Pressor Response to Saralasin (1-Sar-8-Ala-Angiotensin II) Bolus Injection in Hypertensive Patients

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SUMMARY A 10 mg bolus of the angiotensin blocker saralasin was injected 113 times in 68 subjects with essential or renovascular hypertension. Ninety percent of injections caused a transient increase in blood pressure, which correlated with plasma renin activity (PRA) ($r = -0.54$). Mean increase at 2 minutes was 21/13.4 mm Hg ($P < 0.001$) and was independent of pre-injection control blood pressure, with a rapid decrease to or below control values thereafter.

Thirty-seven subjects were studied on successive days before and after furosemide-induced sodium depletion (152 ± 26 mEq [SE] sodium loss). In the low renin group, sodium depletion did not change PRA or the magnitude of the pressor response to saralasin, but significantly decreased control MAP by 13 mm Hg ($P < 0.01$). In normal and high renin patients, MAP was unchanged after diuresis, but PRA increased significantly and the pressor response was attenuated. The net effect of sodium depletion was to reduce the pressor response to saralasin in all renin subgroups by 9 to 12 mm Hg.

Saralasin bolus injection, unlike infusion, saturates available vascular receptors only briefly, eliminating prolonged pressor responses.

A VASODEPRESSOR RESPONSE to intravenous administration of saralasin (1-sar-8-ala-angiotensin II), a competitive inhibitor of angiotensin II, signifies the presence of renin-mediated hypertension. 1-7 We and others have suggested the use of saralasin testing in widespread screening of hypertensive patients.1-8 Because the usual method of saralasin administration, i.e., continuous, pump-controlled intravenous infusion, is not applicable for outpatient screening of large populations, we studied the effects of a single, rapid bolus injection of the drug.5 8 We noted a close correlation of blood pressure responses to a bolus injection as compared to infusion of saralasin in patients with essential and renovascular hypertension, and concluded that the saralasin bolus test has many characteristics of an ideal screening procedure for renin-mediated hypertension.

Severe pressor responses following saralasin infusions have been recently reported.9-12 However, there are few data concerning pressor responses to saralasin bolus administration.9 Since the bolus technique involves rapid delivery of a relatively large quantity of saralasin to the receptor sites as compared to the various infusion techniques described,9-12 it has been predicted that saralasin bolus testing “... will sooner or later, result in a vascular catastrophe”.1 Accordingly, the present report presents a detailed systematic analysis of the pressor responses to 113 bolus injections in 68 hypertensive patients.

Methods

Subjects

The study group consisted of 68 hypertensive patients (44 males and 24 females) who ranged in age from 10 to 62 years (mean age 40.1 years). Sixty-four were Caucasian and four were black. Before entry into the study, all patients were taken off antihypertensive medication for two weeks and then subjected to an extensive inpatient work-up designed to diagnose secondary forms of hypertension. Thirty-five patients were thus found to have essential hypertension and 33 patients were found to have renovascular hypertension. The diagnosis of renovascular hypertension was established by postoperative cure or improvement of hypertension at one year follow-up, as described in the Cooperative Study of Renovascular Hypertension,13 or, in unoperated patients, by unequivocally positive arteriographic and renal vein renin data.14

Study Design

Two weeks prior to saralasin testing a sodium replete diet consisting of approximately 120 to 150 mEq/day of sodium was begun. At this time each patient was interviewed by the investigators, and an informed consent approved in advance by the Human Use Protection and Review Committee of UCLA Medical Center was obtained. In addition to the saralasin tests, each patient had a complete blood count and multiphasic serum analysis (SMA-12, Technicon Corporation), as well as determinations of serum and urine electrolytes, serum creatinine, and supine and upright plasma renin activity (PRA) on the morning of each test.

