EFFECT OF SARALASIN ON PLASMA RENIN ACTIVITY AND ARGinine-VASOPRESSIN IN HYPERTENSIVE MAN

I P Arlart, J Rosenthal, H Wagner, H E Franz

University of Ulm, FGR

Summary

This study was carried out to assess the influence of saralasin (SAR), an angiotensin II-analogue, on peripheral and central angiotensin II-receptors by measurements of plasma renin activity (PRA) and arginine-vasopressin (AVP) release. Before and during i.v. infusion of 10 μg/kg/min of SAR over a 30 minute period, blood samples were obtained from 15 recumbent hypertensive patients (7 renovascular, 8 essential) to determine hormone activities by radio-immunoassay. In 10 patients with a decrease of blood pressure following SAR, PRA increased significantly whereas AVP levels increased significantly in only 7 of these patients. In the remaining 5 patients without a fall of blood pressure, PRA and AVP remained virtually unchanged. The results indicate that an enhanced AVP release may be due to a hypotensive stimulus induced by SAR in angiotensinogenic hypertension. A direct influence of SAR on central receptors is unlikely under the conditions studied.

Introduction

The availability of saralasin (SAR), a competitive angiotensin II (A II)-antagonist, has introduced new ways of investigation of the renin-angiotensin mechanism in different forms of hypertension. Recent studies have demonstrated an increase in systemic blood pressure following intravenous infusion of SAR in patients with a normal sodium balance and under sodium load [1]. In these cases an angiotensin-agonistic action of SAR was postulated. In contrast a depressor effect due to an antagonistic SAR-action was found in high renin hypertension. Furthermore the observation has been made that in normoreninaemic hypertensive patients moderate sodium depletion mitigates the pressor effect of SAR whereas excessive sodium depletion is followed by a decrease in blood pressure [2].

In renovascular or malignant hypertension particularly, pronounced depressor effects of SAR have been described [3]. Results of these studies sug-
gested that SAR may act as a pressor agent when it could fill available vacant vascular A II-receptors, whereas a depressor effect was predominant when SAR had to displace A II from occupied receptors under sodium depletion [4]. In addition a variable receptor response to SAR depending on the plasma concentration of A II and also an altered receptor sensitivity to the analogue could be demonstrated [5]. Thus SAR was shown to decrease blood pressure by blocking the A II-action on the peripheral vasculature and to reduce aldosterone secretion by occupying adrenal cortical receptors. In contrast SAR produces an angiotensin-like effect and reduces renal blood flow under similar conditions by occupying intrarenal receptors. In addition to these effects an A II-action on the central nervous system has been shown which stimulates AVP secretion [6]. Against the background of these results, our study was carried out to assess whether stimulation of renin secretion due to angiotensin blockade or a depressor effect of SAR may influence plasma concentration of AVP in hypertensive subjects.

Patients and Methods

A total of 15 hypertensive patients, 10 male, 5 female, aged 17 to 57 years, underwent routine laboratory tests and angiography to exclude renovascular disease. Thus 8 patients were classified as having essential hypertension and were distinguished from 7 patients with unilateral renal artery stenosis. In all subjects antihypertensive drug therapy was stopped 7 days before hospitalisation. Prior to the study a non-restrictive dietary regimen was observed. Twelve hours before the investigation, 80 mg of furosemide was administered orally. Peripheral venous blood samples were obtained from the recumbent patients before and during a 30 minute i.v. infusion of 10 μg/kg/min of SAR, for determination of PRA and AVP by radioimmunoassay [7,8]. Systemic blood pressure was monitored continuously during the entire investigation.

Results

Following SAR a first group (group I) of 10 patients exhibited a significant decrease of systolic and diastolic blood pressure (P < 0.0005) within 8 to 10 minutes. In 6 of these patients, renovascular disease was proven by arteriography. In all patients of group I PRA increased significantly (P < 0.0025) from 1.79 ± 0.8 to 3.12 ± 0.8 ng/ml/hr, and in 7 patients AVP levels increased significantly (P < 0.005) from 5.16 ± 2.3 to 12.82 ± 3.1 μU/ml. In 3 patients with low basal plasma concentrations of AVP no response was observed under SAR (Figure 1).

In a second group (group II) of patients in which SAR had no depressor effect, only one patient had a renal artery stenosis. Basal PRA was in a lower range than that of group I. Following SAR, renin levels increased only slightly and not significantly (P < 0.1) from 0.62 ± 0.18 to 1.03 ± 0.38 ng/ml/hr whereas AVP levels remained virtually unchanged throughout infusion of the A II-analogue (Figure 2).
Figure 1. Group I. Patients with significant fall of blood pressure (P < 0.0005) following saralasin

Figure 2. Group II. Patients without fall of blood pressure following saralasin
Discussion

