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Carbapenems in Serious Infections

A Risk-Benefit Assessment

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Abstract

The tolerability of the 2 most frequently used carbapenems, imipenem/cilastatin and meropenem, is reviewed. Both of these drugs, but especially imipenem, are potentially neurotoxic and may cause seizures if overdosed relative to renal function and/or bodyweight. The therapeutic margin is considerably narrower with imipenem/cilastatin which cannot be given at doses required for treatment of bacterial meningitis. Meropenem on the other hand, is considerably less prone to cause seizures and its tolerability and efficacy are well documented in 3 relatively large, controlled studies in adults and children with meningitis. They showed that meropenem was as effective and well tolerated as cefotaxime or ceftriaxone. Another potential advantage of meropenem over imipenem/cilastatin is that it can be given intravenously at a high rate without increased risk of nausea or vomiting. An obvious reason for using a carbapenem instead of a cefalosporin for empirical treatment of life-threatening infections is that both imipenem/cilastatin and meropenem have a broader spectrum of activity. They are also more resistant to hydrolysis by the most common β-lactamases, including the class I cephalosporinase frequently produced by *Enterobacter* spp. and *Pseudomonas* spp. and the extended spectrum enzymes, now commonly found in *Escherichia coli* and *Klebsiella* spp.

The importance of the carbapenem antibacterials has increased with time. While resistance to the third generation cefalosporins such as ceftazidime, cefotaxime and ceftriaxone has become increasingly common, the carbapenems remain active against most Gram-negative and Gram-positive pathogens. After more than 12 years of imipenem use, emergence of resistance to this group of antibacterials has been infrequent.[1,2] Problem species include *Stenotrophomonas maltophilia*, *Enterococcus faecium*, *Burkholderia cepacia*, *Corynebacterium jeikeium* and *Enterococcus faecium* which are naturally resistant, and *Pseudomonas aeruginosa* and *Acinetobacter* spp. which may acquire resistance, especially when a carbapenem is used alone.[1-3] The broad spectrum of antibacterial

activity and the frequent possibility of using carbapenem monotherapy instead of combinations should be weighed against potential tolerability concerns related to the use of carbapenems, particularly the risk of seizures.

1. Tolerability of Carbapenems

Carbapenems belong to the β-lactam family of antibacterials and generally share a high degree of tolerability with the penicillins and cefalosporins.[4,5] It should be noted, however, that they have open-lactam metabolites which are stable and which most likely are cross-immunogenic with penicilloyl.[6] Therefore, patients with a history of IgE-mediated (type I) allergy to a penicillin should not be given a carbapenem and vice versa.

Imipenem, when given alone to rabbits as an intravenous bolus injection, is nephrotoxic and causes tubular damage at doses similar to those of cefaloridine, a first generation cefalosporin with a high degree of nephrotoxicity.[6] The nephrotoxicity of imipenem can be completely blocked if it is given together with an inhibitor of the enzyme, dehydropeptidase-I (DHP-I), responsible for renal metabolism of carbapenems.[7] Meropenem and most other carbapenems have been chosen for their lack of nephrotoxicity in animal models and also for having lower degrees of renal metabolism by DHP-I. Thus, most of them do not require coadministration with enzyme inhibitors.

In the course of the clinical development of imipenem/cilastatin, it became clear that this antibacterial, if overdosed relative to renal function and/or bodyweight, had a potential to cause seizures.[8,9] Animal studies have shown that the neurotoxic potential of carbapenems is most probably the result of an interaction with the γ-amino butyric acid A receptor in the central nervous system (CNS).[10] Schliamser et al.[11,12] studied the CNS toxicity of various β-lactam antibacterials and showed that imipenem and the penem antibacterial ritipenem (FCE 22101), which is chemically related to imipenem, were about 10 times more prone to cause epileptogenic EEG changes and seizures than benzylpenicillin on a weight basis. They also showed that the decisive factor for CNS toxicity of a β-lactam antibacterial is the concentration achieved in brain tissue. The concentrations in cerebrospinal fluid were not correlated to epileptogenic activity. Moreover, they demonstrated that meningitis did not increase the risk of seizures in rabbits given β-lactams. There were even indications that meningitis may protect against neurotoxicity. Importantly, these studies also demonstrated that it is the parent carbapenem compound and not the open-lactam metabolite that causes seizures.