Thirty-seven patients were admitted to the UCLA Clinical Research Center and studied in a three-day protocol described in detail elsewhere.8 In brief, saralasin was administered to these patients on two consecutive mornings, beginning the day after admission. The first drug administration was performed while the patients were ingesting the sodium replete diet. The second drug administration was performed the next morning, a state of mild sodium depletion having been achieved by furosemide, 1 mg/kg body weight, given orally at 5 p.m. of the first test day followed by a low sodium diet (10 mEq/day). Before and after sodium depletion, the patients were weighed on a standard balance-type scale. Thus, with regard to sodium balance, each of these patients served as his own control.8

Thirty-one patients were studied as outpatients in the sodium deplete state only. Mild sodium depletion was achieved in these patients by furosemide and dietary sodium restriction, in an identical manner as for the inpatient group.
Eight of these outpatients had repeat saralasin testing several weeks after the initial test.

Altogether, 113 saralasin tests were performed, 37 during sodium repletion and 76 during mild sodium depletion.

Saralasin Testing

A private, quiet, dimly lit room was used for the saralasin tests. All patients were in the supine position. Blood pressure was monitored and recorded every two minutes with an automated ultrasonic device (Arteriosonde 1216, Roche Medical Electronics). The accuracy of the Arteriosonde readings was confirmed in each patient by multiple comparisons with simultaneous readings obtained using a standard sphygmomanometer and stethoscope.

After a one-hour period of blood pressure stabilization, 2 ml of saline were injected through a cannula connected to a venous infusion line. Ten minutes later, a 10 mg bolus of saralasin was administered in the same manner over a two-minute period. The patients were kept unaware of the timing of the injections. Thirty minutes later, saralasin infusion (10 to 50 μg/kg/min) was started and administered for 90 minutes in 37 patients. The remaining 31 patients did not receive an infusion, and the test was terminated 60 minutes after administration of the bolus. After testing, blood pressure was monitored every 10 to 15 minutes with a sphygmomanometer and stethoscope for at least 120 minutes in the outpatients and every hour for 12 to 18 hours in the hospitalized patients.

“Control blood pressure” was considered to be the average of the five Arteriosonde readings just prior to saralasin administration. “Admission blood pressure” was considered to be the average of the first four hourly blood pressures measured by sphygmomanometer immediately after admission to the sphygmomanometer.

Renin Determinations

A radioimmunoassay was used for determinations of plasma renin activity, and all samples were run in duplicate. In our laboratory, this test has a within-assay variation of ±5.6% S.D. Each morning before saralasin administration, peripheral venous samples were obtained for renin determinations with the patient supine for one hour, and after one hour of ambulation. Patients were stratified into renin subgroups by two different methods: 1) The pretest supine, post-furosemide PRA values in all patients were ranked from lowest to highest, and then stratified into three categories of equal size. This permitted saralasin-induced blood pressure changes within each renin category to be analyzed statistically by a stepwise, multiple regression technique in order to derive a best-fitting polynomial for each category, and 2) The 37 patients who were studied both in the salt replete and sodium deplete states on successive days were categorized into absolute renin subgroups by comparison with a normal range (±2 S.D) established in 28 healthy adults studied previously in our laboratory under identical sampling conditions. As in previous studies from our laboratory, sodium depletion, upright PRA values were used for absolute renin categorization.

Results

Magnitude and Duration of Early Pressor Response to Saralasin (113 Bolus Injections)

Figure 1 shows the serial changes in systolic and diastolic blood pressure following saralasin bolus injection (N = 113). Solid horizontal lines indicate mean change in blood pressure and brackets indicate ± S.D.
blood pressure following all 113 saralasin bolus injections, regardless of patient diagnosis, PRA, or, sodium balance. There was a rapid increase of blood pressure in approximately 90% of the group. This agonistic response was of brief duration, generally attaining its peak immediately following the two-minute saralasin injection and never later than the four-minute blood pressure recording. Although there was considerable individual variability, the mean increase at two minutes was 21 mm Hg systolic and 13.4 mm Hg diastolic \( (P < 0.001) \), and at four minutes 11.4 mm Hg systolic \( (P < 0.001) \) and 2.3 mm Hg diastolic (NS). After six minutes most blood pressures were at or below control values. Five patients had transient elevations greater than 50 mm Hg systolic and in seven patients the diastolic pressure exceeded 30 mm Hg. A sustained increase of more than 20 mm Hg diastolic, however, was present in only seven cases at four minutes, one patient at six minutes and in none thereafter. No patients reported any symptoms following saralasin injection.

