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# Safety Profile of Meropenem

## An Updated Review of Over 6000 Patients Treated with Meropenem

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## Contents



## Abstract

Meropenem is a broad-spectrum carbapenem antibacterial with potent antimicrobial activity against a broad range of Gram-negative, Gram-positive and anaerobic bacteria. The second parenteral carbapenem to be introduced worldwide, meropenem has been in clinical use since 1994. Two previous safety reviews have established that meropenem has a favourable and acceptable safety profile. This new review was conducted after the approval of meropenem in the US in 2005 for the treatment of patients with complicated skin and skin-structure infections, in addition to the previously approved indications of intra-abdominal infections and paediatric bacterial meningitis. The analysis includes the clinical trial data from the previous safety reviews, updated with expanded experience across a number of serious bacterial infections, including a large international study in patients with skin or skin-structure infections and further experience in patients with intra-abdominal infections and bacterial meningitis. A total of 6154 patients with 6308 meropenem exposures were compared with 4483 patients treated with comparator agents (4593 exposures), and the paediatric population base for which safety data are available has doubled to over 1000 patients.

The data presented reinforce the favourable safety profile of meropenem. In general, the incidence and pattern of adverse events occurring with meropenem were similar to those of the first carbapenem, imipenem/cilastatin, and to those of the cephalosporin- and clindamycin-based regimens to which it had been compared. The most common adverse events reported for meropenem were diarrhoea (2.5%), rash (1.4%) and nausea/vomiting (1.2%). No adverse event occurred in more than 3% of patient exposures to meropenem, indicating a low overall frequency of adverse events as well as excellent gastrointestinal tolerability. Furthermore, no unexpected adverse events were identified, and the very low incidence of seizures in patients with meningitis was not considered to be drug related. In infections other than meningitis, the incidence of seizures considered by investigators to be related to meropenem treatment was 0.07%. In the new studies that updated the earlier safety data, no new cases of drug-related seizure were reported for any treatment or patient group (meningitis/non-meningitis infections).

In conclusion, meropenem is well tolerated and has good CNS and gastrointestinal tolerability when used for the treatment of serious bacterial infections in a wide range of adult and paediatric patient populations.

Meropenem is a parenteral carbapenem antibacterial with excellent antimicrobial activity against a broad range of Gram-negative, Gram-positive and anaerobic bacteria. Results from the MYSTIC (Meropenem Yearly Susceptibility Test Information Collection) programme, an ongoing global resistance study involving 120 reporting centres in 32 countries, indicate that meropenem continues to exhibit sustained potency and a broad spectrum of activity against antibacterial-resistant bacterial strains, including Enterobacteriaceae, *Pseudomonas aeruginosa* and *Acinetobacter* spp.[1-5]

Three carbapenems are currently licensed in the US for the treatment of serious infections. Imipenem/cilastatin was the first carbapenem antibacterial to be introduced into clinical practice, and it is indicated for the treatment of lower respiratory tract, urinary, intra-abdominal, gynaecological, bone and joint, polymicrobic and skin or skin-structure infections, endocarditis and bacterial septicaemia.[6] Meropenem, the second carbapenem to be available on a worldwide basis, is indicated in the US for the treatment of skin and skin-structure infections, intra-abdominal infections and paediatric bacterial meningitis.[7] Finally, ertapenem is indicated in the US for the treatment of complicated intra-abdominal infections, complicated skin and skin-structure infections, community-acquired pneumonia, complicated urinary tract infections and acute pelvic infections.[8] The continued efficacy of carbapenems such as meropenem and imipenem/cilastatin confirms their place as effective treatment options for severe infections in the hospital setting.

The safety and tolerability profiles of imipenem/cilastatin and meropenem indicate that the most common adverse events during treatment are local injection site reactions, gastrointestinal disturbances and dermatological reactions.[9-13] With ertapenem, the most common drug-related adverse events are gastrointestinal disturbances, infused vein complications, vaginitis in women, headache, phlebitis and/or thrombophlebitis.[14]

Although carbapenems are generally well tolerated, there are two areas of concern with imipenem/cilastatin. The first is an increased risk of seizures, which has particularly been reported at the higher end of the recommended dosage range and in patients with impaired renal function or with a history of CNS disorders.[13,15] As a consequence of these CNS adverse events, imipenem/cilastatin is not approved for the treatment of meningitis. The second area of concern is the potential for imipenem/cilastatin to cause gastrointestinal disturbances (nausea, vomiting and diarrhoea); the risk of these events is largely influenced by the dosage and rate of infusion of the drug.[16,17]

