PRORENIN AND BETA-BLOCKADE IN HYPERTENSION

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Summary

The role of prorenin in relation to beta-blockade has received little attention. We have studied both active renin and prorenin before and during treatment of hypertension with either nadolol or metoprolol in 44 patients. The ratio of active renin to prorenin before treatment was the best predictor of response; the fall in active renin with treatment did not correlate with the fall in blood pressure, whereas prorenin showed an inverse correlation. We suggest that plasma prorenin is an important indicator of the renin status in hypertensive patients.

Introduction

The significance of plasma renin as a predictor of efficacy of beta-blockade in the treatment of hypertension is controversial. Buhler et al demonstrated a close correlation between pre-treatment renin and response to treatment with propranolol [1], but the majority of subsequent studies have failed to repeat their findings [2]. The reasons for this are unclear, although in some studies this can be explained by the inadvertent assay of a combination of both inactive (prorenin) and active renin, the prorenin masking the values of active renin [3].

Prorenin itself has received little attention other than to be recognised as a hazard in renin assay methodology; its physiological role remains unknown. The importance of cardioselectivity of beta-blockers on the secretion of active renin has been studied but this has not been evaluated with respect to prorenin. We therefore examined a selective (metoprolol) and non-selective (nadolol) beta-blocker to compare the effect of these drugs in the treatment of hypertension and to correlate their hypotensive effect with both active renin and prorenin.
Methods

Patients

Forty-eight patients aged 21–65 years with essential (38 patients) or renal (10 patients) hypertension attending a hypertension outpatient clinic were studied. Exclusion criteria were the presence of heart disease, asthma, diabetes mellitus, previous stroke, liver disease or renal failure (serum creatinine >150 μmol/L). All patients gave their informed consent.

Trial design

The trial was of a double-blind placebo run-in design, comparing once daily doses of nadolol with metoprolol. Previous anti-hypertensive therapy (including diuretics) was stopped prior to entry. Following a four week period of control observations on placebo, patients were randomly allocated to receive (double-blind) either nadolol 80mg or metoprolol 100mg tablets. Visits were at −4, −2, 0, 2, 6, 10, 14 and 18 weeks. Initial dose of active drug was one tablet daily commencing at week 0. Dosage was thereafter increased at each visit until either erect diastolic blood pressure was less than 90mmHg or to a maximum of four tablets daily. Patients were seen 24 hours after taking their last tablet; blood pressure and heart rate were recorded after five minutes recumbency, after standing for one minute, and during, at the end of and two minutes after a five minute exercise on a static bicycle ergometer with a 70 watt load. Blood pressure was measured indirectly using a mercury manometer; the diastolic blood pressure was taken as Korotkov phase IV. Each blood pressure recording was the mean of three readings. Patients were requested to maintain their usual dietary sodium intake throughout the study.

Samples for renin and biochemistry were taken after five minutes recumbency, at 0 and 18 weeks. Blood for renin was collected into EDTA tubes on ice and then centrifuged at 4°C, the plasma being stored at −20°C until analysis. Active renin was measured by radioimmunoassay of angiotensin I generated at 37°C for one hour in pH 5.3 buffer [4]. Total renin was estimated by exposing the serum to trypsin (1mg per ml) with angiotensin I generation as above. Prorenin was calculated as total renin minus active renin.

Statistical analysis

Differences between the groups were analysed by Student’s t-test; correlation between blood pressure and renin was by Pearson correlation coefficients and verified by Kendal rank correlation.

