Diltiazem co-treatment in renal transplant patients receiving microemulsion cyclosporin

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
Diltiazem, an antihypertensive agent, was used as a co-treatment to reduce the use of cyclosporin (i.e. Neoral) in renal transplant recipients. Neoral was a relatively new microemulsified cyclosporin formulation. Diltiazem was administered at a dose of 30 mg twice daily in patients weighing less than 60 kg, and at 60 mg twice daily in patients weighing at least 60 kg.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised stable patients with renal allografts who received oral cyclosporin. The exclusion criteria were a persistently low blood pressure (less than 100 mmHg systolic, less than 60 mmHg diastolic), any overriding reason to continue or start taking diltiazem (or verapamil), or a known hypersensitivity to diltiazem. Patients were also excluded at the physician’s discretion, whatever the reason.

Setting
The setting was secondary care. The economic study was carried out in Hong Kong.

Dates to which data relate
The effectiveness and resource use data were gathered between 1997 and 2000. The price year was 1999.

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

Link between effectiveness and cost data
The costing was carried out prospectively on the same sample of patients as that used in the effectiveness study.

Study sample
Power calculations were conducted on the basis of results from published studies. It was calculated that an overall group of 150 patients was required to detect statistically significant differences in the primary outcome measure, with a power of 95% at a significance level of 5%. Eligible patients were identified at the study hospitals. A sample of 114 patients was initially recruited. However, 4 patients were subsequently excluded because they were no longer taking cyclosporin, or were unavailable for assessment. Details on the 4 excluded patients (two in each arm of the trial) were provided for
comparative purposes. Therefore, the final sample considered in the effectiveness analysis comprised 110 patients. There were 55 patients in the diltiazem group and 55 in the placebo group. The mean age of the patients was 42.2 (+/- 10.6) years (age range: 14 - 72) in the diltiazem group and 41.8 (+/- 9.6) years (age range: 21 - 67) in the placebo group. There were 39 women in each of the two groups.

Study design
This was a prospective, double-blind, placebo-controlled randomised trial that was conducted in three hospitals (Queen Mary, Queen Elizabeth and Princess Margaret hospitals). At each hospital the patients were randomised in blocks. The methods of randomisation and blinding were not reported. The length of follow-up was 6 months. The loss to follow-up was unclear but it appears to have been negligible.

Analysis of effectiveness
The analysis of the clinical study was conducted on an intention to treat basis. The outcome measures used were:

- the reduction in cyclosporin dosage;
- blood cyclosporin concentrations, dosages and serum creatinine values just prior to ceasing trial medication, and up to 12 weeks after;
- the creatinine values at 3 and 6 months;
- the occurrence of adverse events or complications;
- the requirement for inpatient or outpatient care, or relevant clinical investigations;
- deaths;
- rejection episodes;
- medication discontinuation; and
- quality of life, which was assessed through the SF-36 questionnaire.

The study groups were comparable at trial entry in terms of the demographics, presence of co-morbidities and disease characteristics. However, significantly more patients had diabetes mellitus in the diltiazem group (10) than in the placebo group (1), (p=0.01).

Effectiveness results
The mean daily reduction in cyclosporin dosage was 30.4% (+/-19.3) in the diltiazem group and 16% (+/- 23.6) in the placebo group (95% confidence interval (CI) for the difference: 14.4% +/- 8.1; p<0.001).

When data from a patient who developed tuberculosis were omitted, the mean daily reduction in cyclosporin dosage was 30.4% (+/-19.3) in the diltiazem group and 18.1% (+/- 17.6) in the placebo group (95% CI for the difference: 12.3% +/- 7; p<0.001).

The mean creatinine value was 140 (+/-45) micromol/L in the diltiazem group and 136 (+/- 29) micromol/L in the placebo group at 3 months. The corresponding figures at 6 months were 131 (+/- 37) micromol/L (diltiazem) and 134 (+/- 28) micromol/L (placebo), respectively.

For diltiazem versus placebo group, the blood cyclosporin concentration levels were:

157 versus 142 ng/mL, just before, or on the day of stopping the trial medication;
118 versus 132 ng/mL, 1 to 3 weeks after stopping; and
127 versus 156 ng/mL, 4 to 12 weeks after stopping.

For diltiazem versus placebo group, the cyclosporin dosages were:
175 versus 200 mg/day just before, or on the day of stopping the trial medication;
175 versus 198 mg/day, 1 to 3 weeks after stopping; and
194 versus 200 mg/day, 4 to 12 weeks after stopping.

