Pressor Responsiveness in Corticosteroid-Induced Hypertension in Humans

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In previous studies short-term cortisol increased cold pressor responses and the rise in forearm vascular resistance accompanying intra-arterial norepinephrine without an increase in overall resting sympathetic nervous activity. The present study examined whether these alterations in pressor response are glucocorticoid or mineralocorticoid effects, or both. Normal male subjects (n=12) received either fludrocortisone, 0.3 mg daily (n=6), or dexamethasone, 3 mg daily (n=6), for 7 days. Hemodynamic studies were performed before and on day 7 of treatment. Fludrocortisone increased body weight from 69.3±1.8 to 71.1±2 kg (p<0.001), cardiac output from 5.0 to 6.0 l/min (±0.1, p<0.01), mean arterial pressure from 82±1 to 91±1 mm Hg (p<0.001), cold pressor responsiveness from 13.0 to 39.0 mm Hg/ml per 100 ml per minute (R units)(±4.3, p<0.01), and forearm vascular response to intra-arterial norepinephrine (F=59.4, p<0.01) and angiotensin II (F=30.8, p<0.01) infusions. Total peripheral resistance fell from 22.0 to 20.1 mm Hg/l per minute (±0.3, p<0.05). Dexamethasone did not increase cardiac output, 5.1 to 5.2 l/min (±0.1), or body weight but did increase mean arterial pressure from 82±3 to 91±3 mm Hg (p<0.001), cold pressor responsiveness from 8.6 to 17.1 R units (±2.8, p<0.05), and forearm vascular response to intra-arterial norepinephrine (F=33.0, p<0.01) and angiotensin II (F=54.9, p<0.01). Total peripheral resistance increased from 21.9 to 24.3 mm Hg/l per minute (±0.4, p<0.01). Thus, short-term fludrocortisone and dexamethasone produced similar rises in pressure: fludrocortisone with an increase in cardiac output and dexamethasone with an increase in resistance. Although hemodynamic patterns differ, increased pressor responsiveness is a feature of both mineralocorticoid and glucocorticoid administration in humans. (Hypertension 1992;19:567-574)

KEY WORDS • blood pressure • cardiac output • glucocorticoids • human studies • mineralocorticoid hypertension • pressor response • vascular resistance • steroids

Corticosteroid excess is a common cause of hypertension in clinical practice. Both corticotropin and cortisol have been shown to increase blood pressure in humans in our own experimental studies. Pressor responsiveness to phenylephrine is augmented by cortisol administration, decreasing the threshold for and increasing the magnitude of the pressor response. Cortisol has also been shown to enhance the pressor effects of both cold pressor stimulation and intra-arterial norepinephrine infusion. Placebo had no effect. At the dosages used, cortisol had both mineralocorticoid and glucocorticoid effects. Mineralocorticoids (deoxycorticosterone and fludrocortisone) and glucocorticoids are known to increase pressor responses to norepinephrine in humans, but human studies with glucocorticoids are conflicting. In the dog, administration of deoxycorticosterone or dexamethasone significantly enhanced the pressor effect of norepinephrine with dexamethasone, but the increase was small in magnitude. The present study investigated pressor responsiveness using a "pure" mineralocorticoid (fludrocortisone) and a "pure" glucocorticoid (dexamethasone) to determine whether the enhanced pressor response is a feature of glucocorticoid activity of steroids, as it is for mineralocorticoid activity.

Methods

Twelve healthy, normotensive male subjects, age range 18–29 years, took part in one of two studies (dexamethasone or fludrocortisone) after having given their written, informed consent. The study was approved by the Medical Research Ethics Committees of the Royal Melbourne Hospital and the Alfred Hospital. Care was taken to exclude subjects with a history of hypertension, peptic ulcer disease, asthma, psoriasis, atopy, hepatitis, Raynaud's syndrome, acquired immune deficiency syndrome, and chronic drug ingestion.

Volunteers were asked to eat, for the duration of the study, a constant diet that was calculated to contain approximately 150 mmol sodium per day. Diet sheets were provided for this purpose.

In the 2 months before the commencement of the study subjects underwent a full blood examination and estimation of serum urea and electrolytes, including creatinine. A series of three cardiac output measure-
ments were also taken using the indirect Fick technique and three sets of resting forearm blood flow determinations using venous occlusion plethysmography (SPG-16 Medasonics, Mountain View, Calif.) to familiarize them with the procedures.

After a 7-day control (C) period (C7–1), subjects (blinded) received 7 days of oral steroid (experiment E) treatment (E1–7). After steroid treatment with either dexamethasone (Oradexon, Organon 1.0 mg orally three times daily) or fludrocortisone (Florinef, Squibb 0.1 mg orally three times daily), there were three further posttreatment (P) observation days (P1–3).