Results

Forty-four patients (35 essential hypertension, 9 renal hypertension) completed the study, 22 patients on each drug. Four patients were withdrawn; one for non-compliance, one for bronchospasm (on nadolol), one for fluid retention (on placebo) and one for an unacceptable increase in blood pressure whilst on placebo.
TABLE I. Blood pressure and heart rate before and after beta-blockade

<table>
<thead>
<tr>
<th>Week</th>
<th>SUPINE</th>
<th>Systolic, Diastolic blood pressure (mmHg, mmHg)</th>
<th>Pulse rate (beats/ min)</th>
<th>ERECT</th>
<th>Systolic, Diastolic blood pressure (mmHg, mmHg)</th>
<th>Pulse rate (beats/ min)</th>
<th>MID EXERCISE</th>
<th>Systolic, Diastolic blood pressure (mmHg, mmHg)</th>
<th>Pulse rate (beats/ min)</th>
<th>END EXERCISE</th>
<th>Systolic, Diastolic blood pressure (mmHg, mmHg)</th>
<th>Pulse rate (beats/ min)</th>
<th>POST EXERCISE</th>
<th>Systolic, Diastolic blood pressure (mmHg, mmHg)</th>
<th>Pulse rate (beats/ min)</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td></td>
<td>Nadolol</td>
<td>165.4, 100.0</td>
<td>86.6</td>
<td></td>
<td>161.9, 102.9</td>
<td>90.8</td>
<td></td>
<td>198.0, 109.8</td>
<td>131.9</td>
<td></td>
<td>193.6, 102.1</td>
<td>132.1</td>
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<td>158.5, 102.9</td>
<td>98.2</td>
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<td></td>
<td>18</td>
<td>152.6, 88.7</td>
<td>59.3</td>
<td></td>
<td>148.0*, 92.2</td>
<td>62.3</td>
<td></td>
<td>174.7, 97.2</td>
<td>127.2</td>
<td></td>
<td>171.3, 90.4</td>
<td>101.0</td>
<td></td>
<td>145.6, 90.6</td>
<td>65.7</td>
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<td>Metoprolol</td>
<td>161.9, 100.9</td>
<td>82.9</td>
<td></td>
<td>162.6, 106.0</td>
<td>89.3</td>
<td></td>
<td>204.5, 112.4</td>
<td>99.7</td>
<td></td>
<td>195.5, 100.7</td>
<td>128.9</td>
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<td>164.9, 105.6</td>
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<td>18</td>
<td>145.3, 88.7</td>
<td>73.9</td>
<td></td>
<td>148.6, 95.7</td>
<td>78.4</td>
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<td>180.5, 98.7</td>
<td>117.1</td>
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<td>177.9, 89.9</td>
<td>120.0</td>
<td></td>
<td>146.1, 92.3</td>
<td>80.8</td>
</tr>
</tbody>
</table>

Differences between blood pressure at week 0 and week 18, p < 0.001 except * where p < 0.05
Effects on blood pressure and heart rate (Table I)

Blood pressure was reduced equally by both drugs before, during and after exercise. Both drugs reduced heart rate, the effect of nadolol being greater than that of metoprolol. After 18 weeks' treatment the mean daily dose of metoprolol was 291mg/day and of nadolol was 189mg/day.

Effects on plasma renin

There was no difference between the two groups in the pre-treatment values of either active renin, prorenin or total renin. There was a slight rise in total renin with treatment (14.5–16.0ng/ml/hour) although this failed to reach significance. Active renin decreased with treatments (2.6–1.7ng/ml/hour p<0.001) and prorenin increased significantly (11.8–14.3ng/ml/hour p<0.02).

Correlation between fall in blood pressure and pre-treatment renin

There was a direct correlation in all patients between the pre-treatment active renin and the fall in systolic (p<0.02, r = 0.37) and diastolic (p<0.02, r = 0.36) pressure whilst standing, and with the diastolic pressure after exercise (p<0.05, r = 0.35). There was a similar correlation with diastolic pressure with nadolol (p<0.02, r = 0.53) but not with metoprolol.

There was an inverse correlation between pre-treatment prorenin and the fall in supine diastolic pressure in all patients (p<0.05, r = -0.33). There was a significant inverse correlation with diastolic pressure whilst supine (p<0.002, r = -0.62), erect (p<0.05, r = -0.43) and after exercise (p<0.02, r = -0.55) with metoprolol, but a lack of correlation with nadolol.