Unlike imipenem/cilastatin, meropenem and ertapenem are not significantly hydrolysed by the renal enzyme dehydropeptidase-1 (DHP-1), and do not have to be given in combination with the DHP-1 inhibitor cilastatin in order to avoid nephrotoxicity and metabolic breakdown.[6,18,19] Given the differences in antimicrobial spectrum, there is a lack of both safety and efficacy trials comparing meropenem with imipenem/cilastatin and ertapenem. However, meropenem was significantly more effective than imipenem/cilastatin in terms of clinical and bacteriological responses in a recently published systematic review comparing these antibacterials in the treatment of patients with severe infections.[20] Meropenem was also associated with a significant reduction in adverse events compared with imipenem/cilistatin. Another recent systematic review and meta-analysis examined 33 randomised, controlled trials of antibacterial monotherapy for febrile neutropenia (21 trials assessed carbapenems; imipenem/cilastatin [11], meropenem [9] and imipenem/cilastatin, meropenem or panipenem [1]).[21] Empirical use of carbapenems resulted in fewer required treatment modifications, but also led to an increased rate of pseudomembranous colitis compared with cephalosporins (i.e. ceftazidime, cefepime, cefoperazone/sulbactam). However, all but one trial reporting pseudomembranous colitis assessed imipenem/cilastatin, which, in general, was associated with more frequent adverse events than other β-lactams (relative risk 1.72; 95% CI 1.45, 2.04 for any adverse event and 2.78; 95% CI 1.00, 7.76 for seizures).

The safety profile of meropenem was first reviewed in 1995, based on data from 3125 patients treated with the drug in the phase III clinical trial programme.[11] The review established that meropenem had an acceptable safety profile, with an overall pattern and frequency of adverse events similar to that of comparator β-lactam antibacterials. Diarrhoea, rash, nausea and vomiting, thrombocytosis, eosinophilia and changes in liver enzyme levels were the adverse events most frequently reported, although they were not necessarily associated with meropenem. There was a similar pattern and incidence of adverse events in both children and adults exposed to meropenem. Initial data suggested that meropenem compared well with other agents in clinical use and was not nephrotoxic.

The incidence of nausea and vomiting was much lower with meropenem than with imipenem/cilistatin.[11] This was despite the fact that meropenem was administered by bolus injection or at infusion rates faster than the 30- to over 60-minutes recommended for the delivery of imipenem/cilastatin at doses of 500mg–2g in adults or 10–40 mg/kg in children to reduce the risk of drug-related nausea and vomiting. The ability to administer meropenem by either intravenous infusion or bolus injection without nausea or vomiting suggested additional flexibility in the clinical management of patients. This is particularly true in instances where rapid administration in lower volumes of fluid may have practical advantages, for example, in the young, elderly and outpatient populations or in patients with either renal or cardiac failure.

Importantly, in the light of the seizure-inducing potential of the carbapenem antibacterial imipenem/cilastatin, the overall incidence of seizures in patients exposed to meropenem was very low and, in patients with meningitis, none of the seizures that occurred were considered to be related to meropenem treatment.[11] These data suggested that meropenem has less neurotoxic potential than imipenem/cilastatin and can therefore be used at effective doses for the successful treatment of bacterial meningitis.

A second safety review performed in 1999 reflected the increasing real-world clinical experience of meropenem and analysed data obtained from nearly 5000 patients.[10] It included additional data from patients with meningitis, intra-abdominal infections, septicaemia and lower respiratory tract infections, as well as from patients with cancer and febrile neutropenia. The review[10] represented a population of more severely ill patients than the first review,[11] which was primarily based on efficacy studies used for product licence submission. The incidence of drug-related adverse events, while slightly higher than in the earlier review numerically, remained very low, confirming the acceptable tolerability profile of meropenem. This low adverse event incidence also supports a favourable safety profile for meropenem in a number of special patient populations, including elderly, renally impaired,

neutropenic and paediatric patients and those with meningitis or cystic fibrosis.[10] No unexpected adverse events were reported, and the incidence and pattern of adverse events was generally similar to those associated with imipenem/cilastatin and both cephalosporin- and clindamycin-based comparator regimens. Few patients treated with meropenem withdrew from treatment because of adverse events. Drug-related adverse events occurred in less than 3% of patient exposures to meropenem, and no relationship between dosage and meropenem-related adverse events was apparent.[10]