Subjects reported at 8 AM on each study day (C3, C1, E2, E4, E7, P2). Supine and standing blood pressure was measured using a London School of Hygiene and Tropical Medicine sphygmomanometer (London, UK), an observer-blind instrument, after the subject had been resting for 20 minutes. Each blood pressure determination was the mean of three consecutive readings. Pulse rate and body weight were recorded. A forearm vein was cannulated, and blood was drawn for measurement of plasma electrolytes, creatinine, urea, glucose, hematocrit, hemoglobin, differential white blood cell count, plasma active and inactive renin concentration, renin substrate, plasma cortisol, and aldosterone concentrations. Subjects collected their own urine for 24-hour analysis of urine electrolytes, and creatinine clearance was calculated.

The concentration of active renin in plasma was determined by incubation with ovine renin substrate under zero order kinetics, using a modification of the method of Thatcher et al,15 and by immunoradiometric assay kit (Marnes La Coquette, France).16 Renin substrate was measured by radioimmunounassay in the presence of excess renin. Plasma aldosterone and cortisol were measured by radioimmunounassay (Ciskit, Sorin Biomedica, Italy, and Amerlex, Amersham, UK, respectively).

On two separate occasions, 7 days apart (C1 and E7), cardiac output (blinded) was measured noninvasively using the indirect Fick technique.14 Ambulatory blood pressure recordings (Spacelabs, Hillsboro, Ore.) were obtained over the 24-hour period before each hemodynamic study. Recordings were made at 20-minute intervals during the day and at 30-minute intervals during the night. Mean systolic and diastolic pressures were calculated as the heart rate. The brachial artery was cannulated (3.0F, 20-gauge, 5-cm catheter, William Cook Australia Pty Limited, Melbourne, Australia), and arterial pressure was monitored via an AE 840 physiological pressure transducer. Resting forearm blood flow measurements were taken on the side of the arterial catheter using strain-gauge plethysmography7 (SPG-16, Medasonics). Cold pressor stimulation was produced by application of ice to the base of the neck of the ipsilateral side for 60 seconds, and forearm blood flow was measured again.

After the testing of cold pressor stimulation, norepinephrine (Levophed, Winthrop Laboratories) was infused into the brachial artery in three successive doses of 6.25, 12.5, and 25.0 ng/ml each for 150 seconds. Forearm blood flow was measured at each dose. After a 30-minute break, allowing for blood flow to return to baseline, angiotensin II (Hypertensin, Ciba) was infused at rates of 4 ml/min at concentrations of 2.0, 4.0, and 8.0 ng/ml each for 150 seconds.

Forearm vascular resistance was calculated from the equation

\[
FVR \text{ (arbitrary units R)} = \frac{\text{mean arterial pressure (mm Hg)}}{\text{forearm blood flow (ml/100 ml/min)}}
\]

where FVR is forearm vascular resistance.

**Results**

**Fludrocortisone Treatment**

**Hemodynamic effects.** The resting supine blood pressures are shown in Figure 1. Systolic and diastolic blood pressures were significantly increased with fludrocortisone treatment. Pressure rose in all six volunteers, and these elevations in arterial blood pressure were also evident in the standing data. There was a consistent decrease in the pulse rate: the supine pulse rate dropped from 56±4 beats per minute on day C3 to 50±4 beats per minute on day E7 (p<0.01), and the standing pulse rate dropped from 70±5 beats per minute on day C3 to 63±3 beats per minute on day E7 (p<0.05). The changes in resting blood pressures were consistent with those of the 24-hour ambulatory blood pressure recordings. Mean ambulatory systolic pressure rose from 121 mm Hg control to 127 mm Hg on fludrocortisone (SED ±1.0, p<0.01), diastolic from 71 to 76 mm Hg (SED ±1.0, p<0.01), and mean arterial pressure from 84 to 90 mm Hg (SED ±1.0, p<0.01). Mean ambulatory heart rate was unchanged.

Resting cardiac output increased from 5.0 l/min on day C1 to 6.0 l/min on day E7 of the experimental period (SED ±0.1, p<0.01). The calculated total peripheral resistance fell from 22.0 mm Hg/l per minute on day C1 to 20.1 mm Hg/l per minute on day E7 (SED ±1.0, p<0.05) (Figure 2).

