Effects of Indomethacin on the Vascular Abnormalities of Bartter’s Syndrome

CARL J. RICHARDS, M.D., ALLYN L. MARK, M.D., DIANNA E. VAN ORDEN, M.D., AND GEORGE J. KALOYANIDES, M.D.

SUMMARY We examined the hypothesis that the vascular abnormalities of Bartter’s syndrome are due to excess production of prostaglandin. Balance studies and vascular reactivity studies were performed before and after indomethacin (200 mg/day) in a patient with Bartter’s syndrome. During documented Bartter’s syndrome, serum potassium rose from 2.1-3 mEq/l in the absence of potassium supplementation, plasma renin activity decreased from 55-3.2 ng/day and peripheral plasma PGA-like activity fell from 1460 ± 220 to 456 ± 71 pg/ml. Before indomethacin, forearm vasoconstrictor responses to brachial arterial infusions of angiotensin II, norepinephrine and to neurogenic reflex stimulation elicited by lower body suction were greatly depressed compared to those of normal subjects. During indomethacin these responses were restored to normal. The dose of intravenous angiotensin II required to increase diastolic blood pressure 20 mm Hg decreased from 160-30 ng/kg/min. These data support the hypothesis that the vascular insensitivity to exogenous angiotensin II, norepinephrine and to neurogenic reflex stimulation observed in this patient with Bartter’s syndrome is due to excess prostaglandin. Moreover, stimulation of the renin-angiotensin-aldosterone system in this syndrome appears to be a compensatory adaptation to excess prostaglandin production.

BARTTER’S SYNDROME is a disorder characterized by hypokalemia, hyperreninemia, hyperaldosteronism, xjuxtaplomerel cell hyperplasia, normotension and resistance to the pressor effects of angiotensin II.1 A prominent feature of this syndrome is the resistance of vascular smooth muscle to the vasoconstrictor action of exogenous angiotensin II. Bartter and colleagues1 originally postulated that the vascular defect is the primary disorder which leads to the genesis of this syndrome. Other investigators2 attributed the vascular insensitivity to the development of tachyphylaxis to angiotensin II. However, as emphasized in our previous study,3 tachyphylaxis to angiotensin II does not adequately explain the observation that many patients with Bartter’s syndrome also exhibit resistance to the vasoconstrictor action of norepinephrine.

Recently, several investigators have reported that administration of drugs which inhibit prostaglandin synthesis reverses or ameliorates the clinical and biochemical features of Bartter’s syndrome.4-7 These observations have called attention to the possible role of excess prostaglandin production in the pathogenesis of this disorder. Moreover, since prostaglandin E and A are known to antagonize the constrictor action of angiotensin and norepinephrine on vascular smooth muscle,8-12 this theory also provides a possible explanation for the refractoriness of vascular smooth muscle to exogenous administration of these agents.

The objective of this study was to evaluate the hypothesis that indomethacin would reverse not only the biochemical abnormalities, but also the refractoriness of vascular smooth muscle to vasoconstrictor stimuli in a patient with documented Bartter’s syndrome.

Methods

MB, a 31-year-old Caucasian male, was discovered to have Bartter’s syndrome at the age of 27 during admission to the University of Iowa Hospital for evaluation of weakness and hypokalemia. Table I summarizes the findings which support the diagnosis of Bartter’s syndrome in this patient. Other studies revealed: 1) normal renal conservation of sodium during a sodium intake of 18 mEq/day; 2) normal urinary diluting capacity; 3) appropriate directional changes in plasma renin activity and aldosterone excretion in response to manipulations of sodium and potassium intake; 4) failure to normalize plasma renin activity and aldosterone excretion during sodium loading, 400 mEq/day, for six days; 5) failure to normalize serum potassium and plasma renin activity during administration of propranolol, spironolactone or triamterene. These studies have been reported in detail elsewhere.3

All studies were performed in the Clinical Research Center of the University of Iowa, with the approval of the Human Studies Committee and the informed written consent of the patient.

