Control of Arterial Pressure and Renal Function During Glucocorticoid Excess in Dogs

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SUMMARY This study was designed to investigate the long-term effects of glucocorticoids on the control of mean arterial pressure (MAP) and renal function. Infusion of 10 mg/day of methylprednisolone (MP), a glucocorticoid with minimal mineralocorticoid activity, for 10 days in six intact conscious dogs maintained on a sodium intake of 78 mEq/day resulted in a decrease in MAP from 98 ± 1 to 89 ± 2 mm Hg, a decrease in sodium lothalamate space to 89 ± 2% of control, and a marked increase in glomerular filtration rate (GFR), effective renal plasma flow (ERPF), and urinary sodium excretion. Chronic infusion of MP at doses of 2–800 mg/day in four dogs maintained on low (5 mEq/day) or high sodium intakes (160–223 mEq/day) also caused increases in GFR and ERPF, as well as natriuresis and decreased sodium lothalamate space, while causing either no change or a slight reduction in MAP. To determine whether glucocorticoids potentiate the chronic effects of angiotensin II (All) on MAP and renal function, MP was infused in dogs undergoing All infusion (5 ng/kg/min). During All hypertension, chronic infusion of 5 or 10 mg/day of MP also resulted in a marked renal vasodilation, natriuresis, and reductions in sodium lothalamate space, while causing small reductions in MAP. Thus, we found no evidence that chronic glucocorticoid excess causes hypertension in dogs, or that glucocorticoids potentiate the blood pressure or renal effects of All. Instead, glucocorticoids tended to reduce MAP, probably because of chronic renal vasodilation, increased excretion of sodium, and volume depletion. (Hypertension 2: 139–148, 1980)

KEY WORDS • glomerular filtration rate • renal blood flow • sodium excretion • body fluid volumes • angiotensin II • methylprednisolone • animal studies, dog

ALTHOUGH adrenal steroids with mineralocorticoid activity are recognized to play an important role in circulatory homeostasis, the importance of the glucocorticoid effects of these steroids in blood pressure regulation, and the mechanisms of glucocorticoid activity on the circulation, are still poorly understood. One observation that suggests glucocorticoids may play a role in blood pressure regulation is the finding that excessive glucocorticoid activity in Cushing's syndrome is usually associated with hypertension.1–4 Patients with Cushing's syndrome, however, usually have inappropriately high secretion of adrenocorticotrophic hormone (ACTH), as well as elevated secretion of adrenal steroids other than cortisone that may play a role in causing hypertension.2–4 Furthermore, many of these patients have hypokalemia, even though their plasma aldosterone concentration may not be elevated, suggesting that excess secretion of mineralocorticoids other than aldosterone may occur in this syndrome.3–4 Thus, there are several abnormalities in Cushing's syndrome, besides excess glucocorticoid activity, that could theoretically produce hypertension. The relative importance of these abnormalities, however, and the role of excessive glucocorticoid activity in causing hypertension is still unclear.

There have been very few studies in which administration of excess glucocorticoids has been demonstrated to cause hypertension. Studies in which hypertension has been produced by glucocorticoid ad-
ministration have usually been conducted in rats, and the doses of steroids used have been as high as 40 mg/kg per day, which is 400-800 times greater than the normal secretion rate of carbohydrate-active steroids. The mechanisms whereby massive doses of glucocorticoids cause hypertension in the rat are not entirely clear, but some investigators have suggested that the elevated blood pressure is caused either by redistribution of body fluid volumes or by increased activity of the renin-angiotensin system due to increased renin substrate production. On the basis of short-term studies, glucocorticoids have also been suggested to potentiate the vasoconstrictor action of angiotensin II (AII). Theoretically, this indirect effect of glucocorticoids could play a role in causing hypertension. In addition, the large amounts of glucocorticoids that are often used would be expected to exert significant mineralocorticoid effects and thereby cause elevations in blood pressure. The relevance, however, of studies where massive amounts of glucocorticoids are infused and of short-term studies on interactions between glucocorticoids and vasoconstrictor agents to the etiology of hypertension associated with Cushing's syndrome and normal blood pressure regulation is not clear.

