Systematic review comparing meropenem with imipenem plus cilastatin in the treatment of severe infections

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CRD summary
This review compared the effectiveness of meropenem with imipenem plus cilastatin in the treatment of severe infections. The authors concluded that meropenem is significantly more effective in terms of clinical response and bacteriologic response, and is associated with significantly fewer adverse events. This was a relatively well-conducted systematic review and the authors' conclusions are likely to be reliable.

Authors' objectives
To compare the effectiveness of meropenem with imipenem plus cilastatin in the treatment of severe infections.

Searching
The Cochrane CENTRAL Register, EMBASE and MEDLINE were searched in March 2004. The search terms were reported and no language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion. The majority of studies were multicentre RCTs.

Specific interventions included in the review
Studies in which patients were treated with an equal dose of meropenem or imipenem plus cilastatin with the same regimen were eligible for inclusion. Any additional treatment had to be given equally in the two randomised groups. Details of the regimens and any additional treatments were not reported in the paper.

Participants included in the review
Studies of adult patients with a lower respiratory tract infection, intra-abdominal infection, skin and soft tissue infection, urinary tract infection, or sepsis were eligible for inclusion. The majority of studies reported that the patients were hospitalised. Four studies reported that the majority of patients were mechanically ventilated.

Outcomes assessed in the review
Inclusion criteria were not stated in relation to the outcomes of interest. Data were extracted on clinical response, bacteriologic response, mortality and adverse events.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed the papers against the inclusion and exclusion criteria. Any differences in opinion were adjudicated by a third party.

Assessment of study quality
The quality of the included studies was assessed on the basis of method of randomisation and concealment of treatment allocation. Two reviewers independently assessed study quality, with any disagreements adjudicated by a third reviewer.

Data extraction
Two reviewers independently extracted the data from the included studies. The data were extracted per protocol, rather than on an intention-to-treat basis. Relative risks (RRs) and 95% confidence intervals (CIs) were determined for each trial.
Methods of synthesis
How were the studies combined?
The studies were combined using the Mantel-Haenszel fixed-effect method. Publication bias was assessed using funnel plots and by calculating the regression of normalised effect versus precision.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared and I-squared statistics. Subgroup analyses were planned, based on different treatment regimens, different sites of infection and the country of origin of the trial. The authors planned to undertake further subgroup analyses if statistical heterogeneity was identified.

Sensitivity analyses were also planned. These were based on changing the inclusion criteria to include all comparative RCTs, regardless of the type of infection or treatment regimen, and by using the DerSimonian and Laird random-effects method for the meta-analysis.

Results of the review
Twenty-seven RCTs were included in the review. The total number of participants was not reported, but was more than 3,802.

Clinical response (27 RCTs) was statistically significantly higher for meropenem than imipenem plus cilastatin (RR 1.04, 95% CI: 1.01, 1.06).

Bacteriologic response (22 RCTs) was statistically significantly higher for meropenem than imipenem plus cilastatin (RR 1.05, 95% CI: 1.01, 1.08).

There was no statistically significant difference in mortality over the course of treatment between meropenem and imipenem plus cilastatin (9 RCTs; RR 0.98, 95% CI: 0.71, 1.35).

There were statistically significantly fewer adverse events with meropenem than with imipenem plus cilastatin (18 RCTs; RR 0.87, 95% CI: 0.77, 0.97). The most commonly reported adverse events were those identified by laboratory tests, such as thrombocytosis and increased hepatic enzymes. Other adverse events included diarrhoea, injection site inflammation, nausea or vomiting, rash and seizure.

No evidence of clinical heterogeneity was found. In all subgroup analyses that consisted of more than one trial, the direction of the result was consistent with the primary analyses. There was no evidence of statistically significant heterogeneity in any of the primary analyses.

There was no evidence of significant publication bias when using either funnel plots or an assessment of regression of normalised effect versus precision for any of the primary analyses (P>0.30 for all comparisons).

The effect of changing the inclusion criteria to include all comparative RCTs, regardless of the type of infection or treatment regimen, did not change the direction of the results for any of the primary analyses. The effect of using a random-effects model also did not change the direction of the results for any of the primary analyses, or make a significant difference non-significant.

The primary meta-analysis of clinical response for meropenem compared with imipenem plus cilastatin was reanalysed as a cumulative analysis, based on the year of publication of the clinical trials included, in order to determine at which point a statistically significant result could have been identified if a cumulative meta-analysis had been employed as new research emerged. A meta-analysis of the 13 trials available in 1995 demonstrated a significant benefit in favour of meropenem (RR 1.03, 95% CI: 1.01, 1.05).

Authors' conclusions
Meropenem is significantly more effective than imipenem plus cilastatin in the treatment of severe infections, in terms of clinical response and bacteriologic response, and is associated with significantly fewer adverse events.
CRD commentary
The review question was clear in terms of the study design, interventions and participants of interest. However, no inclusion criteria were reported in relation to the outcomes of interest. Three relevant electronic databases were searched, with no language restrictions, thus reducing the potential for language bias. The authors made limited attempts to identify unpublished data. However, publication bias was assessed and was not found to be significant. Two reviewers independently carried out the study selection, quality assessment and data extraction processes, thereby reducing the potential for reviewer bias or error. The criteria used to assess the quality of the included studies were appropriate, although the results of the quality assessment exercise itself were not reported.

Details of the included studies were presented in relation to publication type, country of origin, patient characteristics and results. However, no details of the treatment regimens were reported. As the authors pointed out, the inclusion criteria of most of the included trials required that only patients expected to survive the treatment period be randomised, therefore, the included trials were less likely to report a statistically significant difference in mortality. This also has implications for the generalisability of the results of this review.

The authors assessed statistical heterogeneity and performed subgroup and sensitivity analyses. The methods used to combine the studies appeared appropriate. This was a relatively well-conducted systematic review; the authors’ conclusions appear to follow from the evidence presented and are likely to be reliable.

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Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that the cost-effectiveness of meropenem and imipenem plus cilastatin need to be considered, and that further research is currently underway using the results from this systematic review to perform a cost-effectiveness analysis.

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