Clinical and economic benefits of a meropenem dosage strategy based on pharmacodynamic concepts

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
Patients needing antibiotics were given 500 mg of meropenem, a broad-spectrum intravenous carbapenem antibiotic, every 6 hours. A comparator group of patients were given 1,000 mg meropenem every 8 hours.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
Patients visiting the hospital over the course of one year, who had received at least one full day dose of meropenem therapy, were included in the economic analysis. Patients who had received at least 3 days of meropenem therapy were considered in the effectiveness analysis. Patients were excluded if they had received more than one day of antibiotics before meropenem, unless they had not responded to the earlier antibiotic therapy. This meant that this category of patients who had been on meropenem therapy previously was also excluded. Patients were also excluded if their infection was caused by an organism that was resistant to meropenem at the beginning of therapy. They were also excluded if they had a creatinine clearance level of less than 25 mL/minute, because the adjusted dosage they would receive would be the same whether they were on 500 mg every 6 hours or 1,000 mg every 8 hours. Patients who had undergone a prior hospitalisation, during which they had been treated with meropenem for the same infection, were also excluded. Patients receiving meropenem as part of a combination therapy were included.

Setting
The setting was secondary care. The economic study was carried out in Hartford (CT), USA.

Dates to which data relate
The effectiveness evidence and resource evidence were gathered between January 2002 and December 2002. The price year was 2002.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The same patients provided both the effectiveness and the cost data, although some of the cost patients were not included in the effectiveness analysis. The costing was carried out retrospectively.
Study sample
No power calculations were reported. There was no sample selection since all patients meeting the inclusion criteria were included. Of the 136 patients identified as receiving at least one dose of meropenem, 85 patients met the criteria for the economic analysis. Of these, 45 were in the 500-mg group and 40 were in the 1,000-mg group. The patients in the 500-mg group had a mean age of 56.4 (+/- 18.2) years and 71% were male. The patients in the 1,000-mg group had a mean age of 54.2 (+/- 18.5) years and 65% were male. Only 75 patients were included in the effectiveness analysis, 36 in the 500-mg group and 39 in the 1,000-mg group. Ten patients were not included in the effectiveness analysis because they did not receive at least 3 days' meropenem therapy.

Study design
This was a single-centre, retrospective cohort study. The patients were followed up for the duration of their hospital stay.

Analysis of effectiveness
The basis of the analysis was intention to treat. The primary health outcomes used were:

- the response rate (days to normalisation of temperature or lymphocyte count);
- clinical success rate;
- microbiological outcomes;
- adverse events; and
- length of stay (LOS), which was sub-divided into infection-related LOS, meropenem-related LOS, and meropenem-related intensive care unit (ICU) LOS.

Clinical success was defined as the complete or partial resolution of signs of infection at the end of meropenem therapy, or discharge, whichever occurred first. Clinical failure was defined as the persistence of infection, presence of a bacterial superinfection, intolerance of meropenem following an adverse event, or death following an infection.

Microbiological outcomes were defined as successes or failures at the end of therapy or discharge, whichever occurred first. Success was defined as eradication or presumed eradication of infection. Failures included patients with a persistent or presumed persistent infection or a super infection. Patients with no pathogens isolated initially, or subsequently, were categorised as non assessable.

Infection-related LOS was defined as the length of hospital stay between the documentation of infection and the resolution of infection, hospital discharge, or death due to infection, whichever occurred first. Meropenem-related LOS was defined as the length of hospital stay between the start and end of meropenem therapy or discharge, whichever occurred first. Meropenem-related ICU LOS was defined as the length of hospital stay in the ICU between the start and end of meropenem therapy.

At baseline, there were no significant differences between the two patient groups in demographics, severity of illness at the beginning of meropenem treatment (calculated using the Acute Physiological Assessment and Chronic Health Evaluation, APACHE II score), or infection site. There were significantly more patients who had not responded to prior antibiotic therapy in the 500-mg group than in the 1,000 mg group (81% versus 49%; p=0.009). A greater number of patients in the 1,000-mg group were also receiving another antibiotic (46% versus 19%; p=0.027).

Effectiveness results
There was no difference in the rate of response between the two patient groups. The rate of response was 3 days to normalisation of temperature and 4 days to normalisation of lymphocyte count in both groups (the measure of average used was not given).
The clinical success rate was also similar between the two groups, 78% in the 500-mg group versus 82% in the 1,000-mg group, (p=0.862).

One patient in each group had an adverse event.

There was no significant difference between the two groups in terms of microbiological success in patients in which at least one causative pathogen had been identified (30 patients in the 500-mg group and 24 patients in the 1,000-mg group).

There were two bacterial superinfections in the 500-mg group and two in the 1,000-mg group.

There was no significant difference in infection-related LOS, meropenem-related LOS, or meropenem-related ICU LOS between the groups.

