Case Report

Carbapenem associated seizure in a severe melioidosis patient: A case report

Josephine Henry Basil[a], Chee Ping Chong[b,*]

[a]*Master in Clinical Pharmacy Candidate, Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, University Sains Malaysia (USM), 11800 Minden, Penang, Malaysia*

[b]*Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, University Sains Malaysia (USM), 11800 Minden, Penang, Malaysia*

Abstract. The use of carbapenems has been associated with increased risk of seizure with imipenem having a higher propensity to induce seizure as compared to meropenem. As there is limited report on the cross-reactivity between these two agents, clinicians may choose to switch the antibiotic regimen to meropenem whenever an imipenem associated seizure is suspected. We described a 67-year-old woman who was admitted to the intensive care unit due to severe melioidosis. She experienced an episode of myoclonus jerks following two doses of imipenem 500 mg given intravenously at 12 hour interval. Two hours after her first seizure, the patient experienced two more myoclonus jerks which were two hours apart of each other. Imipenem was then discontinued and meropenem 1 g stat and followed by 500 mg every 12 hourly was given intravenously. However, patient continued to experience myoclonus jerks with the first episode occurring four hours after the initiation of meropenem. Phenytoin 100 mg every 8 hourly was given intravenously for the management of seizure. However, the frequency of myoclonus jerks increased to a total of 14 episodes on the next day. The phenytoin therapy was subsequently substituted with intravenous sodium valproate 750 mg stat followed by 400 mg every 12 hourly. With this change in treatment, patient's seizure was resolved. The present case showed the possibility of cross-reactivity in neurotoxicity which occurred across the use of imipenem and meropenem.

Key words: Carbapenem, imipenem, meropenem, seizure, melioidosis

1. Introduction

Melioidosis is a potentially fatal infectious disease caused by an environmental saprophyte, Burkholderia pseudomallei, which is predominantly found in tropical and subtropical areas (1-3). The modes of acquisitions are via inhalation, ingestion and inoculation (3). Inhalation of the aerosolized bacteria or dust particles has been reported to occur during tropical storms. Aspiration of contaminated water can occur during near drowning episodes while inoculation is by contact of wounds, skin abrasions or ulcers with contaminated soil and water (2). In Malaysia, the peak age-specific melioidosis incidence occurred between 41 to 59 years old with the male to female ratio of 3.2: 1 (3). However, the documentation of its global distribution remains limited.

B. pseudomallei have high resistance towards many antibiotics. Currently, ceftazidime (with or without trimethoprim/sulphamethoxazole) or meropenem are the preferred choices of treatment for the acute septicaemic phase of melioidosis (4). Other alternatives are imipenem, amoxicillin/clavulanate, and cefoperazone/ sulbactam (with or without trimethoprim /sulphamethoxazole) (4-6). Maintenance or eradication therapy for a prolonged period is necessary to prevent relapse and recurrence (4). This could be achieved by using the combination of trimethoprim/sulphamethoxazole and doxycycline.

[*]Correspondence: Chee Ping Chong
Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, University Sains Malaysia (USM), 11800
Minden, Penang, Malaysia
Tel: +6 012 534 2685
Fax: +6 04 657 0017
E-mail: jjueping@gmail.com
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The use of carbapenems (imipenem and meropenem) has been associated with increased risk of seizure. However, imipenem has a higher propensity to induce seizure (incidence 1.5% - 3.0%) (7-10) as compared to meropenem (incidence 0.38% - 0.70%) (11, 12). As there is limited report on the cross-reactivity between these two agents, clinicians may choose to switch the antibiotic regimen to meropenem whenever an imipenem associated seizure is suspected. Nevertheless, in the present case, a melioidosis patient who developed imipenem associated seizures continued to experience seizures despite the change to meropenem regimen.

2. Case report

A 67-year-old woman was transferred to intensive care unit (ICU) for impending respiratory failure. She was presented to the emergency department with complaints of cough and shortness of breath for the past two weeks. Her past medical history was diabetes mellitus, hypertension and chronic renal failure. She had no history of seizures or any neurologic disease. Medications before admission include gliclazide, metformin, hydrochlorothiazide and perindopril.

The patient was ventilated and sedated upon transferring to the ICU. Physical examinations revealed mild abdominal distension and right lung air entry reduction. The results of the head and neck, cardiovascular and musculoskeletal examinations were unremarkable. She was hemodynamically supported with norepinephrine and dopamine. Although she was afebrile, her white blood cell (38.6 x 10^3/mm^3) and neutrophil counts (94.4%) were elevated. Her red blood cell (2.5 x 10^3/mm^3), haemoglobin (7.5 g/dL) and hematocrit counts (21.5%) were below normal range. The patient's renal function remained impaired (creatinine clearance of 10 – 20 ml/min) throughout her stay in the ICU.

