ALTERNATE DAY STEROIDS AND BLOOD PRESSURE CONTROL AFTER RENAL TRANSPLANTATION

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Summary

Conversion to alternate day prednisone therapy resulted in a reduction in blood pressure in hypertensive renal transplant recipients.

Plasma renin activity was also reduced and may be connected with the fall in blood pressure.

There was evidence of increased aldosterone activity, possibly mediated by ACTH, but there was no evidence that the fall in blood pressure was due to changes in sodium status.

Introduction

Steroid therapy has been implicated in the aetiology of hypertension following renal transplantation [1]. Sodium retention due to the mineralocorticoid effects of administered prednisone or its metabolites has been proposed as the potential pathogenic mechanism. Hypertension is less prevalent in transplant patients on alternate day steroid therapy [2].

The purpose of this study was:-

(i) To ascertain whether conversion from daily to alternate day prednisone would lead to a reduction in blood pressure in hypertensive transplant recipients.

(ii) To study the effects on the renin-aldosterone system and on sodium status of such a change in steroid therapy.

Patients and methods

Forty-five patients were studied, 25 hypertensive (mean arterial pressure (MAP) >110mmHg) and 20 normotensive. All patients had been transplanted for more than one year and had been receiving base-line prednisone doses for more than six months. All had stable renal function with no renal insufficiency (serum creati-
nine <200μmol/L) and no evidence of transplant renal artery stenosis.

Exchangeable sodium (NaE) was estimated by an isotope dilution technique after intravenous administration of 15 uCi24 Na with a 22 hour equilibration period. The value obtained was expressed in mmol/kg lean body mass, calculated by the formula of Edwards and Whyte [3]. Plasma renin activity (PRA) and plasma aldosterone (P.Ald) were estimated on blood samples taken at 10.00hrs., after an overnight fast and two hours recumbency, and at 12.00 noon after ambulation. PRA was estimated by the radioimmunoassay of angiotensin I using a commercial kit (New England Nuclear). Aldosterone was measured by radioimmunoassay using a modification of the technique described by Frazer, Guest and Young [4].

Urinary aldosterone, urinary sodium and creatinine clearance were measured on a 24hr urine collection which extended over the time-period of blood sampling.

These investigations were carried out on all patients whilst on daily prednisone.

Patients were then converted to alternate-day prednisone, the dose given being equal to twice the daily prednisone dose. Alternate day prednisone was continued for three months and the investigations specified above repeated on the non-prednisone day.

Results obtained on daily and alternate day prednisone were compared using the paired t-test.

Results

Mean arterial pressure fell significantly in the hypertensive patients after changing to alternate day prednisone (MAP on daily prednisone, 125.5mmHg ± 13.0 (SD); MAP on alternate day prednisone 117.7 ± 16.3, t = 3.64, p<0.005) (Figure 1). No change in blood pressure was seen in normotensive patients (MAP 97.7 ± 9.3 on DP, 96.0 ± 9.2 on ADP) (Figure 2).

On daily prednisone, the hypertensive patients had higher levels of plasma renin activity than the normotensives (PRA (lying) 18.5 ± 16.0 cf. 12.2 ± 6.8; PRA (standing) 28.4 ± 35.7 cf. 18.7 ± 7.1). The effects of conversion to alternate day prednisone on the renin-aldosterone system in hypertensive patients can be seen in Table I. There was a marked fall in PRA (Figure 3) and fall in PRA was proportional to the PRA on daily prednisone (r = -0.88, p<0.001) (Figure 4).

Exchangeable sodium was increased slightly, although the difference did not reach statistical significance. Aldosterone levels rose, both lying and standing, and serum potassium fell, providing confirmatory evidence of increased aldosterone activity.

