Clinical Trial

TRIAL OF A TRIAMTERENE-BENZTHIAZIDE COMBINATION (DYTIDE)

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THE USE of thiazide diuretics for the control of oedema in heart failure and other conditions is commonplace. In many instances these drugs are used over long periods, but unfortunately one of the drawbacks of their long-term use can be the development of electrolyte imbalance states, especially hypokalaemia. This is particularly dangerous when associated with digitalis therapy. Hypokalaemia can be prevented by potassium replacement therapy but this is often unpleasant because of the size and number of tablets required, and of their taste. When a patient is having a variety of tablets, the potassium tablets are often the first to be omitted or reduced should he feel out of sorts for any reason.

'Dytide', a preparation of triamterene combined with benzthiazide, has recently been introduced for clinical use. Benzthiazide is a thiazide derivative with an action comparable to hydrochlorothiazide (Ford, 1960). Triamterene, a pteridine derivative, has an effective diuretic and natriuretic action and does not cause a loss of potassium (Wiebelhaus, Weinstock, Brennan, Sosnowski and Larsen, 1961; Crosley, Ronquillo, Strickland and Alexander, 1962; Baba, Tudhope and Wilson, 1962); it has been shown to act on the distal renal tubules (Baba and others, 1964) and a number of investigators have suggested that it therefore augments the action of thiazide derivatives which act on the proximal tubules, while at the same time inhibiting the associated potassium loss (Donnelly, Turner and Sowry, 1962; Cattell and Havard, 1962; Baba; Tudhope and Wilson, 1962; Nielson, 1964). Thus, a combination of triamterene with a thiazide diuretic could be considered to be suitable for treating oedematous patients, especially over a prolonged period, without the need for supplementary potassium therapy. This combination has been used successfully by Golaszewski and Healy (1963) and by Golaszewski, Lazarus and Healy (1964), who found it more effective than triamterene alone.

It was decided to evaluate 'Dytide' in oedematous patients in whom diuretics would normally be used, and to assess its ability to maintain the serum potassium level within normal limits when given over prolonged periods.

Methods and Material

Investigations: Patients were weighed before treat-

ment and twice weekly thereafter while in hospital (with the exception of Case 11). Before diuretic therapy was commenced, and weekly thereafter blood was taken for the investigation of serum electrolytes; the estimation of the serum potassium and urea being undertaken on all occasions and other electrolyte estimations when considered necessary. Before treatment a 24-hour urine specimen was sent for sodium and potassium estimations, which were repeated on the 7th day after starting 'Dytide'. (In three patients, on admission, diuretic therapy could not be withheld for 24 hours, therefore mersalyl was immediately given; in two of these patients it was then possible to withhold other diuretics for a further 24 hours and allow for the appropriate blood and urine collections to be taken.)

Dosage: Each capsule of 'Dytide' contains 50 mg. of triamterene and 25 mg. of benzthiazide. Two capsules were given in the morning and the third capsule in the early afternoon in order to obtain the main diuretic effect during waking hours. This dosage was continued for a week and if the diuretic response proved to be satisfactory the dose was then reduced to two capsules daily, and subsequently, in Out-patients, to two capsules a day on alternate days.

Evaluation of Treatment: The response to therapy was assessed by the improvement in the clinical state, by the diminution of oedema and by the loss of weight.

Associated therapy (digitalis, antibiotics, oxygen, etc.) was prescribed when considered desirable, no potassium supplements were given. The patients were given the standard ward diet without added salt. After discharge the patients were examined in the Out-Patients' Department at fortnightly and monthly intervals as required by their clinical state. They were then weighed and blood was taken on every occasion for serum urea and serum potassium, and for any other investigations considered necessary.

Urea was estimated by the method described by Skeggs (1957), and Marsh, Fingerhut and Kirsch (1957), using the Technicon "Autoanalyser". Sodium and potassium were estimated by flame photometry, and uric acid by the method of Feichtmeir and Wrenn (1955).

Results

Twenty-two patients were investigated, of whom eleven were males and eleven females. The average age of the males was 65 and that of the females 70; that of the group was 68. Eight had had previous diuretic and other therapy at home and were admitted because of a deterioration in their condition.

