Angiotensin II Blockade in Hypertension of Chronic Haemodialysis Patients

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Summary

A P113 saralasin infusion test was performed in 10 patients on long-term regular haemodialysis. Six patients were considered to have hypertension resistant to dialysis treatment and 4 had had their arterial pressure controlled by dialysis.

Five out of 6 resistant and 3 out of 4 controlled patients had a positive response to saralasin associated with normalisation of diastolic arterial pressure.

The value of the saralasin infusion test for the selection of patients for bilateral nephrectomy is critically discussed and we feel that a negative test may be of more value in encouraging more aggressive ultrafiltration in hypertension apparently resistant to dialysis therapy.

Introduction

The role of salt and water overload in the genesis of end stage renal failure hypertension is well documented (Blumberg et al, 1964; Comty et al, 1964). Successful control of uraemic hypertension by dietary sodium restriction and progressive ultrafiltration during regular twice or thrice weekly haemodialysis without hypotensive drugs has been obtained in dialysis-responsive hypertension (Craswell et al, 1972; Vertes et al, 1969). Early reports of total blood pressure control by dialysis and diet (Blumberg et al, 1967; Comty et al, 1966) were not confirmed by later works (Onesti et al, 1968) and bilateral nephrectomy became the mode of treating resistant hypertension.

Attempts to define the role of the renin-angiotensin system in hypertension of dialysis patients have been varied and controversial (Brown et al, 1969; Schalekamp et al, 1973; Vertes et al, 1969; Wilkinson et al, 1970). The relating of exchangeable
sodium to renin levels gave rise to the ‘inappropriate secretion of renin’ hypothesis (Schalekamp et al, 1973) but still the components of vascular reactivity lacked definition.

Recently, the advent of a specific and competitive angiotensin antagonist (1 Sarcosine 8 Alanine Angiotensin II, Saralasin, P113) acting at the vascular receptor level in rats (Pals et al, 1971) and man (Brunner et al, 1973) has permitted us to study the effective contribution of angiotensin II in the maintenance of hypertension in dialysis treated patients.

PATIENTS AND METHODS

Ten patients (5 females and 5 males, age range 24 to 58 years) with a history of long standing hypertension (16 to 120 months) maintained on thrice weekly arteriovenous fistula haemodialysis for 2 to 48 months were investigated for the effect of Saralasin acetate (P113, Eaton Laboratories, Norwich, New-York) on their blood pressure. Four patients were well controlled by dietary sodium restriction and ultrafiltration whilst the remaining six were considered to have resistant hypertension. Six patients had chronic glomerulonephritis, two patients had malignant nephroangiosclerosis and one each lupus erythematosus and chronic pyelonephritis. Five patients were anuric and the remaining five had a residual creatinine clearance of 1.6 to 7.8 ml/min. All hypotensive therapy was stopped at least 7 days before the study in the dialysis resistant hypertensive cases.

The patients were kept recumbent throughout the study. A continuous intravenous infusion of 0.28 mol/l glucose was started at a rate of 0.116 ml/min with a calibrated motor-driven syringe (Harvard Instruments). Blood pressure was measured automatically every 2 minutes with an Arteriosonde Roche model 1217 during the entire study. When the blood pressure was steady for at least 30 minutes, the infusion of saralasin diluted in a 0.28 mol/l glucose solution, was started at a rate of 0.57 n mol/min/kg (low dose infusion) for 30 minutes in the 10 patients. A high dose infusion of P113 (2.58 n mol/min/kg) was then substituted for an additional 30 minutes in 6 of the 10 patients. Following termination of the infusion, blood pressure was recorded for an additional 45 minute recovery period.

This study was performed 4 hours before (10 patients) and repeated one hour after a 4 hour haemodialysis (9 patients).

Haematocrit, plasma sodium (Na) and potassium (K), plasma renin activity (PRA) were measured before and at the end of each P113 infusion period. PRA was measured using a radioimmunoassay technique for angiotensin I generated during incubation at pH 5.6. The interference of Saralasin with the measurement of angiotensin I was not significant in our procedure. The amount of blood withdrawn during the entire study was approximately 50 ml for each patient.
The evaluation of statistical significance was carried out with Student’s t-test or paired data t-test.