The present study was designed, in part, to determine whether chronic administration of a wide range of doses of a glucocorticoid with essentially no mineralocorticoid activity would cause hypertension in the dog. In addition, this study was also designed to investigate the mechanisms whereby glucocorticoids influence regulation of arterial blood pressure. Several theoretical analyses as well as experimental studies suggest that the kidneys play a central role in blood pressure control. Theoretically, glucocorticoids could regulate blood pressure by altering the capability of the kidneys to excrete salt and water. A reduction in renal excretory capability would be predicted to cause sustained Increases in blood pressure, whereas increased capability to excrete salt and water should cause a reduction in arterial blood pressure. Several previous studies suggest that glucocorticoids may increase renal excretory capability. Thus, in the present study, close attention was paid to the chronic effects of glucocorticoids on the control of renal hemodynamics and electrolyte excretion.

Another important goal of the present study was to determine whether glucocorticoids alter the chronic effects of AII on the control of arterial pressure and renal function, since previous short-term studies have suggested that glucocorticoids may potentiate the vasoconstrictor action of AII. To our knowledge, there have been no previous reports on interactions between glucocorticoids and AII in chronic regulation of blood pressure and renal function.

**Methods**

Experiments were conducted in 14 intact, conscious dogs. Polyvinyl catheters were implanted in the femoral arteries and veins under aseptic conditions, and the dogs were permitted to recover from surgery for at least 3 weeks before any experiments were conducted. Antibiotics were administered daily, and rectal temperatures were measured to insure that the dogs were afebrile at the time of the studies. During the recovery and experimental periods, all dogs were fed a low sodium diet (H/D, Riviana Foods, Inc.) that provided approximately 5 mEq sodium and 45 mEq potassium per day. Free access to tap water was permitted at all times.

Approximately 2–3 weeks after surgery, the dogs were housed in individual metabolic cages in a quiet, air-conditioned room with a 12-hour light cycle and fitted with harnesses that contained Statham pressure transducers mounted at heart level. Measurements of electrolyte and water balance, 24-hour recording of mean arterial blood pressure (MAP), and continuous intravenous infusions were performed as previously described. Briefly, one of the femoral artery catheters was filled with heparinized saline (1000 U/ml) and connected to the pressure transducer for continuous recording of mean arterial blood pressure, 24 hours a day on a Grass polygraph (Model 7D); the mean pressure for each hour of recording was determined and used to calculate the daily average arterial pressure for each dog. One of the femoral venous catheters was connected to a roller pump (Sage Instruments, Model 375A) that was used to infuse various solutions continuously 24 hours a day. All solutions were pumped through a disposable millipore filter (Cathivex, Millipore Corp.) to prevent contaminants and bacteria from passing into the venous infusion catheters. The infusion tubing and wires from the transducers were brought out of the top of the cage through a flexible tubing that was attached to the harness; this apparatus permitted the dogs to move freely in the cage but not to turn completely around.

Before the control period, the dogs were trained to lie quietly while blood samples were drawn from a chronic femoral artery catheter and studies of renal function were performed. In all experiments, collection of blood samples and measurements of renal function were begun at approximately 8 a.m. each day, 16–18 hours after the last feeding.

**Experimental Protocols**

Six dogs were maintained on a total sodium intake of approximately 78 mEq/day during the control period and during infusion of excess glucocorticoid. Approximately 5 mEq of sodium was provided in the food, while the remaining 73 mEq was infused intravenously in the form of sterile isotonic saline. After the control period, which lasted at least 5 days, the glucocorticoid methylprednisolone sodium succinate (Solu-Medrol, Upjohn Company) was infused at 10 mg/day continuously for 10 days. This dose of synthetic glucocorticoid has essentially no mineralocorticoid effect and is approximately 10 times the glucocorticoid dose necessary to maintain adrenalectomized dogs in good health. Blood pressure was measured continuously, while urinary excretion of...
sodium, potassium, and water were determined daily. Glomerular filtration rate (GFR), effective renal plasma flow (ERPF), and plasma concentrations of sodium, potassium, and protein were determined at least two times during the control period and at least three times during the 10 days of methylprednisolone (MP) infusion. After infusion of MP was terminated, postcontrol data were obtained for an additional 10 days.