The following outcomes were comparable between the groups:
- the occurrence of adverse events or complications;
- the requirement for inpatient or outpatient care, or relevant clinical investigations;
- deaths, rejection episodes, medication discontinuation and quality of life.

**Clinical conclusions**
The effectiveness analysis showed that the use of diltiazem was safe and effective in reducing cyclosporin use among renal allograft patients.

**Measure of benefits used in the economic analysis**
No summary benefit measure was used in the economic analysis. In effect, a cost-consequences analysis was conducted.

**Direct costs**
Discounting was irrelevant since the costs per patient were incurred during 6 months. The unit costs were not reported separately from the quantities of resources used. The economic evaluation focused only on the cost of medication. Other categories of costs (i.e. investigative tests, hospital inpatient days and outpatient visits) were not statistically different and were not included in the economic analysis. The cost/resource boundary of the study was not explicitly stated, but it appears to have been that of the hospital. Resource use was estimated using actual data derived from the sample of patients involved in the effectiveness study. Local cost estimates were used. These were presumably estimated from the three study hospitals in 1999.

**Statistical analysis of costs**
The costs were presented as mean values with 95% CIs. Statistical tests were performed to test the significance of differences in the estimated costs.

**Indirect Costs**
The indirect costs were not considered.

**Currency**
Hong Kong dollars (HK$). The conversion rate from UK pounds sterling () was assumed to be 1 = HK$12.2.

**Sensitivity analysis**
A sensitivity analysis was carried out in which the price of the medication was varied. More recent local prices of diltiazem (updated to April 2002) were used.
Estimated benefits used in the economic analysis
See the 'Effectiveness Results' section.

Cost results
The mean cyclosporin costs were HK$2,905 (95% CI: 793 - 5,947) in the diltiazem group and HK$3,431 (95% CI: 1,586 - 6,344) in the placebo group, (p=0.011).

The total medication costs were HK$3,562 (95% CI: 1,296 - 7,019) in the diltiazem group and HK$4,171 (95% CI: 1,600 - 7,539) in the placebo group, (p=0.023).

The annual net savings associated with different prices of diltiazem were presented.

Synthesis of costs and benefits
The costs and benefits were not combined because a cost-consequences analysis was carried out.

Authors' conclusions
Diltiazem was a safe strategy for reducing cyclosporin usage in renal transplant recipients and quality of life did not worsen. The use of diltiazem also led to a 15% reduction in drug costs. This would result in annual savings of about HK$ 14.3 million (1.17 million) if diltiazem were used for the 1,800 surviving renal allograft patients cared for in Hong Kong Hospital Authority (HKHA) hospitals.

CRD COMMENTARY - Selection of comparators
The rationale for the choice of the comparator was clear. Placebo was selected as it represented standard care for patients taking long-term oral cyclosporin. It was also appropriate to detect the active value of diltiazem. You should decide whether it represents a valid comparator in your own setting.

Validity of estimate of measure of effectiveness
The basis of the analysis of effectiveness was a prospective, randomised placebo-controlled trial, which was appropriate for the study question. The internal validity of the analysis was further enhanced by several factors. In particular, the double-blind study design, the performance of power calculations, the minimal loss to follow-up, and the baseline comparability of the two groups of patients. The authors described the method used to select the sample in detail, but provided little information on the randomisation and blinding processes.

Validity of estimate of measure of benefit
No summary benefit measure was used because a cost-consequences analysis was conducted.

Validity of estimate of costs
The authors did not explicitly report the perspective adopted in the study, but it appears that costs relevant to the hospital have been considered. The analysis of the costs was restricted to medication expenses. Other relevant categories of costs were excluded because the quantities of resources used for hospitalisations, visits and tests did not differ significantly between the groups. The information on resource use and the quantities of resources used was unclear. The costs were treated stochastically and an extensive sensitivity analysis was performed to account for variations in the drug costs. The price year was reported, therefore making reflation exercises in other settings possible.

Other issues
The authors made some comparisons of their findings with those from other studies that reported more substantial cost-
savings. The authors discussed possible explanations for the differences in terms of estimated cost-savings. The issue of the generalisability of the study results to other settings was not explicitly addressed. Most of the estimates were specific to the institutions considered in the analysis. Therefore, the external validity of the analysis was low. The study referred to patients taking long-term cyclosporin after renal allograft and this was reflected in the authors’ conclusions.

Implications of the study
Diltiazem, as a co-treatment for renal allograft patients, represents a potential cost-saving approach for the health care system in Hong Kong, without affecting quality of life.

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