INFUSION OF ANGIOTENSIN-II ANALOGUE IN TWO PATIENTS WITH UNILATERAL RENOVASCULAR HYPERTENSION

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Summary　　　　The angiotensin-II analogue sar^1-ala^8-angiotensin II ('Saralasin') was administered intravenously in different doses to two patients with unilateral renovascular hypertension. On a sodium intake of 100 meq., infusion of the analogue resulted in a decrease in blood-pressure by 10–20 mm. Hg, a striking sodium retention, and a fall in effective renal plasma flow. In one patient the analogue infusion was repeated after sodium depletion: blood-pressure fell to normal within 10 minutes. After corrective surgery plasma-renin activity returned to normal within 1 day, but in both patients blood-pressure reached normal values only 2–3 weeks later. These results suggest that two mechanisms are acting jointly in the maintenance of the hypertension in these two cases of unilateral renal-artery stenosis.

Introduction

IN hypertensive patients angiotensin-II blockade by the competitive antagonist sar^1-ala^8-angiotensin II ('Saralasin') may cause a reduction in blood-pressure when the renin-angiotensin system is involved in sustaining hypertension.[1-3] Apart from sodium retention, side-effects of the analogue have not been described. Blockade of angiotensin II with saralasin has been advocated to predict surgical curability of unilateral renovascular hypertension, and it has been suggested that if blood-pressure does not fall strikingly, patients should not be exposed to renal-artery angiography or to surgery.[4] We report here the failure of saralasin to normalise blood-pressure in two patients on a daily sodium intake of 100 meq. and in whom unilateral renovascular hypertension was cured by surgery. During infusion of the analogue plasma-renin activity (P.R.A.), renal function, and urinary sodium excretion were measured. In one patient the administration of the analogue was repeated after sodium depletion and again after surgery.

Patients and Methods

Patient 1 is a 35-year-old man with hypertension and intimal fibroplasia of the right inferior segmental renal artery. After nephrectomy peripheral P.R.A. and 24-hour urinary potassium excretion were normal within 1 day. Blood-pressure was still raised 4 days after the operation but fell to normal after 3 weeks. Patient 2 is a 24-year-old woman with hypertension and medial fibroplasia of the right artery probably resulting from a pronounced nephroptosis at the right side.[5] After surgical reconstruction peripheral P.R.A. became normal within 1 day whereas blood-pressure came down in the second week. The relevant laboratory data are shown in the table. Antihypertensive therapy was withdrawn at least 2 weeks before infusion of saralasin. Both patients had a diet containing 100 meq. sodium both before and after surgery. During the observation periods patients were recumbent. Urine was collected in 2-hour periods and blood-pressure was measured every 2 minutes using an automatic recorder ('Arteriosonde 1217', Roche).

Saralasin (Eaton Laboratories, Norwich Pharmacal Co., Norwich, N.Y.) was dissolved in 5% glucose and administered with the help of a Braun 'Unita II' pump. Glomerular filtration-rate (G.F.R.) was measured with ^{125}I-sodium iothalamate (Radiochemical Centre, Amersham) and effective renal plasma flow (E.R.P.F.) simultaneously with ^{131}I-hippuran (Philips Duphar). After an equilibration-time of 2 hours, 2-hour clearances were determined before, during, and after infusion of the analogue. 2-hour samp-