In a second group of four dogs, MP was infused during angiotensin II (AII) hypertension to determine whether excess glucocorticoids potentiate the chronic blood pressure and renal effects of AII. In this series of experiments, sodium intake was maintained at approximately 240 mEq/day throughout the control and experimental periods by intravenous infusion of sterile isotonic saline. After a 5-day control period, [Asp¹, Val¹⁴] AII (Ciba Pharmaceutical Co.) was infused intravenously at a rate of 5 ng/kg/min for 6 days. After 6 days of AII infusion, MP was infused intravenously at a rate of 5 mg/day for 8 days, and then at a rate of 10 mg/day for 6 additional days while the infusion of AII was continued and sodium intake was maintained at approximately 240 mEq/day. Arterial pressure was measured continuously; urinary excretion of sodium, potassium, and water were determined daily; and GFR, ERPF, and plasma concentrations of protein, sodium, and potassium were determined on the last 2 days of each experimental period.

The effect of varying doses of MP on blood pressure and renal function, as well as the influence of sodium intake on the effects of MP, were examined in four additional dogs. In three dogs, the total intake of sodium was maintained at approximately 74-80 mEq/day during 10 days of MP infusion. Thus, after 10 days of MP infusion, there was a net loss of approximately 173 mEq of sodium. Urine volume also increased significantly, but the increase in' urinary potassium excretion averaged 850 ml/day during MP infusion. Water drinking increased significantly, but the increase in water pressure during the 10-day post-control period.

In one additional dog, sodium intake was maintained at a very low level (5 mEq/day) throughout the control and experimental periods and the blood pressure and renal effects of extremely large doses of MP were investigated. After the control period, MP was infused at a rate of 400 mg/day for 6 days, and then at a rate of 800 mg/day for 8 days while changes in blood pressure, renal function, and plasma electrolyte concentrations were determined.

Analytical Methods

The method of Hall et al.¹⁸ was used to determine GFR and ERPF from the total clearances of ¹²⁵I iothalamate (Glofil, Abbott Laboratories) and ¹³¹I iodobipirurate (Hippuran, Mallinckrodt Nuclear) respectively. Filtration fraction was calculated as GFR/ERPF. The volume of distribution of ¹³¹I sodium iothalamate (used as an index of changes of extracellular fluid volume) was determined by the method of Sapirstein et al.¹⁴ Plasma and urine sodium and potassium concentrations were determined by flame photometry (Instrumentation Laboratory, IL 343), and plasma protein concentration was determined by refractometry (American Optical Company). Plasma renin activity was measured by radioimmunoassay of angiotensin I, using a modification of the method of Haber et al.¹⁵ Plasma aldosterone concentrations were also measured by radioimmunoassay procedures (¹²⁵I aldosterone radioimmunoassay, Diagnostic Products).

Statistical Analysis

Control data were compared with experimental data using Dunnet's t test for multiple comparisons.¹⁸ Statistical significance was considered to be p < 0.05. All data and text and figures are expressed as mean values ± standard errors unless otherwise indicated.

Results

Chronic Effects of Methylprednisolone on Blood Pressure and Electrolyte and Water Balance

The changes in MAP, urinary excretion of sodium, water, and potassium, and water drinking that occurred during chronic i.v. infusion of 10 mg/day of MP are shown in figure 1. Mean arterial blood pressure decreased slightly, but significantly, during the first day of MP infusion and remained below the control level throughout the 10 days of infusion. During the control period, MAP averaged 98 ± 1 mm Hg (average of 5 days) and during 10 days of MP infusion, blood pressure averaged 89 ± 2 mm Hg. When MP infusion was stopped, MAP returned toward control levels but there was considerable oscillation of blood pressure during the 10-day post-control period.

Urinary sodium excretion increased significantly on the first and second days of MP infusion. During the control period, urinary sodium excretion averaged 63.1 ± 8.9 mEq/day and increased to 102.8 ± 10.9 mEq/day on the first day of MP infusion. Although urinary sodium excretion returned toward control levels after the third day of MP infusion, sodium excretion averaged 80.4 ± 8.5 mEq/day for the entire 10 days of MP infusion. Thus, after 10 days of MP infusion, there was a net loss of approximately 173 mEq of sodium. Urine volume also increased significantly, averaging 909 ± 120 ml/day during the control period and 1186 ± 147 ml/day during MP infusion. Water drinking increased significantly, but the increase in urine volume exceeded the increase in water drinking and there was a net loss of approximately 850 ml of water during 10 days of MP infusion. Infusion of MP for 10 days also caused a net loss of approximately 169 mEq of potassium; during the control period, urinary potassium excretion averaged 60.3 ± 11.1 mEq/day, while during MP infusion for 10 days, urinary potassium excretion averaged 77.2 ± 7.4 mEq/day.
During Days 1–4 after MP infusion was terminated, approximately 109 mEq of sodium were retained; then urinary sodium excretion increased above control levels, and finally declined back toward control. There was also a marked decline in urine volume on Days 1–4 after MP infusion was stopped, followed by an increase toward control levels. Water drinking decreased toward control levels when MP infusion was terminated. After MP infusion was stopped, urinary potassium excretion decreased to 69.5 ± 7.7 (average of 10 days postcontrol), a level that was not significantly different from the control level.

