Edmonds, C. J., and Wilson, G. M. (1960). *Lancet*, **1**, 505.
Hild, R., and Krueck, F. (1961). *Klin. Wschr.*, **39**, 178.
Kagawa, C. M. (1960). *Edema: Mechanisms and Management*. A Hahnemann Symposium on Salt and Water, p. 309. Edited by John Moyer and Mortons Fuchs. Saunders, Philadelphia.
Laragh, J. H., Reilly, E. B., Stites, T. B., and Angers, M. (1961). *Fed. Proc.*, **20**, 410.
Mulrow, P. J., Lieberman, A. H., Johnson, B. B., and Luetscher, J. A. (1956). *J. clin. Invest.*, **35**, 726.
Pitts, R. F. (1958). *Amer. J. Med.*, **24**, 745.
Sanderson, P. H. (1952). *Biochem. J.*, **52**, 502.
Ulick, S., Laragh, J. H., and Lieberman, S. (1958). *Trans. Ass. Amer. Phycns.*, **71**, 225.
Wiebelhaus, V. D., Weinstock, J., Brennan, F. T., Sosnowski, G., and Larson, T. J. (1961). *Fed. Proc.*, **20**, 409.
Williamson, H. E., Shideman, F. E., and Lesher, D. A. (1959). *J. Pharmacol.*, **126**, 82.

TRIAMTERENE, A NEW DIURETIC DRUG

II. CLINICAL TRIAL IN OEDEMATOUS PATIENTS

BY

W. I. BABA, M.B., Ch.B.

G. R. TUDHOPE, M.D., B.Sc., F.R.C.P.Ed. M.R.C.P.

AND

G. M. WILSON, M.D., B.Sc., F.R.C.P., F.R.C.P.Ed.

Department of Pharmacology and Therapeutics, University of Sheffield

Triamterene has a diuretic effect in oedematous patients (Hild and Krueck, 1961 ; Laragh *et al.*, 1961 ; Donnelly *et al.*, 1962 ; Crosley *et al.*, 1962), producing an increased excretion of sodium and water but a decrease in potassium excretion. Our findings in normal subjects and in adrenalectomized rats suggested that the diuretic action of triamterene is not due to aldosterone antagonism but probably to a direct action on the renal tubular cells (Baba *et al.*, 1962).

The present work describes and compares the various types of responses encountered when hydroflumethiazide, spironolactone, and triamterene were given alone and in combination to patients with chronic salt and water retention.

Patients and Methods

Clinical studies of the action of triamterene were made in 42 patients ; 27 were studied as in-patients and 15 as out-patients.

In-patient Study.—Hydroflumethiazide (100 mg.), spironolactone (400 mg.), and triamterene (200 mg.) were given alone or in combination, according to the plan illustrated in Fig. 1. All the drugs were given at 10 a.m. and urine was collected over 24-hour periods, starting at 10 a.m. each day. Before giving each dose, urine collections were made for two days, during which no drugs were given. Patients admitted to the trial were assigned alternately to Group A or Group B, the grouping determining the order of administration of the drugs. Body-weight was measured daily. All the patients took a normal diet and fluid intake was unrestricted. Blood was taken at least twice weekly for the determination of electrolytes and urea. Urine and serum creatinine levels were estimated at the beginning and end of the period of study.

Out-patient Study.—The effects of prolonged administration of triamterene alone and when combined with hydroflumethiazide or spironolactone were studied in 15 patients with chronic oedema who had all been previously treated for at least three months with oral diuretics. Observations of body weight, degree of oedema, serum electrolytes, and blood urea were made at two-week intervals, and each drug or combination of drugs was given either daily or on alternate days for periods of two weeks. Normal diet and unrestricted fluids were allowed during the trial.

Chemical Methods.—Urinary sodium and potassium were estimated by flame photometry ; triamterene in urine was estimated by fluorimetry (Baba *et al.*, 1962) ; serum electrolytes and urea were determined by routine laboratory methods ; serum and urine creatinine levels were estimated by the method of Owen *et al.* (1954).