RESULTS

Pre-dialysis

Before haemodialysis the control arterial pressures were $171 \pm 9/114 \pm 5$ (n=6) in the dialysis-resistant hypertensive group and $142 \pm 6/90 \pm 3$ (n=4) in the dialysis-controlled hypertensive group. In 8 P113-responsive patients, defined as the patients whose mean arterial pressure (MAP) decreased by more than 10 mmHg, the low dose infusion of P113 induced a mean decrease of MAP of $17.1 \pm 1.1$ mmHg ($p < 0.001$). No further reduction of arterial pressure was obtained when the dose of saralasin was increased to 2.58 nmol/min/kg in 6 patients, suggesting that the blood pressure response to P113 was already maximal with the lower dose. Saralasin infusion induced normalisation of the arterial pressure in 3 out of the 6 dialysis-resistant hypertensive patients. P113 equally lowered the mean blood pressure in the dialysis-controlled hypertension group by an average of $15 \pm 4$ mmHg ($p < 0.05$). Thus, the response to P113 was unrelated to the type of blood pressure control achieved by dialysis alone. Individual results show that 5 out of 6 dialysis-resistant and 3 out of 4 dialysis-controlled hypertensive patients had a positive response to the angiotensin antagonist infusion.

In the P113-responsive patients, the mean predialysis PRA was $30.6 \pm 4.6$ ng/ml/h. This mean is above our range observed in normal recumbent subjects on a restricted sodium intake (1.6 to 10.4 ng/ml/h). However, in one of these patients (ML), P113 induced a $15$ mmHg MAP decrease, despite a PRA within the normal range (8.8 ng/ml/h). No change in haematocrit, plasma sodium and potassium were observed during P113 infusion. Heart rate was unchanged in P113 responsive patients.

Haemodialysis

The four hour haemodialysis performed in 9 out of the 10 patients induced an ultrafiltration weight loss of $1.4 \pm 0.3$ kg, corresponding to $2.5 \pm 0.4\%$ of the control body weight. Haematocrit was raised from $23.4 \pm 1.05\%$ to $24.5 \pm 0.9\%$ ($p < 0.05$). Plasma sodium increased by $3.1 \pm 1.1$ mEq/l ($p < 0.025$) and plasma potassium decreased from $5.34 \pm 0.4$ to $4.38 \pm 0.4$ mEq/l ($p < 0.02$). Haemodialysis was associated with a MAP drop of $13.2 \pm 3$ mmHg ($p < 0.005$) and an increase in heart rate of $10 \pm 2$ beats/min ($p < 0.001$).

Post-dialysis

Nine patients were studied after haemodialysis. Five out of the 6 dialysis-resistant
hypertensive patients normalised their arterial pressure during P113 infusion. In patient BZ who was unresponsive to P113 before haemodialysis, a 1.35 kg ultrafiltration weight loss after dialysis was associated with a 25 mmHg decrease of MAP; subsequently, angiotensin blockade produced a fall of MAP of 9 mmHg and the lowest arterial pressure level reached during P113 infusion was 148/106 mmHg (194/134 before haemodialysis).

In the patients, taken as a whole, the MAP changes induced by P113 were $-13.3 \pm 1.7\%$ of the preinfusion MAP before dialysis and $-13.9 \pm 1.7\%$ after dialysis (no significant difference between these means with paired data analysis). Thus, haemodialysis did not induce any potentiation of the effect of P113 on arterial pressure. No change in heart rate occurred during the antagonist infusion in responsive patients.

The mean post-dialysis PRA (38.6 ± 8.4 ng/ml/h) was higher than the predialysis mean (26.4 ± 4.6 ng/ml/h, $p < 0.05$). During P113 infusion, PRA increased by 13.9 ± 4.9 ng/ml/h ($p < 0.025$). The results are summarised in Table I.

