Effect of Indomethacin in a Patient with Bartter's Syndrome: Evidence against a Primary Role of Prostaglandin in This Disorder

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Summary

It has been claimed that in patients with Bartter's syndrome, enhanced prostaglandin synthesis causes the blunted vasopressor response to angiotensin II. The present study was undertaken to test this hypothesis by administering indomethacin to a patient with Bartter's syndrome. Indomethacin corrected the subnormal pressor response to angiotensin II and lowered plasma renin activity from 115 to 15 ng/ml/hr. This effect was associated with renal sodium retention and a 7% increase in body weight. In contrast, when indomethacin was given but the sodium retention prevented by concomitant administration of furosemide, the blunted vasopressor response to angiotensin II and the hyperreninemia were not corrected. It is concluded that the effectiveness of indomethacin to correct the hyperreninemia and the blunted vasopressor to angiotensin II in the present patient was due in large part to the ability of the drug to correct sodium balance rather than by inhibition of prostaglandin synthesis.

Speculation

Overproduction of prostaglandins does not play a primary etiologic role in the pathogenesis of Bartter's syndrome.

Patients with Bartter's syndrome exhibit a blunted pressor response to exogenous administration of angiotensin II (3). The mechanism underlying the vasopressor resistance to angiotensin II in these patients has not been elucidated. Recent reports suggest that overproduction of prostaglandin by the kidney plays a major role in the pathogenesis of this syndrome (9, 16). Thus, administration of indomethacin, an inhibitor of prostaglandin synthesis, was followed by clinical and chemical improvement in these patients and recovery of their vascular sensitivity to angiotensin II. These findings were felt to suggest that an increased synthesis of prostaglandin locally in the peripheral vascular bed contributed to the vascular insensitivity to angiotensin II in this condition (12, 17).

Another pathogenetic sequence that could account for the lack of pressor response to angiotensin II in Bartter's syndrome invokes a primary defect in renal conservation of sodium, leading to contraction of the plasma volume (4-6). Indomethacin has been shown to cause sodium retention in these patients (9). Thus, restoration of the vascular sensitivity to angiotensin II with indomethacin could result from either the sodium retaining properties of this drug or from its inhibition of peripheral vascular prostaglandin synthesis. The purpose of the present study, therefore, was to clarify the mechanism by which indomethacin corrects the hyposensitivity to angiotensin II in Bartter's syndrome.

CASE HISTORY

A 13-year-old patient was referred because of muscle weakness, growth retardation, salt craving, polyuria, and polydipsia. We had previously shown that this patient has Bartter's syndrome with renal sodium wasting due primarily to a defect in sodium chloride reabsorption at the diluting site of the nephron (7). Physical examination was unremarkable except for height and weight which were both below the third percentile. Blood pressure was 90/60 mm Hg (supine) and 80/55 mm Hg (upright). The following were found in chemical analysis of serum: creatinine, 0.9 mg/100 ml; sodium, 134 mEq/liter; potassium, 1.8 mEq/liter; and chloride, 90 mEq/liter. Arterial blood pH was 7.49, and bicarbonate was 33 mEq/liter. Urinalysis was normal.

MATERIALS AND METHODS

After all drugs had been discontinued (except potassium supplements) for 2 wk, the patient was given a constant diet containing 200 mEq of sodium. After a 7-day equilibration period on this diet, vasopressor responsiveness to angiotensin II, plasma renin activity, and aldosterone concentrations were determined. After these studies, indomethacin (100 mg/day in divided doses) was administered for 4 days. This was followed by an additional 4 days in which indomethacin and furosemide (80 mg/day) were administered concomitantly. On the fourth day on indomethacin alone and on the fourth day of combined indomethacin and furosemide therapy, vasopressor responsiveness to angiotensin II, plasma renin activity, and aldosterone concentrations were restudied. Sodium balance and body weight were carefully monitored throughout all the stages of the study. The pressor response to intravenous angiotensin II infusions was established in the supine position by the technique of Kaplan and Silah (15). Venous blood for the determinations of plasma renin activity (normal, 2.5 μ g/ml/hr) and aldosterone concentrations (normal, 5.0 pg/ml) was drawn in the morning, whereas the patient was supine for at least 1 hr. Plasma renin activity and aldosterone concentrations were measured by radioimmunoassay.

