METABOLIC EFFECTS OF CONVERSION FROM CYCLOSPORINE TO AZATHIOPRINE IN RENAL TRANSPLANT RECIPIENTS

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Summary

The metabolic effects of conversion from cyclosporine (Cys) to azathioprine were studied in 10 non-diabetic renal transplant recipients. Following conversion there was a significant improvement in renal function. There was no evidence of glucose intolerance pre-conversion, and no change in glucose metabolism following conversion. However, fasting cholesterol and triglyceride levels were significantly improved following conversion. The mechanism of this change and its significance needs further investigation.

Introduction

Cyclosporine (Cys) is now extensively used in organ transplantation. However, there are well recognised side effects such as nephrotoxicity and hepatotoxicity [1], and in addition it has recently been suggested that Cys can cause a deterioration in glucose control [2]. Experience in this unit indicated an apparent higher incidence of diabetes using Cys than that previously noted in patients treated with conventional immunosuppression, i.e. azathioprine and prednisolone.

The current protocol for patients receiving cadaveric renal transplants is to convert the immunosuppression at three months from prednisolone and Cys to prednisolone and azathioprine. Hence an opportunity arose to evaluate various metabolic indices before and after conversion.

Method

Ten non-diabetic transplant recipients (age range 21–64 years) with stable renal function were studied at three months post-transplantation. Immunosuppression for the three months following transplantation was Cys (mean dose 7.8±3mg/kg in two equal divided doses) and prednisolone (dose tapered to
30mg on alternate days by two months post-transplantation). At three months azathioprine (100–150mg) was introduced and the Cys was withdrawn – the prednisolone dose remained unaltered at 30mg on alternate days.

Immediately pre-conversion and one month post-conversion a 75gm oral glucose tolerance test was performed after an overnight fast, together with estimation of serum immunoreactive insulin, serum cholesterol and triglyceride, renal and liver function tests. Statistical analysis was performed using paired Student’s ‘t’ test.

Results

The mean Cys level pre-conversion was 164±34ng/ml. There was no significant change in body weight of the patients following conversion (63.8±4.5kg, 63.9±4.5kg).

Renal function was significantly improved by stopping Cys, as judged by the fall in serum urea and creatinine concentrations (Table I).

**TABLE I. Renal function in renal transplant recipients following conversion from cyclosporine to azathioprine (mean values ± SEM)**

<table>
<thead>
<tr>
<th></th>
<th>Pre-conversion</th>
<th>Post-conversion</th>
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<tbody>
<tr>
<td>Creatinine (mol/L)</td>
<td>164±17</td>
<td>136±14*</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>11.0±0.7</td>
<td>7.8±0.7**</td>
</tr>
<tr>
<td>Potassium (mmol/L)</td>
<td>4.5±0.17</td>
<td>4.3±0.17</td>
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*p<0.05, **p<0.01, cf pre-conversion

Fasting blood sugar, fasting immunoreactive insulin, and glucose tolerance was not altered following conversion and there was no evidence of glucose intolerance pre-conversion (Figure 1).

There was, however, a significant fall in serum cholesterol from 7.6±0.3mmol/L to 6.2±0.4mmol/L and in serum triglyceride from 2.4±0.1mmol/L to 1.5±0.2 mmol/L following conversion (p<0.01) (Figure 2), with the mean values of both falling to within the normal range. The changes in serum cholesterol and triglyceride did not correlate with changes in body weight or renal function, or the pre-conversion Cys level.

Discussion

This study demonstrates three metabolic consequences of immunosuppression with Cys in renal transplant recipients:

1. The nephrotoxic effect of Cys was confirmed;
2. There was no evidence for Cys induced glucose intolerance;
3. Stopping Cys resulted in a significant improvement in fasting cholesterol and triglyceride levels.
Changes in renal function are known to affect glucose [3] and lipid metabolism [4], possibly by an alteration in peripheral insulin resistance.

Although an improvement in renal function was observed following conversion, there was no change in serum insulin levels, and it therefore seems unlikely that a change in insulin resistance could account for the improvement in serum lipids.

Prednisolone is known to produce abnormalities in both triglyceride and cholesterol levels [5] although these effects can be minimised by the use of alternate day steroid dosaging as used in this study [6]. Although the dose of prednisolone remained unchanged over the conversion period, Cys has been shown to reduce the clearance of prednisolone, which is almost entirely metabolised by the liver. Thus the effect of a given dose of prednisolone may be greater when Cys is given concomitantly. However, prednisolone is thought to affect lipid levels by inducing hyperinsulinaemia to which the liver remains
selectively responsive, and in this study insulin levels were unaltered over the conversion period. Cys may be affecting lipid metabolism by an independent action on the liver.

References

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