DOES CYCLOSPORINE INHIBIT RENAL PROSTAGLANDIN SYNTHESIS?

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Summary
Urinary PGE$_2$ excretion was measured in female renal allograft recipients being treated either with prednisolone and cyclosporine (Cys) or with prednisolone and azathioprine. The mean urinary PGE$_2$ excretion in patients on Cys of 940pmol/4hr was lower than in patients on prednisolone and azathioprine (2033pmol/4hr) although the difference did not achieve statistical significance. These data are consistent with the hypothesis that Cys inhibits renal prostaglandin synthesis.

Introduction
Cyclosporine (Cys) is a potent nephrotoxin [1]. It is now clear that the renal impairment caused by Cys is not necessarily associated with renal histological changes and that in its early stages it is rapidly reversible when the drug is discontinued [1]. These observations suggest a physiological basis for Cys nephrotoxicity. We have reported a high incidence of sustained hyperkalaemia in renal allograft recipients treated with Cys and shown that this was associated with hyporeninaemia and inappropriately low serum aldosterone levels [2]. Since prostaglandins are a potent stimulus of renin secretion [3] we wondered whether Cys might inhibit their synthesis.

Patients and methods
The study group consisted of female renal allograft recipients receiving either Cys and prednisolone or with prednisolone and azathioprine. All the patients had functioning renal allografts and were studied at a time when their renal function was stable. Four-hourly collections of urine were acidified and then stored at -20°C. The urinary concentration of prostaglandin E$_2$ (PGE$_2$) was determined by radioimmunoassay as previously described [4]. The results were expressed as pmol PGE$_2$ per four hours. The significance of differences between groups was assessed by Student’s ‘t’ test.
Results

The mean urinary PGE$_2$ excretion in patients on Cys was lower than in patients on prednisolone and azathioprine although the difference was not statistically significant (Table I). Five out of 14 patients on Cys had a urinary PGE$_2$ excretion of less than 500 pmol/4 hr in contrast to only one of the 11 patients on prednisolone (Table II).

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Number of Patients</th>
<th>Urinary PGE$_2$ (pmol/4 hr) Mean ± SEM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisolone and azathioprine</td>
<td>11</td>
<td>2034 ± 590</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p &gt; 0.05</td>
</tr>
<tr>
<td></td>
<td></td>
<td>T = 1.90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NS</td>
</tr>
<tr>
<td>Prednisolone and cyclosporine</td>
<td>14</td>
<td>940 ± 218</td>
</tr>
</tbody>
</table>

**TABLE II. Distribution of urinary PGE$_2$ in renal allograft recipients**

<table>
<thead>
<tr>
<th>Urinary PGE$_2$ (pmol/4 hr)</th>
<th>Prednisolone + azathioprine</th>
<th>Prednisolone + cyclosporine</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;500</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>500 – 1000</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>5</td>
<td>4</td>
</tr>
</tbody>
</table>

Discussion

In this study although urinary PGE$_2$ excretion in patients treated with Cys was lower than in those receiving prednisolone and azathioprine the difference was not statistically significant. We therefore cannot conclude with certainty that Cys inhibits renal prostaglandin synthesis although the data strongly suggests that this is so. It is however likely that patients with renal allografts have a glomerular filtration rate (GFR) that is dependent on an intact prostaglandin system. Such a situation obtains during sodium depletion in healthy individuals, in patients with chronic glomerulonephritis and in conditions such as ascites and the nephrotic syndrome where there is an ineffective circulatory volume [5]. In these states, inhibition of renal prostaglandin synthesis leads to a reversible reduction in GFR [5]. The nephrotoxicity of Cys and the rapid improvement in renal function when the drug is discontinued suggests a functional rather than a structural lesion such as would occur with inhibition of renal prostaglandin synthesis.
The prostaglandins PGE$_2$ and PGI$_2$ are potent stimuli of renin release [3] and inhibition of renal prostaglandin synthesis by indomethacin may lead to hyporeninaemia and hypoaldosteronism with consequent hyperkalaemia [6]. We reported that the hyperkalaemia seen in patients on Cys was associated with hyporeninaemia and hypoaldosteronism [2] and suggest that the hyporeninaemia is due to inhibition of renal prostaglandin synthesis. Remuzzi et al [7] have reported that some patients with a haemolytic uraemic syndrome (HUS) lacked PGI$_2$-stimulating factor (PSF) activity in their plasma. Recently, Neild et al [8] found that rabbits treated with Cys had a profound loss of PSF activity in their plasma. Rabbits given acute serum sickness and treated with Cys developed glomerular capillary thrombosis and cortical infarction, lesions were strikingly similar to the changes seen in the HUS [9]. Bone marrow recipients treated with Cys have been reported to develop an illness similar to HUS [10] and it is possible that this is due to inhibition of PSF activity by Cys.

The data of Neild et al [9] and the results of our study suggest that Cys may inhibit prostaglandin synthesis. Inhibition of PGE$_2$ synthesis would explain the reversible nephrotoxicity and hyperkalaemia seen with Cys whilst inhibition of PGI$_2$ production would explain the HUS seen in some patients on Cys and might possibly be the cause of some of the chronic vascular changes hitherto attributed to chronic vascular rejection.

References

5 Dunn MJ, Zambraski EJ. Kidney Int 1980; 18: 609

Open Discussion

VANGELISTA (Bologna) There was work last year from the Minneapolis group which demonstrated that in patients treated with cyclosporine there was a stimulation of the renin angiotensin aldosterone system and it was thought that this was due to the initial stimulation of the autonomic nervous system. How do you explain these different results?

ADU Well, I think it is difficult. I know of the work done in rats showing this but rats are different from humans.

BANKS (Bristol) Was there a relationship between the rise in potassium and the decrease in prostaglandin excretion?

ADU No, we have not done that study, we looked at prostaglandins and creatinine.
UNKNOWN In your Table I you mention a lot of possible renal effects of cyclosporine. You have not mentioned the possible vascular changes which may occur after two or three months of cyclosporine administration without any clinical signs. These are morphological changes not predictable on clinical grounds. I would like to ask you if you have any experience of this type of effect which we have seen in patients on cyclosporine over the last two years?

ADI We suspect that we have seen these types of changes that have been described but when we have looked blind at our biopsies, patients on prednisone and azathioprine and patients on cyclosporine, we have not been able to distinguish histologically between the two groups of patients.

BRYNGER (Chairman) Just one comment regarding the haemolytic uraemic syndrome. We have seen in our patients, and it has been reported in four patients in Canada, an autoimmune haemolytic syndrome. In our cases we have been able or have had to switch to alternative therapy. In the first case it was very severe although it did not affect the kidney function. The second case, it was not that serious, and we changed to conventional therapy and after about six weeks we returned to cyclosporine without any problems. There are a lot of problems with this drug and I will have to work very hard to find out what is going on.

BONOMINI (Chairman) Just a practical question. If you had a son who required a renal transplant would you start with cyclosporine or azathioprine?

ADU I think at the moment if it was a second graft I would always give cyclosporine, and also probably for a first graft.