Angiotensin Blockade as a Rapid Diagnostic Test in Hypertension

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Summary

Saralasin, a specific competitive inhibitor of angiotensin II, was administered to 17 patients with renovascular hypertension and 15 patients with essential hypertension. After modest sodium depletion, a readily apparent vasodepressor response was noted in 16 of the 17 patients with renovascular hypertension and in 4 of the 15 patients with essential hypertension. Before salt depletion, the group differences were not as well defined.

Saralasin (1-sar-8-ala-angiotensin II) [Eaton Laboratories, Norwich, New York] differs from other antihypertensive agents because its blood pressure lowering effect is highly specific. The sole action of this compound is competitive inhibition of angiotensin II (Pals et al, 1971), and prompt lowering of blood pressure in response to its intravenous administration has been equated with ‘angiotensinogenic’ (Streeter et al, 1975) or renin-mediated hypertension (Brunner et al, 1973; Marks et al, 1975). However, the vasodepressor responses occurring with saralasin administration may be critically dependent on the prevailing state of sodium balance (Gavras et al, 1975). To clarify in man the interaction between sodium balance and saralasin responsiveness, we conducted the following prospective, controlled study.

METHODS AND MATERIALS

Thirty-two caucasian adults, 15 with essential hypertension and 17 with renovascular hypertension, were studied in the UCLA Clinical Research Center. Two weeks prior to admission, all antihypertensive medication was discontinued and
a diet of 150 mEq/day sodium was started. All patients had a diastolic blood pressure of at least 90 mmHg, and no patient had malignant hypertension.

Saralasin testing was performed on two consecutive mornings, beginning the day after admission. On test Day 1, the patients were ingesting the 150 mEq/day sodium diet. On test Day 2, the patients were in a state of mild sodium depletion, which was achieved by administering furosemide, 1 mg/kg body weight, orally at 5 pm on Day 1 after that day's study was completed. Thereafter, a sodium-free diet was started. After blood pressure was stable for at least 30 minutes (control level), a 10 mg bolus of saralasin was hand-injected over two minutes into the tubing of an indwelling venous catheter. Thirty minutes after the bolus was given, a constant saralasin infusion (10 μg/kg/min) was then administered over 90 minutes. Blood pressure was monitored with an automated ultrasonic device [Arteriosonde 1217, Roche Medical Electronics].

Determinations of plasma renin activity (Haber method), serum electrolytes and liver function tests, and urinary sodium excretion were performed each morning before saralasin administration.

RESULTS

While patients were admitted to the study on the basis of their diagnosis (i.e. essential or renovascular hypertension), they were subsequently grouped slightly differently — as saralasin responders (n=20) or non-responders (n=12). A 'responder' was considered to be a patient whose blood pressure declined by at least 10 mmHg systolic and 8 mmHg diastolic after saralasin administration on Day 2. Of the 17 patients with renovascular hypertension, 16 were saralasin responders, and one was a non-responder. Of the 15 patients with essential hypertension, four were responders and 11 were non-responders. Responders and non-responders were matched with respect to age, sex, admission levels of blood pressure, urinary sodium excretion, creatinine clearance, and evidence of target-organ damage.

In Figure 1, the diastolic blood pressure changes from control level after saralasin administration are presented (mean ± SEM). On Day 1, with the patients in a salt replete state (average $U_{Na}V=4.5$ mEq/hr), the responder group exhibited a 9 to 10 mmHg average sustained decline in diastolic blood pressure after saralasin administration; the non-responder group showed a modest pressor response. On Day 2, with the patients in a state of mild salt depletion ($U_{Na}V=1$ mEq/hr), the responder group exhibited a significant enhancement of the vasodepressor response, as diastolic blood pressure declined by 20-24 mmHg; the non-responder group showed very little change in blood pressure. Responses to either bolus injection or sustained infusion were not significantly different, and in fact, were closely correlated (r=0.89).

In Figure 2, control levels of plasma renin activity are shown for the two groups on both test days. On the average, renin levels were significantly higher.
Figure 1. Blood pressure changes from control level after saralasin administration (mean ± SEM)

Figure 2. Control plasma renin activity (mean ± SEM)
for responders than non-responders on both Day 1 (salt replete – P <0.01) and Day 2 (salt deplete – P <0.01). Each group responded to salt depletion with an approximate 100 percent increase in level of plasma renin activity.

Of the 17 patients with renovascular hypertension, 10 were saralasin responders on both Day 1 and Day 2. Six patients with renovascular hypertension who were non-responders on Day 1 became clearcut responders on Day 2. One patient with renovascular hypertension had a low level of peripheral renin, non-lateralising renal vein renin data, and no response to saralasin on either day. Five patients had non-lateralising renal vein renins, yet all were cured or improved by operation; 4 of these patients with ‘falsely negative’ renal vein renins were saralasin responders.

Of the 15 patients with essential hypertension, three responded to saralasin on both Day 1 and Day 2, while one responded on Day 2 only. Aside from their plasma renin activity levels, which were grossly elevated on Day 2 in all four patients, these four saralasin responders with essential hypertension were in no way separable from all the other essential hypertensives who had normal or low plasma renin activity and who failed to respond to the blocker. The saralasin responses in these four patients were indistinguishable from the responses seen in the 16 patients with renovascular hypertension.

