

Case Series

Interaction between meropenem and valproate: Not to overlook

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Abstract

Background Valproic acid is commonly used to treat various types of seizures and follows non-linear pharmacokinetics with a therapeutic range of 50 – 150 ug/ml. Several retrospective studies have reported that concomitant administration of VPA and carbapenem lead to decrease in VPA levels significantly and results in failure of seizure control. Different studies suggest the mechanism of interaction as (i) carbapenem may inhibit the gastrointestinal absorption of VPA (ii) meropenem accelerated the glucuronidation of VPA to VPA glucuronide (VPA-G) and inhibited the hydrolysis of VPA-G back to the VPA thus increasing the clearance of VPA and VPA-G and (iii) due to fast erythrocyte distribution of VPA by carbapenem, VPA levels has been reduced. **Purpose** To report four cases who were maintained on therapeutic levels of VPA and had sub-therapeutic levels afterward due to the administration of meropenem. **Method** through CPOE system of AKUH the cases in 2014 were identified who were on valproate-meropenem combination with the available pre and post meropenem valproate levels. **Result** Patients of different age group showed significant reduction in VPA levels within 48 hour of administration of meropenem. **Conclusion** This case series describing the clinical importance of this probable drug interaction and promote its awareness among physicians in Pakistan. If a patient was therapeutic on the same dose of valproate and need broad spectrum coverage, a dose adjustment of valproate should not be done and physicians should consider either alternative broad spectrum antibiotic or renally cleared antiepileptic to avoid this frequently used dangerous drug combination.

Key Words

interaction, meropenem, valproic acid (VPA), therapeutic drug monitoring.

Introduction

Valproic acid an antiepileptic drug is metabolized mainly by liver (cytochrome P450 enzyme system mainly by glucuronidation) and its metabolites are removed by kidneys (Bauer, 2005; Gugler & Unruh, 2012). Because of its complex metabolized system it has many interactions with other drugs (like other anticonvulsants, some antibiotics especially carbapenem etc.) (Patsalos & Perucca, 2003). Several studies supported that the concomitant administration of carbapenem with valproic acid results in significant decrease in valproate levels (Yoon & Kim, 2013). The exact mechanism of interaction is still

unknown but some data suggest that carbapenem may inhibit the gastrointestinal absorption of valproic acid (Patsalos & Perucca, 2003; Torii, Takiguchi, Izumi, Fukushima, & Yokota, 2002) and some suggest that meropenem accelerated the glucuronidation of VPA to VPA glucuronide (VPA-G) and inhibited the hydrolysis of VPA glucuronide back to the VPA by inhibiting hydrolytic enzyme thus increasing the clearance of VPA and VPA-G (Lee, Sun, Lee, Wu, & Wu, 2012; Nakajima et al., 2004) and in one study conducted in rats and human it is suggested that due to fast erythrocyte distribution of VPA by carbapenem, VPA levels has been reduced

(Lee et al., 2012; Ogawa, Yumoto, Hamada, Nagai, & Takano, 2006).

Valproic acid is highly protein bound to albumin (90 -95%) and has a narrow therapeutic index (Gugler & Unruh, 2012) The blood concentration required in the range of 50 – 150 ug/ml to produce the effect (Lee et al., 2012) so albumin level monitoring is also required along with valproate level when patient is on valproate. In children 6-12 years old, reported clearance and half-life of valproic acid is 10-20 ml/h/kg and 6-8 hours as compare to adults in which reported clearance is 7-12ml/h/kg and half-life is 12-18 hours (Bauer, 2005). With other enzyme inducers antiepileptic drugs (like carbamazepine, phenytoin, phenobarbital etc.) clearance rate is higher i.e. 20-30 ml/h/kg (for children) 15-18 ml/h/kg (for adults) and half live shorter i.e 4-6 hr (for children), 4-12 hours (for adults). The reported volume of distribution (Vd) for children is 0.2 L/kg and for adult is 0.15L/kg. (Bauer, 2005) On the other hand carbapenem are sole bactericidal β lactam antibiotic effective against ESBL producing resistant organisms (Hawkey & Livermore, 2012). After an exhaustive literature review we found no study in Pakistan which evaluate this interaction. We presented cases where an interaction between VPA and meropenem led to the severe reduction in VPA levels.

