9-Alpha-Fluorohydrocortisone in the Treatment of Postural Hypotension in Diabetic Autonomic Neuropathy

I. W. Campbell, M.B., M.R.C.P., D. J. Ewing, M.B., M.R.C.P., and B. F. Clarke, M.B., F.R.C.P., Edinburgh, Scotland

SUMMARY

A double-blind crossover study of fludrocortisone, 0.1 mg. twice daily, and placebo is reported in six diabetics with troublesome symptoms of postural hypotension due to autonomic neuropathy. During treatment with the active preparation there was an increase in the lying and tilted systolic blood pressure, a decrease in orthostatic tachycardia, and an increase in the total plasma volume and body weight, but with no change in plasma or urine osmolality. The symptoms of postural hypotension improved in four patients, while two patients with a low serum albumin developed ankle edema during treatment with fludrocortisone. It is concluded that fludrocortisone is effective in diabetics with symptomatic postural hypotension, but should be used with caution in patients with a low serum albumin. DIABETES *24*:381-84, April, 1975.

The use of 9-alpha-fluorohydrocortisone (fludrocortisone) is well documented in the treatment of idiopathic postural (orthostatic) hypotension.[1-6] In diabetic autonomic neuropathy, in which postural hypotension is one of the more prominent and disabling symptoms, there have been only a few reports of its use.[3,5,7] The present study was undertaken to obtain more objective evaluation of the changes produced by fludrocortisone in diabetics with postural hypotension due to autonomic neuropathy using a double-blind crossover technique.

PATIENTS AND METHODS

Six male diabetics with symptomatic postural hypotension with a fall of systolic blood pressure of 30 mm. Hg or greater immediately on changing from the lying to standing position, were selected for study as outpatients. All were impotent with absent testicular sensation,[8] and had confirmatory evidence of autonomic neuropathy with abnormal Valsalva ratios and abnormal sustained handgrip responses.[9] Table 1 shows the details of the patient's age, duration of diabetes, form of treatment, other manifestations of autonomic neuropathy and complications of diabetes. None of the patients had known ischemic heart disease or cardiac failure. All had a blood urea of 40 mg./100 ml. or less with a mean creatinine clearance of 93 ml. per minute (range 60-130 ml. per minute). The two patients (Nos. 4 and 5) with intermittent proteinuria had total plasma proteins of 5.8 gm./100 ml. and 5.6 gm./100 ml., respectively and each had a reduced serum albumin of 3.0 gm./100 ml. (normal range 3.8-5.0 gm./100 ml.). The conduct of the study entailed a randomized double-blind crossover trial comparing fludrocortisone acetate, 0.1 mg. orally twice daily, with an identical placebo likewise given twice daily. The dose of 0.1 mg. twice daily was chosen since the usual recommended range is 0.1 mg.-0.3 mg. daily. Observations were made during four consecutive three-week periods: (1) control ('baseline'), (2) active or placebo, (3) control ('re-equilibration'), and (4) active or placebo. All six subjects were aware of the nature of the study and agreed to participate; each was warned about the possible development of ankle swelling, breathlessness and headache.

The patients were seen regularly during the trial and asked about symptoms of postural hypotension and possible sodium retention. At the end of each three-week period a full physical examination was performed. The blood pressure was recorded in the lying and standing position by sphygmomanometry; blood withdrawn for hemoglobin, packed cell volume, blood urea, serum electrolytes and plasma osmolality;

From the Diabetic and Dietetic Department, and the University Department of Medicine, The Royal Infirmary, Edinburgh EH3 9YW.

Address reprints requests to: I. W. Campbell, Diabetic and Dietetic Department, Royal Infirmary, Edinburgh EH3 9YW.

Accepted for publication January 9, 1975.