Balance Studies

The patient was maintained on a daily, constant-caloric diet containing 150 mEq sodium and 100 mEq potassium. Potassium supplements were provided in the form of potassium chloride. The diet was instituted for a minimum of four days before the initiation of measurements. During period I, the patient received 600 mEq potassium for 10 days. During period II (six days) and period III (eight days),
potassium intake was limited to 100 mEq/day. During period III the patient received indomethacin, 200 mg/day. Intake and urinary excretion of water, sodium and potassium were monitored daily. Fecal losses were not measured. Plasma renin activity and PAG-like activity were measured by radioimmunoassay, reflecting mainly the 13,14-dihydro-PGA metabolite. Plasma and urinary aldosterone were determined by Bio-Science Laboratories.

Vascular Reactivity Studies

The initial study was performed eight weeks after the patient had been maintained on 500 mEq potassium and 150 mEq sodium per day. Serum potassium was 4.2 mEq/L. The second and third studies were performed 22 and 30 weeks, respectively, after the initiation of indomethacin therapy, 200 mg/day. Four days before these studies the patient was maintained on a sodium intake of 150 mEq/day and a potassium intake of 100 mEq/day.

The patient was studied in the supine position in a room maintained at 26–27°C. Forearm blood flow was measured with a mercury-in-Silastic strain gauge plethysmograph. A polyethylene cannula (PE 90) was inserted into a brachial artery percutaneously for measurement of systemic arterial pressure (mm Hg) and for brachial arterial infusion of angiotensin II and norepinephrine. Forearm vascular resistance was calculated by dividing mean systemic arterial pressure (mm Hg) by forearm blood flow (ml/min per 100 ml forearm volume).

After obtaining baseline values, we measured forearm vascular responses to brachial arterial infusions of angiotensin II and norepinephrine 37.5, 75, and 150 ng/min, in studies 1 and 2. Each dose of drug was administered for 4 minutes with observations obtained during the fourth minute of each dose. Ten minutes separated administration of angiotensin and norepinephrine. In studies 1 and 3, we measured reflex forearm vascular responses to lower body suction (application of sub-atmospheric pressure). The patient's body below the iliac crest was enclosed in an airtight chamber connected to a vacuum pump through an adjustable vent to produce graded lower body suction. Lower body suction pools blood in the leg veins, decreases venous return and triggers reflex vasoconstriction by activating baroreceptor reflexes. After obtaining responses to lower body suction, we measured systemic arterial pressure during intravenous infusion of graded doses of angiotensin II. The doses of angiotensin were administered consecutively for 4 minutes each. Observations were obtained during the last minute of each dose at which time arterial pressure had stabilized.

Results

Balance Studies

Figure 1 summarizes the results of the balance study. During period I (days 1–10), sodium and potassium intake were 150 and 600 mEq/day, respectively. Despite this level of potassium intake, serum potassium on day 10 was only 2.9 mEq/l. Plasma renin activity was 22 ng/ml (normal < 4 ng/ml) and aldosterone excretion was 64 µg/day (normal < 16 µg/day).

During period II (days 11–16), sodium intake was maintained at 150 mEq/day, whereas potassium intake was reduced to 100 mEq/day. The patient exhibited marked negative potassium balance with urinary potassium excretion exceeding intake by 619 mEq over the six-day period. By day 16 serum potassium had declined to 2.1 mEq/L. Although sodium balance during this period was positive by 251 mEq, body weight decreased by 3 kg. The positive sodium balance in the face of weight loss probably reflects, at least in part, an intracellular shift of sodium for potassium. By day 16 plasma renin activity had increased to 55 ng/ml and urinary aldosterone excretion had decreased to 24 µg/day, reflecting the divergent effects of hypokalemia on these two variables.

On day 17 indomethacin was started at 200 mg/day while sodium and potassium intake were maintained at 150 and 100 mEq/day, respectively. Over the ensuing eight days potassium intake exceeded urinary potassium excretion by 362 mEq. Sodium balance also became positive and body weight increased from 69.8–72.3 kg. On day 24 plasma renin activity was 3.2 µg/ml and urinary aldosterone excretion was 2 µg/day.

