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

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

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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effects of administered 9α-fluorohydrocortisone in dogs (Wiebelhaus *et al.*, 1961) and in man (Shaldon, 1961, unpublished observation), suggesting that its action is on the distal renal tubule at the site where sodium reabsorption is controlled by aldosterone.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.

and urine volume increased to 750 ml. When SKF 8542 was increased to 200 and 300 mg. daily urinary sodium excretion rose to 10 and 12.5 mEq per 24 hours with no significant alteration in urinary potassium excretion or urinary volume. No patient lost weight. No significant alteration in arterial *p*H, P_{CO_2}, or bicarbonate occurred. "Free water" clearance was reduced and the serum sodium level fell by an average of 3 mEq/l. in 5 out of 10 patients, but the serum potassium levels were unaltered. Endogenous creatinine clearances fell in four patients (Nos. 1, 2, 4, 5) by 20 to 30% (mean

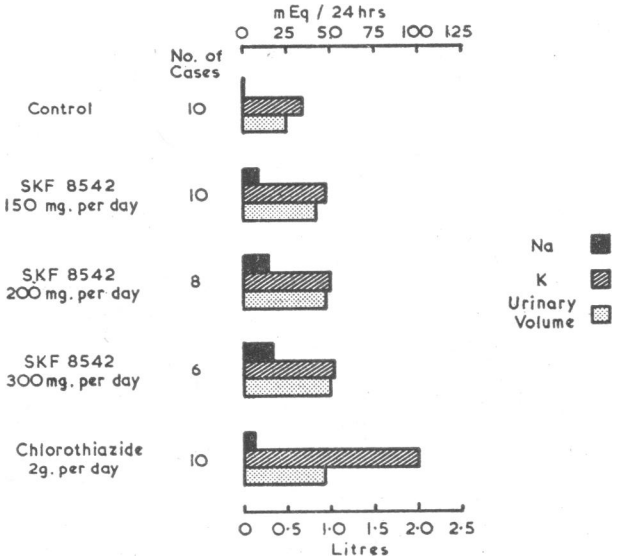

FIG. 1.—The three-day mean urinary volume and sodium and potassium excretion during a control period and during three-day courses of SKF 8542 and chlorothiazide alone. The slight increment in sodium and potassium excretion with SKF 8542 contrasts with the marked potassium loss seen with chlorothiazide alone (see text).

25%). In the remaining six patients there was no significant alteration in creatinine clearances or blood-urea levels. Chlorothiazide 2 g. daily, when given alone, produced a smaller sodium excretion in the 10 patients (mean 4 mEq/24 hours) with a greatly increased potassium loss (mean 100 mEq/24 hours). Two patients (Nos. 1, 2) showed a 30% reduction in creatinine clearance, and serum potassium levels fell in all patients if potassium supplements were not given.

SKF 8542 Combined with Chlorothiazide (Fig. 2).—When SKF 8542, 150 mg. daily, was combined with chlorothiazide 2 g. daily for three days there was a satisfactory sodium diuresis and weight loss in all 10 patients. The mean 24-hour urinary volume increased to 2,000 ml., sodium to 75 mEq, and potassium from 40 to 60 mEq. However, this potassium loss was less than the 100 mEq seen with chlorothiazide alone. Loss of weight averaged 0.3 kg. per day. No significant increase in diuretic efficiency or reduction in potassium wastage was achieved by increasing the SKF 8542 dosage to 200 and 300 mg. daily. In eight patients asymptomatic hyponatraemia (mean reduction of serum sodium 5 mEq/l.) and hypochloraemia (mean reduction of serum chloride 7 mEq/l.) developed. These changes were associated with a reduction in "free water" clearance. Hypokalaemia developed in four patients but hyperkalaemia occurred in two patients after reduction in creatinine clearances (Nos. 5, 7). When the combination of SKF 8542 and chlorothiazide was used for prolonged treatment, potassium supplements became necessary (Fig. 3). The arterial pH, P_{CO_2}, and bicarbonate were not significantly altered during the diuretic response. The blood-urea levels increased from a