Results

Response to Single Doses of Triamterene and of Hydroflumethiazide.—The effects of single doses of triamterene (200 mg.) and of hydroflumethiazide (100 mg.) were compared in patients in hospital. Patients of Group A received triamterene first and hydroflumethiazide second ; in Group B the order was reversed. In both groups the sodium excretion was moderately increased after triamterene, but less so than after hydroflumethiazide in the doses used. Urinary potassium loss, which was increased after hydroflumethiazide was greatly reduced after triamterene (Tables I and II ; Fig. 1).

Response to Combination of Triamterene and Hydroflumethiazide.—The response of hydroflumethiazide was considerably modified in both groups when triamterene was given simultaneously. There was a further increase in sodium and water excretion, whereas potassium excretion was greatly reduced. The sodium excretion and weight loss were greater than with either drug alone (Tables I, II ; Fig. 1).

Comparison of Triamterene with Spironolactone.—In 20 patients the trial was continued by giving triam-

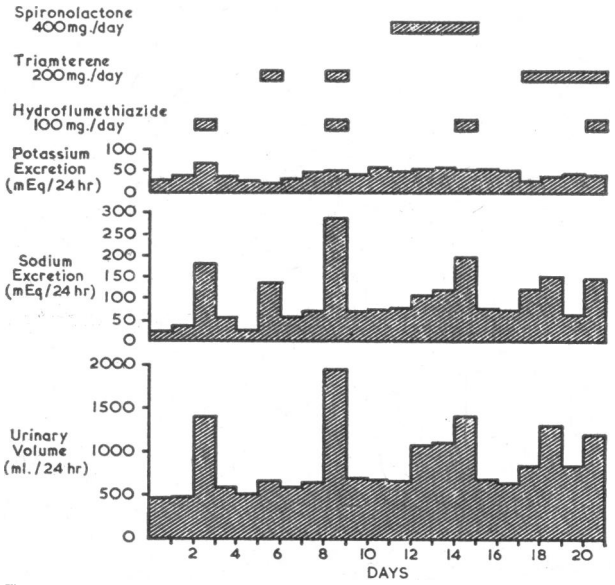

FIG. 1.—Case 4 (Group B, Table I), chronic rheumatic heart disease. Effect of hydroflumethiazide, triamterene, and spironolactone on daily urinary volume and excretion of sodium and potassium.

terene 200 mg. daily for four days, and on the fourth day hydroflumethiazide (100 mg.) was given in addition. In six of these oedematous patients spironolactone (400 mg.) was then given daily for four days, and on the fourth day hydroflumethiazide was also given. Three other patients were studied in a similar manner except that the four days of spironolactone administration preceded those of triamterene. A typical example of the results obtained is shown in Fig. 1; similar results were found with the other patients in this group. The increase in sodium excretion after the first dose of triamterene was found to be greater than that produced by spironolactone. Repeated doses of triamterene were associated with a reduction in sodium excretion in most cases, whereas daily spironolactone produced a progressive increase in sodium excretion (Fig. 1). The average total loss of weight after three days of triamterene treatment was 0.5 kg., and after spironolactone it was 0.43 kg. When hydroflumethiazide was added after three days of either triamterene or spironolactone there was an increase in sodium excretion and weight loss (mean loss of 0.62 kg. with triamterene and hydroflumethiazide and of 0.55 kg. with spironolactone and hydroflumethiazide). With both combinations the potassium excretion was less than that produced by hydroflumethiazide alone (Fig. 1). Serum electrolytes and urea showed no significant changes. After three consecutive doses of triamterene creatinine clearance was unchanged in two patients and reduced by 40–50% in five.

Triamterene Excretion in Urine.—The urine contained 10–88% of the administered dose (200 mg.) of triamterene in 24 hours. A correlation was found between the excess sodium excreted in 24 hours and the total amount of triamterene in the urine (Fig. 2).