BLOOD-PRESSURES AND LABORATORY DATA FOR PATIENTS 1 AND 2 BEFORE AND AFTER SURGERY

	Before surgery	After surgery, day:							After surgery, wk.:		
		1	2	3	4	5	6	7	2	3	4
Patient 1:											
Blood-pressure (mm. Hg)	180/120	165/100	175/120	175/120	180/120	..	..	..	..	130/90	120/80
Plasma volume (ml./kg.)	37	..	..	..	35	..	..	..	..	..	44
P.R.A. supine (ng./ml./hr.)	5	0·4	..	0·4	0·5	..	..	..	..	..	..
P.R.A. upright (ng./ml./hr.)	7·2	..	..	..	..	..	..	..	..	..	..
Renal vein P.R.A. ratio	1·2	..	..	..	..	..	..	..	..	..	..
Aldosterone excretion (µg./24 hr.)	16	..	..	..	0	..	..	..	..	..	..
Serum-potassium (meq./l.)	3·0	4·0	4·8	4·3	4·7	..	..	..	..	4·7	4·7
Potassium excretion (meq./24 hr.)	120	50	48	69	66	..	..	..	..	50	50
Renal vascular resistance (dyne. sec. cm.$^{-5}$)	20,000	..	..	..	19,000	..	..	..	..	..	6500
Patient 2:											
Blood-pressure (mm. Hg)	160/120	170/115	155/105	160/120	160/115	170/120	160/110	140/100	130/90	120/80	120/80
Plasma volume (ml./kg.)	34	..	..	..	..	..	..	..	..	50	..
P.R.A. supine (ng./ml./hr.)	3	1·5	..	..	..	..	..	..	..	2	1·3
P.R.A. upright (ng./ml./hr.)	7·3	..	..	..	..	..	..	..	..	5·1	..
Renal vein P.R.A. ratio	2·7	..	..	..	..	..	..	..	..	..	..
Aldosterone excretion (µg./24 hr.)	10	..	..	..	2	..	..	..	..	..	..
Serum-potassium (meq./l.)	3·9	3·4	3·5	..	..	..	..	..	4·3	4·8	..
Potassium excretion (meq./24 hr.)	50	35	..	..	..	..	..	..	64	65	58
Renal vascular resistance (dyne. sec. cm.$^{-5}$)	17,000	..	..	..	..	..	..	..	..	8000	..

ling of urine was chosen to reduce the influence of incomplete bladder emptying and of dead-space in the urinary tract. Clearances were not corrected for standard body-surface area. P.R.A. was measured by radioimmunoassay for angiotensin I. Normal upper limits of P.R.A. on 100 meq. sodium intake are 3 and 5 ng. angiotensin I per ml. per hour supine and upright, at 8 A.M. and noon, respectively. In patient 2 saralasin was administered also after 2 days' sodium restriction (20 meq. daily) combined with frusemide (40 mg. twice daily by mouth).

The effect of angiotensin-II blockade on the kidney was studied again in patient 2 3 weeks after surgical reconstruction.

Results

In patient 1 (fig. 1) saralasin infused at a rate of 5 µg. per kg. per minute (µg./kg./min.) caused a decrease in blood-pressure from 180/120 to 165/110 mm. Hg. 25 minutes after the dose was increased to 10 µg./kg./min. blood-pressure rose transiently from 165/110 to 185/120 mm. Hg. The rise in blood-pressure was accompanied by an increase in pulse-rate (from 74 to 82 per minute). At that time the patient complained of a mild headache. A further increment of the dose to 18·5 µg./kg./min. again provoked a temporary increase of the blood-pressure from 160/110 to 180/120 mm. Hg after 30 minutes. The pulse-rate increased from 72 to 90 per minute. Doses of
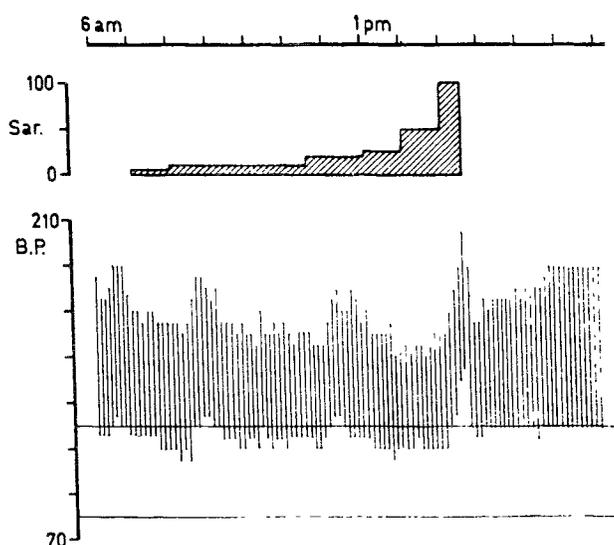

Fig. 1—Patient 1: blood-pressure changes (mm. Hg) during saralasin infusion (µg./kg./min.).