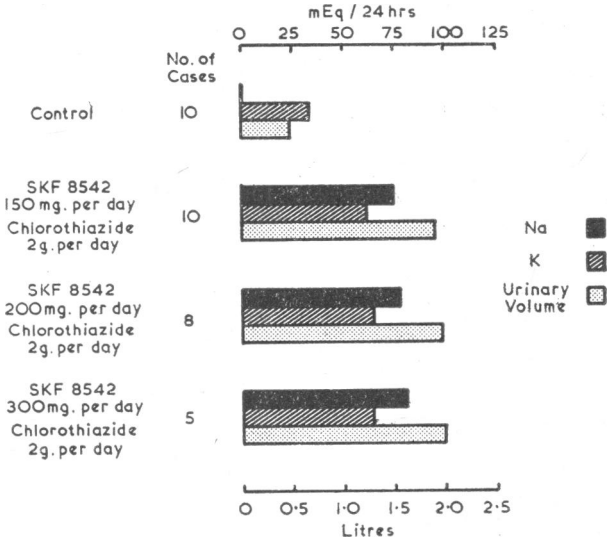

FIG. 2.—The three-day mean urinary volume and sodium and potassium excretion during a control period and during three-day courses of SKF 8542 and chlorothiazide in combination. A successful sodium diuresis with some increase in potassium loss, but less than with chlorothiazide alone, was achieved in all patients. Increasing the dose of SKF 8542 did not affect the sodium diuresis.

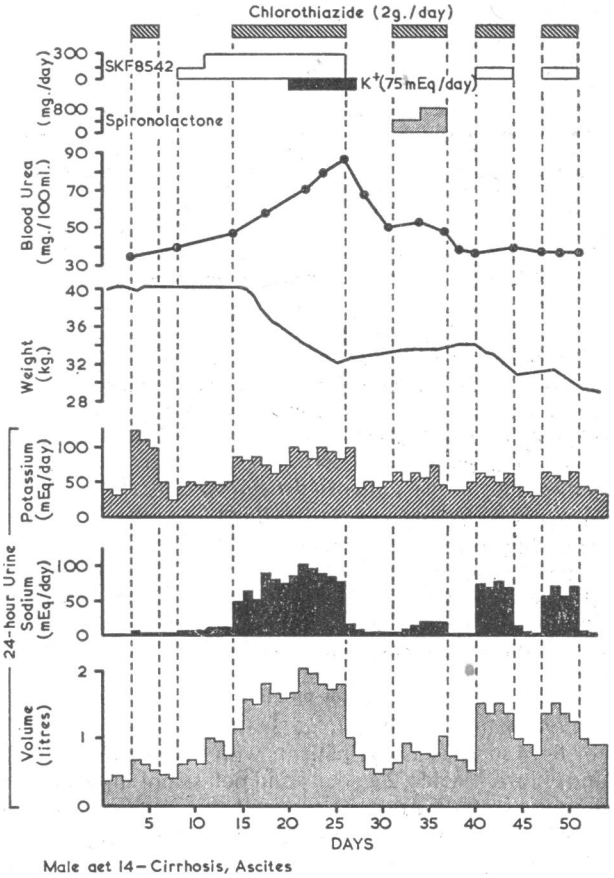

FIG. 3.—Case 1. The patient failed to respond to chlorothiazide or SKF 8542 alone, but on combining the two diuretics a dramatic sodium diuresis ensued. The blood urea rose to 90 mg./100 ml., but the patient also became hypokalaemic and required potassium supplements. On intermitting diuretic therapy the blood urea fell to normal and has remained within normal limits during 14 months of combined SKF 8542 and chlorothiazide therapy three days a week.

control mean of 45 mg./100 ml. (range 20–80 mg./100 ml.) to 70 mg./100 ml. (range 30–120 mg./100 ml.), although two patients showed no alteration in blood-urea levels. Creatinine clearances were reduced by 32% in eight patients (see Table). This reduction in creatinine clearance with elevation of the blood urea appeared during continuous daily diuretic therapy for longer than seven days with a combination of SKF 8542 and chlorothiazide.

SKF 8542 in Combination with Spironolactone and Chlorothiazide (Fig. 4).—In four patients the mean sodium excretion achieved with spironolactone and chlorothiazide was 50 mEq daily. When SKF 8542, 150 mg. daily, was added, the mean sodium excretion

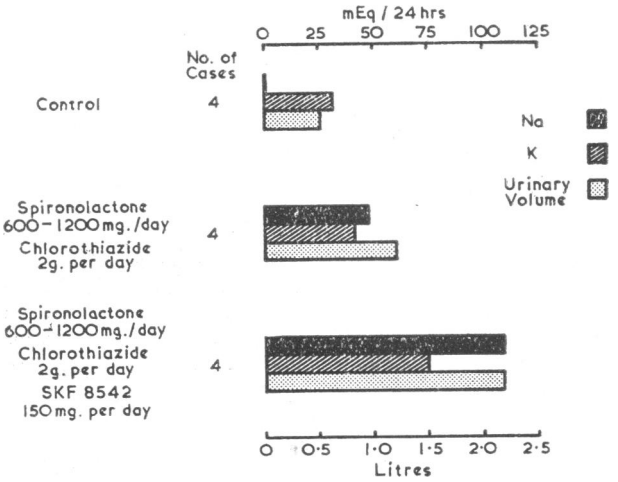

FIG. 4.—The three-day mean urinary volume and sodium potassium excretion during a control period and while the patients were diuresing maximally with spironolactone and chlorothiazide. At this stage the three-day mean sodium excretion was doubled by adding SKF 8542 to the combination (see text).

