Effect of Prostaglandin Inhibition on the Hypertensive Action of Sodium-Retaining Steroids

KEITH MARTIN, M.D., ROBERT ZIPSER, M.D., AND RICHARD HORTON, M.D.

SUMMARY To compare the sodium-retaining action and the effect on blood pressure (BP) of certain steroids, nine normotensive subjects were given fludrocortisone 0.3 mg orally twice a day (b.i.d.), five received deoxycorticosterone acetate (DOCA) 10 mg IM b.i.d., and this was compared to the effect of fludrocortisone or DOCA plus prostaglandin inhibition (PI) or PI given alone. PI was accomplished with either indomethacin 50 mg or ibuprofen 400 mg every 6 hours. All patients received 250 mEq Na\(^{+}\) daily. Fludrocortisone alone caused a cumulative Na\(^{+}\) balance of 305 ± 46 (SE) mEq and a weight gain of 2.5 ± 0.1 kg with escape by Day 7. Mean blood pressure (MAP) increased 9 ± 2 mm Hg in both supine and standing positions by Day 8. When fludrocortisone was continued for 16 days, BP rose 14 ± 1 and 11 ± 1 mm Hg respectively. DOCA caused similar Na\(^{+}\) retention of 485 ± 125 mEq, weight gain of 2 kg, and escape by Day 7; however, no change in BP was observed. PI alone caused retention of 125 ± 49 mEq, weight gain of 1 kg, and escape by Day 4, but no change in BP. In contrast, fludrocortisone with PI added on Day 9 increased BP 21 ± 2 supine (p < 0.01) and 19 ± 2 mm Hg standing (p < 0.001) compared with fludrocortisone alone, but no greater change in Na\(^{+}\) or weight was observed. DOCA plus PI also resulted in no greater Na\(^{+}\) retention or change in weight than DOCA alone; however, BP increased from 86 ± 3 to 98 ± 2 mm Hg (p < 0.01). Similar suppression in PRA and aldosterone was noted in all of the study groups. We conclude that: 1) fludrocortisone has a pressor action in normal humans independent of its effect on sodium balance; 2) DOCA, a pure mineralocorticoid, does not alter BP when given for a period of weeks; 3) PI in normal humans causes some retention of sodium, but does not alter BP; 4) prostaglandin synthesis inhibitors potentiate the pressor action of fludrocortisone and raise BP in DOCA-treated humans, suggesting that vascular prostaglandins play a modulating role in BP control.

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KEY WORDS • blood pressure • fludrocortisone • deoxycorticosterone • prostaglandins • Sodium Retention
retention by itself is not the only mechanism that determines whether these agents are pressor. Neither DOCA nor PI alters the BP in normal subjects. However, fludrocortisone possesses pressor actions that progressively increase the BP after escape from sodium retention occurs. PI alone does not alter the BP in normal humans, but the BP increases when either steroid is added. We conclude from the above findings that prostaglandins play an important role in modulating the BP in man.

Methods

Subjects

Eleven normotensive male volunteers, aged 29 to 59 years, were hospitalized in the Clinical Research Center under informed consent protocol approved by our human research committee.

Subjects were maintained on a repetitive diet containing 250 mEq sodium and 100 mEq potassium and were on unrestricted water intake. Daily 24-hour urine was collected for sodium and potassium, with completeness of collection assessed by urinary creatinine measurement. On alternate days, 8 a.m. supine blood samples were collected for serum electrolytes, plasma renin activity (PRA), and plasma aldosterone. During various phases of the protocol, plasma for arginine vasopressin, norepinephrine, and cortisol were drawn at 8 a.m. Samples were collected through a 21-gauge intravenous butterfly catheter placed 1 hour earlier. Vasopressin was measured by specific radioimmunoassay (RIA) which has a sensitivity of 0.2 and normal hydrated values of 1.8 ± 1.2 μU/ml. The norepinephrine was measured by radioenzymatic assay where random supine values were 326 ± 111 with a sensitivity of 50 ng/liter. All assays have a precision of < 10%. Blood pressures were measured with a mercury sphygmomanometer in the supine (for at least 30 minutes) and standing (after 5 minutes) positions every 6 hours daily. The MAP was estimated from the average daily BP in both the supine and standing position by the formula: mean blood pressure = diastolic + (systolic – diastolic/3). Individuals were also weighed daily.

Study Protocol

Subjects were placed into three protocol groups with some appearing in all three groups during separate times. A 6-day control period preceded each protocol group study.

Group 1

Fourteen subjects were given Na+-retaining steroids. Six subjects received fludrocortisone (Florinef, Squibb) 0.3 mg b.i.d. orally for 8 days, and three received fludrocortisone for 16 days. Five subjects received daily intramuscular injections of deoxycorticosterone acetate (DOCA; Percorten, Ciba) 10 mg twice daily.