**Metabolic effects.** There was no significant change in urine volume or urinary sodium retention during the administration of the fludrocortisone, but there was a subsequent diuresis from 0.92±0.21 l/day on day C3 to 1.36±0.16 l/day on day P2, p<0.05. There was also a significant natriuresis on day P2 with the urinary sodium increasing from 112±18 mmol/day on day C3 to 221±50 mmol/day on day P2 (p<0.01) (Figure 3). There was no significant change in urinary potassium excretion during or after the drug administration.

Plasma sodium concentration [Na] increased from 137±3 mmol/l on day C1 to 141±4 mmol/l on day E7 (p<0.05), and plasma potassium concentration [K] fell (Figure 3). There was no significant change in fasting
plasma glucose concentration. Plasma creatinine concentration was decreased significantly from a pretreatment value of 0.1±0.00 mmol/l on day C3 to 0.09±0.01 mmol/l on days E4 and E6 (p<0.05). Hematocrit fell and body weight was significantly increased (Figure 3). Hemoglobin fell from 144±5 g/l on day C1 to 137±6 g/l on day E7 (p<0.001), and white blood cell count remained unchanged.

**Hormonal changes.** There was a highly significant decrease in plasma aldosterone throughout the whole of the treatment period (days E1-E7), which persisted to day P2 (day C1, 217±77 pmol/l; day E7, 1±0.1 pmol/l, p<0.001). Plasma cortisol also showed a transient fall of a smaller magnitude (day C3, 435±63 nmol/l; day E7, 306±35 nmol/l, p<0.001). Active plasma renin concentration, assayed by both enzyme kinetic (day C1, 28±14 μIU/ml; day E7, 12±3 μIU/ml, p<0.005) and immunoradiometric techniques (day C1, 12±3 μIU/ml; day E7, 4±2 μIU/ml, p<0.05), fell with fludrocortisone administration and was still low on day P2. The total plasma renin concentration was also decreased in a similar fashion. The renin substrate concentration and inactive renin concentrations were unaltered with fludrocortisone administration.

**Forearm vascular responsiveness.** The average rise in mean arterial pressure with cold pressor stimulation was 7 mm Hg before fludrocortisone treatment (day C1) to 20 mm Hg after fludrocortisone treatment (day E7) (SED ±3, p<0.01). The mean increase in the heart rate was 13 beats per minute before and 21 beats per minute after fludrocortisone treatment (SED ±3, p<0.05). The change in forearm vascular resistance to the cold pressor stimulus rose significantly from 13 mm Hg/ml per 100 ml per minute (R units) before to 39 R units after fludrocortisone treatment (SED ±3, p<0.01) (Figure 4).

Norepinephrine and angiotensin II infusion into the brachial artery had no significant effect on the blood pressure or heart rate at the infusion rates used. With both vasoconstrictor agonists there were changes in forearm vascular resistance; fludrocortisone produced a fall in threshold and a shift to the left in the dose-response relation. The average rise in forearm vascular resistance was significantly greater after fludrocortisone treatment with norepinephrine infusion (15.1 R units before fludrocortisone, 41.8 R units after fludrocortisone administration, SED ±3, p<0.05) than with angiotensin II infusion (12.3 R units before fludrocortisone, 26.1 R units after fludrocortisone administration, SED ±3, p<0.05). Maximal responsiveness was not reached at the highest infusion rates, so a comparison of maximum response of forearm vascular resistance was not possible (Figure 4).

**Dexamethasone Treatment**

**Hemodynamic effects.** Dexamethasone treatment produced an increase in supine systolic blood pressure and
mean arterial pressure but not in diastolic blood pressure (Figure 1). Pressure rose in all six subjects. The standing systolic blood pressure was increased as well as the mean arterial blood pressure and, in contrast to the supine observations, there was a significant increase in standing diastolic blood pressure from 83±2 mm Hg (day Cl) to 90±3 mm Hg (day E7). Pulse rate was not significantly altered with dexamethasone treatment. The changes in resting supine blood pressure were consistent with the changes observed with the 24-hour ambulatory blood pressure recordings. Mean ambulatory systolic pressure rose from 121 to 125 mm Hg (SED 1.2, p<0.05) and mean arterial pressure from 84 to 90 mm Hg (SED ±0.7, p<0.01), whereas mean ambulatory diastolic pressure and heart rate were unchanged.

There was an increase in the total calculated peripheral resistance from a pretreatment value of 21.9 mm Hg/l per minute on day Cl to a value of 24.3 mm Hg/l per minute after treatment with dexamethasone (day E7) (SED ±0.4, p<0.01). No significant change in cardiac output from a pretreatment value of 5.1 l/min was observed with dexamethasone treatment (Figure 2).