Prolonged Treatment

Nineteen oedematous patients were studied. All had been treated previously with oral diuretics for several months, and according to their response to this previous treatment the patients were included in one of three groups. Comparisons of the various regimes were made over periods of a fortnight. Examples of the results are shown in Fig. 3.

Group 1

The seven out-patients had previously been controlled satisfactorily with hydroflumethiazide 100 mg. on alternate days and daily potassium supplements.

When triamterene 200 mg. on alternate days without potassium supplements was substituted there was a rise

TABLE II.—*Mean Daily Excretion of Sodium and Potassium (% Control) and Loss of Weight (kg.) Produced by Triamterene, Hydroflumethiazide Alone and in Combination, in Patients of Groups A and B (Table I)*

Group		Triamterene 200 mg.	Hydroflumethiazide 100 mg.	Triamterene 200 mg. Hydroflumethiazide 100 mg.
A	Sodium	+158%	+441%	+647%
	Potassium	−33%	+93%	+14%
	Loss of weight	0·15 kg.	0·6 kg.	0·80 kg.
B	Sodium	+73%	+240%	+419%
	Potassium	−41%	+54%	+11%
	Loss of weight	0·12 kg.	1·01 kg.	1·02 kg.

TABLE I.—*Effect of Triamterene, Hydroflumethiazide, and Triamterene+Hydroflumethiazide on Urinary Sodium and Potassium Excretion in Patients with Chronic Oedema Receiving a Normal Diet*

Group A

Case No.	Age and Sex	Diagnosis	Control. Mean±S.D. of Four Untreated Days		Triamterene 200 mg.		Hydroflumethiazide 100 mg.		Triamterene 200 mg. Hydroflumethiazide 100 mg.	
			Na (mEq/day)	K (mEq/day)	Na (mEq/day)	K (mEq/day)	Na (mEq/day)	K (mEq/day)	Na (mEq/day)	K (mEq/day)
1	F 33	Chronic rheumatic heart disease	5±2·4	25±4·9	39	16	65	109	103	33
2	F 34	,, ,, ,, ,,	37±11·0	64±5·1	52	47	75	47	155	40
3	M 59	,, ,, ,, ,,	27±9·4	49±7·9	38	18	90	86	144	38
4	M 55	Chronic cor pulmonale	125±21·7	52±9·8	285	43	430	134	353	76
5	M 68	,, ,, ,,	80±7·3	46±2·6	149	33	227	67	282	24
6	M 65	,, ,, ,,	110±16·1	44±4·5	113	29	153	70	261	48
7	F 65	,, ,, ,,	14±4·7	22±6·5	30	16	76	34	99	24
8	M 68	,, ,, ,,	10±6·5	17±5·4	21	7	46	43	113	31
9	F 71	,, ,, ,,	22±19·6	28±2·2	53	9	228	66	173	47
10	F 54	Nephrotic syndrome and femoral venous thrombosis	13±5·3	32±8·2	56	32	156	33	235	32
11	F 37	Nephrotic syndrome	38±18·4	53±14·2	95	43	133	115	122	87
12	F 70	Hypertensive heart failure	28±9·5	30±8·9	50	26	92	32	125	17