In 2005, meropenem was granted a supplemental new drug application in the US for the treatment of patients with complicated skin and skin-structure infections, in addition to the existing approved indications of intra-abdominal infections and bacterial meningitis. The current review updates the safety profile of meropenem across an expanded clinical range of serious bacterial infections, including a large international study in patients with skin or skin-structure infections. Furthermore, this review updates existing clinical data in patients with intra-abdominal infections and bacterial meningitis. Additionally, the paediatric population base for which safety data are available has doubled.

## 1. Literature Retrieval and Assessment

A literature search was conducted using the MEDLINE and EMBASE databases. The search encompassed the following dates: 1 January 1999 to 15 October 2006. The searches used were meropenem + approved indications, English only; meropenem + safety/adverse events; and meropenem + bacterial infections. While the focus of the search was limited to clinical studies, meta-analyses were included in the search as a method of verifying that relevant studies had been identified. Reviews, comments, editorials, case reports, retrospective case series and correspondence were all excluded. All results were then manually screened for meropenem use in the treatment of the three indications approved by the US FDA, meropenem in bacterial infections, and meropenem safety and adverse events in all indications.

Publications from the search results were then obtained and manually screened to ensure accordance with the search and indication criteria.

### 1.1 Study Design and Patients

This historical analysis includes all the clinical trial data from the previous safety reviews,[10,11] which were based on 46 efficacy studies, and data from eight additional studies.[22-29] Papers reporting generalised safety data and papers reporting only bacteriological or clinical efficacy data were not included. The new analysis includes seven studies in patients with serious bacterial infections,[22-28] including intra-abdominal infections and skin/skin-structure infections, and one study in patients with meningitis.[29] The comparators in these studies were cephalosporin- and clindamycin-based regimens and imipenem/cilastatin. No efficacy and safety studies comparing meropenem with ertapenem were identified.

The new studies included one of the largest studies of hospitalised patients with complicated skin and skin-structure infections conducted to date, which included over 1000 patients.[23] In total, over 900 paediatric patients were enrolled in the new studies, including 266 children with meningitis.[29] In addition, a *post hoc* subgroup analysis[30] of the study by Fabian et al.[23] in patients with skin and skin-structure infections reported the efficacy and safety of meropenem and imipenem/cilastatin in patients with or without underlying diabetes mellitus.

In 53 studies, written informed consent was obtained from the patients or their guardians, and the study designs were approved by research ethics committees. One study did not report the consent and ethics committee process.

Overall, there were three non-comparative studies and 51 randomised, controlled, prospective, multicentre clinical trials, 47 of them international.[10,11] In the controlled studies, meropenem was compared with imipenem/cilastatin, cephalosporin-based combinations (with or without an aminoglycoside), or clindamycin plus an aminoglycoside. An open-label design was used in all studies except five; three were double-blind, and two studies in patients with meningitis were single-blind.[10,11]

All studies enrolled hospitalised patients with presumed/documented bacterial infections. In one study, after initial treatment in hospital, outpatient parenteral antibacterial treatment was continued in

the convalescent phase for 87 children with intra-abdominal infections.[22]

The main patient exclusion criteria were pregnancy or lactation, known hypersensitivity to study drugs or any β-lactam, recent exposure to other investigational drugs, marked hepatic disease and hepatic or renal failure. Patients with CNS disease, including a history of seizures, were generally excluded, except in meningitis trials.

### 1.2 Treatment

Meropenem was administered intravenously by infusion over approximately 20–30 minutes or by bolus injection over approximately 5 minutes. Intramuscular administration of meropenem was used in three trials.[10,11] Comparator medications were administered at doses recommended by the manufacturers.

### 1.3 Monitoring and Assessment of Adverse Events

Adverse events reported by the patient and/or observed by the clinician were recorded. In all studies, the investigator was required to assess the relationship between the adverse event and the study medication as being either drug-related (definitely, probably or possibly related to study therapy) or not drug-related (probably not or definitely not related to study therapy). Measurement of clinical laboratory parameters was performed before, during and at the end of study treatment and any abnormal results were reported as laboratory adverse events.