**Metabolic effects.** There was a significant diuresis (day Cl, 1.10±0.08 l/day; day E7, 1.5±0.16 l/day, p<0.05) and natriuresis (day Cl, 158±16 mmol/day; day E7, 234±15 mmol/day, p<0.05) observed on day E7 with dexamethasone treatment. There was no significant change in urinary potassium excretion apart from day E2 (day Cl, 83±14 mmol/day; day E2, 117±14 mmol/day, p<0.01).

Plasma [Na] remained unchanged with dexamethasone treatment, but there was a transient decrease in plasma [K] observed on day E4 (Figure 3). There was a significant increase in creatinine clearance observed on day E7 (day Cl, 2.0±0.1 ml/sec; day E7, 2.6±0.2 ml/sec, p<0.05). Plasma urea, hemoglobin, hematocrit, and body weight remained unchanged (Figure 3). Plasma glucose rose from 5.0±0.1 mmol/l on day Cl to 5.8±0.3 mmol/l on day E7, p<0.01. The white blood cell count increased from 5.1±0.4 (×10⁹/l) on day Cl to 8.5±0.9 (×10⁹/l) on day E7 (p<0.05), and differential white blood cell count revealed a significant neutrophilia and a significant decrease in eosinophil count.

**Hormonal changes.** Plasma cortisol concentration fell during dexamethasone administration from 419±77 nmol/l on day Cl to 3±0.3 nmol/l on day E7 (p<0.001), with no change in plasma aldosterone concentration. Total plasma renin concentration assayed by enzyme kinetic technique was increased by dexamethasone administration (day Cl, 187±49 μU/ml; day E7, 292±64 μU/ml, p<0.01) and remained so 48 hours after the cessation of treatment. Active plasma renin concentration remained unchanged. The inactive renin concentration increased with treatment as did the renin substrate concentration (day Cl, 894±121 pmol angiotensin I (Ang I)/ml; day E7, 1,714±224 pmol Ang I/ml, p<0.02).

**Forearm vascular responsiveness.** The average rise in mean arterial pressure with cold pressor stimulation was 4 mm Hg before dexamethasone treatment (day Cl) to 8.0 mm Hg after dexamethasone treatment (day E7) (SED ±1, p<0.01). The mean increase in heart rate was 12 beats per minute before and 23 beats per minute after dexamethasone treatment (SED ±3, p<0.01). The change in forearm vascular resistance to cold pressor stimulus rose from 8.6 R units before to 17.1 R units after dexamethasone treatment (SED ±2.8, p<0.05) (Figure 4).

Norepinephrine and angiotensin II infusions into the brachial artery had no significant effect on the blood pressure and heart rate at the infusion rates used. With each agonist there were changes in forearm vascular resistance, with dexamethasone treatment producing a fall in threshold and a shift to the left of the dose-response curve. The average rise in forearm vascular resistance was significantly greater for norepinephrine infusion (15.1 R units before dexamethasone, 34.2 R units after dexamethasone administration, SED ±7, p<0.05) and angiotensin II infusion (12.1 R units before dexamethasone, 23.1 R units after dexamethasone administration, SED ±4, p<0.05). Maximal responsiveness was not reached at the highest infusion rates, so a comparison of maximum response of forearm vascular resistance was not possible (Figure 4).

**Discussion**

The rise in blood pressure with 7 days of fludrocortisone administration was associated with an increase in cardiac output and a decrease in total peripheral resistance. Dexamethasone administration over 7 days produced similar rises in arterial pressure but a different hemodynamic pattern with no change in cardiac output and an increase in calculated total peripheral resistance.
Both treatments increased vascular responsiveness to exogenous norepinephrine and angiotensin II administration and to cold pressor stimulation. Placebo has been shown previously in a similar protocol not to produce any significant hemodynamic effects. Fludrocortisone administration was associated with an elevation in systolic and diastolic blood pressure. The rise in standing and supine heart rates raises the possibility that the rise in arterial pressure may have been stress induced. However, the 24-hour ambulatory blood pressure.
pressure determinations, which were in agreement with the resting clinic blood pressure determinations, make this unlikely.

Fludrocortisone produced classic mineralocorticoid effects consistent with previous studies. There were no typical "glucocorticoid" effects such as changes in fasting plasma glucose concentration, renin substrate concentration, or renal function observed, but there was a small fall in plasma cortisol concentration.