Group 2

Five subjects were given prostaglandin inhibitors (indomethacin 50 mg orally every 6 hours, three subjects, or ibuprofen 400 mg orally every 6 hours, two subjects) for 8 days.

Group 3

Eleven subjects were given a combination of sodium-retaining steroids (fludrocortisone or DOCA) and prostaglandin inhibitor (indomethacin or ibuprofen). Six subjects received fludrocortisone 0.3 mg orally twice daily for 16 days with the addition of a prostaglandin inhibitor (indomethacin 50 mg orally every 6 hours (four) or ibuprofen 400 mg orally every 6 hours (two) on Days 9 through 16. The protocol was reversed in one subject where indomethacin was given first and then fludrocortisone was added on Day 9. No differences were noted in the results. Five subjects were given both DOCA and oral indomethacin, or ibuprofen.

Statistical analysis used the unpaired t test, with results expressed as mean ± se.

Results

Effect of Sodium-Retaining Steroids on Sodium and Blood Pressure

Fludrocortisone Subgroup

The nine subjects all retained sodium for 7 days resulting in a cumulative retention over the control period of 305 ± 46 (SE) mEq of sodium (fig. 1). In

Figure 1. Change in balance during 250 mEq sodium diet in normal subjects receiving fludrocortisone (Florinef) alone (two groups) or in combination with an inhibitor of prostaglandin synthesis (PI).
close agreement with the calculated changes in sodium balance was the cumulative weight gain of 2.5 ± 1 kg. The study subjects escaped from this effect by Day 8, and their urine sodium rose to intake values. As expected, PRA fell from control values of 2.8 ± 0.8 to 0.5 ± 0.3 ng/ml/hr on Day 8 (supine, p < 0.001) where values remained during the rest of the study period. Plasma aldosterone (PAC) also fell from 4.6 ± 0.6 to 2.1 ± 0.2 ng/dl, p < 0.001. Fludrocortisone also reduced serum potassium from 4.3 ± 0.1 to 3.6 ± 0.1 mEq/liter by Day 8 and to 3.2 ± 0.1 by Day 16, p < 0.001. No change in a.m. plasma cortisol was noted during the study (control 9.6 ± 1.3 vs 10.2 ± 1.1 μg/dl).

Fludrocortisone progressively increased both supine and standing BP during the study period. The MAP increased by 9 ± 2 mm Hg by Day 8 and it continued to rise after escape from sodium to 14 ± 1 and 11 ± 1 mm Hg, p < 0.001, by the Day 16 (table 1 and fig. 2).

**Deoxycorticosterone Acetate (DOCA) Subgroup**

The five subjects in this group retained cumulative sodium of 485 ± 125 mEq which was not different from the effect of fludrocortisone. Similarly, this group gained 2.1 ± 1 kg in weight by Day 8. PRA fell from 1.2 ± 0.4 to 0.1 ± 0.1 ng/ml/hr, and aldosterone changed from 3.6 ± 0.2 to 2.2 ± 0.4 ng/dl, p < 0.05. Serum K⁺ was reduced from 4.6 ± 0.2 to 3.1 ± 0.1 mEq/liter, p < 0.01.

In striking contrast from the effect of fludrocortisone, was the absence of a change in BP throughout the escape and post-escape periods (fig. 3).

**Effect of a Prostaglandin Synthesis Inhibitor**

The five subjects retained 125 ± 49 mEq of sodium with apparent escape from further sodium retention by the fourth day. No difference in sodium balance was seen between those receiving ibuprofen alone and those receiving ibuprofen. The body weight of the study subjects stabilized after a mean increase of 1 kg (fig. 4). PRA was reduced from 2.3 ± 0.4 to 0.6 ± 0.2 ng/ml/hr, p < 0.001, while PAC and serum K⁺ did not change significantly, 5.0 ± 1.0 vs 3.9 ± 0.6 and 4.3 ± 0.1 vs 4.5 ± 0.1, respectively. No change in supine or standing BP was noted from baseline BP during the 8-day period of administration (table 1).

