Meropenem at Recommended Dose Can Cause Potential Risk for Seizure in Hemodialysis Patient

Abdullah Al-Hwiesh1*, Amani Alhwiesh1, Eman Fathi2, Fadwa Mohamed2, Manar Elsayed2, Jameelou Almazan2, Abdullah Alrashidi2, Fatimah Aldehimi2, Azeesa Aldwaihi2, Saad Alqhtani2, Hussin Alsharani2 and Nadia Aluauda2

1Department of Nephrology, King Fahd Hospital of the University, Saudi Arabia
2Department of Nephrology, Security Force Hospital Damam, Saudi Arabia
3Department of Nephrology, Damman Central Hospital, Saudi Arabia

Abstract

Dosage adjustment of meropenem is usually recommended in hemodialysis patient and about 30% of meropenem is cleared during regular hemodialysis session. However, most of published trials excluded patients on regular hemodialysis. Little is known about the exact dosage of meropenem to avoid central nervous system toxicity. Here we report a 65 year old Saudi lady known case of end stage renal failure that was admitted due to pyelonephritis and was started on meropenem as recommended dose, developed tonic clonic convulsion after seventh dose of meropenem and the seizure completely aborted after discontinuation the offending drug. The recommended dosage of 500 mg daily in hemodialysis patients may be still too high in particularly Asians patient, owing to their relative small body mass index.

Keywords: Meropenem; Seizure; ESRD; Hemodialysis

Introduction

Seizures are episode of transient neurologic change due to hyper excitation of neuronal activity in the brain. Seizures are divided into two types: provoked and unprovoked seizure. Provoked seizure occurs with a recognized cause and is not expected to recur in the absence of that particular cause [1]. The incidence of provoked seizures in patients older than age 60 years is estimated at 0.55 to 1 per 1000, with linear increases every decade after age 30 years. Acute stroke, intracranial lesions, metabolic encephalopathy, drugs and alcohol are identifiable causes of provoked seizures [2]. Drugs and drug withdrawal account for 10% of provoked seizures [3]. A range of medications have been identified as a cause of provoked seizures in late life such as: opioids, methotrexate, carbapenems (imipenem, meropenem), penicillin and hypoglycemic agents [3,4]. Meropenem is a broad spectrum antibiotic, works by inhibiting bacterial cell-wall synthesis by binding to penicillin-binding proteins. It metabolized in liver and excreted in urine. Its clinical adverse effects including nausea, diarrhea, constipation, seizure (≤ 1%), urticaria and dysuria [5]. Elderly people are particularly susceptible to drug induce seizure due to high prevalence of impaired drug clearance and poly-pharmacy [1,3]. Carbapenems in general had broad spectrum antibacterial and commonly used in severe complicated bacterial infections [4,6]. Carbapenems have antibacterial activity against mainly gram-negative pathogens. It is well tolerated by most patients, but an important adverse effect of their use is the Central Nervous System (CNS) toxicity [7]. Initial trials reported seizure associated mainly with imipenem in particularly in high dose and elderly patients [8]. Infectious disease of America recommended meropenem over imipenem due to decreases risk of seizure with meropenem [9]. However, there is inconsistency in literature regarding whether there is a difference in the seizure potential between the two Carbapenems. In general the frequency of seizure for imipenem and meropenem is 0.4% and 0.7% respectively [10,11]. Dosage adjustment of meropenem is usually recommended in hemodialysis patient and about 30% of meropenem is cleared during regular hemodialysis session [12]. However, most of published trials excluded patients on regular hemodialysis. Little is known about the exact dosage of meropenem to avoid (CNS) toxicity. Here we report a 65 year old Saudi lady known case of end stage renal failure on regular hemodialysis was admitted due to pyelonephritis and was started on meropenem as recommended dose, developed tonic clonic convulsion after seventh dose of meropenem and the seizure completely aborted after discontinuation the offending drug. The
remedies started. On the 7th day after holding meropenem and intensifying her meropenem was discontinued and ciprofloxacin 250 mg daily was the possibility of meropenem induce seizure was raised. Therefore her cognitive dysfunction and recurrent uncontrolled seizures, no electrolyte disturbance or other concomitant medication explain attack of seizure, nonspecific CT brain, nonspecific EEG changes, No epileti form discharges were recorded Figure 2. Due to recurrent photonic stimulation and hyperventilation produced no abnormality. No epiletiform discharges were recorded. Muscular and movement artifact were recorded.

