Cost-minimisation analysis of piperacillin/tazobactam versus imipenem/cilastatin for the treatment of serious infections: a Canadian hospital perspective


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 (P/T) (4.5 g IV every six hours), a new combination product introduced to the North American market about four years ago, for the treatment of febrile neutropenia and mixed serious infection in non-neutropenic patients.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study looked at adult patients with serious bacterial infections. The inclusion criteria were as follows: aged 16 years and over; prescribed imipenem for a treatment of a serious infection; and not having received more than 72 hours of imipenem before consent. The exclusion criteria were as follows: infection with micro-organisms with known or suspected resistance to imipenem or P/T; hypersensitivity or other serious adverse reaction to imipenem, piperacillin, or P/T; known or suspected meningitis; or pregnancy or lactation.

Setting
Tertiary acute-care hospital. The economic analysis was carried out in Canada.

Dates to which data relate
Effectiveness and resource use data corresponded to patients enrolled in the study between March 1995 and June 1996. The price year appears to have been 1996.

Source of effectiveness data
The evidence for the final outcomes was based on a single study.

Link between effectiveness and cost data
Costing was conducted prospectively on the same patient sample as that used in the effectiveness analysis.

Study sample
Power calculations were used to determine the sample size. (With a sample size of 75 treatment courses per arm, a 68% incidence of clinical success or improvement in the I/C treatment arm, a difference of 20% in clinical outcomes with an alpha of 0.05, and a two-sided test, gave a power of 80%). 150 patients were randomly assigned to either the P/T group
(n=75) or to the I/C group (n=75). It was reported that the groups were well balanced with respect to age; patients were typically in their sixth decade.

**Study design**

This was a randomised, double-blind clinical trial, carried out in a single centre. The duration of the follow-up appears to have been until discharge. The loss to follow-up was not explicitly specified; however it was reported that treatment courses were discontinued due to drug toxicity in 12 I/C treatment course (16%) versus four (5%) P/T treatment courses. Dosage interval extensions were undertaken for patients with impaired renal function. If combination antimicrobial treatment was required, patients could also be prescribed non-study ancillary antibiotics. Dosage adjustments due to renal impairment were required in 9% of the patients in the I/C arm, compared with 16% of the patients in the P/T arm.

**Analysis of effectiveness**

The principle used in the analysis of effectiveness was intention-to-treat. The primary end point of the study was clinical and microbiological success. Clinical success was defined as resolution of fever and clinical signs of infection at 72 hours, with continued resolution and a return to normal temperature for at least four consecutive days in febrile neutropenic patients. In nonneutropenic patients clinical success was defined as complete resolution of signs and symptoms with no evidence of infection. Microbiological success was defined as eradication of the positive baseline culture as determined by negative repeat cultures at the end of therapy. Other outcomes reported were the probable and possible adverse effects, and superinfection (new organism requiring treatment while on study antibiotics). The study groups were comparable in terms of baseline characteristics.

**Effectiveness results**

The effectiveness results were as follows:

The rate of clinical success in the P/T arm was 69% versus 68% in the I/C group (p=0.54) at the end of treatment.

The corresponding values for microbiologic success were 52% in the P/T arm and 48% in the I/C group (p=0.61).

The overall incidence of one or more adverse events was 39% in the P/T group versus 37% in the C/T group, (p=1.0).

However, nausea or vomiting was seen more often in the I/C arm (p=0.03) and there was a trend toward more diarrhoea in the P/T group (p=0.08).

Seizures occurred in two patients, both of whom were in the I/C arm.

The incidence of skin rash was 7% in the P/T arm and 9% in the C/T group.

The rate of superinfection was 7% in the P/T group versus 11% in the C/T group, (p=0.56).

**Clinical conclusions**

Based on the results of the clinical trial, P/T and I/C offer similar clinical, microbiologic, and toxicity outcomes in hospitalised patients with serious infections.

**Modelling**

A decision analytic model was developed using DATA to estimate the costs associated with each of the eight possible therapeutic outcomes.

**Measure of benefits used in the economic analysis**

No summary benefit measure was identified in the economic analysis, and only separate clinical outcomes were
reported. The economic analysis proceeded on the basis of a cost-minimisation analysis due to equivalent health outcomes being observed for the therapeutic strategies considered in the study.

