Reactive hyper-reninaemia to angiotensin blockade identifies renovascular hypertension

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Summary

1. Saralasin and converting enzyme inhibitors SQ 20881 and captopril induced increases in plasma renin activity to greater than 14 ng h⁻¹ ml⁻¹ in 43 out of 44 patients with untreated renovascular hypertension when studied in the seated position and on normal sodium intake. This degree of response was absent in patients with normal-renin essential hypertension and present in only three out of 26 with high-renin essential hypertension.

2. Reductions of greater than approximately 9% in diastolic pressure in response to these three drugs occurred regularly in renovascular hypertension (95%) but also frequently in high-renin (65%) and normal-renin (26%) essential hypertension.

3. Prior sodium depletion abolished the specificity of the renin and depressor responses to angiotensin blockade for renovascular hypertension.

4. Some patients with bilateral renovascular and all with malignant hypertension also exhibited these responses to angiotensin blockade that are characteristic of unilateral renovascular hypertension.

Key words: captopril, converting enzyme inhibitor, renovascular hypertension, saralasin, SQ 20881.

Abbreviations: ANG I, angiotensin I; PRA, plasma renin activity; RVHT, renovascular hypertension; EHT, essential hypertension.

Introduction

Efforts to identify a clinical or laboratory test specific for correctable renovascular hypertension and which is at the same time practical for screening large numbers of patients have been unrewarding. Although in this condition there is increased renin secretion from the ischaemic kidney (Vaughan, Bühler, Laragh, Sealey, Baer & Bard, 1973), peripheral plasma renin activity (PRA) is either absolutely or relatively high in only one-half to three-quarters of all patients with renal artery stenosis (Marks & Maxwell, 1975; Grim, Weinberger, Higgins & Kramer, 1977). In addition, approximately 15% of patients with essential hypertension also have high PRA (Brunner, Laragh, Baer, Newton, Goodwin, Krakoff, Bard & Bühler, 1972). The development of drugs capable of blocking the action of angiotensin II or its formation has provided alternatives to measurement of baseline PRA in studying this problem.

This study evaluates both the responses of blood pressure and PRA to three different angiotensin-blocking drugs: saralasin, an octapeptide competitive inhibitor of angiotensin II; SQ 20881, a nonapeptide converting enzyme inhibitor; captopril, an orally active converting enzyme inhibitor.

Methods

Patients

After complete clinical examinations, 44 patients with renovascular hypertension (RVHT) were given saralasin \( (n = 12) \), SQ 20881 \( (n = 20) \) or captopril \( (n = 12) \) while on normal sodium intake and after being off all medications for at least 2
weeks. Another group of 15 patients with RVHT were studied with saralasin (n = 7) and SQ 20881 (n = 8) after receiving a diet containing only 10 mmol of sodium/day for 4 days. The diagnosis of RVHT was based on renal vein renin studies showing renin secretion from the affected kidney and suppression of renin secretion from the contralateral kidney, along with arteriographic confirmation of the stenosis (Vaughan et al., 1973). The results were compared with those of similar studies in 74 patients with normal-renin essential hypertension (EHT) on normal sodium intake (24 with saralasin, 20 with SQ 20881 and 30 with captopril) and in 24 on low-sodium intake (12 with saralasin and 12 with SQ 20881). Parallel data was also obtained in 26 patients with high-renin EHT on normal sodium intake (10 with saralasin, 10 with SQ 20881 and six with captopril) and in 12 on low sodium intake (seven with saralasin and five with SQ 20881). An additional seven patients with bilateral renal artery stenosis with bilateral renin secretion and five with untreated malignant hypertension were also studied with captopril. Patients consented to the study according to the procedures specified by the institutional Human Rights in Research Committee.