TABLE 1
Details of patients studied

Patient No.	Age (years)	Duration of diabetes (years)	Diabetic treatment	Manifestations of autonomic neuropathy: Diabetic diarrhea	Hypoglycemic unawareness	Gustatory sweating	Complications of diabetes: Peripheral neuropathy	Retinopathy	Proteinuria
1	52	11	Insulin	0	+	0	0	0	0
2	47	23	Insulin	0	+	0	+	P	0
3	64	3	Oral agent	0	0	0	+	0	0
4	54	18	Insulin	+	0	+	+	E	+
5	33	17	Insulin	+	0	+	+	B	+
6	63	11	Oral agent	0	0	0	+	B	0

(P = proliferative, E = exudative, B = background)

and a twenty-four-hour urine collection obtained for sodium and potassium excretion, creatinine clearance and urine osmolality. The patients were weighed and the plasma volume determined using I^{125}-labeled human albumin.[10] Using this method the normal plasma volume for our laboratory is 42.6 ± 5.6 ml./kg. (n = 23). A standardized tilt-table test was performed in which the patients lay horizontally for ten minutes and were then tilted head-up to 70 degrees for a further ten minutes. The blood pressure and heart rate were recorded at one-minute intervals during the twenty minutes. To avoid observer bias the blood pressure was measured with a Hawksley random zero sphygmomanometer[11] with the zero being reset after each reading. The heart rate was measured from an electrocardiograph. For calculation the mean values of the readings in the lying position were taken and compared with the mean values in the tilted position. The plasma volume determinations and tilt-table tests were carried out at the same time of day for each of the four visits.

One subject (No. 6) defaulted while taking the active preparation and the results are therefore analyzed for the other five diabetics.

RESULTS

When the two control and the placebo periods were compared, no significant differences were found in any of the parameters measured. In the following results the placebo period is compared with the period on fludrocortisone therapy.

Blood Pressure and Heart Rate

There were no differences between the blood pressures recorded during the physical examination and those obtained during the tilt-table test. While on the active preparation there was a significant rise in the systolic blood pressure both in the lying and tilted positions (table 2). Although both the lying and tilted diastolic blood pressures also rose while the subject was on the active preparation it was only the latter which reached statistical significance ($P < 0.05$) when compared with the placebo. The effect of the fludrocortisone was therefore to increase significantly both the lying and tilted systolic blood pressure, thus widening the pulse pressure (see figure). The orthostatic tachycardia was significantly decreased on the active preparation (table 2).

Plasma Volume and Body Weight

There was a significant increase in the total plasma volume (mean rise 329 ml.) and body weight (mean rise 3.0 kg.) in all subjects while on the active preparation (see table 2). Because both the total plasma volume and body weight rose significantly, this may explain why there was a less significant rise in the calculated plasma volume expressed as ml./kg.

Blood and Urinary Changes

There were no significant changes between the placebo and the active periods in respect of the hemoglobin level, packed cell volume, urinary electrolyte concentrations, plasma and urine osmolality, and creatinine clearance. There was, however, a significant

TABLE 2
Blood pressure and heart rate responses to tilting in five diabetics with postural hypotension during placebo and fludrocortisone therapy (Mean and S.D.)

	Systolic B.P. (mm. Hg)			Diastolic B.P. (mm. Hg)			Pulse Pressure (mm. Hg)			Heart Rate (beats/min.)		
	Lying	Tilted		Lying	Tilted		Lying	Tilted		Lying	Tilted	
Placebo	149 ±21	110 ±16	P<0.001	87 ±10	76 ±4	P<0.02	62 ±16	34 ±13	P<0.001	78 ±10	97 ±18	P<0.001
Active	180 ±26	154 ±29	P<0.10	95 ±17	88 ±11	NS	85 ±15	66 ±24	P<0.05	76 ±12	86 ±20	P<0.02
	P<0.05	P<0.005		NS	P<0.05		P<0.05	P<0.005		NS	P<0.001	

rise in the serum sodium and a significant fall in the serum potassium while on the active preparation (see table 2).