During period I, plasma PAG-like activity, measured on day six, averaged 1015 ± 85 pg/ml (mean ± SEM). During period II, plasma PAG-like activity, measured on days 14 and 15, was 1,689 and 1,231 pg/ml, respectively. During indomethacin administration, plasma PAG-like activity, measured on days 21, 23, and 24, was 315, 534 and 520 pg/ml.
respectively. In six normal male subjects on no drug therapy plasma, PGA-like activity averaged 628 ± 151 pg/ml.

One week after discontinuation of indomethacin, serum potassium had fallen to 2.4 mEq/l; plasma renin activity and PGA-like activity had increased to 28 ng/ml and 1,536 pg/ml, respectively.

Subsequently, indomethacin was restarted at 200 mg/day and over the past 20 months the patient’s serum potassium ranged between 2.8 and 3.1 mEq/l in the absence of potassium supplementation.

Vascular Reactivity Studies

Table 2 summarizes the baseline hemodynamic data before and during indomethacin in the patient with Bartter’s syndrome; data from 11 normal subjects not receiving indomethacin are also included.

Baseline arterial pressure was within the normal range in all three studies. Baseline forearm blood flow was lower and forearm vascular resistance was higher after indomethacin at the time of the second study than they were at the time of the first study before indomethacin (table 2). However, baseline flow and resistance during indomethacin at the time of the third study did not differ appreciably from values before indomethacin (study 1) or from baseline values determined in 11 normal subjects.

The forearm vasoconstrictor responses to brachial arterial infusions of angiotensin II and norepinephrine (fig. 2) before indomethacin therapy were markedly attenuated compared to the responses of normal subjects. During indomethacin therapy, forearm vasoconstrictor responses to angiotensin II and norepinephrine (fig. 2) were restored to normal. Similarly, whereas reflex vasoconstriction elicited by lower-body suction was impaired before indomethacin therapy, it was restored to normal during indomethacin administration (fig. 3).

Before indomethacin, the dose of intravenous angiotensin II required to increase diastolic blood pressure 20 mm Hg was 160 ng/kg/min. During indomethacin the dose required to raise diastolic blood pressure 20 mm Hg was 30 ng/kg/min. Although in-

<table>
<thead>
<tr>
<th>Table 2. Baseline Hemodynamics</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Study</td>
</tr>
<tr>
<td>Systemic arterial pressure (mm Hg)</td>
</tr>
<tr>
<td>Systolic</td>
</tr>
<tr>
<td>Diastolic</td>
</tr>
<tr>
<td>Mean</td>
</tr>
<tr>
<td>Forearm blood flow (ml/min/100ml)</td>
</tr>
<tr>
<td>Forearm vascular resistance (mm Hg/ml/min/100ml)</td>
</tr>
</tbody>
</table>
domethacin therapy improved the response to intravenous angiotensin II in this patient, it was still above the dose (6–11 ng/kg/min) required to raise diastolic blood pressure 20 mm Hg in normal subjects.18

Discussion

Administration of indomethacin to a patient with Bartter’s syndrome was associated with a decline in plasma PGA-like activity, plasma renin activity and aldosterone excretion to normal levels. Potassium balance became positive and although serum potassium was not restored to normal levels, it was maintained between 2.8 and 3.1 mEq/l in the absence of oral potassium supplements. Moreover, this response has been sustained during more than 20 months of indomethacin-therapy. Our observations are in agreement with the reports of other investigators4 that administration of an inhibitor of prostaglandin synthesis to patients with Bartter’s syndrome reverses the previously described biochemical abnormalities which are characteristic of this disorder, and thus, provide additional evidence for the hypothesis that excess prostaglandin production is causally related to the pathogenesis of Bartter’s syndrome.

The unique feature of the present report is the study of vascular reactivity to humoral and neurogenic stimuli before and during indomethacin administration. Before indomethacin administration we observed decreased vasoconstrictor responses to brachial arterial infusions of angiotensin II, to norepinephrine, and to neurogenic reflex stimulation by lower-body suction. Indomethacin restored the vascular response to angiotensin II, norepinephrine and reflex stimulation to normal, and greatly improved the response to intravenous angiotensin II.