**Chronic Effects of Methylprednisolone on Renal Hemodynamics and Sodium Iothalamate Space**

The changes in GFR, ERPF, filtration fraction (FF), and sodium iothalamate space that occurred during chronic infusion of MP are shown in figure 2. The net losses of sodium and water that occurred during MP infusion were reflected in significant reductions in sodium iothalamate space from 8459 ± 705 ml during the control period to 7841 ± 579, 7654 ± 620, and 7458 ± 401 ml on Days 2, 5, and 9 of MP infusion. Following cessations of MP infusion, sodium iothalamate space increased to values not significantly different from control.

On Days 2, 5, and 9, GFR increased from a control value of 87.6 ± 7.4 ml/min to 119 ± 5%, 119 ± 5%, and 112 ± 5% respectively of the control level during MP infusion. During chronic infusion of MP, ERPF increased to approximately 30%–40% above control while FF decreased 7%–16% below control. When in-

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**Figure 1.** Changes in mean arterial pressure (MAP), urinary sodium excretion ($U_{Na}V$), urinary volume excretion ($V$), urinary potassium excretion ($U_{K}V$), and water drinking during chronic infusion of methylprednisolone in intact dogs maintained on an average sodium intake of 78 mEq/day. Values are means ± SE.

**Figure 2.** Changes in glomerular filtration rate (GFR), effective renal plasma flow (ERPF), filtration fraction (GFR/ERPF) (FF), and sodium iothalamate space during chronic infusion of methylprednisolone in intact dogs maintained on an average sodium intake of 78 mEq/day. Values are means ± SE. C = average control values.
Chronic Effects of Methylprednisolone on Plasma Concentrations of Sodium, Potassium, Protein, Aldosterone, and Plasma Renin Activity

The changes in plasma concentrations of sodium, potassium, protein, aldosterone, and PRA that occurred during chronic infusion of MP are shown in figure 3. Plasma sodium and potassium concentrations did not change significantly during MP infusion. Plasma protein concentration increased transiently on Days 2–3 of MP infusion but then returned gradually toward control levels. When MP infusion was stopped, plasma protein concentration decreased below control levels and remained below control even on the tenth day after MP infusion was terminated. Plasma aldosterone concentration tended to decrease during MP infusion, but these changes were not statistically significant. There were also no significant changes in plasma renin activity during MP infusion.

Chronic Effects of Methylprednisolone on Blood Pressure and Electrolyte and Water Balance During Angiotensin II Hypertension

The changes in MAP, urinary excretion of sodium, water, and potassium, and water drinking that occurred during chronic infusion of AII (5 ng/kg/min), and then during infusion of MP (5 or 10 mg/day) along with AII are shown in figure 4. During chronic infusion of AII in dogs maintained on a high sodium intake (approximately 240 mEq/day), mean arterial blood pressure increased markedly, plateauing at approximately 40 mm Hg above control levels. Urinary sodium excretion decreased significantly on the first day of AII infusion, but then returned to levels not different from control. Urine volume also decreased.
during the first day of AII infusion and then gradually increased to levels slightly above control. Water drinking also increased above control levels, but there were no significant changes in urinary potassium excretion during AII infusion.

Infusion of MP at a rate of 5 mg/day during AII hypertension caused a transient decrease in mean arterial blood pressure on the first day, but then blood pressure increased back to levels not significantly different from those observed during AII hypertension. Infusion of 10 mg/day of MP along with AII caused no further changes in blood pressure. Thus, infusion of MP did not potentiate the blood pressure effects of chronic AII infusion in these experiments.