## 2. Evidence from Clinical Trials

### 2.1 Patients and Trials

A total of 12 206 treatment exposures, experienced by 10 637 patients, were included in this analysis; 6308 were meropenem exposures in 6154 patients. As retreatment was permitted in some trials, there were more exposures than patients. There were no major differences between the meropenem and comparator groups with respect to age, clinical condition or severity of infection. Treatment exposures by infection are summarised in table I. Data on the median and range of the duration of meropenem exposure could not be derived from the available study reports.

### 2.2 Dosage and Administration

In adults, meropenem was administered intravenously, most frequently at a dosage of 1g (n = 2455) or 500mg (n = 1880) every 8 hours.[10,11] In the small number of studies where meropenem was administered intramuscularly, the dosage was usually 500mg every 8 hours. In the paediatric studies, children were treated with 10, 20 or 40 mg/kg of meropenem every 8 hours.

**Table I.** Number of patient exposures by infection type

| Infection type | No. of patient exposures | | | |
|---|---|---|---|---|
| | meropenem (n = 6308) | cephalosporin-based therapy[a] (n = 2804) | imipenem/cilastatin (n = 2567) | clindamycin aminoglycoside-based therapy (n = 527) |
| Intra-abdominal | 1307 | 262 | 698 | 214 |
| Lower respiratory tract | 1346 | 692 | 596 | – |
| Skin and skin-structure | 811 | 96 | 739 | – |
| Urinary tract | 676 | 279 | 332 | 1 |
| Meningitis | 415 | 394 | – | – |
| Septicaemia/bacteraemia | 397 | 319 | 73 | – |
| Fever in neutropenic patients | 379 | 322 | 71 | – |
| Gynaecological | 371 | 2 | – | 312 |
| Pulmonary infections in cystic fibrosis patients | 60 | 21 | – | – |
| Bone and joint | 29 | 1 | – | – |
| Other | 9 | – | 5 | – |

a The cephalosporins used were ceftazidime, cefotaxime and ceftriaxone.

– indicates no data.

**Table II.** Patient exposures leading to adverse events, drug-related adverse events, withdrawals and deaths

| Adverse event | Meropenem (n = 6308) | | Cephalosporin-based therapy[a] (n = 2804) | | Imipenem/cilastatin (n = 2567) | | Clindamycin-aminoglycoside-based therapy (n = 527) | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| Any | 2527 | 40.0 | 1009 | 36.0 | 1076 | 41.9 | 203 | 38.5 |
| Drug-related | 1005 | 15.9 | 340 | 12.1 | 379 | 14.8 | 109 | 20.7 |
| Adverse events leading to withdrawal | 160 | 2.5 | 70 | 2.5 | 82 | 3.2 | 6 | 1.1 |
| Deaths[b] | 273 | 4.3 | 121 | 4.3 | 151 | 5.9 | 0 | 0 |

a The cephalosporins used were ceftazidime, cefotaxime and ceftriaxone.

b During or within 30 days of treatment.

## 2.3 Clinical Adverse Events

The overall incidence of adverse events and all drug-related adverse events was similar among patients receiving meropenem, those receiving imipenem/cilastatin, those receiving cephalosporin-based regimens and those receiving clindamycin-based regimens (table II). Clinical adverse events occurring in at least 0.1% of meropenem exposures that were considered by the investigators to be possibly or probably related to treatment are summarised in table III. The drug-related adverse events that were most frequently reported in association with meropenem were diarrhoea, rash and nausea/vomiting. All other meropenem-related adverse events occurred in less than 0.1% of treatment exposures. Meropenem-related anaphylaxis or Stevens-Johnson syndrome were not reported in any trials.

A similar adverse-event profile was recorded for the comparator regimens, although there was a greater incidence of nausea/vomiting with imipenem/cilastatin and less nausea/vomiting with cephalosporin-based treatments. In the four treatment regimens, the most frequent drug-related adverse events were diarrhoea in association with cephalosporin- and clindamycin-based treatments, and nausea/vomiting in association with imipenem/cilastatin. In a *post hoc* subgroup analysis of 1037 patients with complicated skin and skin-structure infections from the study by Fabian et al.,[23] patients with diabetes mellitus tended to have a higher incidence of gastrointestinal adverse events than patients without diabetes.[30] However, treatment was generally well tolerated, and meropenem and imipenem/cilastatin had similar overall safety profiles.

