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Case Report

MEROPENEM INDUCED REDUCTION IN SERUM VALPROATE LEVEL- A CASE REPORT

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ABSTRACT

Objective: To report a case of meropenem induced reduction in serum valproate level.

Methods: The clinical data of an epileptic patient who experienced a decrease in seizure control due to a drug interaction between valproate and meropenem is described.

Results: The patient was a 26 years old male who was a known case of refractory focal epilepsy and underwent surgery for the same. This patient was on five antiepileptic drugs including valproate. On treatment with meropenem for the management of post surgical site infection due to multi-drug resistant Klebsiella pneumoniae, the patient experienced seizures due to decline in valproate level. Increasing the dose of valproate could not control the seizures. However, changing the antibiotics to a non carbapenem controlled the seizures.

Conclusion: The present report highlights the potential drug interaction between valproate and meropenem. Physicians should thus avoid co-administration of both these agents. If concomitant administration is essential, close monitoring of valproate concentration and clinical monitoring for breakthrough seizures are necessitated.

Keywords: Meropenem, Carbapenem, Serum valproate, Epilepsy, Drug interaction.

INTRODUCTION

In patients with epilepsy, drug interactions have proven to be a major challenge for the maintenance of therapeutic concentrations of antiepileptic drugs. Sodium valproate, one of the most frequently used drug in the treatment of generalized tonic-clonic and partial seizures, has a narrow therapeutic index [1]. carbapenems like meropenem are considered the drugs of choice for treatment of multi-drug resistant (MDR) infections including those caused by extended spectrum beta-lactamase (ESBL) producing organisms [2-4].

carbapenem antibiotics, especially meropenem, may decrease the plasma concentrations of valproate, thus decreasing its therapeutic activity [5-18]. In the present era with increasing incidence of MDR bacterial infections, and increasing utilization of carbapenems, this drug interaction has significant clinical implications to the patient and physician. We report a case of meropenem induced reduction in valproate level and discuss the clinical relevance, potential mechanisms and management of the valproate carbapenem interaction.

CASE REPORT

A 26 years old man, a known case of refractory focal epilepsy was admitted to the hospital for left parietal temporal occipital (PTO) craniotomy and disconnection under transcranial motor evoked potential monitoring. This patient had a history of seizures from 2 years of age and seizure frequency was 2-3 episodes per day with or without generalizations. He was on antiepileptic drugs from childhood and on admission was receiving phenobarbital, valproate, clobazam, oxcarbazepine and lacosamide. During his stay in the hospital, he developed fever and his wound culture grew MDR *Klebsiella pneumoniae*. Hence, the patient was administered meropenem 500 mg twice daily intravenously, adjusted according to his creatinine clearance. The very next day, the patient experienced seizures and thus his valproate dosing frequency was increased from 500 mg twice daily to thrice daily. But patient did not respond to the increase in the dose of sodium valproate. At this point of time, we decided to discontinue meropenem because of the reported potential for interaction between meropenem and valproate. On the day of meropenem discontinuation, the serum valproate level was 21.1 µg/ml (therapeutic range: 50-100 µg/ml). He was started on non carbapenem antibiotic with good response to fever and infection. Seizure control was also achieved. After 14 days of discontinuation of meropenem serum valproate level was 95.7 µg/ml

DISCUSSION

Antiepileptic drugs are commonly prescribed for long periods, to a lifetime in most cases. Many patients require treatment with more than one AED for optimum control for seizure management of concomitant or intercurrent condition, acute or chronic will require additional medication. Antimicrobials are the most frequent class of drugs co administered for patients on multiple medications. Mechanistically, seizure propensity of the β-lactams is related to their binding to γ-amino butyric acid receptors. There are numerous reports of seizure activity associated with imipenem-cilastatin, with seizure rates ranging from 3-33%. For meropenem, Doripenem, and Ertapenem, the seizure rate for each agent is reported as less than 1% [19-22].

Interactions between antiepileptic drugs and antimicrobial agents are of prime importance in the management of epilepsy and infections. Case reports in the literature have shown that co-administration of carbapenems, including meropenem to patients receiving valproate results in a reduction of valproate levels below the therapeutic range which impairs seizure control [4]. The exact mechanism for this interaction is not known. However, several *in vitro* and animal studies have been carried out in attempts to elucidate the mechanisms for carbapenem-valproate interaction. The possible mechanisms that have been suggested include inhibition of

absorption of valproate at the baso lateral membrane of the intestinal epithelial cells; suppression of entero hepatic circulation, increased uptake of valproate into erythrocytes and inhibition of valproate glucuronidase by carbapenem [23-27].

Consistent with other reports, in our patient also serum valproate levels reduced below therapeutic range following meropenem treatment, resulting in seizures. Different studies have reported declines in the range of 66% to 90% [11, 28, 29]. However, in the present case, the % decline could not be determined due to lack of serum valproate concentration prior to initiation of meropenem therapy.

This case confirmed previous literature reports that an increase in valproate dose does not compensate for the reduction in serum valproate concentration caused by a carbapenem [6, 13]. Seizures were controlled only after meropenem treatment was discontinued.

Haroutiunian *et al.* [11] have reported gradual increase in valproate concentration after 8 to 14 days following discontinuation of meropenem. Consistent with the same, in the present case, the serum valproate levels 14 days after discontinuation of meropenem therapy was within the therapeutic range (95.7 μg/ml).

Clinically important antiepileptic drug interactions are frequently observed in medical practice. Since the therapeutic effect of valproate depends on its serum concentration, there may be breakthrough seizures control in patients using valproate with carbapenem antibiotics due to decline in valproate levels.

Therefore, physicians should avoid co-administration of both these agents. If concomitant administration is essential, adverse clinical consequences may be minimized, as appropriate, by individualized dose adjustments guided by careful monitoring of clinical response and measurement of serum valproate concentrations.

CONFLICT OF INTERESTS

Declared None

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