**Clinical conclusions**
Patients on the two dosage strategies did not show any difference in clinical outcomes.

**Measure of benefits used in the economic analysis**
No summary measure of benefit was produced. After concluding that there was no difference in clinical outcomes, the authors carried out a cost-minimisation analysis.

**Direct costs**
No discounting was carried out as the costs were incurred during less than 2 years. The quantities and the costs were not analysed separately, though the unit price of a 500-mg vial and 1,000-mg vial of meropenem was given, as was the average total hospital cost per day. The costs of drug acquisition, concomitant antibiotics, treatment of adverse events, and meropenem-related hospital stay (between the beginning and the end of meropenem therapy or discharge) were calculated. The 2002 average wholesale price was used for meropenem and concomitant medications. The source of the other cost data was actual data from the hospital and the Connecticut Hospital Association. The price year was 2002.

**Statistical analysis of costs**
No statistical analysis of the costs was carried out.

**Indirect Costs**
No indirect costs were calculated.

**Currency**
US dollars ($).

**Sensitivity analysis**
No sensitivity analysis was carried out.

**Estimated benefits used in the economic analysis**
Not relevant as a cost-minimisation analysis was conducted.

**Cost results**
The median total cost was $19,934 (25th percentile $11,895; 75th percentile $27,513) in the 500-mg group and $16,087
(25th percentile $9,969; 75th percentile $23,274) in the 1,000-mg group, (p=0.420).

When the authors excluded the costs of hospital stay and only included the costs of the drugs and treatment of adverse effects, the median costs were $1,035 (25th percentile $563; 75th percentile $1,582) in the 500-mg group and $1,797 (25th percentile $903; 75th percentile $2,622) in the 1,000-mg group, (p=0.008).

**Synthesis of costs and benefits**

Not relevant. The costs and benefits were not combined as the study was a cost-minimisation analysis.

**Authors’ conclusions**

The authors concluded that there was no clinical difference between the two dosing strategies for meropenem (500 mg every 6 hours and 1,000 mg every 8 hours), but that the 500-mg strategy reduced the daily drug acquisition costs associated with antibiotic therapy. This is because the authors focused on a comparison of costs that excluded the costs of the hospital stay. However, when all the costs were included, there was no statistically significant difference between the two groups, and the 500-mg strategy was more expensive.

**CRD COMMENTARY - Selection of comparators**

The choice of the comparator, 1,000 mg over 5 or 30 minutes every 8 hours, is currently the US government approved dosage strategy. You should decide if the comparator represents current practice in your own setting.

**Validity of estimate of measure of effectiveness**

The source of the effectiveness data was a single study. The analysis was based on a retrospective study of patient records in which patients had been allocated non-randomly to the two different dosage strategies. This non-random allocation was subject to relevant biases. For example, it was unclear why patients had been allocated to one or other of the dosing strategies. The two patient groups were not shown to be comparable at baseline and, therefore, there might have been confounding factors affecting the results obtained. The study sample was representative of the study population, as all patients who met the inclusion criteria were included.

**Validity of estimate of measure of benefit**

The authors did not derive a measure of health benefits; the study was one of cost-minimisation. The economic analysis was only concerned with the costs.

**Validity of estimate of costs**

From the hospital perspective adopted, all the relevant categories of costs were included, although the authors do not appear to have assigned sufficient importance to the total costs per patient. In their calculation of the costs of hospital stay, the authors used an average cost per day figure derived from all Connecticut hospitals. This means that important information about each patient's hospital stay will not have been included in the analysis. There was no differentiation between ICU and non ICU days. It was unclear whether the costs of adverse events included staff time, as this was not mentioned as a cost component anywhere in the study. The costs and the quantities were not reported separately, though some individual unit costs were given. It is not clear how these omissions would have affected the conclusions. The resource use quantities were taken from a single study and no other sources, while the prices were taken from the authors' setting and from the regional hospitals. No statistical or sensitivity analyses of the quantities or prices were performed. In addition, no other analysis of the prices was conducted. These facts limit the interpretation of the results. The price year was reported, which will aid any possible inflation exercises.

**Other issues**

The authors made appropriate comparisons of their results with those from other studies. The issue of generalisability to other settings was not addressed. The authors did not present their results selectively. Their conclusions did not reflect
the scope of the analysis, which suffered from the non-randomisation of patients and the lack of comprehensiveness and detail in the cost data, although the authors were aware of these drawbacks. Also, the authors appear to have given undue attention to the elements of the cost data showing the 500-mg strategy to be cheaper, and ignoring the elements that pointed in the opposite direction.

Implications of the study
The authors implied that future research in this area should aim to be prospective and randomised and involve a larger sample size. They also implied that more detailed information on the costs of hospital stay would result in more reliable results.

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