A Case Report on Meropenem and Valproic Acid Drug-Drug Interaction Induced Status Epilepticus

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Abstract

Valproic acid and meropenem is generally co-administrated in neurosurgical cases. Meropenem potentially decreases the valproic acid position, which may beget perioperative turn like seizure. Such serious adverse effect through potential interaction should be taken seriously and made aware by clinicians. Among various neurological emergencies status epilepticus is one of the most important and as it progresses, therapeutic control becomes difficult. Patients receiving antiepileptics and carbapenem group antibiotics concomitantly should be closely monitored due to possible drug interaction between these agents. The authors report a case of a 39-year-old male patient who was admitted with C4-C5 type C injury with neurological deficit due to road traffic accident. His Glasgow Coma Scale score was $E_4M_2V_1$ and graded 'A' on Asia Impairment Scale. Patient was on treatment with valproic acid for existing schizophrenia. He was empirically treated with meropenem as cover antibiotic for infection due to phrenic nerve palsy that allowed secretions to be retained and increase the chance of infection. On third day of admission, he developed 2 episodes of breakthrough seizure in less than 5 minutes. Post status epileptic, Inj. Meropenem was stopped as cover antibiotic and he was treated with Inj. Fosphenytoin, Inj. Midazolam and Inj. Levetiracetam after which no such seizures were observed.

Keywords: Meropenem, Valproic acid, Seizures and Drug interaction.

Introduction

A continuous, generalized, convulsive seizure lasting longer than five minutes or two or more seizures during which the patient doesn't regain baseline consciousness is known as status epilepticus (SE), a serious medical emergency that is linked to severe morbidity and mortality.[1] Numerous neurological or systemic illnesses, including stroke, traumatic brain injury, brain tumor, central nervous system (CNS) infections, electrolytic and metabolic conditions, and anoxic encephalopathy, can also cause epileptic seizures[2,3]. Infections can also cause hospital admissions for people with epilepsy, or they can contract infections while hospitalized. The management of infectious illness comorbidities in patients with epilepsy is thus complicated by medication interactions between AEDs and antibiotics [4]. For instance, rifampicin improves the clearance of lamotrigine, erythromycin, clarithromycin, and isoniazid raise the serum levels of carbamazepine, ethosuximide, and phenytoin[4,5].

An AED frequently used to treat both partial and generalized seizures is valproic acid (VPA). The drug is extensively metabolized in the liver and is known to interact with other AEDs and non-AEDs[6]. Additionally, the use of carbapenems or

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oral contraceptives causes a decrease in serum levels of VPA whereas the use of chlorpromazine causes an increase [5]. A class of antibiotics known as carbapenems is effective in treating illnesses brought on by bacteria that are resistant to a variety of drugs [7]. In case reports by Coves-Orts FJ and retrospective investigations by Spriet I and Haroutiunian S, carbapenems have been demonstrated to lower serum levels of VPA. [8,9,10] The intricate processes governing the interaction between VPA and carbapenems have not yet been thoroughly analyzed [11]. However, it has been suggested that combining these drugs is best avoided because the decrease in serum VPA levels brought on by carbapenems may worsen seizures [8,9].

According to the majority of findings, VPA and carbapenem combination therapy should be avoided unless absolutely essential [8,12]. When co-administering VPA and carbapenems, other AEDs should be temporarily added when simultaneous use is unavoidable. We provide a case report of a patient who experienced epileptic seizures as a result of a potential pharmacokinetic interaction between meropenem and an antiepileptic drug.

Case Presentation

A 39-year-old male patient was admitted with C4-C5 type C injury with neurological deficit due to road traffic accident. His Glasgow Coma Scale score was $E_4M_2V_1$ and graded 'A' on Asia Impairment Scale; Physical examination revealed consciousness tend to fall asleep, closed eyes and normal-sized, normally reactive pupils. Patient was presented with phrenic nerve palsy and brought into intensive care unit with diaphragmatic paralysis. Blood cultures, Procalcitonin, complete blood count, C-Reactive Protein, blood chemistry and CSF samples were obtained where procalcitonin levels were extremely high. He is a known case of Ankylosing spondylitis, Schizophrenia and Hypothyroidism and on treatment with Tab. Valproic acid 750mg, Tab. Levothyroxine 100 µg, Tab. Clozapine 50mg and Tab. Etorcoxib 120mg. The patient was consulted with neurology and infectious disease doctors. Meropenem was started as cover antibiotic for infection due to copious, yellow secretions suggesting the same. On 3rd day of the antibiotic therapy status epilepticus seizures were observed where he developed 2 episodes of breakthrough seizure in less than 5 minutes.Inj. Fosphenytoin 750mg over a period of 2-3 hours followed by 150mg TDS.intravenous (IV) was started. Also, the patient was intubated and mechanically ventilated. EEG revealed generalized epileptiform activity. Inj. Midazolam and Inj. Levetiracetam were added for treatment respectively after which no such seizures were observed and the reaction stopped on the same day. The patient was consulted with neurology and infectious disease doctors daily. Anti-biotherapy with Inj. Meropenem was discontinued after reaction on the same day. On day 21 he was extubated; no seizures had occurred over the following 48 hours. He was discharged from the ICU post stabilization.