Study procedure

All patients were seated for at least 30 min before drugs while their blood pressures were measured automatically at 2 min intervals by Arteriosonde (Roche Medical Electronics) or by direct arterial recordings. A 24 h urine collection was made from each patient beginning on the day before study and assayed for sodium content to assure their level of dietary sodium intake. Blood samples were drawn through previously positioned indwelling venous catheters immediately before drug administration and again at the time of maximal blood pressure change 30 min after saralasin (Case, Wallace, Keim, Sealey & Laragh, 1976) and SQ 20881 (Case, Wallace, Keim, Weber, Sealey & Laragh, 1977) and 90 min after captopril (Case, Atlas, Laragh, Sealey, Sullivan & McKinstry, 1978). Saralasin was infused at the rate of 10 µg min⁻¹ kg⁻¹ for 30 min; SQ 20881 was given as a single, slow intravenous bolus in the dose of 1 mg/kg; captopril was given as a single oral dose of 10–50 mg. PRA was measured by the method of Sealey & Laragh (1975).

Analytical methods

The control blood pressure used for each patient was the average diastolic pressure over 20 min before blood sampling. The average maximal change in diastolic pressure, expressed as a percentage of the control pressure was used for analysis. Non-parametric statistical methods were used to detect differences between two groups (Wilcoxon's two-sample test or Student's t-test where appropriate). All results were expressed as means ± SEM.

Results

The effects of angiotensin blockade on blood pressure and PRA are shown in Table 1. On normal sodium intake, the mean percentage decrease in diastolic pressure of normal-renin EHT was significantly less than that of RVHT to saralasin, SQ 20881 and captopril. Although the mean depressor response to saralasin and SQ 20881 of patients with high-renin EHT were less than that of RVHT, captopril induced similar changes in blood pressure in both groups. PRA after each agent, however, was significantly greater (P < 0.005 or better) in patients with RVHT than in those with normal- or high-renin EHT.

On low sodium intake (Table 1), the mean depressor response of patients with normal-renin EHT was less than that of patients with RVHT (P < 0.01). However, the mean depressor response of high-renin EHT to saralasin and of both normal- and high-renin EHT to SQ 20881 was similar to that of the similarly treated groups of patients with RVHT. Mean PRA after saralasin and SQ 20881 was lower in normal-renin EHT than RVHT (P < 0.005 and < 0.001 respectively). Reactive PRA in the high-renin EHT groups after sodium depletion was not different from that of the patients with RVHT.

Criteria were set for the definition of 'positive' responses in terms of depressor responses and reactive PRA to these three drugs to include a maximum number of patients with RVHT and a minimum number of patients with EHT. A positive depressor response (maximum % change in diastolic pressure) to saralasin was −9.3% or greater after 30 min, to SQ 20881 was −9.4% or greater after 30 min and to captopril −8.5% or greater after 90 min. A positive reactive renin test was defined as 14 ng of ANG I h⁻¹ ml⁻¹ for saralasin (measured after 30 min), 18 ng of ANG I h⁻¹ ml⁻¹ for SQ 20881 (measured after 30 min) and 14 ng of ANG I h⁻¹ ml⁻¹ for captopril (measured after 90 min). With the above criteria 43/44 (97.7%) of RVHT patients had positive reactive renin tests and 42/44 (95.4%) had positive
TABLE 1. Blood pressure and plasma renin changes in response to angiotensin blockade

All values are means ± SEM. Significance: †P < 0.05 compared with RVHT; *P < 0.01 compared with RVHT; ††P < 0.005 compared with RVHT; **P < 0.001 compared with RVHT.