Infusion of 5 mg/day of MP during AII hypertension caused a transient increase in urinary sodium excretion, but then sodium excretion returned to levels observed prior to MP infusion. Infusion of 10 mg/day of MP caused no further changes in urinary sodium excretion. Infusion of MP at 5 or 10 mg/day caused no significant changes in urinary potassium excretion during AII hypertension. There were small but significant increases in average urine volume and water drinking during infusion of 5 or 10 mg/day of MP.

Chronic Effects of Methylprednisolone on Renal Hemodynamics and Sodium Iothalamate Space During Angiotensin II Hypertension

The changes in GFR, ERPF, FF, and sodium iothalamate space that occurred during chronic infusion of AII (5 ng/kg/min) and during infusion of MP (5 or 10 mg/day) along with AII are shown in figure 5. Chronic infusion of AII in dogs on a high sodium diet resulted in a significant increase in GFR to approximately 18% above control levels. However, ERPF decreased by approximately 9% and FF increased markedly during chronic AII infusion. During AII hypertension, sodium iothalamate space also increased to approximately 10% above control.

Infusion of 5 or 10 mg/day of MP caused no significant changes in GFR during AII hypertension. However, infusion of MP at 5 or 10 mg/kg/min did increase ERPF to approximately 19% and 40% respectively above the levels observed during AII hypertension. Therefore, infusion of MP during AII infusion resulted in a marked reduction in FF. Infusion of 5 or 10 mg/day of MP also caused a significant reduction in sodium iothalamate space during AII hypertension.

Chronic Effects of Methylprednisolone on Plasma Concentrations of Sodium, Potassium, Protein, Aldosterone, and Plasma Renin Activity During Angiotensin II Hypertension

The changes in plasma concentrations of sodium, potassium, protein, and aldosterone that occurred during chronic infusion of AII (5 ng/kg/min) and during infusion of MP (5 or 10 mg/day) along with AII are shown in figure 6. There were no significant changes in plasma sodium or protein concentrations during infusion of AII, or during infusion of 5 or 10 mg/day of MP along with AII. Plasma potassium concentration decreased and plasma aldosterone concentration increased significantly during chronic AII infusion, but infusion of MP at 5 or 10 mg/day along with AII caused no further changes in these variables. Plasma renin activity averaged 0.25 ± 0.16 during the control period and then decreased to levels that were undetectable by radioimmunoassay during chronic AII infusion. During MP infusion (5 or 10 mg/day) along with AII, plasma renin activity remained undetectable.
Effects of Chronic Infusion of Varying Doses of Methylprednisolone in Dogs Maintained on Low, Normal, or High Sodium Intakes

The changes in mean arterial pressure, renal hemodynamics, $^{125}$I sodium iothalamate space, and plasma concentrations of sodium and potassium that occurred during chronic infusion of several different doses of MP in dogs maintained on different levels of sodium intake are shown in table 1. Chronic infusion of MP did not elevate mean arterial blood pressure in dogs maintained on low sodium intake (5 mEq/day, G-2), normal sodium intake (73-84 mEq/day, G-3, G-4, G-5), or high sodium intake (160-220 mEq/day, G-3, G-4, G-5). In one dog (G-2) maintained on a low sodium intake (5 mEq/day), infusion of massive doses of MP (400 or 800 mg/day) resulted in a substantial reduction in blood pressure; on the last day of infusion of 800 mg/day of MP, blood pressure averaged only 70 mm Hg, compared to a control value of 88 mm Hg. In all dogs studied, infusion of MP caused marked increases in GFR and ERPF while also increasing urinary sodium excretion and decreasing the total volume of distribution of $^{125}$I sodium iothalamate.

Generally, the increases in ERPF were slightly greater than the increases in GFR, and therefore FF decreased during MP infusion. Infusion of MP over a wide range of dosages caused no consistent changes in plasma concentrations of sodium or potassium.

Discussion

It is widely believed that hypertension associated with Cushing's syndrome is caused mainly by excessive secretion of glucocorticoids. There are also other abnormalities in this syndrome, however, that could increase blood pressure. Cushing's syndrome can occur because of hyperfunction of the anterior pituitary or adrenal cortex as a result of hyperplasia, adenoma, or carcinoma of these glands, and because of excessive production of ACTH-like substances from extraadrenal tumors. In each of these conditions, increased mineralocorticoid activity usually accompanies excessive production of carbohydrate-active steroids. Even though measurements of plasma aldosterone concentration indicate that it is not always elevated in Cushing's syndrome, this finding does not rule out the possibility of excessive mineralocorticoid activity, since secretion of other known adrenal steroids that have significant mineralocorticoid activity, such as deoxycorticosterone and corticosterone, and possibly even undiscovered adrenal steroids, could be increased in these conditions. Also, the observation that hypokalemia does not always occur in Cushing's syndrome (although reductions in plasma potassium concentration have been reported in many studies) does not rule out the possibility of excessive mineralocorticoid activity. Hypokalemia used to be considered the hallmark of hypertension caused by mineralocorticoid excess, but it is now recognized that hypersecretion of mineralocorticoids (i.e., primary aldosteronism) can be associated with normal plasma potassium concentration.

