Evaluation of the use of cefuroxime and cefuroxime axetil in an intravenous oral stepdown program


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
An intravenous-oral step down programme promoting the use of oral antibiotic medication in patients requiring ongoing drug therapy after commencing with parenteral (intravenous) therapy. Specifically the use of cefuroxime and cefuroxime axetil for the prevention and treatment of aerobic infections was examined.

Type of intervention
Treatment; Primary prevention.

Economic study type
Cost-minimisation analysis.

Study population
Inpatients receiving intravenous cefuroxime treatment during the first six months (April-October 1992) of a stepdown programme to prevent or treat aerobic infections following surgery or prophylactic treatment.

Setting
The clinical study was conducted in hospital. The economic study was conducted in Vancouver, British Columbia, Canada.

Dates to which data relate
Effectiveness and resource data were collected between April to October 1992. 1992 prices were used.

Source of effectiveness data
Effectiveness data were taken from a single study.

Link between effectiveness and cost data
Costing was undertaken retrospectively although it is not clear whether costing was undertaken on the same patient sample as that used in the clinical analysis.

Study sample
A random sample of 100 patients who received either prophylactic or empiric/directed (for known or suspected infections) intravenous cefuroxime treatment was selected from the study population. No step down to an oral antibiotic was identified in 78 of these patients, who then formed the 'non-stepdown' group. In addition, a random sample of 50 intravenous cefuroxime courses which involved a stepdown to oral cefuroxime was also identified (the stepdown group). Power calculations were not used to identify the sample size.
In the non-stepdown study group 63% of patients were men, the mean age was 62 (SD 15) years and mean weight was 70 kg (SD 15). In the stepdown group 58% of patients were men, the mean age was 66 (SD 17) years and mean weight was 62 kg (SD 15) (P<0.002).

**Study design**

Single centre retrospective cohort study. Patients appear to have been followed-up for up to 30 days after initiation of treatment. Those accessing the patient records to examine outcomes were blinded.

**Analysis of effectiveness**

The analysis of the clinical study seems to have been based on intention to treat. There were no significant demographic differences between the non stepdown treatment group and the step down group with the exception of weight and APACHE II score.

Prophylactic and empiric/directed treatment courses were evaluated with respect to clinical and microbiological outcomes. For prophylactic regimens, clinical and microbiological outcomes were characterised as a success or a failure, depending on evidence of either a primary site infection (clinical) or primary site cultures (microbiological) within 30 days after surgery. The clinical outcome for empiric/directed treatment was categorised as cure, improvement, failure or relapse according to standard definitions. For the purposes of data presentation, clinical outcomes coded as cure or improvement were grouped together. To be evaluated for microbiological outcome, empiric/directed treatment courses required both clinical and microbiological evidence of infection, based on cultures obtained within 48 hours of start of therapy. Courses were categorised as eradication, colonisation, superinfection, or failure, according to standard definitions. Non-prophylactic treatment courses had to be maintained for at least 3 days to qualify for clinical or microbiological assessment, however it is not clear at what time point these outcome measures were obtained.

The appropriateness of the intravenous treatment, and eligibility for stepdown treatment were also evaluated.

**Effectiveness results**

The clinical and microbiological outcomes for the non step down and step down treatment groups were as follows: 51/78 patients in the non-stepdown group received prophylactic therapy, of whom 46 (90%) had successful clinical outcomes, with 5 (10%) classified as failures. For the stepdown group 4/50 patients received prophylactic therapy of whom 3 were deemed to have successful clinical outcomes and one was classed as a failure (P=0.378). For the microbiological outcomes, 47/51 patients in the non-stepdown group were judged to be successful and four to have failed. In the stepdown group (n=4) there were three successful outcomes and one failure (P=0.325). 27/78 patients in the non-stepdown group received empiric/directed therapy of which 15 were judged to be cured or improved, 2 failed and 10 were unevaluable. In the stepdown group 46/50 patients received empiric/directed therapy of which 38 were cured or improved, 2 failed, 2 relapsed and 4 were unevaluable (P=0.431 excluding unevaluable).

For the microbiological outcomes, the non-stepdown group had 5 cases which were deemed to be eradicated, 3 with superinfection and 19 which were indeterminate. In the stepdown group 12 were deemed to be eradicated, 4 with superinfection, 3 failed and 27 were indeterminate (P=0.396 excluding indeterminate). In the non-stepdown group, 49/78 received appropriate intravenous treatment, and 36/78 were retrospectively considered eligible for stepdown treatment. In the stepdown group (n=50), stepdown was retrospectively considered timely in 32 cases, late in 16 cases and premature in 2 cases.