There was no correlation between the magnitude of the early agonistic response and the control blood pressure \( (r = -0.27) \); i.e., the absolute increase of pressure was similar over the entire range of control blood pressures.

Relation of Early Pressor Response to PRA (113 Bolus Injections)

As seen in figure 2, there was a negative association between PRA and the magnitude of the early agonistic response \( (r = -0.54) \).

For statistical purposes, the study group was divided into three categories of equal sample size according to PRA levels. For each renin-category, a best-fitting polynomial was fit to the early serial blood pressures, using a stepwise multiple regression technique\(^{18}\) (fig. 3). This mathematical model indicates that

a) The time of the peak agonistic response following the start of the saralasin injection was related to PRA level. The peak occurred at approximately 89 seconds in the high renin category, at 115 seconds in the medium renin category, and at 131 seconds in the low renin category.

b) Not only the magnitude of the early agonistic response to saralasin (fig. 2), but its duration as well (fig. 3) correlates with renin level. Thus, the increase in blood pressure occurs more slowly, lasts longer, and is of greater magnitude in the low renin patients than in the other renin categories.

Effects of Sodium Depletion on Pressor Response to Saralasin (74 Bolus Injections)

Thirty-seven patients were studied in an identical manner on successive days before and after administration of furosemide. Furosemide administration resulted in a net sodium loss of 152 ± 26 mEq (sd) and a 2.3% decrease in body weight. Sodium depletion (post-furosemide) attenuated and shortened the duration of the agonistic response to saralasin (fig. 4).

Although net sodium loss and decrease in body weight were not different between renin subgroups following

\[ \text{FIGURE 2. Correlation between log PRA and maximum change in diastolic blood pressure following saralasin bolus injection (N = 113). PRA values used were those obtained in the supine position immediately prior to saralasin testing.} \]

\[ \text{FIGURE 3. Time course and magnitude of early pressor response to saralasin bolus injection (N = 113). The three renin groups are of equal size for statistical purposes. Brackets indicate ± SE. Arrows indicate time of peak agonistic response in each subgroup.} \]

\[ \text{FIGURE 4. Comparison of early blood pressure responses to 74 saralasin bolus injections in 37 patients studied on successive days in the sodium replete and sodium deplete state. Brackets indicate ± SE.} \]
Furosemide administration, sodium depletion had different effects upon control blood pressure and the agonistic responses to saralasin (fig. 5). In the low renin subgroup, furosemide-induced sodium depletion resulted in a significant decrease of control blood pressure (-13 mm Hg MAP, \( P < 0.01 \)) but did not alter the magnitude of the pressor response to saralasin. In the medium and high renin subgroups, sodium depletion did not bring about a significant change of control blood pressure, but attenuated the magnitude of the pressor response to saralasin by 7 mm Hg and 11 mm Hg MAP, respectively. The net effect of sodium depletion was to reduce the maximum mean arterial pressure during the pressor response to saralasin by 9 to 12 mm Hg MAP, as compared to the sodium replete state. Plasma renin activity remained low and unchanged following diuresis in the low renin replete subgroup, and increased significantly in the normal and high renin subgroups (\( P < 0.001 \)).