### *2.3.1 Withdrawals and Deaths*

Patient withdrawals due to adverse events were collectively low for the four treatment regimens, ranging from 1.1% with clindamycin-based therapy to 3.2% with imipenem/cilastatin (table II). The percentage of patients who died during or within

**Table III.** Clinical adverse events occurring in at least 0.1% of meropenem exposures that were possibly or probably related to treatment

| Adverse event | Meropenem (n = 6308) | | Cephalosporin-based therapy[a] (n = 2804) | | Imipenem/cilastatin (n = 2566) | | Clindamycin-aminoglycoside-based therapy (n = 527) | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| Diarrhoea | 155 | 2.5 | 71 | 2.5 | 30 | 1.2 | 20 | 3.8 |
| Rash | 88 | 1.4 | 51 | 1.8 | 37 | 1.4 | 5 | 1.0 |
| Nausea/vomiting | 76 | 1.2 | 11 | 0.4 | 72 | 2.8 | 9 | 1.7 |
| Injection site reactions | 59 | 0.9 | 17 | 0.6 | 28 | 1.1 | 1 | 0.2 |
| Headache | 25 | 0.4 | 2 | 0.1 | 16 | 0.6 | 0 | 0.0 |
| Pruritus | 22 | 0.3 | 5 | 0.2 | 24 | 0.9 | 3 | 0.6 |
| Sepsis | 8 | 0.1 | 4 | 0.1 | 4 | 0.2 | 1 | 0.2 |
| Pain | 6 | 0.1 | 5 | 0.2 | 2 | 0.1 | 1 | 0.2 |
| Other[b] | 6 | 0.1 | 0 | 0.0 | 4 | 0.2 | 0 | 0.0 |

a The cephalosporins used were ceftazidime, cefotaxime and ceftriaxone.

b Other adverse events included constipation, oral candidiasis, glossitis, hypotension and renal failure.

**Table IV.** Incidence of seizures during treatment in patients with infections other than meningitis

| Seizures | Meropenem (n = 5893) | | Cephalosporin-based therapy[a] (n = 2418) | | Imipenem/cilastatin (n = 2567) | | Clindamycin-aminoglycoside-based therapy (n = 527) | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| Total | 22 | 0.37 | 6 | 0.25 | 11 | 0.43 | 2 | 0.38 |
| Drug-related | 4 | 0.07 | 1 | 0.04 | 6 | 0.23 | 0 | 0.00 |

a The cephalosporins used were ceftazidime, cefotaxime and ceftriaxone.

30 days of treatment in the meropenem and cephalosporin groups was identical (4.3%). In the imipenem/cilastatin groups, 5.9% of patients died during or within 30 days of treatment. No patients died in clindamycin-based therapy groups.

#### *2.3.2 Seizures*

Tables IV and V show a breakdown of the reported seizures in the clinical trials, depending on whether patients were being treated for meningitis, an infection associated with seizures, or for other bacterial infections. In the seven most recent studies[22-28] available to update the safety data of meropenem in infections other than meningitis, a seizure was reported in only one meropenem recipient. This case was stated by the investigators to not be treatment-related.[23] Furthermore, no seizures that were considered to be meropenem-related were reported in 137 children with bacterial meningitis treated with that drug.[29]

### 2.4 Laboratory Adverse Events

Table VI summarises laboratory adverse events that occurred in more than 0.2% of meropenem exposures. Overall, there was a similar incidence of events reported in the meropenem, cephalosporin and imipenem/cilastatin treatment groups, and a slightly higher incidence in the clindamycin-based treatment group. The most commonly occurring drug-related haematological adverse event associated with meropenem was thrombocytosis, while the most frequent biochemical adverse events were increases in hepatic enzyme levels. These events occurred at a similar frequency as with cephalosporin-based therapy and imipenem/cilastatin, and at a lower frequency than with clindamycin-based therapy.