Symptoms

Four of the five subjects noticed a marked improvement in their symptoms of postural hypotension while on fludrocortisone. The two subjects with intermittent proteinuria and low plasma albumin developed pitting ankle edema within one week of starting the active preparation and one complained of frontal headache and breathlessness. Both subjects, however, were able to complete their three-week period on the active preparation and once this was stopped, these side effects rapidly subsided. The other three diabetics did not experience any side effects while on the active preparation.

DISCUSSION

Although the syndrome of orthostatic hypotension associated with autonomic dysfunction was first described in 1925 by Bradbury and Eggleston,[12] it was Rundles (1945)[13] who first clearly showed postural hypotension to be a definite feature of diabetic autonomic neuropathy. Since then others have described various aspects of postural hypotension associated with diabetic autonomic neuropathy.[3,5,7,14-22] The anatomical site of the lesion in diabetic postural hypotension is not known with certainty, but has been variously postulated to be on the afferent side of the reflex arc due to involvement of the sensory baro-receptors,[23] a central lesion of the autonomic nervous system,[13] in the efferent sympathetic pathway with deficient stimulation of the smooth muscle of the arterioles[24,25] or a parasympathetic vagal lesion with normal vasomotor tone.[21] A defect in the efferent sympathetic pathway would seem a likely explanation in the diabetic subjects in this present study because they all showed some degree of compensatory tachycardia on assumption of the erect posture, whereas this is usually absent in patients with idiopathic postural hypotension where the lesion is probably central.[26]

TABLE 2 *(Continued)*

Body weight, plasma volume, serum sodium, and potassium in five diabetics with postural hypotension during placebo and fludrocortisone therapy (Mean and S.D.)

Body Weight (kg.)	Total Plasma Volume (ml.)	Plasma Volume (ml./kg.)	Serum Na+ (mmol./liter)	Serum K+ (mmol./liter)
68.9 ±9.3	2,957 ±171	43.1 ±4.5	140.6 ±1.3	4.3 ±0.2
71.6 ±9.3	3,286 ±234	45.9 ±6.2	142.6 ±2.2	3.6 ±0.4
P<0.001	P<0.02	P<0.10	P<0.02	P<0.01

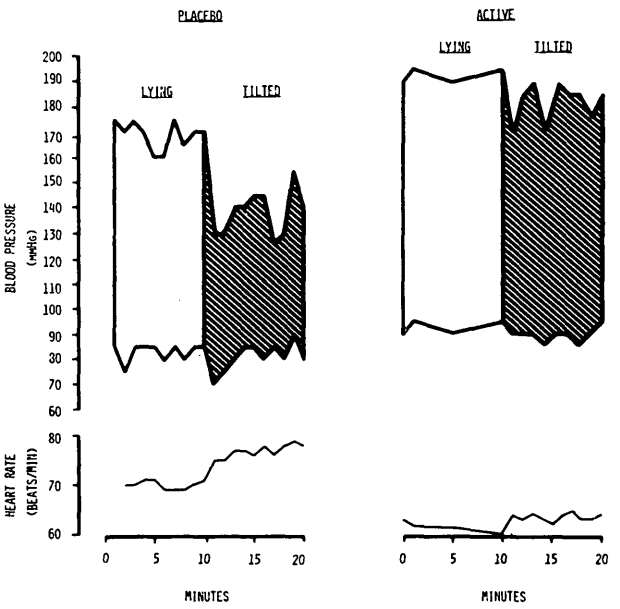

FIG. 1. The blood pressure and heart rate responses to tilting in one patient (No. 3) during therapy with the placebo and fludrocortisone therapy.