RESULTS

The vasopressor responses to angiotensin II infusions in the three phases of the study are summarized in Figure 1. In the control period, the vasopressor response was blunted. The infusion of 0.32 μ g/kg/min increased the mean arterial pressure, diastolic

$$+ \frac{(\text{systolic} - \text{diastolic})}{3}$$

by only 18 mm Hg. After indomethacin therapy, at a similar

Fig. 1. Effects of indomethacin alone and indomethacin plus furosemide on the pressor sensitivity to angiotensin II infusion.

Fig. 2. Effects of indomethacin alone and indomethacin plus furosemide on plasma renin activity, plasma aldosterone concentration, and body weight.

infusion rate of angiotensin II, a 57 mm Hg increment in mean blood pressure was observed. This restoration of vasopressor responsiveness to angiotensin II was paralleled by a 7% gain in body weight and a decrease in the urinary sodium excretion from 190 to 95 mEq in 24 hr. When furosemide was given concomitantly with indomethacin, the body weight returned to control values. Under such conditions, the infusion of the same dose of angiotensin II again resulted in only a modest pressor response as in the control period (23 mm Hg).

As is shown in Figure 2, plasma renin activity and aldosterone concentrations of 115 ng/ml/hr and 9.5 pg/ml, respectively, in the control period fell to 15 ng/ml/hr and 1.2 pg/ml after indomethacin administration. After combined indomethacin and furosemide administration, plasma renin activity and aldosterone concentrations returned towards baseline levels.

DISCUSSION

Our studies show a normalization of the peripheral vascular responsiveness to angiotensin II after 4 days of indomethacin administration in a patient with Bartter's syndrome. This correction of the vasopressor effect of angiotensin II was associated with a 50% decrease in urinary sodium excretion and a gain of 7% in the patient's body weight. When the indomethacin-induced sodium retention was abolished by concomitant furosemide administration and body weight was kept constant, the original pattern of vasopressor insensitivity to angiotensin II was reestablished.

Furosemide administration has been shown to increase both prostaglandin synthesis and plasma renin activity (1, 2). Such humoral effects could potentially account for the blunted vasopressor effect of angiotensin II observed during the combined administration of furosemide and indomethacin to the patient (8, 13). However, such a view is not supported by several recent observations showing that inhibitors of prostaglandin synthetase with indomethacin not only abolishes the prostaglandin releasing effect of furosemide but also attenuates the diuretic induced rise in plasma renin activity (10). Although urinary prostaglandin secretion was not measured in the present study, the large dose of indomethacin used (4 mg/kg) has been shown to be associated with renal prostaglandin depletion even after furosemide administration (10). Thus, it can be safely assumed that prostaglandin synthesis was suppressed in this patient both while on indomethacin alone or during the combined indomethacin and furosemide treatment periods. Taken together, it can be concluded that indomethacin enhances the vasopressor response to angiotensin II primarily by the salt retaining effect of the drug and correction of the patient's contracted plasma volume and not by a prostaglandin-depleting effect. The normalization of vasopressor response to angiotensin II with volume expansion is in accordance with similar observations by several investigators (5, 14, 19).

The present work confirms recent reports of suppression of plasma renin activity and aldosterone concentration during indomethacin therapy in patients with Bartter's syndrome (9-20). However, when the sodium-retaining effect of indomethacin was abolished by concomitant furosemide administration, the level of plasma renin activity and aldosterone concentrations remained substantially elevated. These findings suggest that activation of the renin-aldosterone axis in the present patient is related to volume contraction secondary to renal salt wasting and is not again a direct effect of prostaglandin overproduction on renin synthesis (16).

Although several investigators have demonstrated a defect of sodium chloride reabsorption in the proximal tubule (6) or at the diluting segment of the nephron (7-19), many patients with this syndrome apparently can conserve sodium when challenged with a sodium restricted diet (11). Thus, the relevance of the present data to the pathogenesis of vascular resistance to angiotensin II and to renin and aldosterone hypersecretion in this syndrome may apply only to those patients in whom sodium wasting is prominent.

In summary, indomethacin has been shown to abolish vasopressor insensitivity to angiotensin II and to lower plasma renin activity and aldosterone concentration in a patient with Bartter's syndrome. All of these effects of indomethacin appear to result from expansion of the plasma volume caused by the sodium retaining effect of this drug. Hence, our data suggest that the prostaglandin overproduction does not play a primary etiologic role in the clinical abnormalities of this patient. The physiologic significance of a primary prostaglandin overproduction in the pathogenesis of Bartter's syndrome is still to be determined.

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21. The protocol for this study was approved by the Human Research Committee of the Rambam Hospital, and informed consent was obtained from the patient's parents.
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