Another possible cause of hypertension in Cushing's syndrome is increased secretion of ACTH that occurs in approximately 85% of these patients. Increased plasma concentrations of ACTH have been reported to cause a form of hypertension in sheep that cannot be explained by overproduction of any single, known adrenal steroid. Thus, the hypertension associated with Cushing's syndrome could result from excessive glucocorticoid or mineralocorticoid activity, or it could be caused by some unknown effect of increased ACTH secretion.

One important objective of the present study was to determine whether excessive glucocorticoid activity, without increased mineralocorticoid activity or increased ACTH secretion, would cause sustained hypertension in dogs. The results from our studies indicate that chronic intravenous infusion of a wide range of doses of methylprednisolone (MP), a glucocorticoid with very little mineralocorticoid activity, causes no increase in arterial pressure in dogs. In fact, small but significant reductions in blood pressure were
TABLE 1.  Effect of Chronic Intravenous Infusion of Varying Doses of Methyprednisolone (MP) in Intact, Conscious Dogs on Different Sodium Intakes

<table>
<thead>
<tr>
<th>Groups</th>
<th>MAP (mm Hg)</th>
<th>GFR (ml/min)</th>
<th>ERPF (ml/min)</th>
<th>FF</th>
<th>VTOT (ml)</th>
<th>PNa (mEq/liter)</th>
<th>PK (mEq/liter)</th>
<th>Na intake (mEq/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>88</td>
<td>98.8</td>
<td>294.0</td>
<td>0.366</td>
<td>9996</td>
<td>145.5</td>
<td>4.95</td>
<td>5</td>
</tr>
<tr>
<td>MP - 400 mg/day (6 days)</td>
<td>84</td>
<td>121.5</td>
<td>484.1</td>
<td>0.251</td>
<td>9738</td>
<td>142.7</td>
<td>4.24</td>
<td>5</td>
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<tr>
<td>MP - 800 mg/day (8 days)</td>
<td>77</td>
<td>—</td>
<td>605.4</td>
<td>—</td>
<td>—</td>
<td>139.5</td>
<td>4.36</td>
<td>5</td>
</tr>
<tr>
<td>Control</td>
<td>89</td>
<td>81.1</td>
<td>225.8</td>
<td>0.399</td>
<td>7777</td>
<td>146.8</td>
<td>4.44</td>
<td>73</td>
</tr>
<tr>
<td>MP - 40 mg/day (5 days)</td>
<td>83</td>
<td>107.3</td>
<td>345.5</td>
<td>0.311</td>
<td>7118</td>
<td>146.6</td>
<td>4.38</td>
<td>73</td>
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<tr>
<td>MP - 80 mg/day (7 days)</td>
<td>81</td>
<td>92.8</td>
<td>371.3</td>
<td>0.250</td>
<td>6582</td>
<td>148.0</td>
<td>4.53</td>
<td>74</td>
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<tr>
<td>MP - 80 mg/day + high Na (8 days)</td>
<td>83</td>
<td>130.6</td>
<td>—</td>
<td>—</td>
<td>8040</td>
<td>145.9</td>
<td>4.35</td>
<td>220</td>
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<tr>
<td>Control</td>
<td>85</td>
<td>73.2</td>
<td>168.2</td>
<td>0.435</td>
<td>7084</td>
<td>146.0</td>
<td>4.27</td>
<td>84</td>
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<tr>
<td>MP - 5 mg/day (4 days)</td>
<td>82</td>
<td>94.2</td>
<td>238.1</td>
<td>0.396</td>
<td>7744</td>
<td>144.5</td>
<td>4.15</td>
<td>84</td>
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<tr>
<td>MP - 10 mg/day (4 days)</td>
<td>85</td>
<td>95.0</td>
<td>247.0</td>
<td>0.385</td>
<td>7716</td>
<td>144.8</td>
<td>4.44</td>
<td>81</td>
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<td>MP - 20 mg/day (8 days)</td>
<td>86</td>
<td>102.0</td>
<td>310.5</td>
<td>0.329</td>
<td>7542</td>
<td>144.8</td>
<td>3.98</td>
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<td>MP - 40 mg/day (4 days)</td>
<td>79</td>
<td>107.5</td>
<td>314.8</td>
<td>0.341</td>
<td>7275</td>
<td>144.7</td>
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<tr>
<td>MP - 40 mg/day + high Na (6 days)</td>
<td>84</td>
<td>94.9</td>
<td>316.6</td>
<td>0.300</td>
<td>7854</td>
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<td>66.7</td>
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<td>144.5</td>
<td>4.18</td>
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<td>MP - 2 mg/day (5 days)</td>
<td>95</td>
<td>83.0</td>
<td>182.5</td>
<td>0.455</td>
<td>5677</td>
<td>143.2</td>
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<td>96</td>
<td>81.0</td>
<td>221.0</td>
<td>0.367</td>
<td>5364</td>
<td>144.8</td>
<td>3.95</td>
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<td>MP - 10 mg/day (4 days)</td>
<td>101</td>
<td>82.5</td>
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<td>280.7</td>
<td>0.310</td>
<td>6395</td>
<td>145.5</td>
<td>4.18</td>
<td>73</td>
</tr>
<tr>
<td>MP - 20 mg/day + high Na (6 days)</td>
<td>101</td>
<td>88.8</td>
<td>365.0</td>
<td>0.243</td>
<td>6342</td>
<td>146.0</td>
<td>4.11</td>
<td>160</td>
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</tbody>
</table>