25 to 50 µg./kg./min. resulted in a stable blood-pressure of 150/110 mm. Hg. On 100 µg./kg./min. the blood-pressure rose to 205/145 mm. Hg after 30 minutes. The pulse-rate rose from 74 to 86 per minute. The patient complained of throbbing headache, and the infusion was stopped. 10 minutes later blood-pressure had returned to pre-infusion levels.

The results of the blockade in patient 2 are shown in fig. 2A. In this patient no transient increase of blood-pressure was observed with doses of 8 and 12 µg./kg./min. Increasing the dose to 16 µg./kg./min. resulted in a decrease of blood-pressure from 155/115 to 145/95 mm. Hg. Higher doses were not given. After completion of infusion of the analogue blood-pressure increased to pre-infusion value in about 30 minutes. The effect of the analogue on the blood-pressure in the same patient after sodium depletion is shown in fig. 2B. A normal blood-pressure
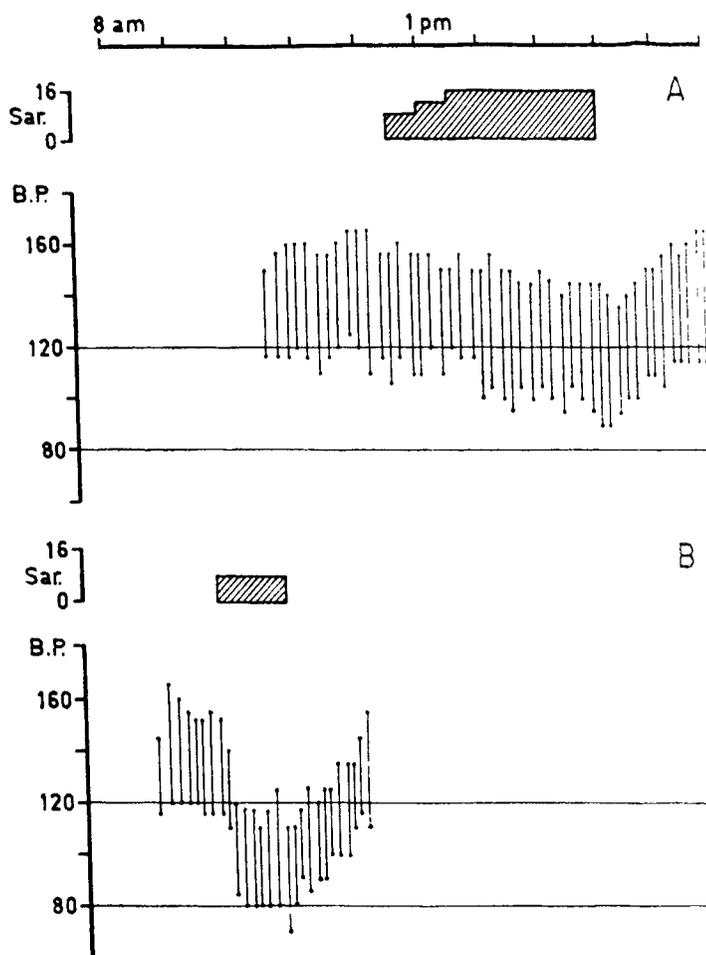

Fig. 2—Patient 2: blood-pressure changes (mm. Hg) during saralasin infusion (µg./kg./min.).

(A) Before sodium depletion. (B) After sodium depletion.

was achieved within 10 minutes using a dose of 8 µg./kg./min. After corrective surgery saralasin infusion had no effect on blood-pressure.

In both patients urinary sodium excretion decreased during saralasin administration, and rose upon withdrawal of the drug. The decrease and increase of sodium excretion paralleled changes in E.R.P.F. The G.F.R. was stable in patient 2 but varied with blood-pressure in patient 1. In both patients P.R.A. increased strikingly during angiotensin blockade, reaching peaks of 15 and 20 ng. angiotensin I/ml./min. in patients 1 and 2, respectively, and falling to control values when the infusion ceased. A decrease of E.R.P.F. and sodium excretion during infusion of saralasin was also observed in patient 2 after surgery. The G.F.R. remained stable, and P.R.A. rose to only 4·5 ng. angiotensin I/ml./min. during the postoperative challenge with saralasin.

