Case Series

Carbapenem induced convulsions in the critically ill – A case series.

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Abstract
Carbapenem induced convulsions are said to be commoner amongst critically ill patients. During a 1½ year study period we observed 4 of 15 patients receiving meropenem and 3 of 7 patients receiving imipenenm develop convulsions in an intensive care unit. The withdrawal of the offending drug rapidly resolved the problem in all but one.

Introduction

Carbapenems are a relatively new class of β – lactam antibiotics, related structurally to the penicillin and cephalosporins. Meropenem and imipenem are the most widely used and have a broad spectrum of activity against aerobic and anaerobic Gram positive and Gram–negative bacteria. Often meropenem is used in the treatment of meningitis as it is acting against the three major pathogens causing bacterial meningitis (Streptococcus pneumoniae, Haemophilus influenzae and Neisseria meningitidis). Meropenem is the only carbapenem approved for use in children younger than 12 years.

These are systemic antibiotics excreted via the kidney as unchanged molecules. Cilastation prevents the metabolism of imipenem in the kidneys by dehydropeptidase-1, thus ensuring high levels of the imipenem in the urinary tract. Renal enzymes that inactivate imipenem do not destroy meropenem. Thus, it can be given without cilastatin. Half-life of both meropenem and imipenem is approximately 1 hour and 90-100% of the dose of meropenem is excreted via urine within 24 hours of administration.

Most frequently reported meropenem related adverse events includes diarrhea, rashes, nausea, vomiting, injection site inflammation and thrombocytopenia1. The important side effects of imipenem are diarrhoea (pseudo membranous colitis), blood disorders, Steven-Johnson syndrome and seizures1. Merapenem is less neurotoxic in comparison to other carbapenems [2]. There is little data in literature on the aspect of adversity among patients receiving intensive care. The aim of this paper was to tabulate neurotoxicity observed with the use of carbapenems and associated risk factors among the critically ill patients receiving treatment in ICU.

Method

We observed all patients who received meropenem or imipenem in a regional ICU over a one and half year period (January 2005 to August 2006). Their demographical data, pre-existing medical illnesses and the reason for admission to ICU were obtained from the hospital records.

The dose, frequency, route and duration of meropenem / imipenem administration was observed including the onset of convulsions. To exclude other likely causes of seizures, following details were also taken:

1. The details of administration of other drugs which are known to cause convulsions.
2. Evidence for cerebral infection, cerebral ischemia and other cerebral insults.
3. Past history of convulsions.

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Investigations were performed to exclude concurrent electrolyte imbalances (serum electrolytes), hypoglycemia (random blood sugar), hypoxia, blood gas abnormalities (blood gas analysis) and renal impairment (blood urea and serum electrolyte). All patients were observed until the carbapenem therapy was stopped and recovered from convulsions. Other abnormal laboratory findings were also noted.

Results

In the ICU, meropenem was given intravenously at a dose of 10 mg/kg every 8 hours for adults and 10-20 mg/kg every 8 hours for children (3 months -12 years). Imipenem was given 10 – 20 mg/kg every 8 hours intravenously.

Fifteen patients (12 males) aged 35 years median (range 2 months - 69 years) were treated with meropenem and 7 patients (5 males) aged 47 years median (range 11-67 years) were treated with imipenem. All received the standard dose of drug according to their body weight. The drug was administered for a median duration of 7 days (range 1 - 18). The first convulsion was noted on the 3rd day median (range 1 – 9 days) following the commencement of carbapenem.

Four of the 15 patients treated with meropenem (26%) developed convulsions. Of these, one patient had renal impairment (blood urea 24 mmol/l, serum creatinine (604 µmol/l). One other had low serum potassium (2.9 mmol/l) at the time of convulsion. One other was suffering from meningitis. None had hypoglycemia or hypoxia. None received any other drugs known to induce convulsions. Two patients who had a past history of convulsions didn't develop any during carbapenem therapy.

Three of the 7 patients treated with imipenem (42%) developed convulsions. Of these, one was a previously diagnosed patient with chronic renal failure and convulsions. One had acute renal failure with multi organ failure and continued to have seizures even after stopping imipenem administration. One patient had pancytopenia due to aplastic anaemia.

Discussion

Several classes of pharmacological agents have been implicated in drug-induced seizures at therapeutic doses. These include antidepressants, neuroleptics, antihistamines, central nervous system stimulants, general and local anaesthetics, and antimicrobial agents.3 Carbapenem is a β- lactam antibiotic known to be epileptogenic and the present study further confirms these findings. We observed a higher incidence of convulsions amongst critically ill patients receiving imipenem (42%) compared with the incidence reported i.e. 0.2-3%.3 The carbapenems are thought to induce convulsive side effects through its inhibitory action on the central gamma amino-butyric acid (GABA) mediated inhibitory transmission 4. The safety margin for neurotoxicity is higher with meropenem compared with imipenem.

The known predisposing factors for β-lactam neurotoxicity includes excessive dose, decreased renal function, damage to blood-brain barrier, pre-existing diseases of the central nervous system, old age and concurrent use of drugs that are nephrotoxic or that may lower the seizure threshold.3 We observed renal impairment, meningitis and electrolyte imbalance predispose to convulsions. On the other hand most recovered fully after cessation of the drug without long term sequelae.

Meropenem and imipenem are potentially neurotoxic and may cause seizures if over dosed relative to renal function and/or body weight 2. Since carbapenems are excreted via the kidney, renal failure leads to accumulation of carbapenem in the blood and induce convulsions. Thus, carbapenems should be used with caution in patients with renal impairment. Adjustment of the dose according to renal function may reduce the risk of seizure.

Epileptogenic reactions of imipenem is related to antibiotic concentration in brain tissue rather than to cerebrospinal fluid concentrations.3 Imipenem is transported through the blood brain barrier principally by passive diffusion but its efflux from the central nervous system through the blood-cerebrospinal fluid barrier is slow3. In

meningitis, inflammatory process of the meninges may damage the blood brain barrier and higher amounts of carbapenem may pass through it increasing the concentration within the brain matter. Therefore, there may be a greater risk of convulsions with carbapenem in patients with meningitis. However, in animal experiments, meningitis did not increase the risk of seizures with carbapenems.2 Neurotoxic potential of imipenem-cilastatin was prohibitive for its use for the treatment of bacterial meningitis2. In contrast, meropenem can be used as it's of low neurotoxic activity.

Pancytopenia is not a known risk factor for imipenem induced convulsions. The one patient in our study with pancytopenia who had recurrent convulsions during the treatment period also had gum bleeding and bleeding into the endotracheal tube. Therefore, the cause for the convulsion may be even structural brain damage.

Conclusion

In our case series we observe convulsions to be a frequent complication following carbapenem therapy in critical illness and to be more likely in patients with renal impairment, electrolyte imbalance and meningeal inflammation. A larger prospective study is needed to ascertain the significance of above mentioned predisposing factors.

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