Meropenem: an updated review of its use in the management of intra-abdominal infections

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Authors' objectives
To determine the efficacy and tolerability of monotherapy with meropenem (MEP) in hospitalised patients with intra-abdominal infections.

Searching
AdisBase (a proprietary database of Adis International) and MEDLINE were searched for medical literature on MEP published in any language since 1983. The search terms used with AdisBase were 'Meropenem', 'ICI-194660', 'ICI-213689' or 'SM-7338', and 'Intra-abdominal-infections'. The search terms used with MEDLINE were 'Meropenem' or 'SM7338' and 'intra-abdominal infections'. The searches were last updated 17 July, 2000. Additional published and unpublished material was obtained by examining the reference lists of retrieved articles and by contacting the company developing the drug.

Study selection

Study designs of evaluations included in the review
No inclusion criteria regarding study design were specified. All of the studies included in the efficacy analysis were multicentre and randomised; one trial was double-blind. A single review was included to determine the tolerability of MEP.

Specific interventions included in the review
Studies were included if they evaluated the use of MEP in patients with intra-abdominal infections. The included trials gave MEP in doses of 1.5 or 3 g/day. Comparison interventions were: imipenem (IMP) or cilastatin (CIL) monotherapy; cefotaxime plus metronidazole; or clindamycin plus tobramycin.

Participants included in the review
No inclusion criteria regarding the participants were specified, other than 'patients with intra-abdominal infections'. The included studies were presented separately according to whether they evaluated MEP in patients with 'moderate', 'moderate to severe' or 'severe' intra-abdominal infections. Three trials also included patients with other infection types, 'serious infections'.

Outcomes assessed in the review
No inclusion criteria relating to the outcomes of interest were specified.

The outcomes presented in the review were the percentages of patients with satisfactory clinical or bacteriological response. Clinical response was satisfactory if symptoms were either cured or improved. Bacteriological response was satisfactory if there was proven or presumptive (satisfactory clinical response but no specimen obtained for culture) eradication of primary pathogens.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
No formal assessment of validity was undertaken.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data
Data were extracted on the following: study author; most common diagnosis; infection severity and site; the number of enrolled patients; drug and dosage; the percentage of patients with satisfactory clinical response; and the percentage of patients with satisfactory bacteriological response.

**Methods of synthesis**

How were the studies combined?
Details of the studies were presented in tables and were combined in a narrative summary.

How were differences between studies investigated?
The studies were grouped in the tables and in the narrative summary according to the severity of intra-abdominal infection.

**Results of the review**

Twelve randomised studies were included in the review: 3 (n = 697) included patients with 'moderate' intra-abdominal infections, 7 (n = 1,222) included patients with 'moderate to severe' infections, and 2 (number of patients unclear) included those with 'severe' infections. A single review (n = 9,514) of 46 trials (45 comparative and 1 non-comparative) was used to determine the tolerability of MEP.

**Moderate infections.**

A satisfactory clinical response was obtained in 92 and 98% of patients with intra-abdominal infections of moderate severity treated with 1.5 g/day MEP in 2 multicentre, randomised trials. Similar results (95 versus 98%) were obtained in a study in which patients received 3 g/day MEP but a reduced dosage of IMP or CIL (1.5 g/day). The bacteriological response rates (95 to 98% for both drugs) were similar to the rates of clinical response in 2 trials, although slightly lower rates were documented in the remaining trial which gave results on a per pathogen basis (87% with MEP versus 93% with IMP or CIL).

**Moderate to severe infections.**

Comparison with IMP or CIL.

The clinical response rates were similar in patients who received either MEP, or IMP or CIL (both 1 g every 8 hours) in 3 multicentre, randomised trials: the clinical response rates ranged from 96 to 100% with MEP, and from 94 to 97% with IMP or CIL. The clinical responses at 2- to 4-week follow-up were similar to those obtained at the end of the treatment. Satisfactory eradication rates were obtained in 84 to 96% of patients receiving MEP, and in 81 to 100% of those receiving IMP or CIL.