**Table 1. Summary of Laboratory Results**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (Fl)</th>
<th>Group 2 (PI)</th>
<th>Group 3 (PI + Fl)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Basal</td>
<td>Day 8</td>
<td>Day 16</td>
</tr>
<tr>
<td>Change in supine BP (mm Hg)</td>
<td>9 ± 2</td>
<td>14 ± 1</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>Change in standing BP (mm Hg)</td>
<td>9 ± 2</td>
<td>11 ± 1</td>
<td>0 ± 1</td>
</tr>
<tr>
<td>PRA (ng/ml/hr)</td>
<td>2.8 ± 0.8</td>
<td>0.5 ± 0.3</td>
<td>0.4 ± 0.3</td>
</tr>
<tr>
<td>Plasma aldosterone (ng/dl)</td>
<td>4.6 ± 0.6</td>
<td>2.1 ± 0.2</td>
<td>2.0 ± 0.3</td>
</tr>
<tr>
<td>Serum sodium (mEq/l)</td>
<td>141 ± 1</td>
<td>142 ± 0.7</td>
<td>143 ± 0.5</td>
</tr>
<tr>
<td>Serum potassium (mEq/l)</td>
<td>4.3 ± 0.1</td>
<td>3.6 ± 0.1</td>
<td>3.2 ± 0.1</td>
</tr>
<tr>
<td>Plasma norepinephrine (ng/l)</td>
<td>331 ± 51</td>
<td>196 ± 35</td>
<td>158 ± 35</td>
</tr>
<tr>
<td>Plasma arginine vasopressin (μU/ml)</td>
<td>0.5 ± 0.1</td>
<td>0.8 ± 0.3</td>
<td>0.4 ± 0.1</td>
</tr>
</tbody>
</table>
FIGURE 3. Change in mean supine blood pressure in normal subjects receiving deoxycorticosterone acetate (DOCA) 10 mg i.m. b.i.d. alone or in combination with prostaglandin inhibitors.

FIGURE 4. Change in sodium balance over an 8-day period in normal subjects receiving a 250 mEq sodium diet during administration of either indomethacin 500 mg q.i.d. or ibuprofen 400 mg q.i.d.

Effect of Sodium-Retaining Steroid and Prostaglandin Inhibitor

Fludrocortisone and PI Subgroup

The six subjects in this group retained the same amount of sodium and increased their weight in a nearly identical fashion during the initial 8 days prior to reaching the escape phase. The addition of prostaglandin synthetase inhibitor on the ninth day appeared to cause a small amount of sodium retention (15 ± 20 mEq), but no further change in urine sodium or weight occurred in the ensuing 7 days comparing Group 2 and 3 (fig. 1). Again the overall weight gain was 2.5 kg and no further weight gain was noted as in Group 1. No difference in PRA, PAC, and serum K+ concentration was observed between Group 1 and Group 3.

The combination of fludrocortisone and PI increased the BP significantly more than fludrocortisone alone. The MAP rose by 21 ± 2 supine and 19 ± 2 mm Hg standing, compared with 14 ± 1, \( p < 0.01 \) and 11 ± 1, \( p < 0.001 \) (fig. 5). However, as noted above, the drug combination did not cause a further change in sodium balance, weight, or alter the suppressed renin-aldosterone status.

DOCA and PI Subgroup

The five subjects retained 530 ± 106 mEq of Na+, and weight gain was 2.1 ± 0.5 kg, which was not different from the effect of DOCA alone over the same interval. PRA 0.1 ± 0.1 ng/ml/hr, PAC 1.1 ± 0.3 ng/dl, and serum K+ 3.3 ± 0.1 mEq/liter also did not significantly vary from values resulting from DOCA administration. However, DOCA and PI was associated with a rise in BP in striking contrast to DOCA alone (fig. 3). The MAP rose from 86 ± 3 to 98 ± 2 mm Hg, \( p < 0.01 \).

Norepinephrine and Arginine Vasopressin

As expected, there was a significant reduction in supine a.m. concentration of norepinephrine on Day 8 as compared with the control values (331 ± 51 vs 196 ± 35 ng/liter, \( p < 0.05 \)) (table 1). No further significant reduction occurred during the additional period of fludrocortisone administration. Similar reductions in norepinephrine occurred with PI plus fludrocortisone.

No changes in arginine vasopressin (AVP) concentrations were noted between the various phases of the study and levels were within limits of normal for the assay in supine hydrated subjects.

Discussion

A full understanding of the mechanism of "mineralocorticoid hypertension" has not been forthcoming despite the many published studies. Sodium retention and volume expansion would be the obvious explanation; however, the present study as well as
previous ones demonstrate that sodium retention does not parallel BP changes. Onoyama and coworkers produced hypertension in dogs with metapyrone, which blocks cortisol synthesis and leads to increased DOC secretion. Gradual sodium repletion was used to indicate that neither changes in sodium balance and volume, or cardiac output, were essential factors. DOCA-salt hypertensive pigs and dogs rapidly develop hypertension without concomitant changes in cardiac output. DOCA produces hypertension in various animal species but does not increase BP in normal humans, as shown in our study. Factors other than sodium retention must be operative in this phenomenon.