Group B

			Control. Mean±S.D. of Four Untreated Days		Hydroflumethiazide 100 mg.		Triamterene 200 mg.		Triamterene 200 mg. Hydroflumethiazide 100 mg.	
			Na (mEq/day)	K (mEq/day)	Na (mEq/day)	K (mEq/day)	Na (mEq/day)	K (mEq/day)	Na (mEq day)	K (mEq/day)
1	F 60	Chronic rheumatic heart disease	96±31·0	62±8·0	210	65	145	53	261	59
2	F 65	,, ,, ,, ,,	75±22·0	55±9·6	294	79	95	36	332	63
3	F 76	,, ,, ,, ,,	18±4·4	32±6·7	26	35	15	8	41	11
4	F 57	,, ,, ,, ,,	37±14·1	31±7·4	189	68	134	19	291	47
5	M 59	Ischaemic heart disease	83±40·3	59±19·5	327	76	50	32	250	56
6	M 75	,, ,, ,,	71±12·2	31±6·0	168	49	173	18	395	31
7	F 56	,, ,, ,,	35±9·0	29±5·1	198	66	76	11	307	40
8	M 72	,, ,, ,,	79±36·6	42±6·5	124	45	121	28	233	48
9	M 68	Femoral venous thrombosis	48±8·5	34±3·6	238	69	139	35	271	35
10	M 54	Nephrotic syndrome	142±36·4	44±11·0	370	62	264	35	502	67
11	F 68	Chronic cor pulmonale	6±2·2	17±0·3	26	25	8	3	70	21

in weight in all the patients although at the end of the fortnight pitting oedema was not usually evident. With this dose of triamterene no rise in blood urea occurred and the serum potassium remained at about the level observed during treatment with hydroflumethiazide and potassium supplements.

When the dose of triamterene was increased to 200 mg. daily there was no increase in weight, and from the point of view of oedema control this was as satisfactory as with hydroflumethiazide on alternate days. However, the serum potassium showed a mean rise of 21%, although it did not go above the normal range, the highest reading being 5.3 mEq/l. In all patients there was an increase in serum chloride (mean +6.4 mEq/l.) and a decrease in serum bicarbonate (mean −4.0 mEq/l.). The blood urea rose on average by 48%, and by the end of the fortnight six of the seven patients had readings above 40 mg./100 ml. In some cases the raised blood urea persisted during the subsequent two-week period of hydroflumethiazide therapy.

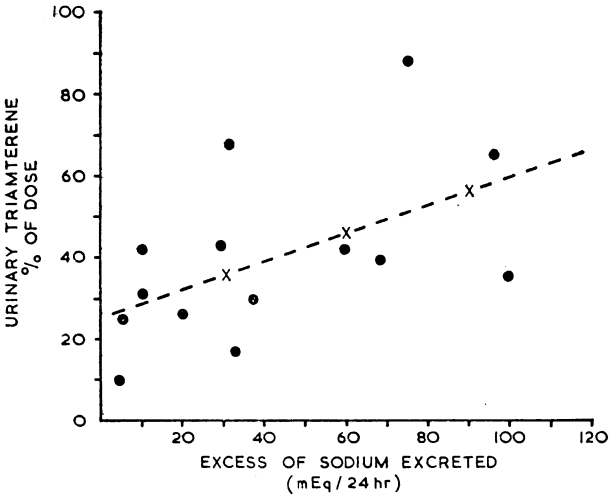

FIG. 2.—Urinary excretion of triamterene during 24 hours after a single dose of 200 mg., showing the correlation between the excess sodium excreted and the amount of triamterene in the urine ($r=0.54$).

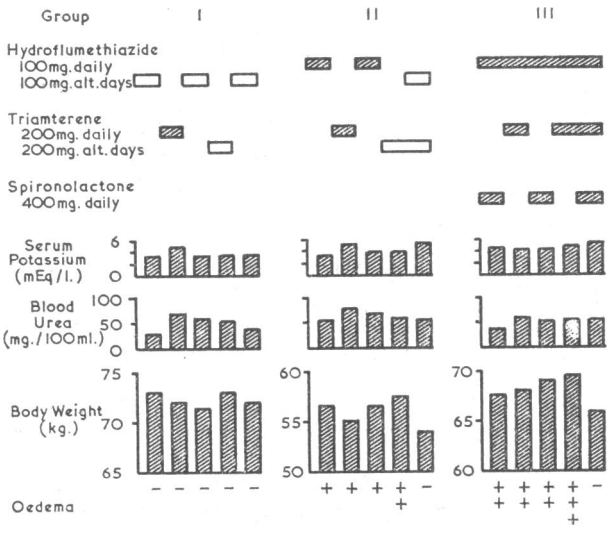

FIG. 3.—Examples of responses to prolonged treatment. Each therapeutic regime was given for a period of two weeks. Group I: Case 6—hypertensive heart disease; Group II: Case 12—thyrotoxic heart disease; Group III: Case 18—chronic cor pulmonale.