On the first day of ICU admission, the patient was diagnosed as having right pleural effusion secondary to community acquired pneumonia. However, her blood, urine and pleural fluid cultures were negative. The initial antibiotic treatments were intravenous (i.v.) cefepime 2 g stat followed by 1 g every 12 hourly and i.v. azithromycin 500 mg once daily. Other drug management included i.v. midazolam 3 mg/hour, i.v. morphine 3 mg/hour, i.v. omeprazole 40 mg every 12 hourly and i.v. hydrocortisone 100 mg every 8 hourly. On day 2 of admission, her chest x-ray showed improvement in the pleural effusion but there were field haziness and fibrotic changes at the right lung. A provisional diagnosis of melioidosis was made and i.v. imipenem 1g stat followed by 500 mg every 12 hourly was initiated at 4 pm. Other added new regimens included i.v.metoclopramide 10 mg every 8 hourly, i.v. erythromycin ethyl succinate 250 mg every 8 hourly and oral oseltamivir 150 mg daily. Cefepime and oseltamivir was discontinued on the next day while azithromycin therapy was completed on day 8 of admission.

On admission day 3, a second dose of imipenem 500 mg was given as scheduled at 4 am, twelve hours after the first dose. Three hours after this dose of imipenem, the patient experienced an episode of myoclonus jerks involving both the upper and lower limbs. She suffered another two more fits at two and four hours apart after the first seizure. Diazepam 10 mg was given intravenously at each episode of seizure. The myoclonus jerks lasted between 5 to 30 seconds and were aggravated by posture, movement and stimuli. Imipenem was then discontinued and i.v. meropenem 1 g stat and followed by 500 mg every 12 hourly was initiated at 12 pm. Despite the change of treatment, another myoclonus jerk occurred at four hour after the initiation of meropenem regimen. Since then, the patient continued to experience five more seizures throughout the day. Besides, she underwent haemodialysis due to anuria.

Intravenous phenytoin 100 mg every 8 hourly was started at the end of admission day 3 for the management of seizure. As there was no significant improvement in the patient's infectious condition, the dose of meropenem was increased to 1 g every 12 hourly on day 4. The haemodialysis was continued for the management of her anuric condition. However, the frequency of myoclonus jerks increased to a total of 14 episodes on day 4 alone despite the administration of phenytoin. Owing to concerns of seizure exacerbation, phenytoin was substituted with i.v. sodium valproate 750 mg stat followed by 400 mg every 12 hourly. On the next day, patient's seizure was resolved after the change to sodium valproate therapy. The antibiotic coverage with meropenem was completed on admission day 9. Sodium valproate regimen was continued until patient was discharged from ICU on day 11.

3. Discussion

Melioidosis has been called "the great mimicker" due to its wide array of clinical manifestations, including pneumonia, disseminated septicaemia, non disseminated septicaemia, suppurative infection, suppurative lesion, pulmonary infiltration and bacteremia (3-13). This disease has a high mortality rate of 30-

70% (13) and diabetes mellitus was found to be the main predisposing condition (3). Other important predisposing factors are renal failure, renal calculi, retroviral infections, malignancy, steroid therapy, alcoholism, occupational exposure, trauma and parenteral drug abuse (1, 2).

Carbapenem is a class of broad spectrum antibiotic which is widely used for severe infections. Imipenem, the first of carbapenems, is formulated in combination with cilastatin, a compound which inhibits the metabolism of imipenem by the kidney (7). Meropenem is structurally different from imipenem due to the addition of a methyl group in the 1-position of the carbapenem moiety (14). This results in greater stability and eliminates the need of co-administration with cilastatin. The carbapenems share a similar β-lactam ring and neurologic adverse effects as the penicillins and cephalosporins. The seizure-inducing potential of the carbapenems is related to the antagonism at the γ-aminobutyric acid (GABA) receptor site by the β-lactam ring (15,16). The GABA neurotransmitters inhibit neuronal activity and propagation. Therefore, by antagonizing the receptor, abnormal neuronal activity is promoted. Cilastatin increases the plasma levels of imipenem and hence increases the seizure propensity of imipenem as compare to meropenem (17).