It is well established that hypertension, particularly when caused by haemorrhage, induces a rise of PRA, A II and AVP [9–11]. In addition it was possible to stimulate plasma levels of AVP in patients with the syndrome of manifest orthostasis [12]. A II and vasopressin were both demonstrated to be effective vasoconstrictor peptides [13]. Acute i.v. infusion of A II was shown to produce definite increases in plasma levels of AVP [6]; in normal subjects supraphysiological plasma levels of A II seem to be necessary for this action [14]. In contrast a suppressant effect of vasopressin on A II was found in man [15]. The influence of A II on central functions, including effects on thirst and drinking, or a pressor reaction, has been shown to be dose-related [16]. In order to block the angiotensin action on central receptors by the analogue SAR, peripheral i.v. administration of the agent was necessary in a concentration one hundred-fold higher than with direct central application. For i.v. administered SAR a concentration of 70 µg/kg/min was required in order to produce central effects [17]. This recommended concentration is ten-fold higher than that used in our own study. Thus it may be possible that SAR in a dose of 10 µg/kg/min blocks peripheral vascular receptors in patients with angiotensinogenic hypertension, producing a depressor effect, but is insufficient to influence central receptors of the neurohypophysis. Increasing AVP levels following SAR could be observed in our study only in patients with a significant depressor action and a significant increase of PRA pointing to an angiotensinogenic hypertension. Otherwise low AVP levels remained unchanged in patients with low or normal renins which could not be stimulated significantly by SAR. This phenomenon may depend on several factors. A main role may be played by the fall of systemic blood pressure inducing a stimulatory effect on AVP release via atrial receptors and arterial carotid sinus receptors, without involving a direct influence of SAR on the neurohypophysis [18]. SAR in the present concentration may have no antagonistic effect on central receptors. The possibility of dose-related agonistic actions has to be considered. In addition the possibility of central receptors, distinct from peripheral receptors, cannot be excluded, and these may have an altered sensitivity for angiotensin-analogues. Conceivably in patients who react to SAR with renin release and a fall in blood pressure, the release of AVP is enhanced.

References


415
Open Discussion

KOKOT (Chairman) Do you think your findings will be of therapeutic importance for the treatment of hypertensive patients?

ARLART I think a better approach would be a converting enzyme inhibitor. Saralasin is different in its actions and it might sometimes be dangerous. Hypertensive crisis has been described after administration of saralasin.

KOKOT Do you think that patients who respond very well after saralasin will be susceptible to treatment by beta-blockers or not?

ARLART Some authors have described a good response to beta-blockers in patients with high renin levels.

KOKOT Do you agree with Laragh's views on this point or not?

ARLART I think Laragh is too optimistic in his results.

WARREN (Southampton) There are some very elegant studies by Dr Ledingham and his colleagues over the last year to show a marked agonist effect of saralasin. In some subjects in whom saralasin is infused there is a rise in blood pressure soon after the beginning of infusion. Have you noticed whether the levels of arginine vasopressin are suppressed in those patients in whom saralasin produces an agonist effect, because this would make it more likely that the observations that you have made are of physiological significance?

ARLART We had no patients with a rise of blood pressure in whom we had measured arginine vasopressin.

WARREN I think if you were to look at some normal subjects very early in the course of saralasin infusion you would quite often find a marked rise in blood pressure in the first few minutes. Most of us have observed that.

ALART Some patients show a rise of blood pressure only five to ten minutes or shortly after the administration, and a return to normal levels after 20 to 30 minutes. Our measurements were done 20 to 30 minutes after the beginning of
infusion of saralasin.

WARREN It would, then, be very interesting if you could go and look at the first few minutes after administration.

DORHOUT MEES (Utrecht) Maybe I missed your point, but I don’t see the evidence for the first conclusion that the renin dependency is more readily shown by this test than by the basal renin levels. I think it is a very important point, of course, and it has been claimed from the beginning of the saralasin infusion test that this would show something more than would basal renin levels. However, I don’t think that up to now anybody has really brought evidence. Our laboratory in Utrecht has shown that there is a linear relationship between the change in blood pressure after saralasin infusion and the starting renin level. Recently this has also been shown, I don’t remember by whom, in the New England Journal, I think, comparing the effect of converting enzyme inhibitor. I have not seen in your presentation evidence for the fact that with a similar renin level some patients do lower their blood pressure after the test and others don’t. That’s what you mean by this conclusion, I suppose. Maybe this is due to the fact that you first determine PRA and after this give furosemide, and then you do the test. My question is also why do you choose this sequence, because you are applying two measures, not only the saralasin but also you give a diuretic?

ARLART We have measured only peripheral renins. In renovascular disease you can find normal levels, but you can find on the involved side enhanced levels of renins. It is not possible to see the endocrine activity of the involved side from peripheral renin levels.

DORHOUT MEES But did you find a group of patients with the same renin levels, some of whom dropped blood pressure after saralasin and others who didn’t. Because that’s the only way you would make the conclusion that there is a difference between renin levels and what you call renin dependency.

ARLART I think the evidence for angiotensinogenic hypertension is the fall of blood pressure following the analogue.