Previous investigators postulated that the attenuated vasoconstrictor response exhibited by patients with Bartter’s syndrome resulted from tachyphylaxis to high circulating levels of angiotensin II.2 According to this theory the improved respon-
siveness to exogenous angiotensin II during indomethacin might have resulted from decreased levels of endogenous angiotensin with an increase in the number of receptors available for occupancy. While this phenomenon might account to some extent for the increased responsiveness to exogenous angiotensin II during indomethacin, it would not explain the increased vasoconstrictor responses to norepinephrine and reflex stimulation. Angiotensin is known to potentiate adrenergic vasoconstriction. Consequently, decreased levels of angiotensin II would be expected to depress vascular responses to norepinephrine and reflex stimulation. The opposite findings of the present study, i.e., increased vascular responsiveness to norepinephrine and reflex stimulation during indomethacin when plasma renin activity and presumably angiotensin were suppressed, support the conclusion that some other mechanism underlies the vascular insensitivity seen in this disorder.

The fact that vascular reactivity to angiotensin, norepinephrine and neurogenic reflex stimulation was depressed before indomethacin and was restored to normal during indomethacin strongly suggests that excess prostaglandin levels mediated the vascular insensitivity observed in our patient with Bartter's syndrome. This theory is supported by the findings of other investigators that prostaglandins E and A inhibit vascular responses to angiotensin II and norepinephrine.

Gill and colleagues have suggested that excessive synthesis of prostaglandins might be the result, rather than the cause, of the impaired vascular responsiveness in Bartter's syndrome. Specifically, Gill et al. stated, "The initial hypothesis of impairment of vascular responsiveness to vasopressor agents as the proximal event remains as a possibility. If there were a defect in resistance arterioles, such that angiotensin II or norepinephrine evoked an excessive release of prostaglandins and thereby produced less than normal arteriolar constriction, then release of renin might be expected to increase to compensate for the decreased effectiveness of angiotensin II and norepinephrine." Our finding that indomethacin restored to normal the vascular responses to angiotensin II, norepinephrine and reflex stimulation makes the hypothesis of a primary defect in agonist-receptor interaction improbable, and suggests that the vascular insensitivity in this syndrome results from excessive production of prostaglandins. Thus, the high plasma renin activity and aldosterone levels, as well as the recently reported increased plasma levels of norepinephrine in patients with Bartter's syndrome, suggest that stimulation of the renin-angiotensin-aldosterone system as well as the sympathetic nervous system reflects a compensatory adaptation to excess prostaglandin production.

At the second vascular reactivity study, baseline forearm resistance during indomethacin was higher than at the time of the first study. This suggested that inhibition of prostaglandin synthesis might alter baseline vascular resistance as well as responses to vasoconstrictor stimuli. We, therefore, performed a third study to determine if this was a reproducible and consistent observation. At the third study, baseline forearm resistance was not increased as it was in the second study. Although the reasons for the difference in baseline vascular resistance during the two studies are not clear, we cannot conclude that indomethacin has a consistent effect in elevating baseline peripheral vascular resistance. Nevertheless, despite the difference in baseline resistance, indomethacin improved the responsiveness of vascular smooth muscle to vasoconstrictor stimuli to a similar extent in both studies.

Although the present study as well as previous studies point to a critical role of excess prostaglandin production in the pathogenesis of Bartter's syndrome, it is not clear whether excess prostaglandin production is primary or secondary to some other initiating factor. Still to be elucidated is the significance of the observation that activity of the kallikrein-kinin system is augmented in patients with Bartter's syndrome. In addition, although inhibition of prostaglandin production reverses most of the abnormalities of Bartter's syndrome, hypokalemia usually persists, although to a less severe degree. The persistence of hypokalemia despite normalization of plasma renin activity and aldosterone raises the possibility that these patients have a primary defect in tubular potassium transport leading to renal potassium wasting, and that this defect may be linked to the pathogenesis of Bartter's syndrome.

References
Effects of indomethacin on the vascular abnormalities of Bartter's syndrome.
C J Richards, A L Mark, D E Van Orden and G J Kaloyanides

Circulation. 1978;58:544-549
doi: 10.1161/01.CIR.58.3.544
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1978 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/58/3/544

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/