Discussion

Saralasin is a specific competitive antagonist of angiotensin-II receptors in vascular smooth muscle and in adrenal cortex of several species.[6-9] Partial agonistic effects have been noted, in particular on the renal vascular bed.[9] Furthermore, saralasin does not block angiotensin-II receptors in adrenal chromaffin tissue, and, in addition, it possesses an intrinsic activity on these receptors.[10,11]

Increase in blood-pressure at different doses of saralasin in patient 1 can be explained by a similar partial agonistic effect of the analogue, either directly on vascular smooth muscle or indirectly by a release

of catecholamines. The striking rise in blood-pressure with the high dose of 100 μg./kg./min. demonstrated that administration of saralasin is not without risk.

Infusion of saralasin had an agonistic effect on the renal vascular bed in the two patients; in patient 2 before as well as after surgery. Sodium was retained, paralleling a decrease of E.R.P.F. A similar pattern is seen in healthy people during infusion of angiotensin II or noradrenaline.[12,13] In rabbits a dose-related increase of renal blood-flow was found when the analogue was superimposed on exogenous angiotensin II. However, renal blood-flow decreased during blockade when the endogenous angiotensin-II activity was suppressed by sodium loading.[9] Further studies about the influence of saralasin infusion on the E.R.P.F. in patients with unilateral renovascular hypertension or essential hypertension and with or without a stimulated renin-angiotensin system by sodium depletion are required, but these effects on E.R.P.F. do suggest the presence of a sodium-loaded state in patients with unilateral renovascular hypertension.

In both patients the infusion of saralasin was accompanied by only a slight decrease in blood-pressure. However, surgery was successful in both cases. Normalisation of blood-pressure followed that of P.R.A. by 2–3 weeks. The failure of the saralasin infusion to lower blood-pressure to normal in these two patients may be explained by the sodium balance. A normal blood-pressure was obtained by infusion of the analogue in patient 2 after preceding sodium depletion, and happened in a short time using a relatively low dose of the analogue. The importance of the sodium balance in renin-dependent hypertension has been shown by Brunner et al.[2] A blood-pressure reduction by angiotensin-II blockade in malignant hypertension was reversed by sodium loading. These workers found increased sensitivity to blockade in bilateral renal-artery stenosis following sodium depletion. Similar results were found using SQ 20,881, an inhibitor of the converting enzyme of angiotensin I to angiotensin II before and after sodium depletion.[14]

Thus, in unilateral renovascular hypertension also blood-pressure increase seems to be maintained by both an angiotensin-II-mediated vasoconstriction and by sodium retention. Indeed, in experimental unilateral renovascular hypertension in rats with the contralateral kidney left untouched this sodium retention occurs before a demonstrable rise in basal peripheral P.R.A.[15,16]

In conclusion, it is possible that infusion of saralasin could become a unique and simple screening test for renin-dependent hypertension or in predicting surgical curability of unilateral renal-artery stenosis,[4] but only after previous sodium depletion.

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AMŒBIC INFECTION OF THE EYE

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Summary   A healthy Huntingdonshire schoolteacher of 32 had mild unilateral keratoconjunctivitis and uveitis which did not respond to treatment. 6 months later progressive indolent corneal ulceration, pain, and loss of vision led to a corneal graft, which was rejected. A free-living soil amœba, Acanthamœba polyphaga, was repeatedly isolated from the affected eye. A Lincolnshire farmer of 59 developed an identical clinical condition which required enucleation of the eye after a year. A similar Acanthamœba was grown from his eye tissue. These are the first eye infections caused by free-living amœbæ to be reported in the U.K.

Introduction

Two genera of free-living soil amœbæ have been associated with human infections: Naegleria in the Vahlkampfiidæ family and Acanthamœba or Hartmannella in the Hartmannellidæ. Both have " limax "—i.e., slug-like—trophozoites which in the acanthamœbæ have thorn-like processes or " acanthopodia " (fig. 1) on the hyaline zone.

Naegleria sp., especially N. fowleri, are a well-established cause of acute primary amœbic meningoencephalitis in young adults, which is usually rapidly fatal.[1] Carter reviewed sixty-nine definite or possible cases with a worldwide distribution.[2]

Acanthamœba sp. are occasionally recovered from the nasopharynx of children [3,4] when tissue-cultures are

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