Figure 6 categorizes individual patients by PRA levels and shows the maximal mean arterial pressure following saralasin administration in the sodium deplete state as compared to the “control” blood pressure in the sodium replete state. Each data point thus represents the pressor effect of saralasin as influenced by sodium depletion. The average maximal increase of mean arterial pressure above control values for the entire group was 13.2 mm Hg. Six subjects had increases of greater than 20 mm Hg, and only one subject had an increase of greater than 30 mm Hg. The random distribution among renin subgroups demonstrates that sodium depletion resulted in elimination of the peak blood pressure differences otherwise seen between renin subgroups (see above, figures 2 and 3).

Sustained and Rebound Pressor Responses to Saralasin (113 Bolus Injections)

Because of the known within-patient variability of in-hospital blood pressures,20 a minimum significant pressor response is considered to be an increase of diastolic blood pressure of 10 mm Hg. Application of this definition in figure 1 indicates that only five of 113 bolus injections resulted in sustained elevation of blood pressure at ten minutes. No patients exhibited a sustained pressor response at 20 or 30 minutes after the bolus injection.

At one, two, and three hours after cessation of saralasin administration, four subjects had diastolic blood pressures which exceeded their admission values by 12 to 18 mm Hg. None of these patients had any complaints nor demonstrated any untoward signs or symptoms.

Discussion

Saralasin testing compares favorably with renin determinations in the diagnosis of renin-mediated hypertension.1 3 6 7 21 In most patients with renovascular hypertension or high-renin essential hypertension, saralasin evokes a prompt, readily apparent vasodepressor response; no such response occurs in patients with normal or low renin essential hypertension, unless they are stressed by sodium depletion and upright posture.9 22 22 Saralasin administration is generally regarded as safe,21 but certain patients have exhibited a paradoxical pressor effect after receiving the drug, occasionally associated with acute hypertensive symptoms.1 9 10 11 12 Thus, marked elevations in blood pressure may constitute an uncommon, but potentially dangerous major side effect of saralasin testing.

The published articles concerning the pressor response to saralasin are limited to the infusion technique.9 12 There appear to be three types of pressor responses which may occur during and following a saralasin infusion: 1) an initial transient pressor response occurring in almost all subjects,
lasting a few minutes, then quickly disappearing; 2) a sustained pressor response occurring largely in low renin patients and lasting up to 30 minutes or for the duration of the infusion; and 3) a rebound pressor response occurring in some high renin patients one to three hours after termination of the infusion.

In contrast, the bolus injection resulted in only the initial transient pressor response (figs. 1 and 4), which generally was maximal at the end of the two-minute injection, decreasing thereafter. In only five of 113 bolus injections was there a sustained elevation of blood pressure (increase of diastolic pressure greater than 10 mm Hg) at 10 minutes (fig. 1), and no patients exhibited a sustained pressor response at 20 or 30 minutes after the injection. No symptomatic rebound hypertension was observed.

The difference in the pattern of the pressor reaction following a bolus injection versus a slow infusion may be explained by the "rate theory" of drug receptor interaction. According to this theory, antagonists stimulate first and then block as the stimulation fades. The stimulation results from the initial process of coupling between drug molecule and receptor substance. Following administration of a bolus, there is an immediate saturation of available vascular receptors which causes a prompt rise of the arterial pressure. Saralasin has a plasma half-life of only 3.2 min so that its concentration is maximal at the termination of the bolus and diminishes rapidly thereafter. This results in a largely unidirectional reaction, i.e., uncoupling of the receptors. The reaction during prolonged saralasin infusion, on the other hand, is a dynamic equilibrium between coupling and uncoupling, so that the pressor effect may last until the infusion is terminated.

The initial transient increase in blood pressure of 21 mm Hg systolic and 13.4 mm Hg diastolic which occurred in almost all patients is of similar magnitude to that which occurs during saralasin infusion. Nevertheless, there was considerable individual variability, and approximately 5% of the pressor responses exceeded 50 mm Hg systolic (5 patients) or 30 mm Hg diastolic (7 patients) (fig. 1). Since there was no correlation between the magnitude of the early agonistic response and the baseline blood pressure \( r = -0.27 \), it is possible that pressor increases of this magnitude might be hazardous in those patients with very high blood pressures. If this small subset of patients can be identified, however, or if the pressor responses can be attenuated and/or predicted, then the saralasin bolus test could have wide potential as a screening procedure (see below).

