Escape from Sodium-Retaining Effects of Deoxycorticosterone in Hypotensive and Hypertensive Dogs[1] (34879)

JAMES T. HIGGINS, JR.[2]
(Introduced by O. M. Helmer)

Departments of Medicine, Indiana University School of Medicine, Indianapolis, Indiana 46202; and Veterans Administration Hospital, West Haven, Connecticut 06516

It has been known for many years that normal subjects escape from the sodium-retaining effects of the mineralocorticoid hormones after several days of exposure to excessive amounts of these hormones (1, 2). Patients with aldosterone-secreting adrenal cortical tumors also exhibit escape from the renal effects of the excessive aldosterone (3), and although these patients appear to develop hypertension in most cases, it is not thought that elevation of blood pressure is necessary for escape from aldosterone by the kidneys. Dogs are able to escape even more rapidly than humans, without detectable increase in blood pressure during a brief period of hormone administration (4). To be sure that small increases in blood pressure or adrenergic tone do not play a role in escape, the response to deoxycorticosterone acetate (DOCA) was studied in dogs in which hypotension and catecholamine depletion were produced with guanethidine and hydralazine.

The role of blood pressure in escape was further examined by giving pressor doses of ephedrine to dogs which could not escape from DOCA because of thoracic inferior vena caval constriction (4).

Materials and Methods. Dogs of both sexes, ranging from 10 to 20 kg in wt, were housed in metabolism cages. Each morning the dogs were fed a synthetic diet which provided approximately 80 cal/kg/day; 0.2 g of N/kg/day; 4 meq of Na/kg/day, 1.2 meq K/kg/day, plus essential vitamins and minerals. This diet was specially prepared in pelleted form by Nutritional Biochemicals Corporation, formula no. 65817. It was also prepared in gelatinous form with agar in the laboratory so that dogs which refused to eat could be force-fed to maintain constant intake. Water was provided *ad libitum*. Residual bladder urine was obained by catheterization each morning to complete the 24-hr collection, and total daily urinary excretion of sodium and potassium was determined for each animal.

After the dogs were trained to lie quietly on the table, arterial blood pressures were obtained by direct puncture of a femoral artery with a 19-gauge thin wall, short bevel needle mounted directly on a Statham P23Db strain gauge pressure transducer. Pressures were read from a recording oscillograph. Mean arterial pressure was obtained electronically utilizing an average circuit with a time contant of 0.2 sec.

After a period of stabilization on the diet, urine collections were begun and control blood pressure was measured. Two experimental procedures were then carried out in each normal dog to determine the effect of hypotension upon ability to escape, with a period of stabilization between studies. In one study, the dog was given deoxycorticosterone acetate (DOCA) in oil, 10 mg intramuscularly/day, before feeding. When urinary sodium excretion rose to control levels indicating escape from DOCA, the blood pressure was lowered with a combination of guanethidine sulfate (20 mg orally in the mornings) and hydralazine HCl (50 mg orally mornings and evenings). In the second study, the blood pressure was first lowered with the same dosage of guanethidine and hydralazine and then DOCA (10 mg/day)

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TABLE I. Mean Arterial Blood Pressure (MAP) in Dogs in Which Blood Pressure Was Lowered Before DOCA Was Given (Exp. I) and in Dogs Which Had Escaped from DOCA Before Hypotensive Drugs Were Given (Exp. II).

Exp.	n	MAP during: Control	Escape	Drugs	Drugs and escape
I	6	128 ± 9		90 ± 7[a]	84 ± 6[a]
II	5	128 ± 8	128 ± 10		96 ± 16[b]

[a] $p < 0.001$.
[b] $p < 0.005$.

was begun, while continuing urine collections.

In two dogs, sodium retention was produced by constricting the thoracic portion of the inferior vena cava. These dogs were given ephedrine sulfate in divided doses throughout the day at levels sufficient to raise the mean arterial blood pressure 15–30 mm Hg. One dog was given DOCA (10 mg/day) throughout the experiment.

Renal plasma clearance measurements of creatinine (Cr) and para-aminohippurate (PAH) were made with the animal in the postabsorptive state without prior hydration. Priming and sustaining infusions of Cr and PAH were given to insure constant plasma levels, and clearances were calculated as the means of three consecutive 20-min periods.