**Clinical conclusions**

The authors concluded that there were no differences in outcomes between the stepdown and non-stepdown treatment groups, particularly as stepdown therapy usually occurs after a period of responsive parenteral cefuroxime treatment. However, stepdown treatment was only used in a small proportion of all intravenous cefuroxime treatment courses and was considered to be late in a third of stepdown cases.
Measure of benefits used in the economic analysis
Since the effectiveness analysis showed no difference in the clinical benefit between the two treatment options, the economic analysis was based on the difference in costs only.

Direct costs
Only the costs of cefuroxime and cefuroxime axetil were estimated, based on 1992 costs. Specifically these included drug acquisition, preparation and delivery costs. No discounting was conducted. The cost of therapy per day and per treatment course were calculated.

Currency
US dollars ($).

Sensitivity analysis
No sensitivity analysis was conducted.

Estimated benefits used in the economic analysis
Not applicable.

Cost results
The mean costs per day and duration of treatment with prophylactic therapy were:

Non-stepdown: $25.08 (SD 8.02), 2.9 days (SD 2.8).

Stepdown: $17.08 (SD 5.66), 8.0 days (SD 3.3) (intravenous $29.94 (SD 7.29), 4.0 days (SD 2.9)), oral $6.86 (SD 1.16), 4.0 days (SD 2.5)).

There were no significant differences between the non-stepdown and stepdown mean costs per day, but the duration of treatment was significantly longer in the stepdown programme (p=0.001).

The mean costs per day and mean duration of empiric/directed therapy were:

Non-stepdown: $26.21 (SD 7.19), 4.9 days (SD 4.3).

Stepdown: $15.66 (SD 6.03), 9.7 days (SD 4.2), (intravenous drug $24.50 (SD 7.11), 4.6 days (SD 3.7) and oral 7.62 (SD 1.74), 5.1 days(SD 2.4)).

The difference in mean cost per day and mean duration of treatment were statistically significant (P<0.001).

Synthesis of costs and benefits
Not applicable.

Authors' conclusions
The authors concluded that there were no differences in clinical outcomes between parenteral and oral administration of cefuroxime and that there was a significant difference in the mean costs of therapy with the stepdown therapy being lower than the non step down therapy ($15.66 compared with $26.21 for empiric/directed therapy). They noted that the introduction of stepdown therapy had only had a small impact on the level of oral treatment in its first six months. The authors also noted that although the study was limited by its size and observational nature, the use of oral cefuroxime should be promoted as an alternative to parenteral therapy in cases where conversion is feasible, as this will reduce the costs of treatment.
CRD COMMENTARY - Selection of comparators

A justification was given for the comparators used. Cefuroxime axetil is the oral version of the parenteral cephalosporin cefuroxime. The use of the same stepdown agent as for parenteral therapy was thought to reduce the reluctance of physicians to switch to prescribing oral therapy rather than parenteral therapy.

Validity of estimate of measure of benefit

The estimates of benefit were derived from a small observational study and as such are highly likely to be biased. Although the two groups were selected randomly, the non-stepdown group was formed from a subgroup of the random sample. Some of the analyses were conducted on very small patient numbers (for example, information on prophylactic patients in the stepdown group was based on a sample of just four patients).

Validity of estimate of costs

Insufficient details were provided of the source and nature of costs used. Insufficient information was provided on the dosage of cefuroxime used in the non step down treatment group. There were significant flaws in the analysis of the treatment costs. The total average costs of treatment for stepdown versus non-stepdown treatment were not provided. Instead, costs were presented as ‘average cost of treatment per day’. It is therefore not surprising that significant differences between the two groups were found: there were no significant differences in duration of parenteral treatment between the two groups, and the stepdown group then went on to received the much cheaper oral antibiotic for 4-5 days, thus reducing the average cost of treatment per day by a significant amount.

Other issues

This study is methodologically flawed, in terms of the effectiveness data, the cost data, and in the analysis, and its results should be treated with a great deal of caution.

Implications of the study

There is a need for a well designed randomised controlled trial to determine the clinical impact and costs of oral alternatives to parenteral therapy using cefuroxime. In addition the costs and effectiveness of educating professionals to make use of step down therapy programmes needs also to be examined.

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