increased to 100 mEq daily, urine volumes increased from 1.2 to 2.2 litres, and potassium excretion rose from 30 to 40 mEq per 24 hours.

Overall Results

In all 10 patients the ascites was satisfactorily controlled. Four patients died from liver-cell failure while in hospital. At necropsy the kidneys were normal histologically although azotaemia had been present. The other six patients left hospital with their ascites controlled. Four patients developed azotaemia during continuous intensive diuretic therapy with SKF 8542 and chlorothiazide. However, blood-urea levels fell to normal when the combination of SKF 8542 and chlorothiazide was given three days per week instead of daily. This relaxation in diuretic therapy was possible only when the ascites was controlled.

Follow-up Results

Four patients (Nos. 1, 2, 3, 4) continued treatment for 6–14 months as out-patients with SKF 8542, 150 mg., and chlorothiazide, 2 g., daily and potassium supplements. Two patients (Nos. 3, 4) received this combination for five days weekly, and two for three days per week—one on alternate days (No. 2) and one (No. 1) on consecutive days. One patient (No. 3) died after six months with a perforated peptic ulcer. At necropsy no ascites was present and the kidneys were histologically normal. One patient (No. 4) redeveloped ascites after four months' out-patient treatment, and in spite of increasing the dosage of SKF 8542 to 300 mg. daily she ultimately required spironolactone to control her ascites. The other two patients (Nos. 1, 2) have remained reasonably symptom-free for 14 months. During this time the ascites has been controlled and strict dietary salt restriction has been employed.

Side-effects

Three patients developed loose bowel motions and some nausea while on SKF 8542, and one patient (No. 5) discontinued treatment because of this; in the other two patients the upset was transient. No depression of white blood cells has been observed after 14 months' drug therapy. Blood-pressure was not significantly affected, but no patient was hypertensive at the start of the trial. Urinary deposits have repeatedly shown no abnormalities microscopically.

Discussion

SKF 8542 and spironolactone have similar effects, and it was originally suggested that SKF 8542 was an antagonist of aldosterone (Crosley *et al.*, 1961). However, the drug acts in the absence of aldosterone, indicating a direct independent effect on the renal tubule. The potentiation by SKF 8542 of the sodium diuresis in four cirrhotic patients maintained on maximal doses of spironolactone supports the hypothesis that it inhibits sodium resorption independently of an aldosterone-blocking mechanism. The reduction in free water clearance suggests that its principal site of action is at the level of the distal tubule; a similar reduction in free water clearance has been observed with spironolactone (Shaldon, 1960). The development of hyponatraemia and hypochloraemia is probably secondary to the reduction in free water clearance with consequent retention of water in excess of sodium and chloride. The previously reported potassium-retaining effects of SKF 8542 (Donnelly *et al.*, 1962) were not clearly demonstrated in cirrhotic patients. The failure to achieve potassium conservation may have been partly due to the addition of chlorothiazide, although loss of potassium still occurred when SKF 8542 was used alone. This might be due to hyperaldosteronism which was not sufficiently counteracted by SKF 8542. The reduction in potassium loss when SKF 8542 was combined with chlorothiazide was similar to that seen when spironolactone and chlorothiazide were given together (Shaldon *et al.*, 1960), although with both combinations potassium supplements were still required for long-term use.

SKF 8542 definitely reduced the glomerular filtration rate, particularly when the drug was used with chlorothiazide. Elevation of the blood urea (Laragh *et al.*, 1961; Donnelly *et al.*, 1962) and reduction in glomerular filtration rates (Baba, personal communication, 1962) have also been observed when SKF 8542 was given alone to oedematous patients and normal subjects. The reduction in glomerular filtration rates in dogs following intravenous chlorothiazide has been attributed to a direct action of that drug in redistributing renal blood-flow within the kidney (Spencer, 1960). We have, however, rarely noted a reduction in glomerular filtration rate when an intravenous load of a thiazide diuretic is given to cirrhotic patients (Shaldon *et al.*, 1962). Such studies of SKF 8542 are limited by the absence of a suitable intravenous preparation, and further work is necessary to clarify the mechanism responsible. The normal urinary deposit and renal histology preclude a direct toxic action, and the reversible nature of the

azotaemia with intermittent use of SKF 8542 suggests there is some reversible effect on renal blood-flow.