**DISCUSSION**

The pathogenesis of hypertension complicating end-stage renal failure is unknown. It is certain that salt and water retention, as well as increased activity of the renin-angiotensin system, each play a role, but the exact manner in which they act or interact, remains uncertain. In the present study we have confirmed that in the majority of our patients, angiotensin II is responsible in part for the maintenance of the elevated resting arterial pressure. This fact is not surprising as 6 of our patients were selected because of a dialysis-resistant hypertension. This type of hypertension has often been associated with an elevated PRA and has been treated in the past by bilateral nephrectomy (Onesti et al, 1968; Toussaint et al, 1966, Vertes et al, 1969; Wilkinson et al, 1970). In our resistant patients, although renin levels were elevated (24.1 ± 4.4 ng/ml/h) compared with the dialysis-controlled patients 14.8 ± 5.2 ng/ml/h (0.2 < $p$ < 0.3), bilateral nephrectomy has never been considered, as our policy is to control arterial pressure with beta-blocking agents, sodium restriction and progressive ultrafiltration. Therefore the value of the saralasin infusion test in these resistant patients appears to be limited, in contrast to Lifschitz et al, 1975, and Trust et al, 1976, who recommended this test as helping in the selection of patients for bilateral nephrectomy.

However, in case BZ, a young girl with malignant hypertension and borderline elevation of PRA, a negative saralasin test encouraged us to control her hypertension by more vigorous ultrafiltration during dialysis. Thus we feel that a negative response to P113 in a hypertensive dialysis patient is likely to be of more value than a positive test which is anyway, in our experience, always associated with an elevated PRA.

The fact that arterial pressure was normalised in all saralasin responders but
<table>
<thead>
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<th>Patients</th>
<th>Age</th>
<th>Sex</th>
<th>Residual c. creat. ml/min</th>
<th>Duration Dialysis (mos)</th>
<th>Blood Pressure mm Hg Before HD (1)</th>
<th>After HD</th>
<th>Plasma Renin Activity ng/ml/hr (3) Before HD</th>
<th>After HD</th>
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<tr>
<td>AR</td>
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</table>

Dialysis-Resistant Hypertension

Dialysis-Controlled Hypertension

(1) Haemodialysis
(2) Maximal effect during administration of Angiotensin II antagonist
(3) Normal range in recumbent normal subjects on restricted sodium intake (1.6 to 10.4 ng/ml/hr)
one, suggests that future developments with this compound may permit it to be used as a therapeutic agent for dialysis-resistant hypertension.

References

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Open Discussion

DONKER (Groningen) It has been suggested that PRA increases during P113 infusion by blocking the positive feedback between angiotensin II and renin production. From the data from Dr Marks and also from our experience I have doubts about that; PRA only increases during blockade when the blood pressure decreases. When the patient is on a normal sodium diet and you are giving him Saralasin and his blood pressure does not respond, the PRA does not increase.

MIMRAN I could answer from my own experience in normal people. Usually plasma renin activity stays the same during Saralasin infusion. The fact that

518
PRA went up with Saralasin when blood pressure went down shows that the renin-angiotensin system was overactive in these people. In these patients, in fact, there was a correlation between the decrease in blood pressure and the increase in plasma renin activity.

ROSENFELD (Tel Aviv) Will you comment please on the importance of sodium balance to the response to Saralasin infusion; actually the same question I was wanting to ask Dr Marks?

MIMRAN Well, the results really do not show very clearly that sodium balance has any effect in these patients; but as everybody knows the vasculature of these people is probably rigid when compared to normal people or to essential hypertensive or renal-vascular hypertensive patients, and I do not have any evidence to give you about the change in reactivity. In fact, in essential hypertensive patients, when you deplete sodium with Lasix or some other diuretic, you get potentiation of the effect of Saralasin. Sodium balance probably plays a role. This is I think a very complicated point in assessing the effect of this antagonist, because it depends on the sodium balance, and that is why probably we might have some false positive reactions.

CHAIRMAN - ANDREUCCI You mention in your abstract that a negative response to P113 was valuable in indicating the need for more vigorous ultrafiltration in blood pressure control. We usually try to check the dry weight quite frequently, and then to keep the patient's weight a little bit higher than the dry weight. What do you mean by more vigorous ultrafiltration? What is the dry weight?

MIMRAN I, also, can ask this question, what is the dry weight in a patient and how do you define it? This patient who was hypertensive was not responsive to an angiotensin blocker. The only way to control blood pressure was probably through the volume component.