In previously reported cases, the onset of carbapenem-induced seizure ranges from immediately after initiation of therapy to 29 days after the first dose (9-18). In the present case, the onsets of seizures were relatively fast, which were 15 hours and 4 hours respectively after the first dose of imipenem and meropenem regimen. Carbapenem treatment has been predominantly associated with generalized tonic-clonic seizures while the less commonly associated seizures are focal seizures and myoclonus (9,10-18,19). However, there is limited documentation on persistent myoclonus jerks across the use of imipenem and meropenem in the same patient as observed in the present case.

Reviews on previously reported cases showed that excessive dose of carbapenem therapy, specifically in patients with renal dysfunction, and pre-existing central nervous system abnormalities or seizure history were associated with an increased risk of carbapenem-induced seizures (9-20). Because of the extensive renal elimination, doses of both imipenem and meropenem should be adjusted in renal impairment (7). Nevertheless, dosages exceeding the recommended dose were received by the patient in the present case. Based on the patient's creatinine clearance, the appropriate dose of imipenem should be 250 mg (rather than 500 mg) every 12 hourly (21) while meropenem should be administered at 500 mg (rather than 1 g) every 12 hourly (22). These excessive dosages plus the renal dysfunction have placed the patient at risk of seizure. The history of seizures during the imipenem therapy on day 3 of admission further predisposed the patient to the risk of seizure when meropenem treatment was initiated.

The Naranjo probability scale (23) was used to assess the level of causality of the adverse event. The result showed a probable relationship (score of 7) between the patient's seizures on day 3 of admission and imipenem therapy. Since imipenem has a short half life (approximately 3 hours in renal dysfunction) and is removed by hemodialysis (21), nearly all of the previous administered imipenem doses have been eliminated out from the patient's body on admission day 4. Considering the dose-dependent basis of carbapenem-induced seizure (7-20), the seizure episodes during day 4 were unlikely induced by imipenem. Use of the Naranjo scale also indicated that meropenem was possibly (score of 5) the cause of the convulsions throughout day 4 of admission. All other concomitant drugs have been evaluated for the possibility of inducing seizures. Seizures secondary to cefepime (24), azithromycin (25), hydrocortisone (26) and oseltamivir (27) have been documented in previous reports. However, detail analysis on the onset and duration of seizures in this patient had ruled out the possibility of convulsion induced by the above mentioned drugs. A re-challenge would further confirm the causality of seizure, but this was not considered safe in this patient. Additionally, the patients did not have any underlying medical conditions like head trauma, central nervous system abnormalities, infection of the central nervous system, acute metabolic changes and alcoholism which can precipitate seizure.

Controls of carbapenem-induced seizures in the previous reports were achieved with anticonvulsants and/or by discontinuation of the antibiotic (9). Benzodiazepines are recommended as the first-line of treatment for the seizures, followed by agents which enhance GABA neurotransmission (20-28). In the present case, monotherapy of IV diazepam or addition of IV phenytoin failed to control patient's myoclonus jerks. The use of phenytoin was not appropriate in this patient as a previous report showed that it may aggravate myoclonus by worsening patient's gait (29). Indeed, guidelines have advised that

phenytoin should be avoided in patients with myoclonus seizures (30, 31). A recent review (20) discourages the use of valproate in carbapenem-induced seizure as carbapenems can significantly reduce the serum concentration of valproate (32, 33). Interestingly, the use of valproate in this patient was effective as the seizure frequency was gradually reduced and halted. However, the serum level of valproate was not monitored in the present case.

The use of antibiotic with minimum risk of seizure should be considered in this patient. Ceftazidime with more favourable neurotoxicity profile than carbapenems is currently the first-line antibiotic for the treatment of severe melioidosis (4). An open-label, randomized trial showed that the overall mortality rate did not differ significantly between patients treated with ceftazidime and imipenem (34). Another observational study found that the outcomes of severe melioidosis patients treated with ceftazidime were similar to those managed by meropenem (35). Therefore, ceftazidime is a preferred choice than carbapenems in the present case. In fact, when the diagnosis of melioidosis was made in this reported case, clinician should have used i.v. ceftazidime 2 g every 8 hourly if the patient's renal function was normal (4), especially when the patient developed seizure at using imipenem. However, the dose of ceftazidime should be reduced to i.v. 2 g every 24 hourly for this patient as her renal function was impaired (creatinine clearance of 10-20 ml/min).

In conclusion, carbapenems therapy in excessive doses may induce myoclonus jerks in severe melioidosis patient with renal dysfunction. In order to avoid this neurotoxicity, the doses of carbapenems should be adjusted based on the patient's renal function. Other alternative with better neurotoxicity profile such as ceftazidime should be used in this kind of patients.

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