Cefepime versus vancomycin plus netilmicin therapy for continuous ambulatory peritoneal dialysis-associated peritonitis


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
The health technologies examined in the study were once-daily cefepime (a fourth-generation cephalosporin) and the combination of vancomycin plus netilmicin, used for the treatment of continuous ambulatory peritoneal dialysis (CAPD) peritonitis.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients aged 18 years or older who had been on CAPD therapy for more than 4 weeks before the onset of peritonitis. Numerous exclusion criteria were reported: completion of antibiotic therapy for peritonitis within 28 days; active exit-site infection, tunnel infection, and/or subcutaneous leakage; signs and symptoms of septicaemia with oral temperature greater than 38.5°C and/or systolic blood pressure less than 100 mmHg; known history aminoglycoside toxicity; pregnancy; etc.

Setting
The study setting was hospital. The economic study was carried out at the Department of Medicine and Pathology, Queen Elizabeth Hospital, Hong Kong.

Dates to which data relate
Effectiveness and resource use data were collected between 1 January 1998 and 30 June 2000. The price year was not reported.

Source of effectiveness data
The effectiveness evidence was derived from a single study.

Link between effectiveness and cost data
The costing was undertaken prospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations were retrospectively performed based on the existing sample size and the estimated power of the study was stated to have been 0.45 to detect a difference at the 0.05 level in a measure that was not reported. All CAPD
patients presenting with symptoms suggestive of peritonitis were assessed for suitability for inclusion in the study between 1 January 1998 and 30 June 2000. Eighty-one consecutive subjects were recruited and allocated to two groups:

- group A, patients administered cefepime, 2-g intraperitoneally (IP) loading dose (dwell for more than 6 hours), followed by 1 g/d IP for 9 more consecutive days; and
- group B, patients administered vancomycin, 1 g intravenously (IV), and netilmicin, 80-mg IP loading dose (dwell for more than 6 hours), followed by vancomycin, 1 g IV day 7, and netilmicin, 40 mg/d IP for 9 more consecutive days.

Eight patients were then excluded and, as a result, 39 patients (mean age 58+/−14, 23 men) remained in group A and 34 (mean age 59+/−10, 18 men) in group B. Baseline characteristics in terms of primary disease, duration of dialysis and connecting system were given.

**Study design**
The study was an open-label, randomised, controlled, clinical trial, carried out in a single centre (Department of Medicine and Pathology, Queen Elizabeth Hospital). Patients were randomised to the groups by drawing sealed envelopes containing one of the two different treatment regimes. Patients were followed for 28 days after completion of therapy and were assessed on days 1, 5, 10, and 28 for clinical outcome and adverse reactions.

**Analysis of effectiveness**
An intention to treat analysis was conducted. The primary health outcomes used in the analysis were given by the type of pathogens isolated (gram-positive, gram-negative, and culture-negative results), as rates of primary response (disappearance of signs and symptoms of peritonitis, and clearing of the peritoneal dialysate on day 10), complete cure (no relapse for 28 days after completion of antibiotic therapy), relapse (peritoneal dialysate cleared on day 10, but peritonitis recurred attributed to the same organism within 28 days after completion of antibiotic therapy), and failure (when patients required modification of therapy on days 5 through 10 or peritoneal dialysate cell count greater than 100/mL on day 10). Side effects were also reported. Statistical analyses were conducted to show the comparability of groups in terms of sex ratio, age, primary diagnosis, duration of dialysis therapy, and use of different connecting system.

**Effectiveness results**
The effectiveness results were as follows:

- With respect to the type of pathogens isolated, gram-positive, gram-negative, and culture-negative results accounted for 41% (16 episodes), 18% (7 episodes), and 41% (16 episodes) in group A, respectively, and for 41% (14 episodes), 21% (7 episodes), and 32% (11 episodes) in group B, respectively.

- The primary response rate was 82% in group A and 85% in group B. Complete cure rate was 72% in group A and 76% in group B. Relapse rate was 10% in group A and 9% in group B.

- The rate of failure was 18% in group A and 15% in group B. There were no significant side effects in either group, except for one patient in group A, who reported instillation pain.

- No differences between the groups reached statistical significance at the 0.05 level in a two-tailed test.