Group II

The six out-patients had been treated previously with hydroflumethiazide 100 mg. daily and daily potassium supplements. This regime had not kept them entirely oedema-free and minimal pitting was usually detectable at the ankles.

Triamterene 200 mg. daily was also not effective in relieving their oedema, and again there was a rise in serum potassium and blood urea. Further increase in oedema developed when triamterene was given only on alternate days. Similar changes in serum potassium and blood urea occurred as in the Group I patients.

A combination of hydroflumethiazide 100 mg. and triamterene 200 mg. both together on alternate days with no potassium supplements was then tried. In all cases there was a conspicuous loss of weight and at the end of the fortnight no pitting oedema was detectable. The serum potassium was in the range 3.3–4.0 mEq/l. and there was no rise in blood urea.

Group III

These six patients had persistent oedema in spite of prolonged daily treatment with hydroflumethiazide, spironolactone, and potassium supplements. Two were studied as out-patients and four in hospital. Continuation of the hydroflumethiazide but substitution of triamterene 200 mg. daily in place of spironolactone and potassium led to an increase in weight, oedema, and blood urea. However, when hydroflumethiazide. spironolactone, and triamterene were all given together daily there was a reduction in weight and loss of oedema. The blood urea remained above the normal range. More prolonged therapy has been continued in these patients.

Two patients with hitherto intractable oedema had shown persistently low serum sodium values.

Case 16.—A housewife aged 33 with chronic rheumatic heart disease had previously taken daily hydroflumethiazide 100 mg., spironolactone 800 mg., and potassium supplements for 10 months, but, despite this, she had considerable oedema and the sodium concentration in the serum was reduced to 127mEq/l. Triamterene (200 mg.) daily was added to her previous therapy including the potassium supplements. After one week on this regime she lost 7 kg. in weight and the oedema cleared completely (Fig. 4). There was a rise in the serum sodium level to 140 mEq/l; however. there was also a rise in serum potassium to 9.6 mEq/l. and in blood urea to 82 mg./100 ml. After triamterene and potassium supplements were withdrawn, on account of the hyperkalaemia and impending uraemia, there was a decrease in sodium and water excretion and the weight began to increase. The serum sodium dropped to 123 mEq/l. and there was a reduction in potassium level to 4.9 mEq/l.

A similar diuretic response was obtained in Case 17, a housewife aged 50, with chronic cor pulmonale and severe congestive heart failure. She had a considerable degree of oedema and ascites. She had previously received hydroflumethiazide, spironolactone, and potassium supplements, but, despite this, the oedema was persistent and her serum sodium concentration was reduced to 124 mEq/l. In this case, triamterene 200 mg. daily was given in addition to spironolactone and hydroflumethiazide, but in view of the experience with the previous case potassium supplements were stopped. After three weeks on this regime the oedema had cleared completely, and the serum sodium level was remaining steady at about 138 mEq/l., the serum potassium at 3.6 mEq/l., and the blood urea at 40 mg./100 ml.

Side-effects

Apart from the rise in serum potassium and blood urea, no serious undesirable effects have so far been noticed. No change has been found in haemoglobin concentrations, leucocyte count, and blood film. No albuminuria or haematuria has been produced, but the faint blue colour of the urine has been consistently observed. A few patients have complained of looseness of bowel motions, which rapidly reverted to normal on discontinuing triamterene administration.

