Seizure worsening caused by low serum valproate levels from an interaction between valproate and meropenem

Valproat ve meropenem arasındaki etkileşime bağlı olarak serum valproat düzeyinin düşmesinin ortaya çıkardığı nöbetler

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ABSTRACT
We present an interaction of meropenem with valproate in an epileptic child, leading to seizure exacerbations owing to the rapid lowering of serum valproate concentration. An increase of seizure frequency and somnolence were observed in the patient after the addition of meropenem to the treatment, and a rapid decline of valproate serum concentrations was observed after two doses of meropenem. This decline was the most likely cause of the increase in seizure frequency. The dosage of valproate was raised and meropenem was stopped. Two days later, the seizures stopped. Five days later, the serum valproate concentrations raised to three fold, and they rose to therapeutic levels four weeks later. To avoid drug interaction that reduces the serum concentration of valproate, meropenem in epileptic patients using valproate for the treatment of epilepsy should be administered cautiously. If concomitant administration is essential, close observation of serum concentration of valproate and clinical course of the patient are necessary.

Keywords: Carbapenems, Drug interactions, Meropenem, Seizures, Valproate

ÖZET

Anahtar kelimeler: İlaç etkileşimi, Karbapenemler, Meropenem, Nöbetler, Valproat

Introduction
Meropenem, is a carbapenem antibiotic, and has a broad spectrum of antimicrobial activity. Valproate is widely used in the treatment of epileptic seizures in children. In recent years, low serum concentrations of valproate were reported in children and adults receiving concomitant treatment with meropenem [1]. We present an interaction of meropenem with valproate in an epileptic child, leading to seizure exacerbations owing to the rapid lowering of serum valproate concentration.

Case report
This report describes a fourteen-year-old epileptic inpatient girl who had received concurrent treatment with meropenem for the treatment of lobar pneumonia and pleuresia, and
valproate for the treatment of epilepsy. The patient has been
epileptic since three-months of age, with motor and mental
retardation, and has been diagnosed as Lennox-Gastaut
syndrome. The patient was receiving valproate + lamotrigine
+ clobazam + levetiracetam treatment by oral route during
the last three years because of resistant seizures. Serum
levels of valproate were observed within the therapeutic
range (50 – 100 µg/ml) during the follow-up period.

The patient was admitted to the emergency department
with the complaints of cough, fever, malaise, and feeding
difficulty during the last four days. She was examined as
dyspneic, tachypneic, cyanotic, and dehydrated. Ceftriaxone
and vancomycin were started as an initial therapy for lobar
pneumonia. On the 2nd day of hospitalization, her fever and
respiratory distress were relieved. On the 3rd day, serum
level of valproate was 68.31 µg/mL, within the therapeutic
range (Table I). On the 4th day, the patient was clinically
worse and pleurisy was diagnosed on the chest X-ray and
ultrasonography. Meropenem was started on the 5th day with
1 gr of dose twice daily intravenously, and ceftriaxone was
discontinued. On the 6th day the patient became lethargic,
and numerous generalised myoclonic seizure episodes
occurred involving her face, arms, and legs. After two doses
of meropenem, serum level of valproate, was 12.18 µg/mL.
The increase in seizure frequency and somnolence were
considered to be due to the rapid decline of valproate serum
concentration after addition of meropenem to the treatment.
This situation was the most likely cause of increase in
seizure frequency. The dosage and frequency of valproate
were raised from 1000 mg/day (500 mg, every twelve hours)
to 1050 mg/day (350 mg, every six hours), with nearly the
same dose, and meropenem was stopped on day seven.

After meropenem therapy was discontinued, piperacillin/
tazobactam was started in addition to vancomycin. Two
days later, the seizures were taken under control. Five days
later, the serum valproate concentration rose to three-fold
and four weeks later, on day 36, concentrations rose up to
therapeutic levels (Table I). The drug interaction probability
scale indicates a highly probable drug interaction between
valproate and meropenem use in our patient. For this reason,
the seizures were considered to be related to the concurrent
administration of meropenem and valproate.

Antibiotherapy was completed on day 18, the patient
recovered from pneumonia and pleurisy, and was discharged
from the hospital.

Discussion
Meropenem is a carbapenem antibiotic with a broad spectrum
of activity against gram-positive and gram-negative aerobic
and anaerobic organisms [2]. It has been used in critically
ill patients with severe infections, such as pneumonia and
sepsis. The risk of seizure occurrence increases in patients
using carbapenems [3]. Meropenem has a lower risk (0.02 -
0.1%) [4] of seizure than imipenem (0.4 - 0.9%), probably
due to structural differences, and their lower affinity for
gamma-aminobutyric acid receptors in the central nervous
system [2]. For this reason, meropenem is considered one of
the best choices for patients with severe infections who have
epilepsy or other neurologic diseases.

Valproate is a widely used anti-epileptic drug in the
treatment of epilepsy including generalized tonic-clonic

Table 1. Valproate serum levels, valproate dose and frequency, and seizures during meropenem therapy. Valproate serum levels before,
during, and after meropenem therapy. After the patient was discharged on day 18, the serum level of valproate increased up to 58.11 µg/
ml on day 36.