Case No. 1

A 6-year-old, 18.2 kg male child, with a history of intractable seizures and was on Ketogenic diet admitted in Tertiary Care Hospital, for Gastrostomy tube insertion. At the time of admission, he was on antiepileptic drugs valproate 250mg three times a day, levetiracetam 250mg three times a day, Lamotrigine 25mg two times a day, topiramate 37.5mg two times a day , phenobarbital 75mg at bed time and

clonazepam 0.25mg two times a day because he had a history of intractable seizures. After Pre-operative assessment feeding gastrostomy was done under general anesthesia. Postoperatively patient was being treated empirically with ceftriaxone which was switched later on to meropenem, as recommended by the hospital's neurology team. Post operatively the antiepileptic medicines were switched to IV administration. Baseline blood valproate level was 53.9 ug/ml when he was taking sodium valproate 250mg orally three times a day. After 48 hour of being treated with meropenem with a dose of 360 mg every 8 hourly, the patient's valproate level fell to <10 μ g/ml and patient showed the issue of fits like activity (muscle twitching) for which meropenem was discontinued and the patient was given a bolus dose of IV valproate (400mg) and the valproate maintenance dose was changed to 200mg IV every eight hourly along with the addition of IV phenytoin 60mg every 12 hourly and oral lacosamide 12.5 mg every 12 hourly. After these measures had been implemented, the patient remained seizure-free with improved neurological symptoms and has discharged on oral phenytoin, valproate, levetiracetam, lamotrigine, clonazepam, lacosamide and phenobarbital.

Case No. 2

A 62 year old male having known case of hypertension, diabetes diagnosed with squamous cell carcinoma of right buccal mucosa admitted in tertiary care hospital with a complaint of non-healing lump in right cheek for last 3 months. On December 2014, after baseline investigations, right composite resection with mandibulectomy, right neck dissection, feeding gastrostomy and free fibular flap was performed without any intraoperative complications. On the night of operation day patient became hypoxic and tachypnoeic for which CPR

was done for 10 minutes and patient was revived and shifted to ICU and kept on ventilator. Empirically piperacillin-tazobactam was started for 6 days Chest CT scan with contrast was done which showed no evidence of pulmonary embolism. MRI brain was done which showed hypoxic brain injury. He had some episode of seizures and GCS dropped to 2/10. Myoclonic jerks was also noticed later for which a bolus dose of IV valproate 1500 mg followed by 500 mg every 8 hourly given. Blood valproate level was 57.0 ug/ml noted after 6 days of dosing. Later on, tracheostomy was done and empirically meropenem was started at the doses of 1g every 8 hourly. After 48 hours of dosing, valproate level rapidly decreases to < 10 ug/ml for which patient was given the bolus dose of 1500 mg followed by 1000 mg IV three times a day but there was no improvement in seizure like activity after which the valproic acid discontinued and switched to other antiepileptic (levetiracetam and midazolam). After making the patient seizure free, patient was discharged on antihypertensive, insulin, and valproic acid, levetiracetam, clonazepam with nursing home healthcare services.

Case No. 3

A 33 year old female having known case of pancreatic pseudo cyst admitted with myoclonic jerk of limb for one day for which one stat dose of IV midazolam given along with routine antiepileptic drugs (clonazepam PO 1 mg three times a day +levetiracetam 500 mg PO three times a day+ IV valproate 500mg three times a day). MRI brain, CSF DR and culture along with EEG done. In her initial workup TLC count was increased for which Meropenem, Acyclovir was started empirically. Her blood valproate level was 57.6 ug/ml on dose of sodium valproate 500mg IV three times a day. After 32 hour of being treated with meropenem, the patient's valproate

level fell to 20.7 µg/ml for which meropenem was discontinued and piperacillin/tazobactam was started. After 22 hours of dc meropenem patient valproate level rise to 37.0 with a same dose of valproate without any seizure like activity. During hospital stay her GCS dropped for which CT scan of brain done which showed thalamic infarct. Code was ran as per the discussion with family and decided for withdrawal of care. Patient expired after 07 days of admission.