Urinary sodium and potassium were analyzed by flame photometry, creatinine by the method of Folin and Wu (5), and para-aminohippurate by the method of Smith *et al.* (6). Significance of differences between group mean values was determined by the t test.

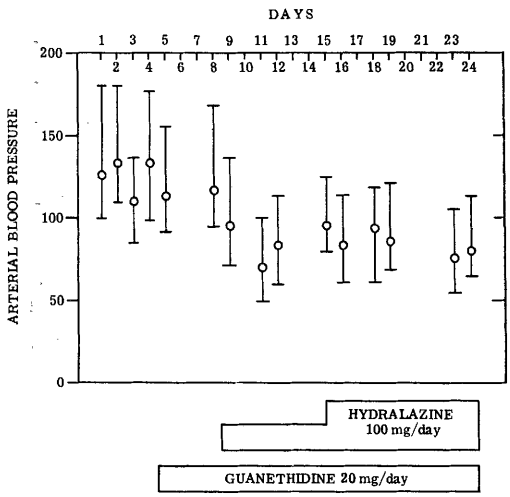

FIG. 1. Systolic, diastolic, and mean arterial blood pressure of a dog during control and hypotensive drug administration.

Results. The combination of hydralazine and guanethidine was very effective in lowering blood pressure of normal dogs. As shown in Table I, mean arterial pressure was significantly lowered in each group given drugs. Figure 1 illustrates the sustained effect of hydralazine and guanethidine on the systolic, diastolic, and mean arterial pressures of an animal given the drugs over a 20-day period. Orthostatic hypotension, a well-recognized result of the α-adrenergic blocking property of guanethidine therapy in humans, was evidenced by signs of faintness whenever the dogs were held erect.

When DOCA was administered to six dogs made hypotensive with drugs, escape from renal retention of sodium occurred in all six within 1 to 4 days. The blood pressure remained at hypotensive levels throughout (Table I). A slight increase in urinary potassium excretion usually accompanied the increase in sodium excretion. Figure 2 illustrates a typical DOCA escape response in one animal.

In five dogs the blood pressure was lowered after the dog had already escaped from DOCA. In each case there was a transient reduction in sodium excretion with the onset of hypotension, followed in 1–5 days by resumption of sodium balance despite continued hypotension and DOCA administration (Figs. 3, 4). Urinary excretion of potassium fell coincident with the reduction of blood

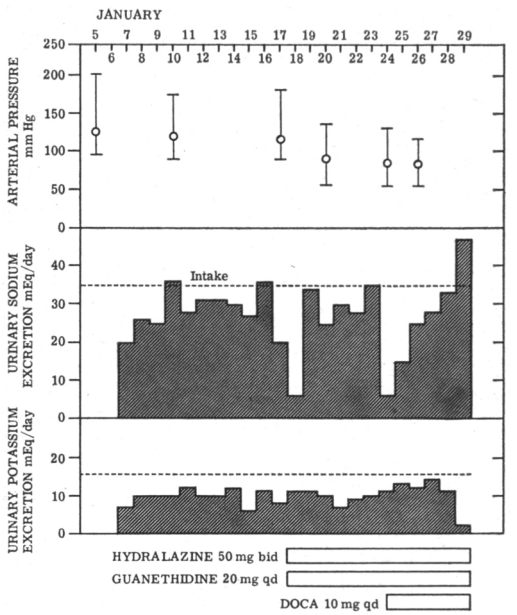

FIG. 2. Arterial blood pressure and electrolyte balance of a dog made hypotensive with drugs and then given DOCA, demonstrating renal escape from DOCA despite hypotension.

pressure and sodium excretion (Fig. 3). This urinary sodium to potassium relationship is the reverse of that seen with the beginning of DOCA administration, and suggested that the transient sodium and potassium retention following blood pressure reduction might be caused by decreased renal perfusion. This interpretation was confirmed by repeating the study in one dog and determining renal clearance of creatinine (C_{Cr}) and para-aminohippurate (C_{PAH}). As shown in Fig. 4, during control observations C_{PAH} was 157 ml/min and C_{Cr}, 49 ml/min; after DOCA escape C_{PAH} was 160 ml/min and C_{Cr}, 43 ml/min; during hypotension C_{PAH} averaged 132 ml/min and C_{Cr} 30 ml/min.

