CYCLOSPORINE AND SHORT ISCHAEMIA: A NEW MODEL OF EXPERIMENTAL ACUTE RENAL FAILURE IN RATS

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Summary

To determine whether a mild episode of ischaemia may be a factor in the production of cyclosporine (Cys) toxicity, right nephrectomy was performed in three groups of Charles River rats: I. Ischaemia (left renal pedicle clamping) for 20 minutes, without treatment; II. Ischaemia of 20 minutes, followed by IP Cys 60mg/kg BW/day; III. Sham (no ischaemia) followed by Cys as in Group II. The rats were sacrificed after four days.

Cys plus ischaemia produced a lower creatinine clearance (136±15μl/min/100g BW, p<0.001) and a higher FENa per cent (0.94±0.14, p<0.05), FEK (1.07±0.02, p<0.01) compared with ischaemia alone creatinine clearance 261±39, FENa per cent 0.61±0.08, FEK 0.54±0.08, FEH2O -0.04±0.005. Histology showed more vacuolisation of tubular epithelial cells in the Cys plus ischaemia group than in the ischaemia alone group.

Introduction

Cyclosporine has been found to have a major clinical advantage over conventional immune suppressants in renal transplantation [1]. However, nephrotoxicity with high doses is a well-documented side-effect [2]. This is sometimes manifested as acute renal failure.

The mechanism of Cys renal injury is not established. As a consequence of only minor renal damage in normal laboratory animals, it is very difficult to produce an experimental Cys acute renal failure model [3,4].

The aim of the present study was to examine the renal toxicity of Cys on a kidney exposed to a short ischaemia time. This being a simulation of renal transplantation without the immunological component.

Material and methods

Charles River rats of both sexes weighing between 250–320g were used. All rats underwent right nephrectomy under ether anaesthesia. Immediately following the nephrectomy, the rats were divided into three experimental groups.
Group I. Left renal pedicle occlusion for 20 minutes.

Group II. Left renal pedicle occlusion for 20 minutes and Cys 60mg/kg BW/day intraperitoneal.

Group III. Sham operated rats and Cys 60mg/kg BW/day.

Immediately after the operation the rats were placed in individual metabolic cages. The experiment lasted four days. Cys was given every day, in a dose of 60mg/kg BW intraperitoneal. At the end of the experiment blood was withdrawn from the aorta and the left kidney was removed for histology. Creatinine, sodium, potassium and osmolality were determined in the blood and in the last 24-hour urine collection. Creatinine clearance, fractional excretion of sodium, potassium and water were calculated using standard formulae.

Mean, standard error of the mean were calculated. One way analysis of variance was used to assess significance, and p<0.05 was considered significant.

Results

The different glomerular and tubular function parameters are given in Table I.

<table>
<thead>
<tr>
<th></th>
<th>Group I ischaemia alone n=6</th>
<th>Group II Cyst+ischaemia n=10</th>
<th>Group III Cys – no ischaemia n=6</th>
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</thead>
<tbody>
<tr>
<td>Creatinine clearance*</td>
<td>216±39</td>
<td>136±15**</td>
<td>318±24</td>
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<tr>
<td>µl/min/100g BW</td>
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<tr>
<td>FE%Na</td>
<td>0.61±0.08</td>
<td>0.94±0.14**</td>
<td>1.17±0.08</td>
</tr>
<tr>
<td>FEK</td>
<td>0.54±0.08</td>
<td>1.07±0.1**</td>
<td>0.85±0.87</td>
</tr>
<tr>
<td>FEH₂O</td>
<td>−0.04±0.005</td>
<td>−0.1 ±0.015**</td>
<td>−0.01±0.001</td>
</tr>
</tbody>
</table>

* Mean ± SE n = number of rats.

** Significantly different from the respective values in Group I.
(p at least <0.05)

By analysis of variance the rats with Cys and ischaemia showed a larger creatinine clearance (p<0.001), a higher FE%Na (p<0.05), FEK (p<0.003) and a lower FEH₂O (p<0.001) compared with the group with ischaemia alone (untreated with Cys). The creatinine clearance was similar in the group of ischaemia without Cys as in the group with Cys without ischaemia. Light microscopy showed tubular epithelial cells vacuolisation in all groups studied, and was more pronounced in the Cys plus ischaemia group (Figure 1).

Discussion

Only prolonged administration of a high dose of Cys results in significant impairment of kidney function while lower doses are associated with minor changes in renal function [3,4].
Figure 1. Light microscopy in different experimental groups. Group I: ischaemia alone. Group II: Cys plus ischaemia. Group III: Cys alone. Tubular epithelial vacuolisation are seen in all groups, but is much more pronounced in the Cys plus ischaemia group.

The present study demonstrates that the administration of Cys for a short period of time, will result in acute renal failure, if the kidney was previously exposed to a short ischaemic insult. This type of acute renal failure is characterised by an important reduction in GFR, increased FE$_{\text{Na}}$ and FE$_{\text{K}}$ and impressive histological damage.

The potentiation of Cys nephrotoxicity by gentamicin [5] or mannitol [6] have been recently described. However, it seems that our model in which ischaemia is used as a synergistic factor, gives a better simulation of the immediate post-transplant, non oliguric situation. This model will offer the possibility of studying different therapeutic approaches, such as calcium entry blocker drugs. This is under current investigation in our laboratory.

References

Open Discussion

CHAIRMAN You showed in your Table a minus sign before the free water clearance so that is a negative free water clearance?

IAINA Yes, they still concentrate their urines.