Diltiazem use in tacrolimus-treated renal transplant recipients

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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
The effects of using diltiazem as a first-line antihypertensive agent in renal transplant patients who received tacrolimus-based immunosuppressive treatment were evaluated. The mean average daily dose of diltiazem was 213.95 mg/day.

Type of intervention
Other: Management care (post-transplant).

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients who underwent renal transplantation. Of those patients, only those who were administered tacrolimus, mycophenolate mofetil and prednisone as initial immunosuppressive treatment were included in the study. Patients entitled to receive antihypertensive treatment had at least three mercury sphygmomanometer blood pressure (BP) measurements with either a systolic reading greater than 140 mmHg or a diastolic reading greater than 90 mmHg. No further inclusion or exclusion criteria were reported.

Setting
The setting was tertiary care, a medical-surgical university-affiliated centre that provided post-transplant care. The economic study was carried out in Canada.

Dates to which data relate
The effectiveness data were collected between March 1997 and March 2002. The cost data were reported for the fiscal year 2003.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was most probably carried out respectively on the same sample of patients as that used in the economic analysis.

Study sample
The sample size was not determined in the planning phase of the study. In addition, power calculations were not performed retrospectively. The study sample comprised consecutive patients who underwent renal transplantation in the authors' setting. From the initial sample size (n=373), 277 patients were excluded since they did not meet the inclusion
criteria. Overall, 96 patients were included in the study. Of these, 64 patients (64.1% male) formed the diltiazem group (diltiazem was administered in the first post-transplant week before their first hospital discharge) and 32 patients (50.0% male) formed the control group (diltiazem was not administered in the first post-transplant week). The mean age of the patients was 46.35 (+/- 12.3) years in the diltiazem group and 46.01 (+/- 14.4) years in the control group.

**Study design**
The analysis was based on a retrospective cohort study that was conducted at a single centre. The data on each patient were collected for a 24-month period. Blinded assessment was not reported. It was reported that one patient in the control group was lost to follow-up during the study period, but the reason for this was not reported. In addition, two patients in the control group switched over to treatment with diltiazem 6 months after the transplant. However, the sample sizes of the two groups did not alter and these two patients were treated as controls in the analysis.

**Analysis of effectiveness**
The basis of the analysis was intention to treat. The primary outcome was the level of renal function up to 2 years post-transplant. The secondary outcomes included:

- BP control,
- tacrolimus doses and tacrolimus levels,
- serum creatinine and creatinine clearance,
- the number of biopsy proven acute rejection episodes (acute rejection rate),
- the cases of tacrolimus nephrotoxicity,
- patient and graft survival,
- chart-recorded side effects of tacrolimus and diltiazem, and
- the number of antihypertensive medications administered to the patients in the two groups.

The authors reported that the patients in the two groups were comparable at baseline in terms of demographic and other baseline characteristics.

**Effectiveness results**
There was no difference in the level of renal function between the two groups over 2 years.

There were also no differences in graft and patient survival, which were 96.9% and 98.4%, respectively, in the diltiazem group and 100% and 100% in the control group. The authors reported that graft loss was recorded in one patient in the diltiazem group, while one patient with a functioning graft died due to sepsicaemia.

The mean systolic and diastolic BPs and the number of antihypertensives administered were not statistically significantly different between the two groups during the study period.

The overall incidence of side effects was not statistically significantly different between the two groups (23.4% in the diltiazem group versus 15.6% in the control group).

The differences between the two groups in results for serum creatinine and creatinine clearance, tacrolimus dose, the number of tacrolimus dose changes and tacrolimus levels at 2 weeks and 3, 6, 12 and 24 months after transplantation were not statistically significant.

The acute rejection rate was similar in the two groups (15%). Ten acute rejection episodes developed in the diltiazem
group versus 5 in the control group. No cases of tacrolimus nephrotoxicity were reported in either group.

Clinical conclusions
The authors concluded "diltiazem use is efficacious and acceptably safe in renal transplant recipients treated with tacrolimus-based immunosuppressive therapy".

Measure of benefits used in the economic analysis
The authors did not derive a summary measure of benefits. In effect, a cost-consequences analysis was performed.

Direct costs
The health service costs included in the analysis were for tacrolimus, laboratory-based tacrolimus levels and diltiazem. The costs and the quantities were reported separately. The drug costs were derived from the local hospital-based pharmacy, while the quantities of resources used were derived directly from the effectiveness analysis. Discounting was not relevant as the costs were incurred during 2 years. All the costs were reported for the year 2003. The study reported the average cost per patient.

Statistical analysis of costs
The costs were treated deterministically.

Indirect Costs
The indirect costs were not included in the analysis.

Currency
Canadian dollars (Can$).

Sensitivity analysis
The authors did not carry out any sensitivity analyses.

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

Cost results
The combined cost (mean +/- standard deviation) of diltiazem, tacrolimus and tacrolimus levels was Can$8,602.82 (+/- 4,841.53) in the diltiazem group and Can$7,887.10 (+/- 5,054.02) in the control group.

Synthesis of costs and benefits
The costs and benefits were not combined.

Authors' conclusions
Diltiazem is effective and acceptably safe to be used as a first-line antihypertensive with tacrolimus. In addition, it is cost-neutral for tacrolimus use.

CRD COMMENTARY - Selection of comparators

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The choice of the comparators was explicitly justified. They represented current practice in the authors' setting. You should decide if they represent widely used therapeutics in your own setting, or whether other comparators from other therapeutic options could also have been relevant.

Validity of estimate of measure of effectiveness
The analysis was based on a retrospective cohort study and, since the participants were not randomly assigned to each group, it is possible that confounding might have occurred. In addition, the retrospective nature of the study represents a limitation to internal validity. However, the authors carried out an extensive statistical analysis to deal with possible biases. The study sample was representative of the study population and the patient groups were shown to be comparable at analysis. Therefore, confounding factors may be low. The sample size was not determined in the planning phase and no power calculations were conducted to assure a certain power of the results. It is therefore possible that some of the results obtained were due to chance.

Validity of estimate of measure of benefit
No summary measure of benefits was derived and the study is therefore characterised as a cost-consequences analysis. The reader is referred to the comments in the 'Validity of estimate of measure of effectiveness' field (above).

Validity of estimate of costs
Although the perspective adopted in the economic analysis was not reported, it could not have been societal since the indirect costs were not included. It seems that only the drug costs have been included. Relevant costs, for example the costs of side effects, acute rejection episodes and graft loss, were not included in the analysis. These costs might have resulted in an overestimation of the cost-effectiveness of the use of diltiazem. The costs and the quantities were reported separately, which would allow the analysis to be easily extrapolated to other settings. However, the costs were treated deterministically and no sensitivity analysis was conducted to assess the robustness of the estimates used. This may limit the interpretation and the generalisability of the study findings. The price year was reported and discounting was not relevant.

Other issues
The authors did not compare their findings with those of published studies, although this might have been due to the lack of published literature in this specific area. The issue of generalisability was not directly addressed. The authors do not appear to have presented their results selectively and their conclusions reflect the scope of the analysis. The study enrolled patients who had renal transplantation and this was reflected in the authors’ conclusions. The authors acknowledged that their study lacked statistical power.

Implications of the study
The authors did not make any explicit recommendations for changes in policy or practice. However, they suggested that the results of their study demonstrated that diltiazem “can be considered as a first-line antihypertensive” in patients who had a renal transplant and are under tacrolimus-based immunosuppressive therapy. The authors did not make any recommendations for future research.

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