Pharmacokinetic and economic evaluation of piperacillin/tazobactam administered as either continuous or intermittent infusion with once-daily gentamicin

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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
Piperacillin-tazobactam, administered as a continuous infusion with and without gentamicin, was compared with piperacillin-tazobactam administered as an intermittent infusion, with and without gentamicin.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The population of interest was ultimately patients with serious infections. In particular, those where Pseudomonas aeruginosa and/or Enterococcus species were known or suspected pathogens. The study sample was drawn from a healthy population.

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

Dates to which data relate
The dates to which the effectiveness evidence related were not reported. The resources used for infusion were taken from a study published in 1997. The costs were derived for the fiscal year 1997 to 1998.

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

Link between effectiveness and cost data
The effectiveness data were collected from 12 healthy volunteers. The cost data were collected from 296 patients treated with piperacillin-tazobactam at the hospital during the 1997-1998 fiscal year.

Study sample
Power calculations, to estimate the sample size required to detect statistically significant differences in the costs or effects, were not reported. The study sample comprised 12 healthy volunteers. There was no evidence to suggest that the study sample was representative of the potential patient population with serious infections.
Study design
The study was a single-centre pharmacokinetic study with a crossover design. The 12 patients first received a continuous infusion of piperacillin-tazobactam and a single high dose of gentamicin. Then, after a washout period, they received an intermittent infusion of piperacillin-tazobactam and a single high dose of gentamicin. The authors did not report any procedures to mask the participants or investigators to the treatment method during administration of the therapy, or the assessment and analysis of the outcome.

The duration of follow-up was the length of the infusion. All 12 patients completed the continuous infusion part of the study. One patient withdrew from the intermittent infusion part of the study for reasons unrelated to the study, which were not reported.

Analysis of effectiveness
The basis of the analysis, in terms of intention to treat or treatment completers only, was not reported.

The primary outcomes were pharmacokinetic parameters for piperacillin before and after the administration of gentamicin. These were:

- the steady state concentration of piperacillin administered by continuous infusion;
- the maximum concentration of piperacillin administered by intermittent infusion;
- the elimination half-life of piperacillin administered by intermittent infusion;
- the area under the concentration-time curve for piperacillin administered by intermittent infusion.

Effectiveness results
For the continuous infusion of piperacillin, the mean steady state concentration of piperacillin was 28 (standard deviation, SD=6.9) microg/mL before the administration of gentamicin, and 29.7 (SD=7.0) microg/mL for the 9 hours following the absolute peak gentamicin concentration, (p=0.30).

The mean maximum concentration of piperacillin administered by intermittent infusion was 232 (SD=54) microg/mL before the introduction of gentamicin, and 253 (SD=83) microg/mL after, (p=0.67).

The mean elimination half-life of piperacillin administered by intermittent infusion was 0.81 (SD=0.22) hours before the introduction of gentamicin, and 0.89 (SD=0.23) hours after, (p=0.32).

The mean area under the concentration-time curve for piperacillin administered by intermittent infusion was 354 (SD=132) microg hours/mL before the introduction of gentamicin, and 315 (SD=73) microg hours/mL after (p=0.39).

Clinical conclusions
The authors concluded that administering once-daily gentamicin to healthy volunteers, who were receiving piperacillin-tazobactam as either a continuous or intermittent infusion, did not alter the pharmacokinetic parameters of either piperacillin or gentamicin. There was no clinically or statistically significant interaction.

Measure of benefits used in the economic analysis
The outcomes were reported in a disaggregated way and, as such, this was a cost-consequences analysis.

Direct costs
The resource quantities and the costs were not reported separately. The resource use and cost data were obtained from a time and motion study published in 1997, and from data for 296 patients treated in the 1997 to 1998 fiscal year. The direct costs to the hospital were included in the analysis. The costs of the acquisition, preparation and administration of
the antibiotics were included in the analysis. The unit cost data were obtained from two sources, the hospital unit cost data and the average wholesale price from the Red Book 1998. The price data referred to the 1997 to 1998 fiscal year. Discounting was not conducted due to the short timeframe of the study, which was less than one year. The study reported the average costs.

**Statistical analysis of costs**
A statistical analysis of the costs was not reported.

**Indirect Costs**
The indirect costs were not included in the analysis as they were not appropriate to the perspective of the study.

**Currency**
US dollars ($). No currency conversion rates were reported.

**Sensitivity analysis**
One-way sensitivity analyses were conducted on the dose regimen and the unit costs of the intermittent infusion of piperacillin.