Abbreviations: MAP = mean arterial pressure, representing the average pressure measured continuously during the control or experimental periods; GFR = glomerular filtration rate; ERPF = effective renal plasma flow; FF = filtration fraction; VTOT = total volume of 131I Na - iothalamate distribution; PNa = plasma sodium concentration; PK = plasma potassium concentration.

observed during chronic infusion of MP. These observations are consistent with clinical studies that have demonstrated that large doses of glucocorticoids can be administered in humans for long periods of time with very little incidence of hypertension, unless there is evidence of underlying renal disease.5

There have been reports of increased blood pressure, estimated by the tail-cuff method, during chronic administration of cortisone, corticosterone, or MP in rats.6-7 An explanation for the differences between the studies in rats and the results obtained in dogs in the present study is not apparent but may be related to differences in dosages used or in the methods used for measuring blood pressure. In the rat studies,6,7 extremely large doses of glucocorticoids have often been used, and it is recognized that almost all adrenal steroids, as well as synthetic glucocorticoids, have some mineralocorticoid activity, es-

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especialiy at extremely high doses. It is also possible that measurements of systolic pressure for only a few minutes may not be representative of the average blood pressure throughout the day, especially if blood pressure is for some unknown reason more labile during glucocorticoid excess. Previous studies have indicated that blood pressure may fluctuate markedly from hour to hour, so that a few minutes of blood pressure recording may not provide an accurate assessment of the daily blood pressure under certain experimental conditions. In the present study, mean arterial blood pressure was measured continuously, 24 hours a day, so that an extremely accurate assessment of changes in arterial blood pressure could be made. Our results clearly demonstrate that MP, a glucocorticoid with minimal mineralocorticoid activity, does not elevate arterial pressure in the dog when administered at doses ranging from 2-800 mg/day for periods of 4-27 days. These observations, when taken together with the observation that there is a very low incidence of hypertension during glucocorticoid therapy in patients without renal disease, suggest that excessive glucocorticoid activity may not be the cause of hypertension in patients with Cushing's syndrome; factors other than increased glucocorticoid activity should be examined as possible causes of hypertension in Cushing's syndrome.