Discussion

Due to its broad-spectrum action against both gramme positive and gramme negative bacteria, meropenem, one of the antibiotics in the carbapenem family, is used in the empirical treatment of nosocomial infections. Meropenem, one of the various carbapenem antibiotics, is frequently used in neurosurgical facilities because it doesn't contain the seizure-causing compound cilastatin [13]. Antiepileptic medication called valproic acid is frequently used to treat seizures, including partial seizures, generalised seizures, and status epilepticus. Valproic acid is frequently used for prophylaxis against seizures in brain injury and neurosurgery due to its broad-spectrum epileptic control [14]. The glucuronide molecule, which is produced by the enzyme uridine diphosphate glucuronyltransferase (UDPGT), is expelled in bile up to 50% of the time (glucuronidation) [15]. To convert this substance into a free form of valproic acid that can be reabsorbed through enterohepatic circulation, the gut bacterial flora is crucial [15,16]. Only 10% of the remaining valproic acid is metabolised by cytochrome P450, with the majority of the remaining half being broken down by β-oxidation [16].

Meropenem and valproic acid interact with uncertain full mechanism of action [16,17,18]. Two hypotheses account for the decreased valproic acid levels with meropenem co-administration [19,20]. According to Kojima's study, meropenem's

broad-spectrum antibacterial effect reduces the gastrointestinal flora, which in turn slows the conversion of valproic acid's glucuronide compound form to the free form, which can then be reabsorbed via enterohepatic circulation [21]. According to the second idea, meropenem increases glucuronidation, which raises the amount of glucuronide molecules that are excreted by the liver. It also causes less hydroxylation, which reduces the amount of gastrointestinally re-absorbable valproic acid [22].

In this case, we report we describe a patient who was admitted to the intensive care unit with a C4-C5 type C injury, neurological deficit graded 'A' on Asia Impairment Scale, and other injuries as a result of an automobile accident. Blood samples were taken for blood cultures, complete blood counts, C-Reactive Protein, Procalcitonin, blood chemistry, and CSF tests where his Procalcitonin levels were elevated. He is currently receiving treatment with Tab. Valproic acid 750 mg, Tab. Levothyroxine 100 g, Tab. Clozapine 50 mg, and Tab. Etorcoxib 120 mg for his known cases of Ankylosing Spondylitis, Schizophrenia, and Hypothyroidism. Doctors who specialize in infectious diseases and neurology both spoke with the patient. As a preventative measure against infection, meropenem was empirically administered to him. On the third day after being admitted, he experienced 2 breakthrough seizures in less than 5 minutes. Following his diagnosis of post-status epilepticus, the cover antibiotic Inj. Meropenem was stopped, and he was treated with Inj. Fosphenytoin, Inj. Midazolam, and Inj. Levetiracetam. Over the ensuing 48 hours, no more seizures were noted. After stabilization, he was released from the ICU.

After the administration of carbapenems, serum VPA levels drop to subtherapeutic levels, according to a study by Chi-Ren Huang. Within 24 hours of starting therapy with either high or low doses of carbapenems, the levels of VPA were reduced. Carbapenems have the potential to cause seizures and may also cause antiepileptic medication serum levels to decrease [23]. Clinicians need to be aware of this potential combination since it could have major negative consequences. This case report offers compelling evidence of the potential epileptic activity of meropenem and the possibility for pharmacological interactions with antiepileptic medications. This relationship needs to be managed by clinicians due to the clinical and financial implications. Antiepileptic drug serum levels should be monitored in patients taking carbapenem antibiotics and antiepileptic medications concurrently. The concurrent use of these two medications should be avoided if at all possible.

Conclusion

One of the most significant neurologic emergencies is status epilepticus, and as its duration lengthens, therapeutic control becomes increasingly challenging. Due to a potential drug interaction between antiepileptics and antibiotics from the carbapenem group, patients receiving both medications at the same time should be continuously watched.

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