Several methods have been suggested for the treatment of postural hypotension including physical measures such as elastic tights, anti-gravity suits, abdominal binders, and postural training by tilting up the head of the bed during sleep, all of which are cumbersome; and drugs including ephedrine, fludrocortisone, and more recently the combination of a monoamine-oxidase inhibitor and tyramine.[27] Fludrocortisone has been considered to be an effective drug for the treatment of postural hypotension irrespective of the cause[28] and the action is considered to be by producing sodium retention with an increased extracellular fluid volume.[29] It may also produce some degree of constriction in partially denervated blood vessels,[30] and increase the water content of the vessel walls thereby reducing their distensibility.[31] There are, however, few detailed studies of its action in diabetes mellitus.

The present double-blind crossover study shows that the subjective and objective evidence of improvement in the postural hypotension of diabetics with autonomic neuropathy corresponds with the mineralocorticoid effect of fludrocortisone with an increase predominantly in the systolic but also in the diastolic blood pressure, and a significant rise in the serum sodium and fall in the serum potassium. In such diabetics, therefore, a possible effect of long-term fludrocortisone might be hypertensive disease. However, without treatment, these same patients would experience disabling symptoms with potential

damage of the central nervous system due to cerebral hypoxia.

Although the mean plasma volume increased while on the active preparation, these results should be interpreted with some caution because of the known variation in plasma volume of normal subjects when repeated.[10] In this study the increase in plasma volume was not enough in itself to account completely for the increase in body weight and the remainder of the increase may be explained by an isotonic expansion of the extracellular fluid volume secondary to sodium and water retention.

We conclude that fludrocortisone should be worthy of trial in diabetics with troublesome symptoms of postural hypotension due to autonomic neuropathy. Though a fixed dose of fludrocortisone, 0.1 mg. twice daily, was used in the trial, in clinical practice this would have to be adjusted to the need of the individual patient, both in terms of control of postural hypotension and the avoidance of possible side effects. Since edema only occurred in the two patients with a low serum albumin, plasma proteins should be measured routinely before starting fludrocortisone in diabetics with postural hypotension, and if the serum albumin is low, then fludrocortisone should be used with caution because the resultant increased sodium retention together with the already lowered oncotic pressure would be more liable to produce edema.

ACKNOWLEDGMENT

We thank Dr. L.J.P. Duncan for allowing us to study patients under his care, and Professor K. W. Donald for his help and encouragement.

We also thank Mr. J. Cowie and his staff at the Medical Renal Unit, Royal Infirmary, Edinburgh, for meauring plasma and urine osmolalities.

The fludrocortisone and placebo tablets were supplied by E. R. Squibb and Son, Ltd.

REFERENCES

[1]Hickler, R. B., Thompson, G. R., Fox, L. M., and Hamlin, J. T.: Successful treatment of orthostatic hypotension with 9-alpha-fluorohydrocortisone. N. Engl. J. Med., *261*:788-91, 1959.

[2]Schirger, A., Hines, E. A., Molnar, G. D., and Thomas, J. E.: Idiopathic orthostatic hypotension. JAMA *181*:822-26, 1962.

[3]Schatz, I. J., Podolsky, S., and Frame, B.: Idiopathic orthostatic hypotension. JAMA *186*:537-40, 1963.

[4]Frick, M. H.: 9-alpha-fluorohydrocortisone in the treatment of postural hypotension. Acta Med. Scand. *179*:292-99, 1966.

[5]Shear, L.: Orthostatic hypotension. Arch. Intern. Med. *122*:467-71, 1968.

[6]Bannister, R., Ardill, L., and Fentem, P: An assessment of various methods of treatment of idiopathic orthostatic hypotension. Quart. J. Med. *38*:377-95, 1969.

[7]Finch, P. J.: Extensive autonomic neuropathy in diabetes. Proc. Roy. Soc. Med. *64*:803-04, 1971.

[8]Campbell, I. W., Ewing, D. J., Clarke, B. F., and Duncan, L. J. P.: Testicular pain sensation in diabetic autonomic neuropathy. Br. Med. J. *2*:638-39, 1974.