The increase in cardiac output observed after the 7-day treatment period was probably due to a positive salt and water balance as manifested by an increased body weight. The initial fall in calculated total peripheral resistance is presumably a baroreceptor-mediated compensatory mechanism. Later, there is elevated total peripheral resistance and a near normal cardiac output. We have previously reviewed possible mechanisms for fludrocortisone-induced hypertension.
Glucocorticoid administration is a well-recognized cause of arterial hypertension in humans. In contrast to mineralocorticoid hypertension, glucocorticoid hypertension in humans and animals can be produced in the absence of a high salt intake. In our present study dexamethasone administration was associated with systolic hypertension with an increase in calculated total peripheral resistance. Previous studies with dexamethasone have not shown any increase in plasma volume, which is in contrast to the effect of cortisol in humans.

There is no clear correlation between the degree of hypervolemia and the increase in cardiac output. In the present study there was no change in cardiac output, no initial sodium retention, and no hemodilution with dexamethasone, which produced classic glucocorticoid but no in vivo mineralocorticoid effects.

The major finding of the present study was the unequivocal increase in pressor responsiveness with the pure glucocorticoid dexamethasone.

In humans the digital vascular reactivity to norepinephrine in patients with Cushing's syndrome of whatever cause is increased, despite the absence in some patients of elevated arterial pressure. Cardiac output is not elevated in all patients, suggesting peripheral mechanisms may play a role in the etiology of the hypertension. Reis and Leperi and Christiani observed potentiation of the response of conjunctival blood vessels to norepinephrine after pretreatment with various topically applied natural and synthetic adrenocortical steroids. Digital reactivity was increased in normotensive subjects pretreated with oral prednisolone. Cortisol administration increased the pressor responsiveness to phenylephrine and lowered the threshold dose for angiotensin II pressor response. Cortisol administration increased cold pressor responsiveness and augmented the rise in forearm vascular resistance seen with intra-arterial norepinephrine infusion. Short-term adrenocorticotropic treatment produced a small increase in sensitivity to phenylephrine but not angiotensin II. Others have not seen changes in pressor response with acute administration of glucocorticoid.

Glucocorticoids are known to inhibit phospholipase A. The consequent decrease in vascular vasodilatory prostanoid formation may increase the pressor responsiveness to endogenous agonists, but in previous studies in humans, indomethacin treatment did not modify hydrocortisone-induced changes in pressor responsiveness. Glucocorticoids may increase the responsiveness to epinephrine and norepinephrine by inhibition of catechol-O-methyl transferase. The role of changes in activity of the sodium-potassium pump in patients with glucocorticoid excess is still unclear. Receptor sites for steroids, including glucocorticoids, have been demonstrated in vascular tissues. The antglucocorticoid RU486 prevented the potentiation of the pressor response to norepinephrine, angiotensin II, and vasopressin by exogenously administered steroid and unmasked the enhancing effect of endogenous steroids on pressor responsiveness to endogenous vasoconstrictors.

Thus, glucocorticoids may exert a direct effect on the vascular smooth muscle to potentiate pressor responsiveness.

Interpretation of whole body vascular reactivity studies in animals and humans is complicated in that pressor responsiveness reflects the total algebraic sum of the pressor and depressor reflexes as well as any related changes in blood flow. Factors in addition to alterations in fundamental reactivity may operate, such as variation in organ responsiveness in selective vascular beds. Our present study was designed to examine pressor responses in the forearm vascular bed. Local vascular responsiveness, uncomplicated by systemic reflexes, was determined, using doses of norepinephrine and angiotensin II that did not alter blood pressure or heart rate.

Short-term treatment with both fludrocortisone and dexamethasone produced enhanced vascular responsiveness to both the reflexly induced constrictor effects of the cold pressor test and the constrictor effects of locally administered norepinephrine and angiotensin II. The decreased threshold observed argues for a functional change leading to the enhanced pressor responsiveness rather than a structural change. The results are consistent with previous studies reporting enhanced pressor responsiveness in chronic steroid treatment.

The mechanisms of the observed enhanced pressor responsiveness were not addressed.

If the increase in vascular reactivity seen with these steroids was the major factor in the rise in blood pressure, peripheral resistance should increase. This was not the case for fludrocortisone, suggesting that for this steroid, at least in the short term, changes in pressor responsiveness are not the primary cause of the hypertension.

In summary, over the 7-day study period both treatments produced similar rises in arterial pressure. Dexamethasone, acting as a pure glucocorticoid, achieved this with an increased total peripheral resistance while fludrocortisone, acting as a pure mineralocorticoid, raised pressure in association with an increased cardiac output. Both treatments increased pressor responsiveness to cold, norepinephrine, and angiotensin II.

In conclusion, an augmented pressor responsiveness secondary to steroid administration appears to be due to a functional change in smooth muscle activity produced by steroids with mineralocorticoid, glucocorticoid, or both, activities. The data suggest that the increased pressor responsiveness is not the major cause of the rise in blood pressure.

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