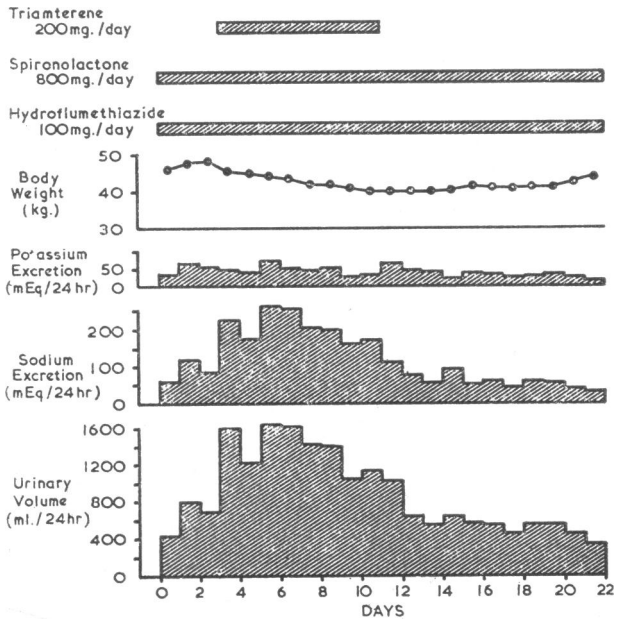

FIG. 4.—Chronic rheumatic heart disease. Effect of triamterene +hydroflumethiazide+spironolactone on daily body weight, urinary volume, and excretion of sodium and potassium.

In addition to the studies described above, six patients received triamterene in the larger dose of 300 mg. daily for 14 days. Four of these developed diarrhoea and two had nausea and vomiting after four days of this dosage. The symptoms were rapidly relieved after stopping the drug. As with the other patients receiving daily triamterene, there was a rise in the level of the blood urea in all these cases, but no other toxic manifestations were found.

However, it is obviously too early to assess the potential toxicity of this drug in man.

Discussion

Triamterene produced an increase in sodium excretion and a considerable decrease in potassium excretion in oedematous patients. The increase in water and sodium excretion was found to be much less than that produced by hydroflumethiazide in the doses used. However, the two drugs produce their effect by different mechanisms, so that triamterene potentiates the action of hydroflumethiazide when given simultaneously, producing a further increase in water and sodium excretion and a decrease in potassium excretion.

Our results in oedematous patients support our finding that the mechanism of action of triamterene is different from that of spironolactone. The effect of repeated doses of spironolactone produced a progressive increase in sodium excretion, whereas in most cases repeated doses of triamterene led to progressive decrease during the three-day period. The potassium-retaining action of triamterene was found to be greater than that of spironolactone. Prolonged administration of triamterene produced an increase in serum potassium level, and additional potassium should not be given when patients are treated with triamterene either alone or in combination with hydroflumethiazide. Triamterene was found to potentiate the action of spironolactone and hydroflumethiazide when all three were given together, which further suggests that triamterene has a different mechanism of action from that of spironolactone.

Prolonged administration of triamterene produced a rise in the serum levels of potassium and chloride and in blood urea and a decrease in serum bicarbonate level. The rise in blood urea may be explained by reduced glomerular filtration; repeated doses of triamterene over a three-day period produced a decrease in creatinine clearance in most patients.

It appears from our studies that administration of triamterene and hydroflumethiazide on alternate days produces no rise in blood urea. This regime was of considerable value in the treatment of patients whose oedema was persistent when treated with hydroflumethiazide alone. Daily administration of triamterene and hydroflumethiazide again produced a rise in level of blood urea.

The combination of triamterene, hydroflumethiazide, and spironolactone has proved of value in the treatment of refractory cases of oedema, but the level of serum potassium must be watched carefully.

It is evident from our studies that triamterene when given alone is a weak diuretic agent. Its main therapeutic use is in combination with a thiazide, or with spironolactone and a thiazide in treatment of refractory cases of oedema.