Saralasin testing in these 32 patients did not cause hypotension, cardiac irregularities, or consistent changes in serum electrolytes, liver function tests, or urinary volume or composition.

DISCUSSION

The synthesis of saralasin was first reported in 1971 by Pals and co-workers, who also showed its specificity of action. Brunner et al (1973) reported the use of this angiotensin blocking agent as a diagnostic tool in 12 hypertensive patients. Streeten and associates (1975) have reported an extensive experience with saralasin infusions, with all patients in a salt deplete state prior to administration of the blocker.

In the present series, 32 patients with renovascular or essential hypertension received saralasin before and after salt depletion. After furosemide-induced natriuresis, the blocker evoked a vasodepressor response in 16 of 17 patients with renovascular hypertension and in all four high-renin essential hypertensive patients tested. Without sodium depletion, these responses failed to occur or were very modest. Thus, the results of the study substantiate the importance of prior sodium depletion in saralasin testing, which, when performed as described herein, is a rapid, effective, and safe method to diagnose renin-mediated hypertension.

In an earlier report, we noted that bolus injections of saralasin produced a blood pressure response comparable to that seen during sustained infusions (Marks et al, 1975). The present data confirm and expand that comparison: post-bolus and intra-infusion blood pressures are not significantly different.
(Figure 1). While sustained infusions may have a therapeutic value (Brunner et al., 1974), bolus injections are entirely adequate for diagnostic purposes. Saralasin testing in this manner requires that the patients are not receiving concomitant antihypertensive medication. The patient must also demonstrate a stable level of genuinely elevated arterial pressure after mild salt depletion.

Streeten et al. (1975) observed that all saralasin responders in their series had independent evidence of potentially pathogenic renal or renovascular lesions, i.e. renal underperfusion. We cannot confirm this observation since several patients in our series with high-renin hypertension and normal renal anatomy and function responded to the blocker. These responses constitute direct in vivo evidence that overactivity of the renin-angiotensin system is at least partially responsible for elevated arterial pressure in certain cases of essential hypertension. The significance of these responses in patients with essential hypertension, in relation to treatment and prognosis, remains to be established.

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Open Discussion

KENNEDY (Glasgow) Out of the 16 patients three had positive results. If this is a false positive result, this according to my arithmetic is 20%. Is a 20% false positive result highly accurate?

MARKS I think the test is highly accurate as a test for renin mediated hypertension. It is not specific for renovascular hypertension. All three of those patients were patients with very high renin levels, patients with normal arteriograms, no renal arterial stenosis, no renal lesion of any kind, but with extremely high renin levels; just as high as the patients with renal vascular hypertension that we saw. They responded to the drug, implying to us that they must have had a renin or angiotension dependent blood pressure. They did not have renovascular hypertension, but they had a renin-mediated hypertension. This figure of 15 to 20% goes along well with published references to a high renin sub-group of essential hypertensive patients, and we were pleased to see it in this small series. Our incidence of Saralasin responsiveness among patients with essential hypertension corresponded to those other published series.

KENNEDY Can I ask, for my interest, what you did with these patients, and what you labelled them? Did they still have ‘essential hypertension’?

MARKS We have not had a formal programme of certain drug therapies for patients who responded to Saralasin versus patients who did not. I think it might be interesting - all three of these patients are controlled on beta blocking agents plus other medications. I am not sure what that means.

KENNEDY Are you therefore saying that the test is a useful primary non-invasive procedure for selecting those patients who should be subjected to invasive and more detailed investigations for renovascular hypertension?

MARKS Yes, absolutely.

ANDREUCCI (Naples) What happened with the patient who had renovascular hypertension and has not responded? Did he undergo revascularisation? If yes, what happened to his hypertension?

MARKS Yes, that patient interested us, too. The one patient out of the 17 with renovascular hypertension who did not respond to Saralasin, either before or after salt depletion, was a lady of 42 years with fibromuscular disease of the renal arteries, who had normal peripheral renin levels and no response to Saralasin, who, on the basis of her arteriogram alone, was operated upon and had a renal arterial bypass. She is now normotensive. There was absolutely no evidence in this woman, other than her arteriogram, that the renin-angiotension system was involved in the maintenance of her hypertension. Perhaps the people who talked about other mechanisms will help us to answer the question.

HABERAL (Ankara) Did you use this drug for treatment or just for diagnosis?

MARKS For treatment only in the last patient I showed, and only for a 12 hour
infusion. Our ethics committee are very stringent and we have approval only for use as a diagnostic test. It was only with emergency ethics committee approval that we were able to do it on this one. I hope that we will be able to try some more in the future.

DONKER (Groningen) Dr. Marks, you have information or data concerning the renal blood flow and the urinary sodium and water excretion during the infusion of Saralasin, both before and after sodium depletion. As P113 is a competitive antagonist of angiotension II, one would expect during the infusion an increase in renal blood flow and a loss of sodium and water.

MARKS No. We did not study the urinary sodium excretion during the rather short period of time we gave this drug. I think that is a very valuable thing to do, but I think you will need to do it for more than a bolus injection.

DONKER Two or four hours?

MARKS Yes, I think it needs to be done.