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<tr>
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<th>Normal-renin essential hypertension</th>
<th>High-renin essential hypertension</th>
<th>Renovascular hypertension</th>
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<td>I. Normal sodium intake</td>
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<td>Decrease in diastolic pressure (%)</td>
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<td>After saralasin</td>
<td>+0.6 ± 1.3**</td>
<td>-7.8 ± 2.0*</td>
<td>-18.6 ± 2.9</td>
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<td>After SQ 20881</td>
<td>-6.7 ± 0.8**</td>
<td>-13.5 ± 1.5††</td>
<td>-20.3 ± 1.3</td>
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<td>After captopril</td>
<td>-7.6 ± 0.9*</td>
<td>-14.5 ± 2.2</td>
<td>-13.6 ± 1.8</td>
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<td>Plasma renin activity (ng of ANG I h⁻¹ ml⁻¹)</td>
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<td>After saralasin</td>
<td>2.9 ± 0.2**</td>
<td>6.8 ± 1.2††</td>
<td>55.4 ± 12.0</td>
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<td>After SQ 20881</td>
<td>5.6 ± 0.7**</td>
<td>11.9 ± 1.3**</td>
<td>73.0 ± 9.4</td>
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<td>After captopril</td>
<td>4.6 ± 0.5**</td>
<td>10.2 ± 1.3††</td>
<td>36.2 ± 4.7</td>
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<td>II. Low sodium intake</td>
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<td>Decrease in diastolic pressure (%)</td>
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<tr>
<td>After saralasin</td>
<td>-8.4 ± 2.7*</td>
<td>-22.2 ± 5.4</td>
<td>-19.4 ± 3.8</td>
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<tr>
<td>After SQ 20881</td>
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<td>-19.5 ± 2.5</td>
<td>-16.9 ± 3.4</td>
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<td>Plasma renin activity (ng of ANG I h⁻¹ ml⁻¹)</td>
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<tr>
<td>After saralasin</td>
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<td>60.1 ± 22.2</td>
<td>96.6 ± 14.8</td>
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<tr>
<td>After SQ 20881</td>
<td>23.1 ± 5.2††</td>
<td>64.0 ± 15.4</td>
<td>64.5 ± 12.3</td>
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depressor response tests. Of patients with high-renin EHT, 3/26 (11.5%) had positive reactive renin tests and 17/26 (65.4%) had positive depressor-response tests. In the group of 74 patients with normal-renin EHT, none had a positive reactive renin test and 19 (25.7%) had positive depressor response tests.

Seven patients with bilateral renal artery stenosis and bilateral renin secretion were studied with captopril. Of these, six had positive depressor response tests and four had positive reactive renin tests. An additional five patients with untreated malignant hypertension were also studied with captopril. All five had positive depressor response tests (mean -23.5 ± 2.2%) and positive reactive renin tests (mean 32.0 ± 6.2 ng of ANG I h⁻¹ ml⁻¹).

Discussion

The data indicate that, under the testing conditions as defined, reactive hyper-reninaemia and depressor responses to angiotensin blockade occur in nearly all patients who meet the generally accepted definition of surgically correctable RVHT. However, reactive hyper-reninaemia was found to be a more specific test than no patients with normal-renin EHT and only 12% of patients with high-renin EHT exhibited the same degree of responses. In contrast, depressor responses occurred in 26% of normal-renin and in 65% of high-renin EHT patients.

A crucial prerequisite for the test is normal sodium intake, since patients with EHT who had undergone prior dietary sodium depletion exhibited responses that could not be distinguished from those of patients with RVHT. In addition, patients with malignant hypertension also exhibited similar depressor and renin responses. Thus the test is not applicable in patients who have severe hypertension and neuroretinopathy. Some patients with bilateral renovascular hypertension also exhibited the same responses as those with unilateral disease. However, there are no data to determine whether this group would have a better surgical result compared with the others with bilateral disease who did not exhibit these responses.

The findings suggest that patients who are clinically suspected of having renovascular hypertension (i.e., by age, presence of an abdominal bruit, severity, history of drug resistance) would be ideal candidates for testing. Of the three drugs, only SQ 20881 is not likely to be available in the next year or two. It is not certain whether the same responses of blood pressure and of PRA are elicited in patients who are receiving antihypertensive medications. Our results suggest that diuretic treatment may alter the state of sodium balance and produce more 'false-positive' tests. On the other hand, Re, Novelline, Escourrou,
Athanasoulis, Burton & Haber (1978) have shown that SQ 20881 will enhance renal renin secretion from ischemic kidneys in patients treated with propranolol.

The mechanism by which the hyper-reactive renin rise occurs in RVHT is unclear but could result from both systemic or renal baroreceptor stimulation or from interruption of feedback inhibition of angiotension II on renin release.

Acknowledgments

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References