Although the mean of several arterial blood pressure measurements in two dogs with thoracic inferior vena caval constriction was 119 $\pm$ 8 mm Hg, this value was not significantly different from normal, probably due to the small sample. Nevertheless, administration of ephedrine sulfate three times daily produced increased blood pressure for several hours throughout the day. Three courses of ephedrine administration, 2–8 days in duration, to the two dogs with thoracic inferior vena cava constriction failed to increase sodium excretion, and the dogs continued to retain almost all dietary sodium. Figure 5 illustrates the response of one dog.

Discussion. The results of this study are of interest in two areas. First, does blood pressure elevation play a causal role in renal escape from the salt-retaining effects of mineralocorticoid hormones, and second, what is the role of the sympathetic nervous sytem in renal sodium conservation.

Detectable elevations of blood pressure have not been found during short-term administration of DOCA to dogs [(7), and present work]. However, it seemed possible that slight elevations of pressure, obscured by the limitations inherent in taking blood pressure of conscious animals, might play a role in renal escape from DOCA. This possibility is further supported by the observation that patients with primary hyperaldosteronism are in a constant state of escape, and are usually found to have hypertension (3). In

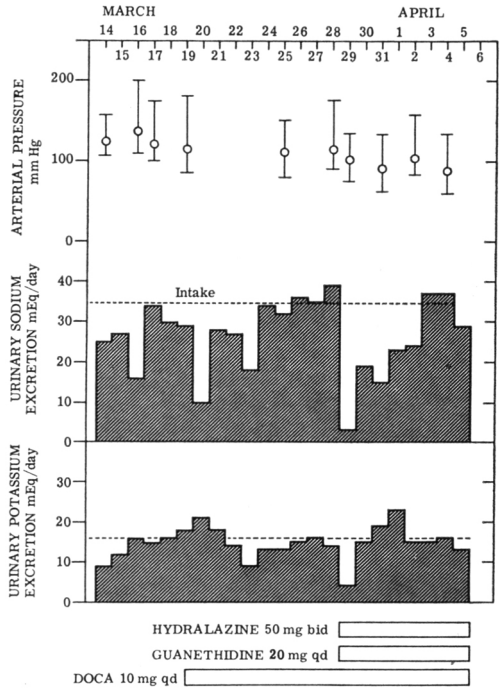

FIG. 3. Resumption of sodium balance during hypotension in dog which had escaped from deoxycorticosterone.

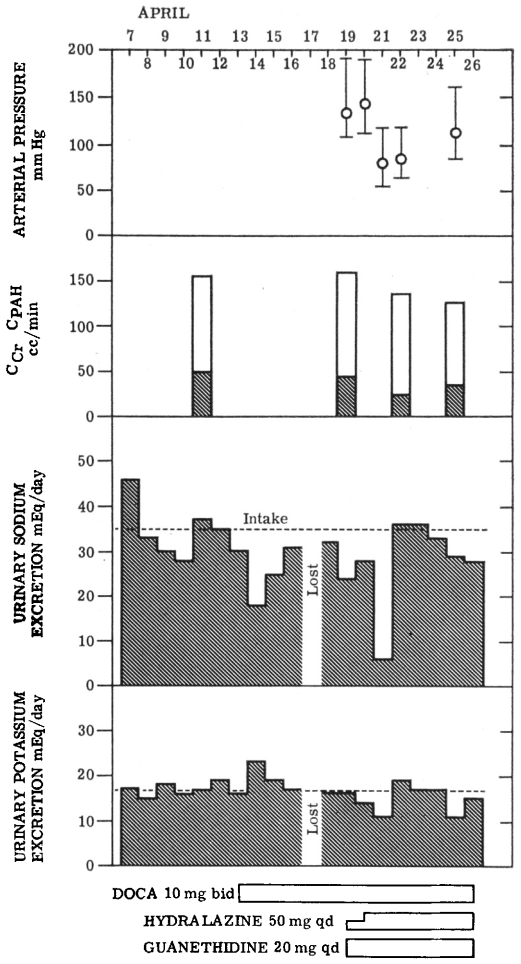

FIG. 4. Resumption of sodium balance despite decreased renal perfusion during hypotension in dog which had escaped from DOCA.