**Table V.** Incidence of seizures during treatment exposures in patients with meningitis

| Seizures | Meropenem (n = 415) | | Cephalosporin-based therapy[a] (n = 394) | |
|---|---|---|---|---|
| | n | % | n | % |
| Total | 35 | 8.43 | 48 | 12.18 |
| Drug-related | 0 | 0.00 | 0 | 0.00 |

a The cephalosporins used were ceftazidime, cefotaxime and ceftriaxone.

### 2.5 Patient Subgroups

#### *2.5.1 Skin and Skin-Structure Infections*

With the addition of the new studies, adverse event data were available for a total of 811 patients with skin or skin-structure infections who had been treated with meropenem (table I); 96 patients with skin/skin-structure infections were treated with cephalosporin-based therapy, and 739 were treated with imipenem/cilastatin. In general, similar proportions of meropenem, cephalosporin and imipenem/cilastatin recipients experienced drug-related adverse events, although there was a tendency for a higher incidence of nausea with imipenem/cilastatin.

#### *2.5.2 Intra-Abdominal Infections*

A total of 2481 patients with intra-abdominal infections were treated in the studies included in this analysis; 1307 with meropenem, 698 with imipenem/cilastatin, 262 with cephalosporins and 214 with clindamycin-based treatment (table I). Adverse-event profiles across the four treatment groups were similar.

#### *2.5.3 Meningitis*

In the specific meningitis studies,[10,11,29] 413 patients were treated with meropenem and 393 with cephalosporins (cefotaxime or ceftriaxone); in studies not specific to meningitis, two additional meningitis patients were treated with meropenem and one with a cephalosporin (table I).[10,11] Meropenem displayed a safety profile similar to that of the cephalosporins; 63 (15.3%) patients treated with meropenem and 48 (12.2%) patients treated with

**Table VI.** Laboratory adverse events occurring in more than 0.2% of meropenem treatment exposures

| Laboratory adverse event (% patients) | Meropenem (n = 6308) | | Cephalosporin-based therapy[a] (n = 2804) | | Imipenem/cilastatin (n = 2566) | | Clindamycin-aminoglycoside-based therapy (n = 527) | |
|---|---|---|---|---|---|---|---|---|
| | total | drug-related | total | drug-related | total | drug-related | total | drug-related |
| **Haematology** | | | | | | | | |
| Thrombocytosis | 2.3 | 1.3 | 1.7 | 1.2 | 1.6 | 1.2 | 7.0 | 4.6 |
| Eosinophilia | 0.6 | 0.5 | 0.6 | 0.5 | 0.5 | 0.4 | 1.3 | 1.3 |
| Thromboplastin level decreased | 0.5 | 0.3 | 0.2 | 0.2 | 0.2 | 0.2 | 0.6 | 0.2 |
| Anaemia | 1.0 | 0.0 | 1.1 | 0.0 | 1.6 | 0.1 | 0.9 | 0.0 |
| Prothrombin time decreased | 0.4 | 0.2 | 0.1 | 0.1 | 0.2 | 0.2 | 0.8 | 0.4 |
| Thrombocytopenia | 0.4 | 0.2 | 0.5 | 0.0 | 0.6 | 0.2 | 0.2 | 0.0 |
| Leukocytosis | 0.2 | 0.0 | 0.1 | 0.0 | 0.2 | 0.0 | 0.8 | 0.4 |
| **Biochemistry** | | | | | | | | |
| ALT level increased | 5.2 | 3.7 | 4.2 | 2.6 | 3.2 | 2.4 | 8.2 | 5.7 |
| AST level increased | 4.3 | 2.9 | 3.5 | 1.9 | 3.0 | 2.3 | 7.0 | 4.6 |
| Alkaline phosphatase level increased | 2.2 | 1.2 | 1.6 | 0.6 | 2.6 | 1.5 | 4.9 | 1.7 |
| Lactic dehydrogenase level increased | 1.3 | 0.7 | 1.2 | 0.6 | 0.6 | 0.5 | 3.2 | 1.5 |
| Creatinine phosphokinase level increased | 0.8 | 0.6 | 0.1 | 0.6 | 0.2 | 0.2 | 0.2 | 0.0 |
| Bilirubinaemia | 0.7 | 0.2 | 1.0 | 0.2 | 0.7 | 0.2 | 0.9 | 0.8 |
| Creatinine level increased | 0.4 | 0.1 | 0.6 | 0.1 | 0.5 | 0.2 | 0.4 | 0.2 |
| NPN level increased | 0.3 | 0.1 | 0.4 | 0.1 | 0.1 | 0.0 | 0.0 | 0.0 |
| BUN level increased | 0.3 | 0.0 | 0.2 | 0.1 | 0.2 | 0.1 | 0.2 | 0.0 |
| Hypokalaemia | 0.2 | 0.0 | 0.2 | 0.0 | 0.2 | 0.1 | 0.2 | 0.0 |
| Hypoproteinaemia | 0.2 | 0.0 | 0.2 | 0.0 | 0.1 | 0.0 | 0.2 | 0.0 |