**Case Presentation**

A 65 years old Saudi lady known case of diabetes mellitus since more than 20 years with diabetic retinopathy, neuropathy and nephropathy end stage renal failure on regular hemodialysis three time per week, four hour duration through right prenchath for 2 year. Also known case of hypertension, coronary heart disease status post stent and cerebrovascular disease old right cerebral artery stroke. She was maintained on insulin, amlodipine, calcium carbonate, one alpha and folic acid. Her blood sugar and blood pressure was well controlled. She was admitted to our hospital due to pyelonephritist and was started on meropenem 500 mg daily as her urine culture grew klebsella pneumonia. On 7th day of antibiotic patient started to be confused, agitated with incoherent speech, disoriented with visual hallucination and she developed recurrent attack of generalized tonic clonic seizure that lasted for about 1 min each. Due to that, she was loaded with phenytoin then 100 mg every 8 h and her condition deteriorated with more episodes of tonic clonic seizure, so valoropic acid was added. CT brain showed multiple scattered hypodense areas seen more on the left occipital region, right high frontal region, at the medial aspect of right cerebelluar hemisphere and the vermis. Left aspect of midbrain and left aspect of the pons tiny spots of hypodensity diffuse periventricular white matter hypodensities. No mass effect or midline shift. No hemorrhagic lesion. No intra or extra axial collection.

Recommended dosage of 500 mg meropenem daily in hemodialysis patients may be still too high in particular Asians patient, owing to their relative small body mass Index.

**Discussion**

Carbapenem in general had abroad spectrum antibacterial and commonly used in sevious complicated bacterial infections [6]. Carbapenems have antibacterial activity against mainly gram-negative pathogens. It is well tolerated by most patients, but an important adverse effect of their use is the CNS toxicity [7]. Initial trials reported seizure associated mainly with imipenem in particularly in high dose and elderly patients [6]. Infectious disease of America recommended meropenem over imipenem due to decreases risk of seizure with meropenem [9]. However, there is inconsistency in literature regarding whether there is a difference in the seizure potential between the two carbapenem. In general the frequency of seizure for imipenem and meropenem is 0.4% and 0.7% respectively [8,9]. In recent meta-analysis by Joan et al. [13] the ORs for risk of seizures from imipenem, meropenem, ertapenem and doripenem compared with other antibiotics were 3.50 (95% CI 2.23, 5.49), 1.04 (95% CI 0.61, 1.77), 1.32 (95% CI 0.22, 7.74) and 0.44 (95% CI 0.13, 1.53), respectively. In studies directly comparing imipenem and meropenem, there was no difference in epileptogenicity in either risk difference or pooled OR analyses [13].

It is worth noting, that the main risk factors for carbapenem induce seizure are higher dose and renal impairment as meropenem
mainly excreted by kidney. However, there is conflicting result in literature regarding other risk factors (previous CNS injury, or history of seizure and concomitant medication known to decrease seizure threshold) [14,15].

The pool safety studies for carbapenem have identified the frequency of seizure in 0.4% and 0.2% for meropenem and ertapenem respectively. The absolute risk of seizure with carbapenem compared to non carbapenem antibiotic is still low. However most of meropenem trials associated with CNS toxicity have excluded patients on regular hemodialysis [16]. Little is known about the exact dosage of meropenem to avoid central nervous system toxicity. The molecular weight of meropenem is 383.5 g/mol, the plasma half-life is approximately 1 h in adults with normal renal function. Plasma half-life is increased and clearance of the drug is decreased in patients with renal impairment, about 30% of meropenem is cleared during regular hemodialysis session [17]. Drug clearance is highly dependent on the method of renal replacement, filter type, and flow rate. Appropriate dosing requires close monitoring of pharmacologic response, signs of adverse reactions due to drug accumulation [14]. The mechanism of seizure provocation by carbapenem is multifactorial; it’s related to the drug’s ability to reduce inhibition of epileptic discharges by blocking the amino butyric acid (GABA). A receptor; to its action on -Amino-3-Hydroxy-5-Methyl-iso xazole Propionate (AMPA) and N-Methyl-D-Aspartate (NMDA) receptor complexes (which may be secondary to the drug’s action on GABA receptors); or to its penicillin-like activity [18].

Common (CNS) symptoms of carbapenem toxicity including disorientation, incoherent speech, agitation, restlessess and visual hallucination [15]. The high protein binding, high volume of distribution and increase permeability of blood brain barrier of meropenem may hinder rapid tissue elimination after CNS toxicity [16,17].

Our patient is un-uric and has small bodyweight which lead to accumulation of meropenem recommended dose leading to classical CNS toxicity that completely disappeared after removing the offending drug. Therefore, our case report highlighted that the recommended dose of 500 mg meropenem on daily basis for conventional hemodialysis patient may be still too high in particular un-uric with small body weight, so heath care providers awareness about meropenem CNS toxicity would avoid unnecessarily extensive investigation, hospitalization and potential devastation complications.

References