Renal function was not affected by the change in prednisone regime (serum creatinine 156 ± 86μmol/L to 154.0 ± 99μmol/L), nor was there any significant change in weight (67.6 ± 13.7 kg to 66.0 ± 14.9kg). There was no difference in urinary sodium (144 ± 49.2mEq/24hrs and 133 ± 60.2mEq/24hrs), indicating that dietary sodium was similar during both studies.
Figure 1. Effect of change from daily to alternate day prednisone on mean arterial pressure in hypertensive patients.

Figure 2. Effect of change from daily to alternate day prednisone on mean arterial pressure in normotensive patients.
Figure 3. Effect of change from daily to alternate day prednisone on PRA (lying) in hypertensive patients

Figure 4. Relationship of PRA on daily prednisone to change in PRA on conversion to alternate day prednisone
<table>
<thead>
<tr>
<th></th>
<th>Plasma renin</th>
<th>Plasma renin</th>
<th>Exchangeable</th>
<th>Plasma</th>
<th>Plasma</th>
<th>Serum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>activity (lying)</td>
<td>activity (standing)</td>
<td>sodium (mmol/Kg LBM)</td>
<td>Aldosterone (lying)</td>
<td>Aldosterone (standing)</td>
<td>potassium (mEq/L)</td>
</tr>
<tr>
<td>Daily Prednisone</td>
<td>18.5 (± 16.0)</td>
<td>28.4 (± 37.7)</td>
<td>50.7 (± 9.6)</td>
<td>77.1 (± 74.0)</td>
<td>252.7 (± 278)</td>
<td>3.94 (± .39)</td>
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<tr>
<td>Alternate Day Prednisone</td>
<td>12.6 (± 9.2)</td>
<td>15.6 (± 12.3)</td>
<td>55.3 (± 14.3)</td>
<td>157.9 (± 181)</td>
<td>334.9 (± 290)</td>
<td>3.74 (± .39)</td>
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<tr>
<td>Paired t-test</td>
<td>t = 3.64</td>
<td>t = 2.65</td>
<td>t = 1.51</td>
<td>t = 2.46</td>
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<tr>
<td>p</td>
<td>p&lt;0.005</td>
<td>p&lt;0.01</td>
<td>N.S.</td>
<td>p&lt;0.02</td>
<td>N.S.</td>
<td>p&lt;0.01</td>
</tr>
</tbody>
</table>
Discussion

The fall in blood pressure demonstrated in these hypertensive patients after converting to alternate day prednisone confirms the findings of other workers [5,6]. The reduction in plasma renin activity may play an important role in this fall in blood pressure, although no direct correlation between change in blood pressure and change in PRA could be demonstrated. It does, however, lend support to our findings of the importance of renin in the aetiology of hypertension after transplantation [7].

The plasma renin activity may be reduced in these patients, not because of a fall in renin production, but because of a reduction in the output of angiotensinogen (plasma renin substrate) by the liver. The output of angiotensinogen is influenced by steroid hormones and has been shown to be increased in conditions of steroid excess, e.g. Cushing's syndrome, glucocorticoid therapy and oral contraceptives [8].

On alternate day prednisone, aldosterone levels were found to be elevated, despite lower PRA. Confirmatory evidence for increased aldosterone activity is given by the reduction in serum potassium and slight elevation in exchangeable sodium. Aldosterone secretion is governed by PRA, potassium and sodium status and by ACTH. It has been suggested that there is less suppression of the pituitary-adrenal axis on alternate day prednisone therapy [9]. Increased production of ACTH on conversion from daily to alternate day prednisone may be the stimulus for aldosterone secretion in these patients.

There was no evidence that the improvement in blood pressure control on alternate day steroids was due to or mediated by changes in sodium intake or retention.

References

1 Sampson D, Kirdani RY, Sandberg AA, Murphy GP. *Invest Urol* 1972; 10: 1, 66
5 Reed WP, Lucas ZJ, Cohn R. *Lancet* 1970; ii: 747
9 Sampson D, Albert DJ. *J Urol* 1973; 109: 345