All the above results were generated in animal models. However, Wong et al.[13] showed that when children with bacterial meningitis were treated with imipenem/cilastatin 25 mg/kg 4 times daily, 7 out of 25 patients developed seizures which were considered to be due to the drug and the trial was prematurely terminated.

Contrary to the findings with imipenem, the 3 randomised comparative studies of the use of meropenem (doses of 40 mg/kg up to 2g, 3 times daily) published so far, have shown a low degree of seizures during treatment and satisfying clinical cure rates (table I).[14-16] The relatively high frequencies of neurological sequelae in the patients in these studies were most probably due to the fact that audiological examinations were performed in all patients; a majority of sequelae were hearing deficiencies.

An adverse event which seems to be specific for imipenem/cilastatin is the relatively frequent complaint of nausea which occurs when imipenem/cilastatin is administered rapidly (faster than 0.5g of imipenem/30 min of imipenem). This seems to be less of a problem with meropenem which can be given as a 5 to 10 minute bolus injection of 1g without increased frequencies of nausea compared with slower infusion rates.[17]

2. Comparison of Imipenem/Cilastatin and Meropenem

The studies mentioned in section 1 showed similar efficacy and tolerability profiles for meropenem and third generation cefalosporins in the treatment of bacterial meningitis. With regard to

Table I. Studies comparing the efficacy and tolerability of meropenem and third generation cefalosporins (cefotaxime or ceftriaxone) for the treatment of bacterial meningitis

Reference no.	Treatment	Clinical cure in evaluable patients no. (%)	Neurological sequelae in evaluable patients no. (%)	Seizures on treatment (all patients treated) no. (%)
14	Meropenem	23/23 (100)	16/28 (57)	0/28 (0)
	Cefalosporin (cefotaxime or ceftriaxone)	17/22 (77)	11/28 (40)	0/28 (0)
15	Meropenem	75/75 (100)	21/98 (21)	5/98 (5)
	Cefalosporin (cefotaxime or ceftriaxone)	62/64 (97)	10/98 (10)	3/98 (3)
16	Meropenem	75/78 (96)	34/78 (43)	15/129 (12)
	Cefalosporin (cefotaxime)	71/75 (95)	29/75 (39)	22/129 (17)

this indication, meropenem is clearly the only well documented carbapenem currently available which can be used. Indeed, there is a lower risk that the causative organism is resistant to meropenem than to other antibacterials. However, in none of the studies investigating meningitis treatment was a cefalosporin-resistant organism considered a problem.

In studies in which imipenem/cilastatin and meropenem were compared for the treatment of infections other than meningitis, there were no observed differences in terms of frequencies or types of adverse events reported, and there were no clinically significant differences in the efficacy of the 2 antibacterials.[17] This was also true for most of the trials in which a carbapenem was compared with another antibacterial or antibacterial combination. In 2 trials (one which compared ciprofloxacin and imipenem/cilastatin for the treatment of severe pneumonia, and another in which imipenem/cilastatin was compared with piperacillin/tazobactam for the treatment of intra-abdominal infections), the clinical results indicated that imipenem/cilastatin was less effective than the comparator.[18,19] However, these studies appear to be exceptions to the rule that a carbapenem is at least as affective as a comparator agent.

It should be noted that when used as recommended by the manufacturer, as is normally the case in clinical trials, the risk of seizures with imipenem/cilastatin is low and probably not higher than that with other β-lactam antibacterials. Thus, when infections other than those in the CNS (i.e. those requiring very high doses) were treated there were no significant differences between meropenem and imipenem in terms of tolerability or efficacy.[17]

3. Conclusions

Carbapenems are well tolerated and effective antibacterials for monotherapy of serious infections. Imipenem/cilastatin and meropenem are comparable except for the treatment of meningitis where meropenem but not imipenem/cilastatin can be used due to a higher neurotoxic potential of imipenem.

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