The diuretic response to the combination of SKF 8542 and chlorothiazide is excellent and all patients lost their ascites. The drug was active within a few hours of administration, and, unlike spironolactone, need not be given on consecutive days to obtain a diuretic response. In no patient could the administration of SKF 8542 be related directly to the production of hepatic precoma or coma. The maximal effective dose was between 150 and 200 mg. daily, given in two doses daily. Long-term follow-up of four patients showed only one patient who reaccumulated ascites while on combined SKF 8542 and chlorothiazide therapy. There have been no toxic effects with 14 months' continuous use of the drug.

SKF 8542 is an effective diuretic in patients with cirrhosis and intractable ascites, particularly when given in combination with a proximal tubular diuretic of the thiazide series. The similarity to spironolactone suggests a distal tubular site of action through a mechanism not dependent upon the blockade of aldosterone.

Summary

The effect of triamterene (SKF 8542), a new pteridine diuretic, alone and in combination with chlorothiazide has been assessed in 10 patients with ascites due to cirrhosis of the liver. When given alone SKF 8542 produced only a small sodium diuresis without clinical alteration of the ascites. However, when combined with chlorothiazide the previous diuretic resistance to both diuretics individually was abolished and a satisfactory control of ascites was achieved in all cases.

The similarity of action to spironolactone suggests it acts on the distal renal tube, although potassium depletion did occur and supplements were necessary when the drug was combined with chlorothiazide. SKF 8542 significantly increased the sodium diuresis in four patients already receiving spironolactone and chlorothiazide. This observation confirmed previous suggestions that SKF 8542 produces a sodium diuresis independently of an antagonism of aldosterone.

Glomerular filtration rates were reduced by an average of 30% during continuous combined diuretic therapy with SKF 8542 and chlorothiazide, but reverted to control levels when intermittent therapy was given. No direct evidence of nephrotoxicity was found. Two patients have been maintained for 14 months on intermittent SKF 8542 and chlorothiazide without adverse side-effects.

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RHEUMATIC HEART DISEASE COMPLICATING PREGNANCY

THE REMOTE PROSPECTS

BY

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The purpose of this communication is to consider the remote effects of child-bearing on women afflicted by rheumatic heart disease.

A prospective study of rheumatic heart disease complicating pregnancy was begun in the National Maternity Hospital on January 1, 1948. During the following eight years 539 pregnancies were observed in 385 women. Distinctive features of the series were the high parity of the mothers and the fact that therapeutic abortion was never performed. This combination of circumstances provided an unusual opportunity to observe the effects of child-bearing on the course of the disease and at the same time to assess, albeit in a negative sense, the value of therapeutic abortion.

Immediate Results

The immediate results have been published (Drury *et al.*, 1954; O'Driscoll *et al.*, 1957). Some points relevant to the present context are worthy of reiteration. Deaths that occurred during pregnancy or within an arbitrary period of one year of confinement were regarded as having been related to pregnancy. There was no such death in 475 booked cases and 7 deaths in 64 unbooked cases. Not one of the 7 women who died had been seen at the hospital previous to admission in heart failure. At that time the period of gestation was 16 weeks or more in every case (Table 1). The mothers were notable for their comparative youth and low parity. The woman with 10 children died from rupture of a classical caesarean section scar several weeks before term.

TABLE I.—*Details of Seven Fatal Cases*

Age	23	24	25	27	28	37	39
Gravida	1	1	1	2	1	3	10
Gestation in weeks on admission	30	16	31	32	30	20	30

The conclusions were that adequate care can virtually eliminate maternal deaths from this disease, and that therapeutic abortion is a dangerous substitute for adequate care.

Remote Results

Whether repeated child-bearing and the consequent stress of caring for a young family would materially affect the remote prospects of these mothers remained in doubt. In order to answer this question a follow-up of the 378 women who survived delivery by more than a year was undertaken in January, 1961. All had then been delivered between 5 and 13 years previously. Of the 378 women, 356 (94.2%) were traced, 16 (4.2%) had emigrated, and 6 (1.6%) were untraced. The emigrants went to Britain (12), U.S.A. (3), and Canada (1). On