Because hypertension has been observed in some patients with renal disease during chronic administration of glucocorticoids, and because glucocorticoids have been reported to potentiate the acute vasoconstrictor effects of AII, we also investigated in the present study the chronic interactions between AII and glucocorticoids in regulating blood pressure. Presumably, if glucocorticoids potentiate the chronic effects of AII on vascular resistance and renal function, this could lead to sustained elevations of blood pressure. To our knowledge there have been no previous reports in which chronic interactions between the blood pressure and renal effects of AII and glucocorticoids have been investigated. Results of the present study suggest that the long-term effects of AII in causing renal vasoconstriction and in elevating blood pressure are not potentiated by glucocorticoids, since chronic infusion of 5 or 10 mg/day of MP in dogs infused with AII (5 ng/kg/min) caused no further increases in renal vascular resistance or blood pressure. In some instances, MP infusion actually resulted in a significant reduction in arterial blood pressure, and in all dogs studied renal vascular resistance was reduced during chronic administration of MP. Thus, in dogs infused with AII, as well as normal dogs, chronic infusion of MP actually tends to lower blood pressure and renal vascular resistance.

The reductions in blood pressure that occurred during MP infusion in intact dogs as well as those infused with AII were associated with sustained reductions in sodium iothalamate space, sustained decreases in renal vascular resistance, and transient natriuresis. Several theoretical analyses as well as experimental studies indicate that chronic increases in renal excretory capability, such as those observed during MP infusion, could result in sustained reductions in blood pressure. Thus, the effects of glucocorticoids to lower blood pressure may be due primarily to its actions on renal excretion of salt and water. It is possible, however, that other mechanisms, such as a reduction in ACTH secretion, may play a role in reducing blood pressure during administration of excess glucocorticoids.

The rise in urinary sodium excretion observed during MP infusion can be accounted for by the increase in filtered sodium load. The filtered sodium load, measured on Days 2, 5, and 9 of MP infusion, increased an average of 1970 µEq/min in normal dogs maintained on approximately 80 mEq of sodium per day, while urinary sodium excretion increased an average of only 17.3 mEq/day, or approximately 12 µEq/min. Therefore, total reabsorption of sodium increased markedly during chronic infusion of MP. Whether the rise in sodium reabsorption occurred as a primary effect of MP, or as a compensatory response to increased GFR and filtered load of sodium, however, cannot be determined from the results of the present study.

The mechanisms responsible for the renal vasodilation and increased GFR observed during chronic infusion of MP in the present study are not entirely clear, but certainly these changes cannot be due to an increased extracellular fluid volume since there was a negative sodium balance and a reduction in sodium iothalamate space during MP infusion. In addition, there was a chronic reduction in arterial pressure that would tend to lower GFR and renal blood flow. It is also unlikely that the changes in renal vascular resistance and GFR during MP infusion were caused by changes in electrolyte concentration or hematocrit, since these factors remained relatively constant. Although infusion of MP did cause a transient increase in plasma protein concentration, this change would tend to decrease the net filtration force at the glomerular capillaries and therefore lower GFR if it had any effect at all. The rise in plasma protein concentration may have blunted the rise in GFR caused by renal vasodilation during glucocorticoid administration.

Methylprednisolone could cause renal vasodilation and increased GFR through its effects on metabolism of glucose and protein. It is well established that excess glucocorticoids produce a tendency toward hyperglycemia and glycosuria, as well as catabolism of proteins and a rise in plasma amino acids. Several experimental and clinical studies have demonstrated that increased blood levels of glucose or amino acids, due to intravenous infusion, result in marked elevations in GFR and renal blood flow. However, the exact mechanisms whereby increases in blood glucose or amino acids elevate GFR and renal blood flow remain obscure.

One interesting observation in the present study was that chronic infusion of MP did not elevate plasma renin activity, even though there was a negative sodium balance and a chronic reduction in blood pressure, both of which would tend to stimulate renin activity.
release. However, the filtered load of sodium was also increased during MP infusion, which would tend to increase distal tubular delivery of sodium (and chloride as well). These changes have been demonstrated in many acute experiments to be a potent stimulus to reduce renin release, and could account for the lack of an increase in plasma renin activity observed in the present study during MP infusion.

In summary, we found no evidence in the present study that chronic high levels of glucocorticoid result in hypertension in dogs. Instead, chronic administration of a wide range of doses of methylprednisolone, a glucocorticoid with very little mineralocorticoid activity, caused small but consistent reductions in MAP. Our chronic blood pressure lowering effect.

Glucocorticoid administration, however, did have important effects on the kidney to increase GFR, ERPF, and urine excretion of sodium and water; these actions of glucocorticoids led to a reduction in sodium iothalamate space, and are probably responsible for their chronic blood pressure lowering effect.

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