Case Report

Drug Interaction between Valproic Acid and Meropenem: A Case Report

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Valproic acid and meropenam 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*

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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[1]. Meropenem is always for empirical and definite treatment due to the low prevalence of drug-induced seizure among carbapenem group antibiotics[2]. Valproic acid, one of a number of antiepileptic agents that have shown good efficacy in preventing and treating perioperative seizures, is also widely used[3]. When both drugs are administered to the same patient, however, various studies have found an apparent drug interaction between the meropenem and valproic acid that resulted in a decrease in the serum level of valproic acid, which can lead to a perioperative seizure[4-10]. The present report shows the change of valproic acid levels with time sequences after co-administration of valproic acid with meropenem in a neurosurgical patient.

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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 glucuronyltranferase (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].

As previous reports, in the presented case a rapid decrease of serum level of valproic acid after administration of meropenem was observed, falling from 66.51 ug/ml to 18.96 ug/ml after 24 hours of meropenem use[12-14]. According to the desired therapeutic level of valproic acid of 50-100 ug/ml, the level of valproic acid of the patient was critically low, which was identified in five days in the previous reports of Clause et al and De Turck et al[13,14]. However, seizure was not observed in other patients due to co-administration of phynyltoin and in patients with indication of valproic acid in the presented patient for prophylaxis against perioperative seizure.

The higher dosage of valproic acid did not result in an increased serum level during administration of meropenem in the presented patient, as was found in earlier reports[13,14]. In addition, in the presented patient, the change from oral form to injection did not seem to result in any benefit, because the oral bioavailability of valproic acid was more than 90%, therefore insignificantly different serum level of oral and injection form[3,4]. The previous report of Nacarkucuk et al showed to recovery level of valproic acid after meropenem was stopped in a few days. However, the patient in this current report was not evaluated for valproic level after meropenem was stopped[12]. There have been only a few reports of drug interactions between other carbapenems and valproic acid[17].

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.

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อันตรกิริยาของยาระหว่างกรดวาลโพรอิคและเมอโรพีเนม: รายงานผู้ป่วย 1 ราย

วิชัย สันติมาลีวรกุล, สุทธิพร ภัทรชยากุล, ศรัญญู ชูศรี

กรดวาลโพรอิคและเมอโรพีเนมมักถูกใช้ร่วมกันในผู้ป่วยประสาทศัลยศาสตร์ เมอโรพีเนมสามารถลดระดับของกรดวาลโพรอิคเป็นผลให้เกิดการชักก่อน/ระหว่าง/หลังผ่าตัดยังไม่เคยมีการรายงานอันตรกิริยาของยาระหว่างกรดวาลโพรอิคและเมอโรพีเนมในประเทศไทย ผู้นิพนธ์รายงานผู้ป่วยที่ไม่สามารถควบคุมอาการชักหลังจากได้รับกรดวาลโพรอิคร่วมกับเมอโรพีเนม การประเมินระดับของกรดวาลโพรอิคช่วงเวลาต่าง ๆ หลังได้รับเมอโรพีเนม พบว่าการลดระดับของกรดวาลโพรอิคอย่างรวดเร็วขณะใช้ยากันชักตัวอื่นร่วมไม่ก่อให้เกิดการชัก สิ่งสำคัญคือแพทย์ต้องตระหนักอันตรกิริยาของยาระหว่างกรดวาลโพรอิคและเมอโรพีเนม การหลีกเลี่ยงการใช้ยาทั้งสองร่วมกัน การตรวจเตือนระดับกรดวาลโพรอิค และการให้ยากันชักอื่นร่วมด้วยเป็นการแก้ไขปัญหาที่เหมาะสม