The Potentiating Effect of ACTH and of Cortisone on Pressor Response to Intravenous Infusion of L-Nor-Epinephrine.* (18962)

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Despite extensive investigation of the pharmacodynamic and therapeutic action of adrenocorticotrophin (ACTH) and cortisone, there have been but few reports on the effects of these agents on the circulation. Several reviews have summarized current knowledge (1,2). Adrenal steroids have been shown to prevent shock in adrenalectomized dogs(3) and to sustain experimental renal hypertension in adrenalectomized rats(4). Progressive insensitivity to nor-epinephrine has been noted in adrenalectomized dogs subjected to stress. Reactivity to nor-epinephrine was restored by adrenal cortical extract (ACE) but not by desoxycorticosterone acetate glucoside(5,6). Single injections of ACE potentiated the blood pressure response to previously ineffective concentrations of nor-epinephrine in adrenalectomized dogs but not in normal controls(7).

In humans treated with ACTH or cortisone hypertension has been irregularly noted (8-10). A rise in the tetraethylammonium chloride (TEAC) floor has been described in normotensive and hypertensive patients receiving ACTH and cortisone(11). However, others have noted(12) no definite change in the pressor responsiveness to epinephrine, nor-epinephrine, or tetraethylammonium chloride in patients treated with cortisone and only slightly increased pressure responses in patients treated with ACTH. In normotensive human subjects, the pressor effect of epinephrine and nor-epinephrine has been enhanced by pre-treatment with desoxycorticosterone acetate(13).

The present communication describes the effect of cortisone and ACTH on the pressor response of normotensive human subjects to l-nor-epinephrine.

Methods. Three normotensive patients were studied. Repeated tests were performed in the same laboratory by the same personnel. All experiments in the same patient were carried out at the same time of day, from 1 to 3 hours after a light meal. An intravenous infusion of 5% glucose in water was administered through a No. 19 gauge needle into an antecubital vein. A constant rate infusion apparatus with variable gear ratios (Braun, Melsungen) was connected to the D/W infusion by a No. 25 needle inserted into the rubber tubing of the intravenous apparatus close to the needle in the antecubital vein. Two milliliters l-nor-epinephrine, 1:1,000† was diluted in 250 ml of 5% dextrose in water. This could be administered at the rate of 0.26, 0.45, 0.72, 1.1 and 1.7 ml per

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†Kindly supplied through the courtesy of the Winthrop-Stearns Research Institute.

minute. The heart rate was calculated from electrocardiograms (direct writing electrocardiograph); the blood pressure was measured by the auscultatory method. When all apparatus had been attached and the glucose infusion had been started, the pulse rate and blood pressure were measured every 2 minutes until a steady state had been achieved (approximately 30 to 40 minutes). The infusion of l-nor-epinephrine was then begun and that of dextrose in water was stopped by clamping just distal to the insertion of the No. 25 needle. The observations were repeated every minute for 5 minutes and then every 2 minutes until a steady state could be demonstrated (usually at least 12 to 14 minutes). In 2 patients (Cases 1 and 2) the initial infusion speed of 0.45 ml per minute (3.6 μg per minute) was followed by similar observations at 3 more rapid rates of infusion of nor-epinephrine (5.8, 8.8 and 13.6 μg per minute). In the third patient (Case 3) the infusion of nor-epinephrine was maintained at 0.26 ml (2.1 μg) per minute, for 30 to 40 minutes.

Results. Case 1, M.B., a 28-year-old male, BIH No. M17695 entered for therapy of erythema nodosum and rheumatoid arthritis. During the first 9 days of hospitalization salicylates, tripelennamine hydrochloride (pyribenzamine) and penicillin were prescribed; there was no change in the clinical course. On the 10th day cortisone administration was started, 100 mg twice daily for five days and then 50 mg twice daily. Dramatic subsidence of joint and skin pain and fever were noted shortly after administration of cortisone(14). Fig. 1 demonstrates the results of infusions of nor-epinephrine in this patient before cortisone and 24 hours after starting oral cortisone. During the period of cortisone administration the pressor response to all concentrations of nor-epinephrine was consistently greater than that found before treatment. The resting pulse rate on cortisone therapy was notably lower (approximately 65 to 70) than before any therapy was administered (approximately 95 to 100).