<table>
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<th>Day 3</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
<th>Day 9</th>
<th>Day 17</th>
<th>Day 36</th>
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<tr>
<td>Valproate serum levels (µg/mL)</td>
<td>68.31</td>
<td>12.18</td>
<td>36.7</td>
<td>39.06</td>
<td>58.11</td>
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<tr>
<td>Treatment with meropenem</td>
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<td>Two doses, every 12 hours</td>
<td>Discontinued</td>
<td>No</td>
<td>No</td>
<td>No</td>
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<tr>
<td>Seizures</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<td>Dose (mg) and frequency of valproate</td>
<td>500, every 8 hours</td>
<td>500, every 8 hours</td>
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<td>350, every 8 hours</td>
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and partial seizures [2]. This drug is heavily attached to plasma proteins and largely metabolized in the liver by glucuronidation (70%). Beta-oxidation, omega-oxidation and hydroxylation are minor pathways in the metabolization of valproate. All carbapenems, including meropenem, have lowered the serum concentration of valproate in epileptic patients to a sub-therapeutic level. Because serum valproate concentration was not decreased by carbapenems in hepatectomized rats, the liver is considered as the key organ for the decrease of valproate concentration by carbapenems. Valproate-glucuronidase in human liver microsomes, and especially in cytosol, was inhibited by carbapenems [5]. The interaction between valproate and a carbapenem (panipenem/betamipron) was first reported by Nagai et al [6] in two children in 1997. Other cases have been reported since then; as in our case, seizures have occurred during concomitant therapy of valproate and meropenem [1,2,7,8].

Decline in valproate serum concentration and seizures were observed within 24 hours after concomitant administration of valproate and meropenem in our patient. The most rapid decrease of serum valproate within 24 [7] and 36 hours [6] were reported in other studies. In some other reports, this decline was observed within three to seven days after the initiation of meropenem to patients receiving valproate therapy [1]. This rapid decline in serum concentration of valproate is not explained with enzyme induction because this mechanism usually requires several days [9]. Inhibition of plasma protein binding of valproate by carbapenems has been suggested for the interaction between valproate and carbapenems [5,7]. Valproate has a high protein-binding ratio (90 - 95%), whereas, meropenem is a low (2%) protein bound drug. For this reason, these rapid declines may not be explained by the mechanism of competition in protein binding [10]. The most comprehensive research study on this topic was undertaken by Yokogawa et al [10]. They studied the effects of meropenem on valproate metabolism in rabbits, because metabolism of this drug is similar to that in humans. This study indicated that urinary excretion of valproate-glucuronide, and suppression of valproate-glucuronide hydrolysis in the liver were increased at the time of concomitant administration of valproate and meropenem [10]. Furthermore, suppression of valproate-glucuronidase hydrolysis in the gastrointestinal tract was also increased in this concomitance [10]. The mechanisms of rapid decline of valproate serum concentration has been elucidated by recent studies. Some studies have indicated that the clearance of valproate is increased by meropenem by increasing the urinary excretion of valproate glucuronide [7,8,10]. Other mechanisms in which decreases occur in the serum levels of valproate by carbapenems are: inhibition of the hydrolysis of valproate glucuronide, increase in the glucuronidation of valproate, suppression of enterohepatic recirculation of valproate, and increase in the erythrocyte distribution of valproate, which induce the decrease in serum levels of valproate [11]. The reduced blood levels of valproate at a fairly short time period in our patient may be caused by decreased hydrolysis of valproate-glucuronide conjugation resulting from eliminating of microorganism with beta-glucuronidase activity owing to antibacterial drugs. For these reasons, reabsorption of free valproate decreases.

Carbapenems may induce seizures during acute neurologic diseases as intracranial infections, hemorrhage, stroke, trauma, and tumors [3,9]. None of these have occurred in our patient during concomitant therapy of valproate and meropenem.

In the reported cases to date, none of the antibiotics (i.e. ceftazidime, cefotaxime, amikacin, vancomycin, ampicillin, tobramycin, and clindamycin) other than carbapenems have caused a decline of the serum concentration of valproate. In addition, serum valproate concentrations increased after the termination of carbapenems according to these reports [1]. Rapidly changed serum concentrations of valproate is not consistent with the induction of enzymes participated in valproate metabolism process.

Serum valproate concentration was decreased while under meropenem treatment and gradually returned to normal levels after cessation of meropenem in a reported 14-year old girl with cystic fibrosis and multidrug resistant pulmonary infection with intravenous antibiotics [12]. Her serum valproate concentration kept low despite elevated daily dosing of valproate and a loading dose. Finally, on the 18th day of cessation of meropenem the blood valproate level reached its normal value. The daily doses were increased, however, the loading dose was not used in our case. The low blood levels of valproate until the 36th day may be related with inadequate dose of valproate without the loading dose. Conversely, seizures were controlled after two days and the serum valproate concentration rose to three-fold after the discontinuation of meropenem and increased daily valproate doses. Therefore, the loading valproate dose with increased daily doses may be used to increase the blood valproate levels.

Clinicians should be aware of the interaction between valproate and carbapenems and of the possible clinical consequences like increasing the frequency of epileptic seizures and/or status epilepticus. To avoid drug interaction that reduces the serum concentration of valproate, care should be taken when administering meropenem in epileptic
patients using valproate for the treatment of epilepsy. If possible, another antibiotic, except carbapenems, should be used in patients using valproate or the antiepileptic therapy should be switched to another drug other than valproate. However, this second option may not be feasible in many patients if their seizures are controlled only with valproate. In addition, if the antiepileptic drug regime has changed, at least two – four weeks will be required for sufficient levels of the new antiepileptic drug to be attained [1]. If concomitant administration is essential, close observation of serum concentration of valproate and clinical course of patient are necessary.

There were not plasma levels of other antiepileptic drugs excluding valproate.

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References