**Estimated benefits used in the economic analysis**
See the 'Effectiveness Results' section.

**Cost results**
Using hospital-based costs, the total costs for 296 patients given an infusion of piperacillin were:

- $144,814 for a 4-hourly intermittent infusion of piperacillin 3.375 g;
- $96,542 for a 6-hourly intermittent infusion of piperacillin 3.375 g;
- $90,414 for an 8-hourly intermittent infusion of piperacillin 4.5 g; and
- $78,806 for a continuous infusion of piperacillin (500 mg/hour) plus a 4.5 g loading dose.

Using hospital-based cost data, the net savings associated with constant infusion were:

- $66,008 versus a 4-hourly intermittent infusion of piperacillin 3.375 g;
- $17,736 versus a 6-hourly intermittent infusion of piperacillin 3.375 g; and
- $11,608 versus an 8-hourly intermittent infusion of piperacillin 4.5 g.

The costs did not include the costs of therapeutic failure, adverse events or side-effects. The authors reported that no adverse events were observed during the conduct of the study.

**Synthesis of costs and benefits**
The costs and the benefits were not combined in this cost-consequences study.

The sensitivity analysis gave the following results.

Using average wholesale price data, the costs were:
$182,055 for a 4-hourly intermittent infusion of piperacillin 3.375 g; 
$121,370 for a 6-hourly intermittent infusion of piperacillin 3.375 g; 
$115,069 for an 8-hourly intermittent infusion of piperacillin 4.5 g; and 
$101,972 for a continuous infusion of piperacillin (500 mg/hour) plus a 4.5g loading dose.

Using average wholesale price data, the net savings associated with constant infusion were:

$80,083 versus a 4-hourly intermittent infusion of piperacillin 3.375 g; 
$19,398 versus a 6-hourly intermittent infusion of piperacillin 3.375 g; and 
$13,097 versus an 8-hourly intermittent infusion of piperacillin 4.5 g.

**Authors' conclusions**
The administration of once-daily gentamicin to volunteers receiving piperacillin-tazobactam by continuous infusion or by intermittent dosing did not alter the pharmacokinetic parameters of piperacillin or gentamicin. The continuous infusion resulted in lower hospital costs compared with the intermittent infusion, mainly due to a reduction in the labour and supply costs.

**CRD COMMENTARY - Selection of comparators**
The choice of the comparator was justified on the grounds that intermittent infusion is the traditional method used to administer piperacillin-tazobactam. You should decide if this is a widely used health technology in your own setting.

**Validity of estimate of measure of effectiveness**
The effectiveness data were derived from a single study. The study was a pharmacokinetic study using a crossover design in healthy volunteers. This study design was appropriate for the stated aim, which was an evaluation of the pharmacokinetic properties of the antibiotics. However, it was not adequate for an evaluation of the clinical effectiveness of the antibiotics. The study sample, healthy volunteers, was not representative of the study population, patients with serious bacterial infections.

The study did not report the use of power calculations. It is unclear whether the study sample was large enough to detect a statistical difference between the pharmacokinetic parameters. Therefore, the lack of statistically significant differences could have been due to chance rather than equivalence.

**Validity of estimate of measure of benefit**
The authors did not derive a summary measure of health benefit. The authors reported that they conducted a cost analysis. However, the study design was inadequate to demonstrate therapeutic equivalence between the primary outcome measures and was, in fact, a cost-consequences analysis.

**Validity of estimate of costs**
The costs and the quantities were not reported separately. All the categories of cost relevant to the study perspective were included in the analysis. However, although, the methods stated that the labour costs were included in the analysis, the method of estimating and reporting these costs was unclear. The source of the resource use quantities was a time and motion study carried out in the hospital, which was published in 1997. Two sources of prices were used, the authors' setting and a published source. A statistical analysis of the resource use or prices was not reported. The date to which the prices related was reported. Sensitivity analyses of the dose regimen and the source of the unit costs were conducted. Since all the costs were incurred over a short timeframe, discounting was unnecessary and was not reported. Currency conversions were not required for the study setting and were not reported.
Other issues
The authors made appropriate comparisons with the results of their earlier studies of different dosing regimens. The issue of generalisability to other settings was not adequately addressed, due to the limited sensitivity analysis and design of the study. The authors commented that practice in their hospital was similar to practice in other hospitals. The study enrolled healthy volunteers. The authors generalised their conclusions about the costs and therapeutic impact to a population of patients with serious infections, without supporting evidence from evaluations of clinical effectiveness.

Implications of the study
The authors report that this study did not identify a statistically or clinically significant interaction when high-dose gentamicin was combined with continuous or intermittent infusion of piperacillin-tazobactam. They suggest that further research is needed to assess possible interactions with other aminoglycoside beta-lactam combinations. The authors concluded that it is crucial to develop methods to treat infections that are both clinically sound and cost-effective.

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