Case 2, T.S.P., a 35-year-old woman, BIH

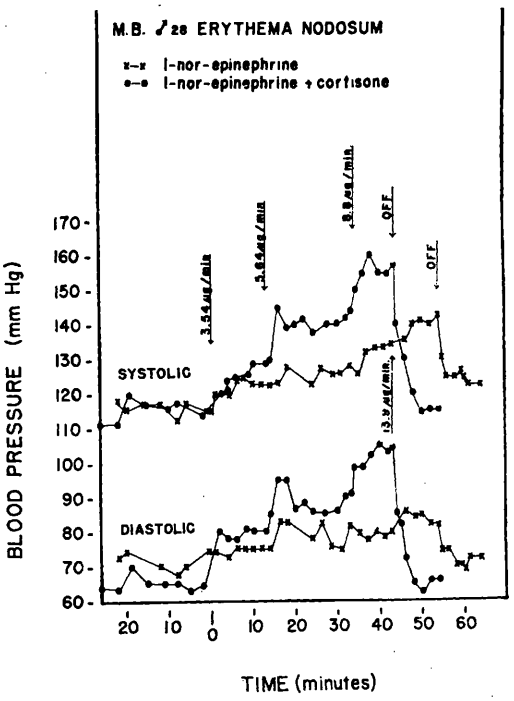

FIG. 1. Case M.B. Blood pressure response to intravenous infusion of varying concentrations of nor-epinephrine before (x———x) and during (•———•) oral cortisone.

No. 18755 was admitted for ACTH therapy during an acute exacerbation of multiple sclerosis. Studies were performed before, during, and after ACTH therapy as indicated in Table I. No other agents were administered. Six infusions were performed during ACTH therapy; 3, before ACTH and 24 and 72 hours after omission of ACTH. The data (Table I) indicate a striking increase in systolic pressor response to nor-epinephrine during ACTH therapy compared to the response before ACTH was administered and when ACTH was omitted. The resting pulse rates were somewhat lower during ACTH therapy.

Case 3, M.K., a 41-year-old woman, BIH No. M19859 was admitted for ACTH therapy of rheumatoid arthritis of 3 years' duration. Although the clinical diagnosis of scleroderma was considered, the histologic diagnosis from a skin biopsy was senile atrophy (elastosis) of skin. Seven infusions of nor-epinephrine were carried out: 3 prior to ACTH; two, 24 and 100 hours after starting ACTH; one 36 hours after omission of ACTH; and one,

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TABLE I.

Exp.	Protocol	No. of eosinophils per mm³	Avg systolic blood pressure, mm Hg					
	Rate of infusion L-nor-epinephrine		0	3.5 μg/min	5.7 μg/min	8.8 μg/min	13.9 μg/min	0
I	Control	75	105	109	114	127	143	104
II	ACTH, 90 mg daily		108	123	130	140	154	108
III	ACTH, 180 mg daily for one day		110	117	124	132	143	109
IV	ACTH, 180 mg daily for 4 days		110	131	138	153	165	110
V	ACTH, 180 mg daily for 5 days	16	113	135	142	154	>170	118
VI	ACTH omitted for 24 hr	464	110	116	119	125	138	
VII	ACTH omitted for 72 hr		109	114	122	131	151*	
VIII	ACTH, 180 mg daily for 4 days	6	108	120	129	142	158	
IX	ACTH, 180 mg daily for 5 days		109	132	144	154	165	
			Avg pulse rate, beats per min					
	On ACTH		80	71	69	67	65	
	Off "		95	84	78	71	68	

* Distended bladder.

48 hours after administration of cortisone. The data (Fig. 2) demonstrate the striking difference between the pressor response to nor-epinephrine during ACTH therapy as compared to the response to 3 infusions performed prior to ACTH and one performed 36 hours after omission of ACTH. Subsequently cortisone, 50 mg every 8 hours was administered by mouth for 48 hours and the experiment was repeated. The systolic pressor response to nor-epinephrine was notably greater than during the control period and as great as during ACTH administration. This was true not only when the magnitude of the rise was expressed as mm of mercury but also when the rise was expressed as a per cent of the resting blood pressure. The diastolic blood pressure changes were similar to the systolic but not as striking. The resting blood pressure on ACTH and cortisone was higher than the resting value obtained during the pretreatment period.