**Clinical conclusions**
The effectiveness analysis has indicated that the results would be consistent with the therapies being equally effective, although, on average, the vancomycin group did better.

**Measure of benefits used in the economic analysis**
Although the effectiveness analysis showed that there was no statistically significant difference in the effectiveness of
the two drugs, the number of successfully cured patients was used as the benefit measure in the economic analysis and was derived from the effectiveness analysis.

**Direct costs**
Discounting was not relevant due to the short time horizon of the analysis. Resource quantities and unit costs were reported separately only for the peritonitis-related hospitalisations. The resource/cost boundary adopted was that of the hospital. The costs included direct drug costs and hospitalisations. The estimation of costs and quantities was based on actual data obtained from the Department Manager of the author’s institution. The data on the resources used in the analysis were gathered from 1 January 1998 to 30 June 2000. The price year was not reported.

**Statistical analysis of costs**
No statistical analysis of costs was reported.

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

**Currency**
US dollars ($).

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

**Estimated benefits used in the economic analysis**
The number of successfully cured patients (complete cure rate) was 28 out of 39 subjects in group A and 26 out of 34 patients in group B.

**Cost results**
The number of peritonitis-related hospitalisations were 84 patient-days in group A and 115 patient-days in group B. The cost of 1-patient-day of hospitalisation was approximately $300. Drug acquisition costs were $100 for cefepime and $34 for vancomycin plus netilmicin. Total costs in each group were not reported.

**Synthesis of costs and benefits**
A cost-effectiveness analysis was performed to synthesise costs and benefits in the study: the total costs of each group were divided by the number of successfully cured patients in the respective group. The average cost per cured patient was $1,039 in group A and $1,371 in group B.

**Authors' conclusions**
The authors concluded that cefepime and the combination of vancomycin plus netilmicin were equally effective and did not differ in terms of cost-effectiveness, therefore cefepime (once daily) was a safe and cost-effective alternative to vancomycin plus netilmicin in the treatment of CAPD-associated bacterial peritonitis.

**CRD COMMENTARY - Selection of comparators**
The authors did not provide a justification for the selection of the health technologies in the study and it appeared that other drug therapies were available, but were not included in the analysis. You should consider whether they represent widely used interventions in your own setting.
Validity of estimate of measure of effectiveness
The effectiveness analysis was based on a randomised design, which was appropriate for the hypothesis of the study. However, although statistical analyses showed the comparability of groups with respect to demographic and clinical characteristics, a major limitation of the analysis was the small sample size. The authors acknowledged that approximately 300 patients should have been recruited in each arm of the study to give a power of 0.8 at a significance level of 0.05. However, it is not easy to obtain this number of peritonitis patients in a single centre.

Validity of estimate of measure of benefit
The benefit measure was derived directly from the effectiveness analysis. The choice of the benefit estimate was not explicitly justified. Since effectiveness outcomes did not differ significantly between groups, it would have been interesting to have adopted a summary benefit measure, also based on patient preferences, especially in consideration of the different length of hospital stay between the groups, which could have affected quality of life as perceived by patients and caregivers. Also lacking was any renal impairment measure, which might have tipped the balance towards cefepime.

Validity of estimate of costs
The cost estimates appeared to be quite specific to the study setting (Hong Kong hospital) and statistical analyses were not carried out to enhance the external validity of the study results. Overall, the cost analysis was not reported satisfactorily, mainly because very few details were indicated in the study. Unit costs and quantities were reported separately only for the length of hospital stay and it was not stated which cost items were included in the analysis. Finally, the price year was not reported. It should also be noted that any claim regarding cost-effectiveness should be based on the incremental change in resource use (valued by monetary cost) for a given change in benefit in moving from one technology to another. This was not performed here. Also, the comparator technology needs to be shown to be the next best or the only established technology, and, again, this was not shown here.

Other issues
The generalisability of the results to other settings was quite limited, as no sensitivity analyses were conducted. The authors did make some comparisons of their findings with those of other studies.

Implications of the study
The authors claimed that adoption of cefepime appeared to be particularly advantageous to avoid the risk of reduction of valuable renal function of dialysis patients and that it is cost-effective. However, as described above, these claims are not entirely supported by the evidence, particularly given the small sample, lack of measure of renal impairment, and inappropriate economic analysis.

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