Summary

The action of triamterene (2,4,7-triamino-6-phenylpteridine) has been studied in 42 oedematous patients—27 as in-patients and 15 as out-patients. Triamterene produced an increase in sodium and water excretion. Its natriuretic effect was found to be less than that of hydroflumethiazide. Like spironolactone, it potentiates the action of hydroflumethiazide, producing a further increase in sodium excretion and a decrease in potassium excretion. Its potassium-retaining action was greater than that of spironolactone, and potassium supplements should not be given when patients are treated with a combination of triamterene and hydroflumethiazide. Triamterene alone was not effective in patients whose oedema was persistent when treated with hydroflumethiazide alone, but in these cases improvement followed when the drugs were given together. Prolonged daily administration of triamterene alone or with hydroflumethiazide produced a rise in blood urea; however, this effect was not observed when the combined therapy was given on alternate days. This has proved the most satisfactory regime. Triamterene, hydroflumethiazide, and spironolactone given together were found effective in patients with otherwise persistent oedema.

W.I.B. is in receipt of a grant from the Iraqi Ministry of Education. We are grateful to Dr. K. Hardy, Medical Superintendent, Wharncliffe Hospital, and to the nursing staffs of the Royal Infirmary, Sheffield, and of Wharncliffe Hospital, Sheffield, for their willing co-operation, and to the technicians of the Department of Therapeutics, Univer-

sity of Sheffield, for their assistance. We thank Messrs. Smith Kline and French for the supply of triamterene.

REFERENCES

Baba, W. I., Tudhope, G. R., and Wilson, G. M. (1962). *Brit. med. J.*, **2**, 756.
Crosley, A. P., Ronquillo, L., Strickland, W. H., and Alexander, F. (1962). *Ann. intern. Med.*, **56**, 241.
Donnelly, R. J., Turner, P., and Sowry, G. S. C. (1962). *Lancet*, **1**, 245.
Hild, R., and Krueck, F. (1961). *Klin. Wschr.*, **39**, 178.
Laragh, J. H., Reilly, E. B., Stites, T. B., and Angers, M. (1961). *Fed. Proc.*, **20**, 410.
Owen, J. A., Iggo, B., Scandrett, F. J., and Stewart, C. P. (1954). *Biochem. J.*, **58**, 426.

USE OF A PTERIDINE DIURETIC (TRIAMTERENE) IN TREATMENT OF HEPATIC ASCITES

BY

STANLEY SHALDON, M.A., M.D., M.R.C.P.
Lecturer in Medicine

AND

JILL A. RYDER, M.Sc.
Biochemist

From the Department of Medicine, Royal Free Hospital, London

Triamterene (2,4,7-triamino - 6 - phenylpteridine ; SKF 8542) has been shown to produce a sodium diuresis with potassium retention in oedematous patients (Laragh *et al.*, 1961 ; Donnelly *et al.*, 1962). This is not dependent upon a direct antagonism of aldosterone (Liddle, 1961), for the effect is seen in the adrenalectomized subject not on salt-retaining steroids. Nevertheless, the drug is capable of reversing the sodium-retaining and potassium-wasting effects of administered 9α-fluorohydrocortisone in dogs (Wiebelhaus *et al.*, 1961) and in man (Shaldon, 1961, unpublished observation), suggesting that its action is on the distal renal tubule at the site where sodium reabsorption is controlled by aldosterone. These unique properties have prompted its study in 10 cirrhotic patients with ascites. Such patients are known to be suffering from secondary hyperaldosteronism and are often resistant to diuretics such as thiazides or mercurials, and have in addition excessive potassium loss in the urine.