Discussion. In previous studies of the pressor response to epinephrine and nor-epinephrine a variety of methods have been used for the administration of these agents. This may, in fact, explain the variable results obtained(12). The validity of conclusions drawn from our data is predicated upon the reliability and reproducibility of the results obtained with the technic we have utilized. In Case 3 (Fig. 2) 4 infusions without ACTH, 2 infusions during ACTH therapy and one infusion during cortisone therapy were performed. The preinfusion systolic blood pressure in 4 control experiments ranged from 96 to 104 mm of mercury and averaged 101 mm of mercury. During the infusion of nor-epinephrine in the same experiments the means of the systolic blood pressure ranged from 126 to 132 mm of mercury and averaged 129 mm. The findings during ACTH therapy are in striking contrast; the mean systolic resting blood pressures were 108 and 112 mm and mean systolic blood pressures during nor-epinephrine infusions were 158 and 161 mm. Similarly, of the 9 studies performed in Case 2, there was no overlap (except in infusion No. 7), between the systolic blood pressure response to l-nor-epinephrine without ACTH and that observed during ACTH therapy. In period 5 of the 7th infusion in this case an unexpectedly high systolic blood pressure was observed; the patient was suffering considerable discomfort from a distended bladder. Additional studies in other patients of the pressor response to epinephrine and nor-epinephrine have also demonstrated the reproducibility of the blood pressure response during successive infusions in the same patient on

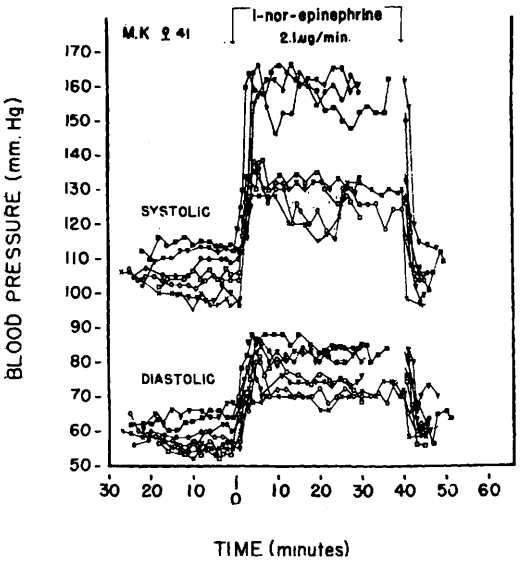

FIG. 2. Case M.K. Pressor response to intravenous infusions of 2.1 µg/min of nor-epinephrine. Open symbols represent observations obtained prior to ACTH or after its omission. Solid symbols represent observations made during ACTH (●——● and ▲——▲) and during oral cortisone (■——■) administration.

different days. These results indicate that variability of technic or variable response of the patient can be eliminated as the basis for the altered sensitivity to nor-epinephrine.

The present data are consistent with the hypothesis that ACTH increases the pressor response to nor-epinephrine by the release of C-11 oxysteroids from the adrenal cortex. Previous observations by others of increased resting blood pressure in patients on DCA therapy alone and the observation that DCA potentiated the response to nor-epinephrine (13) suggested the possibility that ACTH had stimulated DCA production. It is noteworthy that both case 2 and case 3 gained weight during ACTH therapy. However, cortisone alone (Case 3) is at least as effective as ACTH in increasing sensitivity to nor-epinephrine.

The mechanism of action on the cardiovascular system of the C-11 steroids requires further study. The data of Fritz and Levine (15,16) indicate that C-11 oxysteroids act locally on the small splanchnic vessels in animals by sensitizing them to the action of nor-epinephrine. The observations of Brust *et al.*(11) demonstrating the effect of ACTH and cortisone in counteracting the usual depressor effect of TEAC is also consistent with a direct effect (rather than one of reflex origin) on the vasculature. The hypothesis that ACTH and cortisone sensitize the vasculature of man to endogenous nor-epinephrine may explain the elevation of the resting blood pressure during ACTH and cortisone therapy which had been previously noted by others and has also been observed in this study. Similarly, the hypertension of Cushing's disease, previously without adequate explanation, may result from sensitization by increased amounts of C-11 oxysteroids to endogenously formed nor-epinephrine. It is of interest that Goldenberg has reported increased sensitivity to nor-epinephrine in patients with essential hypertension(17). However, no conclusions can be drawn at the present time concerning the relationship between the altered sensitivity to nor-epinephrine demonstrated here in normotensive patients and the genesis of essential hypertension.

Summary. 1. The pressor response to an intravenous infusion of 2.1-13.9 µg per minute of l-nor-epinephrine was studied, using a constant rate infusion apparatus, in 3 patients before and during the administration of ACTH and cortisone. 2. Striking potentiation of the blood pressure response to nor-epinephrine was noted within 24 hours after administration of 90-180 mg ACTH daily or 150-200 mg cortisone daily. The potentiating effect disappeared within 36 hours after the omission of these agents.

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