a The cephalosporins used were ceftazidime, cefotaxime and ceftriaxone.

**BUN** = blood urea nitrogen; **NPN** = non-protein nitrogen.

cephalosporin-based regimens had a drug-related adverse event. There were three withdrawals due to adverse events and seven deaths in the meropenem group, compared with two withdrawals and 11 deaths in the cephalosporin group. The incidence of seizures was higher in the cephalosporin group than the meropenem group (table V), although no seizure in either group was considered to be related to study therapy.

#### 2.5.4 Other Infections

The updated and historical safety data of this review includes over 3000 meropenem exposures in other indications, including lower respiratory tract, urinary tract and gynaecological infections, septicaemia/bacteraemia and neutropenic fever (table I). The overall patterns and frequencies of adverse events with meropenem and the comparator regimens in these indications were similar and no unexpected findings or concerns were noted.

#### 2.5.5 Paediatric Patients

Children treated with meropenem mainly had meningitis (n = 383), lower respiratory tract infections (n = 382), intra-abdominal infections (n = 166) and skin or skin-structure infections (n = 131). The overall safety profile of meropenem was similar to that of the cephalosporin agents, with 16% of meropenem-treated children (188/1148) and 11% of cephalosporin-treated children (115/1030) in comparative trials experiencing drug-related adverse events. The only adverse events related to therapy with meropenem that were experienced by more than 1% of paediatric patients were diarrhoea (4.5%) and rash (2.2%). Other meropenem-related gastrointestinal adverse events were uncommon (seven episodes of vomiting and one of nausea). In comparative studies, 15 (1.3%) withdrawals and five (0.4%) deaths occurred in meropenem recipients, compared with nine (0.9%) withdrawals and six (0.6%) deaths in cephalosporin recipients.

## 3. Discussion

This analysis, based on over 6000 patient exposures, reflects recent expanded experience with meropenem that includes patients with skin and skin-structure infections. Meropenem was approved in the US in 2005 for the additional indication of treatment of complicated skin and skin-structure infections. Further experience with meropenem in intra-abdominal infections and bacterial meningitis was also included, notably a study of 266 children with meningitis, 137 of whom received meropenem and 129 who received cefotaxime.[29] The data reinforce the favourable safety profile of meropenem. In general, both the incidence and the pattern of adverse events seen with meropenem were similar to those of comparator regimens of imipenem/cilastatin and cephalosporin- or clindamycin-based treatment. The clinical trials did not identify any unexpected adverse events, and the proportion of treatment discontinuations because of adverse events was low.

The drug-related clinical adverse events most frequently reported with meropenem were diarrhoea, rash and nausea/vomiting, none of which occurred in more than 3% of patient exposures; this indicates a low overall frequency of adverse events. The most common laboratory adverse events were thrombocytosis and increases in liver enzyme levels.

The increased seizure rate associated with clinical use of imipenem/cilastatin[15,31,32] has made neurotoxicity an important consideration with the carbapenems. It is accepted that risk factors likely to be associated with higher seizure rates in imipenem/cilastatin-treated patients are impaired renal function, pre-existing CNS disorders or infection, a history of seizure, and the specific dose administered.[15,20] In the current review, a higher incidence of drug-related seizures was noted with imipenem/cilastatin (0.23%), than with meropenem (0.07%) and cephalosporin-based (0.04%) therapy in patients without meningitis, confirming that meropenem has good CNS tolerability. However, no new cases of drug-related seizure were reported for any treatment or patient group (meningitis/non-meningitis infections) in the eight[22-29] new studies that updated the safety data.