**Direct costs**
Costs were not discounted due to the short time frame of the cost analysis. Quantities were reported separately from the costs. Cost items were reported separately. Cost analysis covered the costs of treatment of the primary infection, failure, superinfection, and adverse reactions to the study drugs. The data on resource use included doses of the study and non-study drugs, laboratory tests, diagnostic tests, physician consultations, and hospitalisation days spent on medical and critical care wards. Hospitalisation costs included the nursing and ancillary healthcare professional labour and nutrition costs. The perspective adopted in the cost analysis was that of the study hospital. Costs for resource consumption by each study patient were based on data obtained from institutional and provincial sources. The price year appears to have been 1996. Cost analysis did not cover the labour costs of support staff (janitorial, patient escort services) as it was assumed they were fixed and would not be directly affected by study patients.

**Statistical analysis of costs**
An intention-to-treat analysis of the data, using the Wilcoxon rank-sum test, was performed on the total cost associated with treatment of a serious infection.

**Indirect Costs**
Not included.

**Currency**
Canadian dollars (Can$).

**Sensitivity analysis**
To test the robustness of the study results a series of one-way sensitivity analyses was conducted on the clinical and cost parameters of the model, including the probabilities of the different health outcomes obtained from the clinical trial. Threshold values were also identified.

**Estimated benefits used in the economic analysis**
Not applicable.

**Cost results**
The mean total cost per patient in the P/T group was Can$15,211 (95% CI: Can$11,429 - Can$18,993), compared with Can$14,232 (95% CI: Can$11,421 - Can$17,043) in the I/C group (p=0.32), resulting in a mean cost difference of Can$979. Sensitivity analyses revealed that the superiority of I/C over P/T for successful treatment of serious infections was sensitive to changes in the cost of hospitalisation and drug efficacy for either drug.

**Synthesis of costs and benefits**
Costs and benefits were not combined since the economic analysis was reduced to a cost-minimisation analysis.

**Authors’ conclusions**
Under base-case conditions, this pharmacoeconomic analysis showed that I/C was a cost-effective alternative to P/T for the dosage regimen studies. However this finding was sensitive to plausible changes in both clinical and economic parameters.
CRD COMMENTARY - Selection of comparators

The strategy of using I/C was regarded as the comparator since it was introduced more than a decade ago into the US marketplace and was used on the formulary in the study institution. You, as a database user, should consider whether this is a widely used health technology in your own setting.

Validity of estimate of measure of effectiveness

The effectiveness results are likely to be internally valid given the randomised nature of the study design, power calculations performed, and the intention-to-treat analysis conducted. The study groups were comparable in terms of baseline characteristics. The study sample appears to have been representative of a heterogeneous study population of patients with serious infections.

Validity of estimate of measure of benefit

The analysis of benefits was based on therapeutic equivalence of treatment alternatives. The economic analysis therefore included only costs.

Validity of estimate of costs

Resource quantities were reported separately from the costs and adequate details of methods of cost estimation were given. It appears that all important direct cost elements were included in the cost analysis. The price year was specified. It is not entirely clear whether cost analysis was based on true costs, charge data, reimbursement data, or a combination of all three. The perspective adopted in the cost analysis (hospital's perspective) was specified. The effects of alternative procedures on indirect costs were not addressed since they were deemed less relevant in the management of acute infections in hospitalised patients. Statistical analyses appear not to have been performed on resource consumption, but were conducted on cost data.

Other issues

The authors' conclusions appear to be justified given the randomised nature of the study design, and the sensitivity analyses performed to address the robustness of the study results. The issue of generalisability to other settings or countries was not addressed (it is not clear whether the sensitivity analysis was broad enough to address generalisability). Appropriate comparisons were made with other studies. The study sample was meant to be representative of a heterogeneous study population of patients with serious infections; which was deemed to permit an assessment of the relative cost-effectiveness of the study drugs when used for a multitude of infections, as would be expected in a tertiary acute-care hospital setting.

Implications of the study

This study was conducted to determine the feasibility of replacing I/C at the study institution. However, with regard to the results achieved in this study, P/T has not been replaced I/C on the formulary in the study institution.

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