addition, the natriuretic response to a saline load, throught to be mediated by the same renal mechanism as escape, is augmented in patients with hypertension (3, 8). The present studies, however, show that renal escape from the salt-retaining effects of DOCA can occur even in the presence of drug-induced hypotension, thus providing direct evidence that elevation of blood pressure is not necessary for escape. These findings are consonant with studies showing that the diuresis produced by saline loading takes place even after constriction of the renal arteries or suprarenal aorta (9).

The possibility of a positive or negative role of the sympathetic nervous system in escape is suggested by findings in patients and animals with heart failure. It is generally accepted that there is increased adrenergic activity in heart failure (10). There is uncertainty as to whether this increase is beneficial or deleterious since it may impair sodium excretion even while supporting cardiac function, and administration of both sympathomimetic and sympatholytic drugs have been proposed to agument sodium excretion in patients in heart failure (11, 12). Dogs with TIVC constriction are like patients with heart failure in that neither can escape from sodium-retaining steroids (4), and the effect of a sympathomimetic drug on sodium excretion by these dogs was tested. Ephedrine was the sympathomimetic agent chosen in the present studies because it can be given orally, possesses actions similar to epinephrine, and elevates blood pressure over a several-hour period (13). Although no attempt was made to examine the relative alpha and beta adrenergic effects on vascular parameters, it was clear that ephedrine in pressor doses produced no increase in sodium excretion in the dogs with TIVC. These findings indicate that increasing the blood pressure and stimulating other adrenergic receptors does not augment

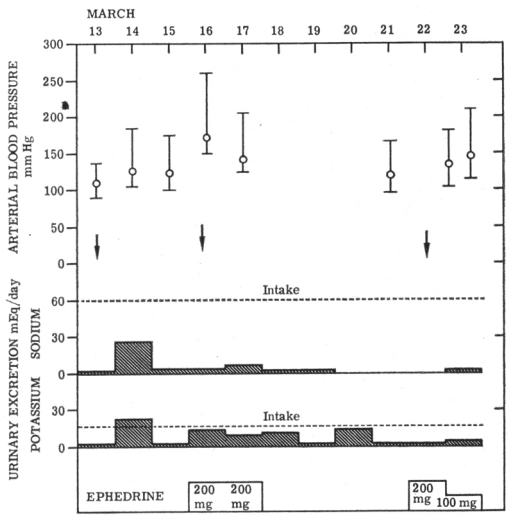

FIG. 5. Failure of ephedrine to increase sodium excretion despite blood pressure elevation in dog with thoracic inferior vena caval constriction. (Arrows indicate paracentesis for removal of ascitic fluid.)

renal sodium excretion in this condition. Furthermore, the administration of large doses of the α-adrenergic blocking agent guanethidine to normal dogs did not modify the normal renal escape from DOCA indicating that α-adrenergic activity is not essential for DOCA escape.

Summary. The ability of the mammalian kidney to escape from the sodium-retaining effects of mineralocorticoid hormones has not been thought to depend upon increases in blood pressure or renal perfusion. However, chronic exposure to excess endogenous or exogenous adrenal cortical hormones results in hypertension, and it seemed possible that early small increments in blood pressure might play a role in escape. To evaluate this, hypotension was produced with drugs in dogs, and their ability to escape was studied. A combination of hydralazine and guanethidine effectively lowered blood pressure but did not prevent or delay renal escape from deoxycorticosterone. Production of hypotension after escape resulted in sodium retention for 1 day, but then sodium balance resumed despite continued hypotension and lowered renal blood flow and filtration. Mean arterial blood pressure in dogs with thoracic inferior vena caval constriction was not significantly below normal, and elevation of blood pressure with ephedrine failed to increase sodium excretion or permit renal escape from deoxycorticosterone. These studies indicate that neither increased blood pressure nor α-adrenergic tone is necessary for renal escape from the salt-retaining effects of mineralocorticoid hormones.

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