The gastrointestinal safety of antibacterial agents is an important treatment consideration, especially in seriously ill patients, the elderly and children. The excellent gastrointestinal tolerability of meropenem was confirmed by this analysis, with nausea/vomiting occurring in 1.2% of recipients, compared with 2.8% of imipenem/cilastatin recipients. Indeed, unlike imipenem/cilastatin, meropenem can be administered by bolus injection over 3–5 minutes, while

the recommended intravenous infusion time of imipenem/cilastatin to minimise nausea is 15–60 minutes, depending on the dose.[6]

Antibacterial-associated gastrointestinal infections are of concern in hospitalised patients, who are often elderly or immune compromised. *Clostridium difficile* is the most important cause of nosocomial diarrhoea in adults, and is associated with a clinical spectrum ranging from mild diarrhoea to severe life-threatening pseudomembranous colitis.[33] The main predisposing factor for *C. difficile* diarrhoea is antibacterial therapy, notably with third-generation cephalosporins, clindamycin and broad-spectrum penicillins.[34,35] Preventive measures to minimise *C. difficile* superinfection include judicious selection of antibacterials, and strategies to prevent transmission and cross-infection in the hospital. Most cases of *C. difficile*-associated diarrhoea respond adequately to first- or second-line treatment with metronidazole and vancomycin, respectively.[33] However, recent experience suggests that treatment failure is becoming more frequent,[36] and recurrent disease can be very difficult to treat. Although all antibacterials may predispose patients to *C. difficile* infection and should be used with caution, the carbapenems are active *in vitro* against *C. difficile*, and there is evidence to suggest that meropenem is active against a wider range of isolates than imipenem/cilastatin.[9,37,38] A systematic review of bacterial or fungal superinfection in patients with hospital-acquired infections identified 1431 patients treated with third generation cephalosporins, fluoroquinolones, piperacillin/tazobactam and carbapenems between 1990 and 2003, including 323 patients treated with meropenem.[38] Although *C. difficile* was implicated in 4.1% of superinfections, no cases were associated with meropenem, ciprofloxacin or piperacillin/tazobactam. Furthermore, in a recent hospital outbreak in Canada, all *C. difficile* isolates were found to be susceptible to metronidazole, vancomycin, meropenem and rifampicin (rifampin), but resistant to bacitracin, cefotaxime, ciprofloxacin and levofloxacin.[39] Over 80% of these isolates were also resistant to ceftriaxone, clarithromycin, gatifloxacin and moxifloxacin.

The prescribing information[6-8] for carbapenems cautions against their administration in patients with a history of penicillin hypersensitivity, and a risk of cross-hypersensitivity between penicillin and imipenem approaching 50% has been reported.[40] A recent review of retrospective studies[41] suggested that the actual risk of cross-hypersensitivity is similar for both meropenem and imipenem/cilastatin, at between 9% and 11%, although approximately 26% of patients with reported penicillin hypersensitivity had positive skin tests with carbapenems in one study. The risk of cross-hypersensitivity with ertapenem has not yet been investigated.

Changes in levels of biochemical markers of renal function, such as creatinine or blood urea nitrogen, were uncommon in patients receiving meropenem in the present analysis. A previous review reported the excellent safety profile of meropenem in elderly or renally impaired patients and concluded that the drug was suitable for use in these patient groups.[42] In this study,[42] the overall incidence and type of adverse events in elderly and renally impaired patients was similar to that seen in younger patients and those with normal renal function. No clinically significant changes in biochemical markers of renal function were seen in either patient cohort.

Reports have been published of an apparent interaction between meropenem and the anticonvulsant valproic acid, which leads to generally reduced serum valproic acid levels.[43-47] In some cases, potentially subtherapeutic levels of valproic acid may be reached, increasing the risk of seizures.[43,45,47] Similar interactions have been reported with the carbapenem panipenem/betamipron,[48,49] which could suggest a class effect. In several, but not all reports, the observed reduction in valproic acid levels with meropenem was associated with seizure exacerbation.[44,46] A search of the literature did not identify reports of meropenem interacting with other anticonvulsants.

## 4. Conclusions

Based on the findings of this expanded and updated analysis of the meropenem safety data, meropenem is well tolerated and has good CNS and gastrointestinal tolerability in patients with serious bacterial infections, including special patient populations such as patients with meningitis and paediatric patients. The findings fully support previous safety reviews of meropenem.[10,11]

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