Comparison with the cefotaxime-metronidazole combination.

Three trials comparing MEP with a cephalosporin-based regimen consisting of cefotaxime (1 or 2 g every 8 hours) plus metronidazole (0.5 g every 8 hours) reported contrasting results. Patients receiving MEP (1 g every 8 hours), however, achieved high rates (91 to 95%) of satisfactory clinical response in all trials. The bacteriological eradication rates with MEP were consistently similar to those achieved with cefotaxime-metronidazole in the 2 trials reporting these data.

Comparison with the clindamycin-tobramycin combination.

The data from one multicentre, randomised, double-blind study suggested that MEP (1 g every 8 hours) produced similar clinical response rates to clindamycin (0.9 g every 8 hours) plus tobramycin (15 mg/kg per day): the rates were 96% following treatment with MEP and 93% with clindamycin-tobramycin. The rate of satisfactory clinical response was maintained at a follow-up of 4 to 14 and 28 to 42 days later. The bacteriological response rates were 96 and 93% after treatment with MEP and clindamycin-tobramycin, respectively. These rates improved to 100% in both treatment groups at the 4- to 14-day follow-up, but dropped to 94% in the MEP group at the 42-day follow-up.
Severe infections.

MEP and IMP or CIL demonstrated similar clinical efficacy in 2 comparative trials, which recruited patients with serious infections and included over 50 patients each with severe intra-abdominal infections. Administered at dosages of 3 g/day, the clinical response rates were 82 and 96% with MEP, versus 81 and 77% with IMP or CIL. The bacteriological response rates were also similar: 68 and 78% with MEP versus 70 and 70% with IMP or CIL.

Tolerability.

An overview of tolerability data from 46 trials (n=9,514) showed that the overall incidences of adverse events, drug-related adverse events (definitely, probably, or possibly related to the drug), and adverse events leading to withdrawal and mortality were similar between MEP and its comparators, i.e. other therapeutic regimens. These results were generally supported by those from trials involving patients with intra-abdominal infections, which showed a similar incidence of clinical adverse events with MEP and comparator regimens.

Cost information

The results of three cost analyses comparing the direct drug-related costs of MEP and monotherapy with IMP or CIL were presented in a table. In the two cost analyses that compared bolus administration of MEP with infusion, bolus administration was associated with a delivery cost-savings of approximately 30% in an Australian study and 45% in a UK study. The savings were related to the use of fewer consumables, and slightly lower labour costs in one study. Any differences in the total direct costs between the various MEP and IMP or CIL regimens were predominantly a reflection of these differences in delivery costs.

Authors' conclusions

The extensive comparative clinical data demonstrated that MEP can be used effectively as empirical monotherapy in moderate to severe intra-abdominal infections. It also showed potential in the most severe forms of infection, although experience in this infection type remains limited. Compared with standard combination regimens, MEP offers the benefits of ease of administration without the need for monitoring. It also offers improved central nervous system tolerability, compared with IMP or CIL, with the option of a higher maximum dosage; this may be a particular advantage in patients with severe intra-abdominal infections.

CRD commentary

This review presented a thorough overview of the data pertaining to MEP in intra-abdominal infections. It was based on quite an extensive literature search, which incorporated searching of two databases, as well as identifying relevant papers from reference lists of retrieved articles and contacting manufacturers.

The inclusion criteria relating to the intervention and participants of interest were applied to the search results, although these were very broad. No formal validity assessment of the included trials was carried out, though the authors did place emphasis on the findings from stronger study designs. The data extracted from the included studies were appropriate to the review question, although it was unclear how many reviewers were involved at this, or any other, stage of the review. The included studies were presented in tables and appropriately combined in the narrative summary.

The authors' conclusions appear to follow from the results of the review.

This review included information on the pharmacology and pharmacokinetics of MEP, as well as the efficacy and tolerability.

Implications of the review for practice and research

Practice: The authors state that MEP can be used effectively as monotherapy in moderate to severe intra-abdominal infections.

Research: The authors did not state any implications for further research.
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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.