The Investigation

The 10 patients with portal cirrhosis and ascites gave no history of alcoholism or previous hepatitis (see Table). All patients excreted less than 1 mEq of sodium per 24 hours in the urine on a daily sodium intake of 22 mEq. Before referral to the Royal Free Hospital they had required at least one paracentesis and were classified as "resistant" cases of ascites because of failure of previous diuretic therapy, which had included thiazides, mersalyl, and spironolactone. Strict dietary sodium restriction had not been practised. On admission the patients were put to bed and received daily 22 mEq of sodium and 60–90 mEq of dietary potassium without supplements ; protein intake varied from 60 to 80 g. daily, but was constant in the individual patient ; the fluid intake was measured but not restricted, and the patients were weighed daily. Urine collections were made over 24-hour periods, beginning at 8 a.m. Biochemical methods used included sodium and potassium in serum and urine by flame photometry, chloride by potentiometric titration (Sanderson, 1952), urea (Archer and Robb, 1925), and creatinine in serum and urine (Hare, 1950). The 24-hour endogenous creatinine clearance was used as an index of the glomerular filtration rate. Urinary and serum osmolality were measured with a Fiske osmometer. Arterial blood *p*H, Pco_2, and bicarbonate were measured with an Astrup radiometer (Astrup *et al.*, 1960).

After a control period of three days all 10 patients received chlorothiazide 2 g. daily for three days. Urinary electrolytes returned to baseline three to five days later, and then 150 mg. of SKF 8542 was given daily for three days. Eight patients then received a further three-day course of SKF 8542, 200 mg. daily, and finally six patients received a three-day course of SKF 8542, 300 mg. daily. All 10 patients also received a three-day course of SKF 8542, 150 mg. daily, in combination with chlorothiazide 2 g. daily. Eight patients then received 200 mg. of SKF 8542, and five received 300 mg. of SKF 8542 daily, both in combination with chlorothiazide 2 g. daily for three days. In addition, after a suitable period had elapsed with return to control urinary excretion of sodium, four patients were placed on chlorothiazide 2 g. daily and spironolactone 600–1,200 mg. daily. The amount of spironolactone was increased until no further increment in urinary sodium excretion occurred. At this stage 150 mg. of SKF 8542 daily was added to the combination for three days.

The results are expressed as the three-day mean urinary volume, sodium, and potassium excretion for each patient.

Results

Control Period.—In all 10 patients the basal level of 24-hour urinary sodium excretion was less than 1 mEq, and the mean 24-hour urinary potassium excretion was 40 mEq and 24-hour urinary volume 500 ml. Weight changes were negligible and no patient was losing weight.

SKF 8542 (Fig. 1).—SKF 8542, 150 mg. daily, increased the mean 24-hour urinary sodium excretion to 7 mEq, the potassium excretion rose to 50 mEq,

Clinical and Biochemical Data

Case No.	Age and Sex	Aetiology of Cirrhosis	Blood Urea (g./100 ml.)	Creatinine Clearance (ml./min.)	Outcome
1	14 M	Cryptogenic	35 (80)	100 (60)	Alive at 14 months on intermittent SKF 8542, chlorothiazide, and K supplements. Blood urea 40 mg/.100 ml.
2	60 F	,,	40 (90)	75 (30)	Alive at 14 months on intermittent SKF 8542, chlorothiazide and K supplements. Blood urea 45 mg./100 ml.
3	49 F	,,	30 (30)	90 (90)	Died after 6 months' therapy; no ascites at post mortem; kidneys normal
4	60 F	,,	20 (90)	120 (40)	Alive at 14 months, relapsed on SKF 8542 after 6 months, re-required spironolactone. Blood urea 45 mg./100 ml.
5	70 M	,,	80 (120)	50 (25)	Died in hospital from liver failure. Kidneys normal
6	62 F	,,	60 (90)	50 (35)	,, ,,
7	60 M	,,	70 (100)	45 (25)	,, ,,
8	33 F	,,	50 (70)	50 (35)	,, ,,
9	31 F	,,	30 (30)	120 (120)	Left hospital: not available for follow-up
10	19 F	,,	45 (60)	90 (70)	,, ,,

Figures in parentheses represent maximal changes seen during combined diuretic therapy with chlorothiazide and SKF 8542.