[9]Ewing, D. J., Campbell, I. W., Burt, A. A., and Clarke, B. F.: Vascular reflexes in diabetic autonomic neuropathy. Lancet *2*:1354-56, 1973.

[10]Report by the international committee for standardization in haematology (ICSH): panel on diagnostic applications of radioisotopes in haematology. Br. J. Haematol. *25*:801-14, 1973.

[11]Wright, B. M., and Dore, C. F.: A random-zero sphygmomanometer. Lancet *1*:337-38, 1970.

[12]Bradbury, S., and Eggleston, C.: Postural hypotension: report of three cases. Am. Heart J. *1*:73-86, 1925.

[13]Rundles, R. W.: Diabetic neuropathy: general review with report of 125 cases. Medicine (Balt.) *24*:111-60, 1945.

[14]Swartz, J. M., and Stine, L. A.: Visceral neuropathy complicating diabetes mellitus. Amer. J. Med. *5*:610-15, 1948.

[15]Berner, J. H.: Orthostatic hypotension in diabetes mellitus. Acta Med. Scand. *143*:336-40, 1952.

[16]Muri, J. W.: Nocturnal diarrhoea in diabetes mellitus. Acta Med. Scand. *146*:143-45, 1953.

[17]Odel, H. M., Roth, G. M., and Keating, F. R.: Autonomic neuropathy simulating the effects of sympathectomy as a complication of diabetes mellitus. Diabetes *4*:92-98, 1955.

[18]Malins, J. M., and French, J. M.: Diabetic diarrhoea. Q. J. Med. *26*:467-80, 1957.

[19]Aagenes, O.: Neurovascular examinations on the lower extremities in young diabetics. p. 120. Published by C. Hamburgers Bogtrykkeri A/S, Copenhagen, 1962.

[20]Texter, E. C., Danovitch, S. H., Kuhl, W. J., Tomhave, W. G., and Haddy, F. J.: Physiologic studies of autonomic nervous system dysfunction accompanying diabetes mellitus. Am. J. Dig. Dis. *7*:530-44, 1962.

[21]Friedman, S. A., Frieberg, P., and Colton, J.: Vasomotor tone in diabetic neuropathy. Ann. Intern Med. *77*:353-56, 1972.

[22]Frank, H. J., Frewin, D. B., Robinson, S. M., and Wise, P. H.: Cardiovascular responses in diabetic dysautonomia. Aust. N.Z. J. Med. *1*:1-7, 1972.

[23]Sharpey-Schafer, E. P., and Taylor, P. J.: Absent circulatory reflexes in diabetic neuritis. Lancet *1*:559-62, 1960.

[24]Martin, M. M.: Involvement of autonomic nerve-fibres in diabetic neuropathy. Lancet *1*:560-65, 1953.

[25]Keen, H.: Auonomic neuropathy in diabetes mellitus. Postgrad. Med. J. *35*:272-80, 1959.

[26]Bannister, R.: Degeneration of the autonomic nervous system. Lancet *2*:175-79, 1971.

[27]Lewis, R. K., Hazelrigg, C. G., Fricke, F. J., and Russell, R. O.: Therapy of idopathic postural hypotension. Arch. Intern. Med. *129*:943-49, 1972.

[28]Leading article: Management of postural hypotension. Br. Med. J. *2*:247-48, 1970.

[29]Seager, L. H.: Pressor action of fluorohydrocortisone in orthostatic hypotension. Tufts Folia Med. *9*:56-61, 1963.

[30]Schmid, P. G., Eckstein, J. W., and Abboud, F. M.: Effect of 9-α-fluorohydrocortisone on forearm vascular responses to norepinephrine. Circulation *34*:620-26, 1966.

[31]Tobian, L., and Redleaf, P. D.: Ionic composition of the aorta in renal and adrenal hypertension. Am. J. Physiol. *192*:325-30, 1958.