Case No. 4

A 63 year-old female with known case of status epilepticus since age of 5 years, hypertension, status asthmatics since 2009 and anoxic brain injury admitted in emergency care of Tertiary Care Hospital with seizures, high grade fever (100°F) from last 3 days, cough, burning micturition since last night. At the time of admission, she was on antiepileptic drugs valproate 500mg two times a day, Lamotrigine 100mg two times a day, lacosamide 50 mg two times daily. In emergency ward, for control of seizures, patient received one shot of IV levetiracetam, diazepam and valproic acid and for urinary tract infection, ceftriaxone was started empirically. CT head was also done which showed severe hydrocephalus for which family declined for neurosurgical intervention. Because of focal seizures on left side her oral lamotrigine and lacosamide dose adjusted along with the addition of oxcarbazepine, topiramate, IV levetiracetam, valproate and Phenytoin. Later on patient discharged on IV antibiotic Meropenem for 7 days (based on urine culture which showed >10,000 cfu/ml of E.coli sensitive to meropenem and fosfomycin only), valproate 500 mg three times a day, topiramate 75 mg two times daily, oxcarbazepine 450 mg two times a day, phenytoin 300mg bed time, levetiracetam 1000mg three times daily, lacosamide 100mg two times daily and

lamotrigine 150 mg two time daily. Blood valproate level was 92.4 ug/ml when she was on sodium valproate 500mg three times a day. After 07 days of being treated with meropenem, she readmitted with breakthrough seizures with the valproate

level fell to <10µg/ml due to which all Antiepileptic drugs were readjusted. It should be notified that on 11th day of completion of meropenem VAL level rise to 48.8 (D11), 65.5 (D37), 87.6 (D58) and 90.2 (D88).

Table 1: Meropenem-Valproate Interaction Case Reports

*levels available after 168 hour

Patient Age (Yrs.)	Gender	Weight (Kg)	VPA Dose mg/day	Pre Meropenem Level (ug/ml)	Post Meropenem Level (ug/ml)	Effect on VPA Concentration (↓by %)	Meropenem Exposure (hours)
06	M	18.2	750	53.9	<10	81.44	48
62	M	74	1500	57.0	<10	82.45	48
33	F	60	1500	57.6	20.7	64.00	32
63	F	85	1500	92.4	<10	89.17	168*

Discussion

The bioavailability of IV and oral valproate is approximately 100% that's why there will be no change in levels after switching from oral to IV valproate (Bauer, 2005). Valproate follow non-linear pharmacokinetics in terms of protein-binding saturation that's why we observed reduced valproate serum levels during meropenem treatment, despite an increased maintenance dose and multiple loading doses, resulted in recurrence of seizures. Valproate levels only increased significantly after meropenem treatment was stopped which we can observe in case no 4. It should be noted that all valproate levels should be measured just before the next dose of any time after the attainment of steady state in 3-5 half-lives- thus representing the trough levels. For example the calculated half-life of patient is 7 hour ($t_{1/2} = 0.693 * V_d / Cl \Rightarrow 0.693 * 3.64 L / 0.36L/hr$) so the level can be obtained at any time after the 1.5 day of dosing (5 half-lives= $5*7 hr = 35$ hours). Furthermore in the presence of other enzyme inducer antiepileptic drugs the clearance of valproate is higher so the doses needs to be adjusted accordingly.

There are many studies published on interaction of valproic acid and meropenem in which some experts suggest to avoid this dangerous interaction and some suggest to monitor the levels closely and use higher doses of VPA or add other antiepileptic's temporarily as well (Vélez-Díaz-Pallarés et al., 2012; Yoon & Kim, 2013) but the present study findings suggested that higher doses of VPA will not produce the beneficial effect because of its non-linear pharmacokinetic nature because after the administration of meropenem, the competition between VPA and meropenem will be started for protein binding which results in increase in unbound concentration of VPA in plasma which then distributed to liver cells where it is metabolite and then excreted through kidney. So that the level of VPA in plasma and brain tissues would be significantly decreased (Hobara, Hokama, Ohshiro, Kameya, & Sakanashi, 2002).

Conclusion

The prescribing physician must be aware about this concomitant drug interaction and the correct time of taking the level based on

the half live of VAL in that patient. The concomitant use of carbapenem should be avoided, replacing antibiotic empirically or according to the culture wherever possible for patients taking valproate long term to control epilepsy. Due to these retrospective evidences, our Pharmacists have keen knowledge to counsel the physicians about this pharmacokinetic interactions and hold these type of combinations.

Competing Interests

The Author declare that there is no conflict of interest.

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