We and others have demonstrated a close positive correlation between PRA and vasodepressor response to saralasin. In the present report, the initial pressor response to saralasin bolus showed a negative correlation with PRA level (obtained at the time of drug injection) \( r = -0.54 \) (fig. 2), i.e., the lower the renin the greater the early rise in blood pressure after saralasin bolus administration. A similar relationship between renin level and sustained pressor response has been demonstrated during saralasin infusion. Presumably, in low renin patients more vascular receptors are unoccupied by circulating angiotensin than in normal and high renin states, so that the partial agonistic effect of a given dose of saralasin will be greater and last longer (figs. 2 and 3).

The mechanism of the protective effect of sodium deple-

tion differs according to renin subgroups. In the normal and high renin subgroups, furosemide-induced diuresis did not change the control blood pressure, but clearly attenuated the magnitude of the initial pressor response (fig. 5). In these two renin subgroups, negative sodium/fluid balance resulted in the anticipated increase of PRA (fig. 5), thus shifting patients to the right in the PRA pressor-response curve (fig. 2). In the low renin subgroup, who exhibited the most marked pressor response to saralasin, a comparable degree of sodium depletion failed to either attenuate the absolute magnitude of the pressor response or to raise the PRA (fig. 5). Diuresis itself, however, caused a significant decrease of control blood pressure in this subgroup, so that an equivalent pressor response to saralasin in the sodium-depleted state resulted in a lower absolute maximal blood pressure than in the sodium replete state. These results support the hypothesis that low renin hypertension is primarily volume mediated and that saralasin-responsiveness is related to PRA.

The question which remains to be answered is: Is the saralasin bolus test dangerous, and likely to "sooner or later, result in a vascular catastrophe"?

In estimating patient risk, it is pertinent to compare the maximal blood pressure rise after saralasin to spontaneous changes in blood pressure during daily activities. Utilizing continuous 24-hour blood pressure measurements, it has been shown that transient increases of 50 to 60 mm Hg diastolic occur frequently during emotional stress in both normotensive and hypertensive subjects. Even mild isometric exercise equivalent to carrying a 10 kg suitcase may increase the diastolic pressure by up to 45 mm Hg. Similar striking increases of blood pressure with isometric exercise have been reported by others. Thus, even the most extreme rises in blood pressure following saralasin bolus are less than those reported during daily activities in hypertensive individuals.

The saralasin bolus test is, therefore, considered to be reasonably safe after modest salt depletion, when the pressor effect will rarely be greater than the patient's ambulatory, salt replete blood pressure, regardless of renin classification. The decision as to "risk" in any given patient obviously depends upon a physician's perception of risk-benefit, and must be made on a case-by-case basis.

Taken altogether, data from the present study and several companion studies strongly suggest that saralasin bolus testing should be used in a large field trial. Based on our relatively large experience, the following guidelines are offered: 1) the patient should have a reasonably competent cardiovascular status, i.e., a transient increase or decrease in blood pressure would not place the patient in severe jeopardy; 2) blood pressure should be no higher than 130 mm Hg diastolic; 3) mild, but not extreme sodium depletion (150 to 200 mEq or 2 to 3% of body weight reduction) should be instituted before testing; 4) the patient should be in the supine position with a stable elevated level of blood pressure; 5) the patient should be receiving no concomitant antihypertensive medication at the time of the test; 6) a vasodepressor response to saralasin is a decrease in blood pressure by 10/8 mm Hg, persisting for at least 8 minutes. Under these conditions, saralasin bolus testing is a relatively safe and highly accurate diagnostic procedure. The simplicity of the test suggests that it may be used as an office procedure.
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