgery\(^3\). Up to 50% is excreted in bile in the glucuronide compound, which is synthesized by uridine diphosphate glucuronyltransferase (UDPGT) enzyme (glucuronidation)\(^11\). Gastrointestinal bacterial flora is important to change this compound to a free form of valproic acid that is able to be re-absorbed through enterohepatic circulation\(^4,11\). The remaining half of the valproic acid is mostly metabolized by β-oxidation while only 10% is metabolized via cytochrome P450\(^4\).

The full mechanism of drug interaction between meropenem and valproic acid is unknown\(^4,12-14\). Two hypotheses attempt to explain the lower levels of valproic acid during meropenem co-administration\(^5,16\). According to the study of Kojima, the broad-spectrum action against bacteria of meropenem decreases the gastrointestinal flora, which in turn causes a decreased rate of change of the glucuronide compound form of valproic acid to the free form, which is able to be re-absorbed via enterohepatic circulation\(^15\). The second theory postulates that the meropenem enhances glucuronidation, which increases the biliary excretion of glucuronide compounds, and leads to decreased hydroxylation, which in turn, lowers the level of gastrointestinal re-absorbable valproic acid\(^10\).

In conclusion, due to the rapid decrease level of valproic acid of meropenem and less benefit to increase the dosage of valproic acid to achieve the therapeutic level, the avoidance of co-administration of valproic acid and meropenem in cases when co-administration is necessary. Serum valproic acid levels should be closely monitored and co-administration of other antiepileptic agents considered.

Potential conflicts of interest
None.

References
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