Fludrocortisone, however, produces hypertension when given to humans. This is despite the fact that the sodium retention from DOCA is quite similar to that of fludrocortisone. The escape from both steroids occurs in a nearly identical fashion, yet the BP continues to increase in the post-escape phase. Fludrocortisone is not a "pure" mineralocorticoid since this synthetic steroid possesses a 10- to 15-fold greater glucocorticoid activity than cortisol. Nevertheless, this would be only equivalent to 6-10 mg of cortisol; plasma cortisol in our patients was unchanged, and glucocorticoid administration does not produce hypertension. The conclusion is that fludrocortisone must have an alternate action in addition to its mineralocorticoid and glucocorticoid properties. An effect on cation turnover and membrane permeability in vessels has been postulated. A similar conclusion that fludrocortisone has unique pressor activity has been reached by Butkus et al. in studies of sheep. Clinically, it is well known that hypertension often appears in patients with adrenal insufficiency or in congenital adrenal hyperplasia given fludrocortisone replacement. The knowledge about its pressor activity when given to patients with autonomic insufficiency and to normal subjects in the present study should lead to caution in its use.

Additional factors in mineralocorticoid hypertension include alterations in circulating pressor agents, enhanced vascular responsiveness, and altered vasodepressor systems. Enhanced vascular sensitivity has been demonstrated in subjects given exogenous norepinephrine. However, the lack of changes in BP after administration of adrenergic blocking drugs reduces this possibility as well as the observation in dogs that plasma norepinephrine decreases during mineralocorticoid administration, although hypertension does not develop in the renal denervated rat. In the present study, norepinephrine declined or did not change from control levels despite development of hypertension. The increase in vascular responsiveness is probably secondary to the decrease in norepinephrine and angiotensin.

Vasopressin levels are elevated in the malignant phase of mineralocorticoid hypertension in the rat. Although vasopressin might be operative as a pressor substance in this situation, increased levels are probably secondary to fluid depletion of this model. Hyperresponsiveness to vasopressin has also been demonstrated in DOCA-salt hypertension in rats. In our human study, a.m. plasma AVP levels did not vary throughout the study protocol. There is, therefore, no evidence to explain the different effects of fludrocortisone and DOCA as due to detectable changes in these circulating pressor agents.
Hypokalemia (3.0 mEq/liter) has also been reported to produce enhanced vascular reactivity. Again, however, the potassium depletion and hypokalemia produced by DOCA was little different from that of fludrocortisone. The vascular changes produced by DOCA-salt in rats appear to be independent of potassium balance.

Vascular and renal prostaglandins have been implicated as modulating factors of blood pressure in a number of species. Prostaglandin (PG) IE₂ and I₄ are potent vasodilators. Angiotensin II (All) increases the release of PGE-like substances from perfused rabbit mesentary, and systemic All increases PGE levels in urine. Bradykinin may exert its vasodilatory action through local PG production, as indomethacin blocks this vascular action. Prostaglandin synthesis inhibition heightens the dose response to both All and norepinephrine.

We have previously reported that, during the escape from mineralocorticoids, urine PGE does not increase, suggesting that escape is not the result of increased renal PG production. This does not reduce the possibility of enhanced vascular production of PGE₂ or PGI₁ since extrarenal production is not reflected by changes in excretion.

Prostaglandin inhibition causes mild sodium retention and the site of action is the ascending loop of Henle or the distal tubule. We detected no change in either supine or standing BP over an 8-day period with escape from sodium retention by Day 4. This is in contrast to other species where increased BP occurs in both rabbit and dog. In certain strains of rats, PI reduces BP since PGE₂ is pressor in this group. Widely varying species differences, therefore, exist with respect to prostaglandins. Another example is that PGE is completely cleared by the canine lung, however, we have shown that a significant fraction of PGE escapes metabolism during passage through the human lung in situ.

Our study indicates that two different drugs affecting the cascade of prostaglandin synthesis in the arachidonic acid pathway can alter the BP during steroid administration. Fludrocortisone alone was associated with a progressive increase in BP; however, when PI was added there was a more severe BP increase. The effect of PI on BP was more dramatic in the DOCA group where DOCA alone did not alter BP. When DOCA and PI were combined, a highly significant increase in MAP of 12 mm occurred (p < 0.01). This observation strongly indicates that, although sodium retention is part of the underlying phenomenon, additional factors must be operative that prevent the development of hypertension during DOCA administration in man. The observation that BP changes occur from both indomethacin and ibuprofen suggests that the action of these drugs is via prostaglandin inhibition. In a previous study we showed that these doses reduced urine PGE by 80%. Use of DOCA and PI may be a good human model for considering multiple systems involved in certain types of human hypertension since the level of known vasopressors are depressed. Vascular prostaglandins may be operative as one of the systems regulating BP in man. In the presence of increased sodium-retaining steroids, inhibition of prostaglandin synthesis causes hypertension to develop de novo or accentuates it.

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