There was a positive correlation between the ratio of active to prorenin before treatments and the fall in systolic (p<0.01, r = 0.40) and diastolic (p<0.005, r = 0.42) pressure whilst standing, and the systolic (p<0.005, r = 0.45) and diastolic (p<0.025, r = 0.37) pressure after exercise, without any difference between either drugs.

Relation between fall in blood pressure and changes in renin

There was no correlation between the fall in blood pressure and the fall in active renin when the groups were assessed either separately or together.

There was an inverse correlation between the increase in prorenin and the fall in systolic (p<0.05, r = -0.36) and diastolic (p<0.05, r = -0.34) pressure whilst standing and with the diastolic pressure after exercise (p<0.005, r = -0.49), without any difference between the two groups.

There was a positive correlation between the change in ratio of active to prorenin and the fall in systolic (p<0.02, r = 0.39) and diastolic (p<0.05, r = 0.32) pressure whilst standing and the diastolic pressure after exercise (p<0.02, r = 0.42). There was a significant correlation in the nadolol group with the fall in systolic pressure after exercise (p<0.02, r = 0.55).
Relation of active renin to prorenin

There was a within-patient correlation between active renin and prorenin prior to beta-blockade (p<0.025, r = 0.34); the correlation was stronger after treatment (p<0.001, r = 0.55).

Discussion

The presence of a circulating inactive precursor of renin, so-called prorenin, has been the subject of recent review [5]. Its response to both physiological stimuli and drugs differs from active renin [6], and as prorenin constitutes the majority of circulating renin the inadvertent assay of total renin (active + prorenin) may mask any correlation between the hypotensive effect of beta-blockade and renin. This may explain the failure of some studies to find such a correlation, but negative results in others which have measured active rather than total renin are more difficult to explain.

The role of prorenin as a predictor of response to beta-blockade has not previously been evaluated, although Atlas et al [7] have demonstrated an inverse correlation between an increase in prorenin and the fall in systolic pressure during treatment with propranolol. It is likely however, that in their studies the value of prorenin was underestimated as they used a cryo-activation procedure which we believe to be less efficient than the use of a proteolytic enzyme such as trypsin.

We have demonstrated a correlation between the reduction in blood pressure to beta-blockade and both the pre-treatment active renin and its ratio with prorenin. In addition we have demonstrated some correlation with pre-treatment prorenin. The effect of beta-blockade was correlated both with the rise in prorenin and the change in ratio of active to prorenin, but not with the fall in active renin alone. This suggests that prorenin may be a better indicator of renin status than active renin which is more sensitive to variation from posture and salt intake. Also, because the fraction of prorenin is much greater than active renin, only a small proportion of prorenin needs to be cryo-activated (e.g. during collection and storage of samples) to significantly alter the assay value of active renin. These results demonstrate the importance of estimating both active renin and prorenin in order to recognise important correlates with treatment.

We found little difference between the selective and non-selective beta-blocker except on the correlation between their hypotensive effect and the pre-treatment values of renin, which is difficult to explain. Some debate has centred on the relevance of cardioselectivity to the effect of beta-blockers on renin secretion [8]. We did not demonstrate a difference between the two drugs on either the fall in active renin or the rise in prorenin with treatment.

These findings strongly support the concept that not only is the renin status of hypertensive patients relevant in their response to beta-blockade but suggest that the mode of action of the drugs may be related to the renin-angiotensin system. The best responders to beta-blockade were patients with a high ratio of active renin to prorenin, i.e. a high active renin and low prorenin. We would like to postulate that the in vivo activation of prorenin to active renin in such patients
is accelerated and that beta-blockade reduces activation of prorenin and tends to return the system to normal. Observation of a stronger correlation between active and prorenin within patients after treatment also supports this.

We conclude from the results of this study that plasma renin is an important indicator of the response to treatment of hypertension with beta-blockers. It is necessary to measure both active renin and prorenin as the ratio between the two offers the best indicator of response. We suggest that this study helps to explain some of the current controversy.

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