Neurotoxicity of Carbapenem Antibacterials

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Summary

Similar to other β-lactam antibacterials, carbapenems have a neurotoxic potential that seems to be higher than that of the penicillins and cephalosporins. Seizures have been reported in several large studies of patients treated with imipenem/cilastatin. However, it seems clear that the main factor increasing the risk of neurotoxicity with imipenem/cilastatin is administration of excessive dosages relative to bodyweight and/or renal function. If the manufacturer’s dosage recommendations are followed, the risk of seizures in patients receiving this combination is minimal. With meropenem, a newly registered carbapenem, the safety margin with respect to neurotoxic reactions has been increased compared with imipenem and meropenem can be used at higher doses than imipenem/cilastatin. Since the neurotoxicity of β-lactam antibacterials seems to be caused by an interaction with γ-aminobutyric acid (GABA) receptors, other drugs with a similar mechanism of action, such as fluoroquinolone antibacterials, should be used with caution when combined with carbapenems.

1. Overview of β-Lactam Neurotoxicity

β-Lactam antibacterials are known to be potentially neurotoxic and cause epileptogenic changes on the electroencephalogram (EEG) and seizures in experimental animals. Seizures can also occur in patients, if the drugs are administered at excessively high doses. As reviewed by Schliamser et al.,[1] factors that increase the risks of neurotoxicity are direct application of the antibacterial on or into brain tissue and the use of very high dosages relative to renal function and/or bodyweight.

A series of studies[2-5] showed that the decisive factor for neurotoxicity of β-lactam antibacterials was the drug concentrations achieved in brain tissue. Contrary to what might have been expected, the concentration in the CSF did not influence the risks of neurotoxic reactions.[3,4] In those studies, meningitis did not increase the neurotoxicity of benzylpenicillin (penicillin G) in an experimental model, in which rabbits received high intravenous doses of antibacterials and epileptogenic EEGs or seizures were used as endpoints.

An important consequence of the above findings is that the decisive pharmacokinetic factor related to neurotoxicity is the passage of the antibacterial across the blood-brain barrier (the barrier formed by the end-capillaries and the glia cells in the brain). The passage across the blood-CSF barrier (the choroid plexus) is of no consequence whatsoever for the risk of neurotoxicity when a β-lactam antibacterial is used.

In their study, Schliamser et al.[5] found marked differences in the neurotoxic potential of various β-lactam antibacterials. In comparison with benzylpenicillin, imipenem/cilastatin and a penem antibacterial, ritipenem (FCE 22101), were similar to each other and approximately 10 times more neurotoxic per weight unit. Possible reasons for that are discussed in section 2.
2. Neurotoxicity of Imipenem/Cilastatin

In the evaluation of the results of the phase I to III trials of imipenem/cilastatin, seizures that were considered related to the drug occurred at a frequency of 0.2% in 3470 patients. That frequency was higher than expected. Calandra et al. [7] analysed patients who had neurotoxic reactions while receiving treatment with imipenem/cilastatin and found that only when the antibacterial was given at high dosages relative to renal function and/or bodyweight was there an increased risk of seizures. There also seemed to be a correlation between pre-existing disorders of the CNS and an increased risk of seizures during imipenem/cilastatin treatment.

In another study of 1951 patients treated with imipenem/cilastatin, Pestotnik et al. [8] found that the only risk factor was administration of excessive dosages. They used a prospective surveillance system that warned prescribing physicians when recommended dosages of imipenem/cilastatin were exceeded. The frequency of seizures in their patients was only 0.2%. That frequency was considerably lower than the 6% reported by O’Donovan et al. [9] in a retrospective analysis of imipenem/cilastatin recipients. Also, Townsend et al. [10] found high frequencies of neurotoxicity in patients whose dosages were not carefully monitored; 11% had any type of neurotoxic reaction and 3% had seizures.

In general, most of the reports of seizures caused by or appearing in conjunction with imipenem/cilastatin treatment describe patients who have received high dosages and/or who had other obvious risk factors for neurological reactions. [11-14]

Two reports have indicated an increased risk of neurotoxicity to imipenem/cilastatin in patients concomitantly treated with cyclosporin. [15,16] However, others have suggested that the combination of cyclosporin and imipenem/cilastatin is favourable, since the cilastatin component seems to reduce the nephrotoxicity of cyclosporin. [17,18]

The high correlation between dosage and risk of neurotoxic reactions to imipenem/cilastatin was further supported by a study of Wong et al. [19] They treated children who had bacterial meningitis with imipenem/cilastatin at a dose of 25 mg/kg every 6 hours (dosage refers to imipenem). Seizures occurred in 7 of 21 patients and the study was terminated prematurely.

In the literature, there is a report of 1 sporadic case of a child with pneumococcal meningitis treated with imipenem/cilastatin at high dosages without seizures occurring. [20] Another sporadic case of imipenem/cilastatin treatment of meningitis was reported by Stuart et al., [21] who treated a neonate with 20 mg/kg/day. That child developed seizures during treatment, but it should be remembered that seizures are common in patients with meningitis irrespective of what treatment is given. In the same series, another 62 neonates were treated without neurotoxic reactions. The same high degree of safety of imipenem/cilastatin was reported in a series of 61 neonates treated with imipenem/cilastatin at dosages ranging between 40 and 103 mg/kg/day; seizures were reported in none of these children. [22]

It seems clear from the above studies that imipenem has the potential to cause neurotoxic reactions with seizures if used in overdose and that this is a factor that limits the use of very high dosages. An obvious consequence is that the usefulness of imipenem for the treatment of bacterial meningitis is limited.

An issue that has been discussed but not thoroughly studied is whether the parent drug, the open β-lactam metabolite of imipenem, or both are responsible for the neurotoxic reactions. Unpublished studies in rats have shown that the neurotoxicity of ritipenem, which has similar metabolic pathways to imipenem and other carbapenems, is drastically increased by cilastatin (S.R. Norruby et al., unpublished observations). This strongly indicates that it is the parent compound rather than the metabolite which is neurotoxic, since ritipenem is significantly metabolised to the open b-lactam metabolite in the rat, a metabolism that is effectively inhibited by cilastatin.