TABLE 1

Case No.	Diagnosis	Age	Sex	Clinical Response	Loss of Wt. on 7th day in lbs.	Total stay in hospital in days	Wt. loss at end of hospital stay
1	Hypertension	68	F	satisfactory	5	14	7
2	Cor pulmonale						
3	Chronic bronchitis	63	M	satisfactory	8	15	8
	Mitral incompetence						
	Auricular fibrillation	71	F	satisfactory	9	28	10
4	Kyphoscoliosis						
	Pneumonia—cor pul.	63	M	satisfactory	12	35	15
5	Rheumatic ht. disease						
	Auricular fibrillation	63	F	satisfactory	4	30	36
6	Cardiomyopathy						
	Auricular fibrillation	66	M	satisfactory	10	14	17
7	Cardiomyopathy ? Myeloma						
	Auricular fibrillation	76	M	satisfactory	25	17	36
8	Cor pulmonale						
	Chronic bronchitis	73	M	satisfactory	8	28	39
9	Rheumatic ht. disease	51	M	satisfactory	8	10	8
10	Rheumatic ht. disease	67	F	satisfactory	6	14	9
11	Acute myocardial infarct.	66	F	satisfactory	N.K.	35	N.K.
	Left ventricular failure.						
12	Ischaemic ht. disease	74	F	partial response	5	21	4
13	Cor pulmonale	70	M	partial response	7	14	10
	Chronic bronchitis						
14	Cardiomyopathy	63	M	partial response	10	17	16
15	Coarctation of aorta	59	M	partial response	+3	10	+3*
16	Hypertension	78	F	partial response	8	24	23
	Digitalis intoxication						
17	Rheumatic ht. disease	76	F	partial response	6	24	12
18	Cor pulmonale	67	M	no response	1	13	—
	Chronic bronchitis						
19	Nephrotic syndrome	70	F	no response	5	58	—
20	Hypertension	72	F	no response	2	14	3†
21	Ischaemic ht. disease	66	M	no response	nil	17	nil
	Left ventricular failure						
22	Cor pulmonale	65	F	drug stopped	8	17	—
	Chronic bronchitis			side effects			

* See text for explanation

† Defaulted after 1st. O-P appt.

In one patient the fluid retention was caused by the nephrotic syndrome secondary to renal amyloidosis and in the remaining 21 patients it was caused by cardiac failure. Heart failure was attributed to cor pulmonale in six patients, valvular heart disease (5), ischaemic heart disease (3), hypertension (3), and coarctation of the aorta in one. In the remaining three cases the cause of the heart failure was obscure but in two of these three patients it was probably due to alcoholic cardiomyopathy.

Of the 21 patients treated, 11 showed a successful clinical response, six a partially successful clinical response and five were considered failures.

Successful Response

Eleven patients were maintained reasonably symptom-free, without side effects, with 'Dytide' as the only diuretic. Four had clinically detectable ankle oedema but this was their usual "normal" state and was not considered significant.

Partially Successful Response

Six patients were considered only partially

successful. Four of these (Cases 12, 13, 14 and 16, in Table 1) showed an initial favourable response to 'Dytide' alone but either deteriorated or failed to maintain this response and required the addition of twice-weekly mersalyl injections. The mersalyl injections were not required until after 10, 11, 16 and 2 weeks respectively. Three of these four patients (12, 13, and 16) had had several previous admissions for exacerbations of chronic heart failure and had been previously receiving daily diuretics. Patient No. 16, with hypertensive and ischaemic heart disease, had been admitted with digitalis toxicity. She improved with treatment and was discharged from hospital without ECG evidence of digitalis toxicity but unfortunately died two weeks later at home in severe left ventricular failure. A fifth patient (15) with severe coarctation of the aorta and congestive failure had previously responded to vigorous hospital treatment with digoxin, thiazides, mersalyl and paracentesis abdominis. His oral diuretic was changed to 'Dytide' and the mersalyl (2 cc. once weekly) was continued; he was maintained well and oedema-free for six months. The sixth patient

TABLE 2
VARIATION IN SERUM POTASSIUM LEVELS

Case no.	No. of times serum K < 3.5*	No. of times K = 3.5—4.0*	No. of times K = 4.0—5.0*	No. of times K = 5.0—5.5*	No. of times K < 5.5*
1	Nil	2	5	Nil	Nil
2	1	1	2	Nil	Nil
3	Nil	1	5	1	Nil
4	1	2	5	Nil	Nil
5	1	4	2	Nil	Nil
6	Nil	Nil	5	1	Nil
7	Nil	2	3	Nil	Nil
8	Nil	1	8	Nil	Nil
9	Nil	Nil	4	Nil	Nil
10	Nil	Nil	1	2	Nil
11	Nil	Nil	4	Nil	Nil
12	Nil	1	4	Nil	Nil
13	1	1	4	Nil	Nil
14	Nil	3	6	Nil	Nil
15	Nil	3	2	Nil	Nil
16	Nil	Nil	3	Nil	Nil
17	Nil	Nil	2	Nil	1

* Figures given in mEq./litre.

(17) had responded well as an in-patient but when seen at Out-patients two weeks after discharge she was rather more breathless, with increase in weight and a slight ankle swelling. Her 'Dytide' was increased from two to three capsules daily but unfortunately she died in her sleep ten days later.

Poor Response

In four patients a satisfactory diuresis was not obtained using 'Dytide'. One patient aged 67 with severe cor pulmonale, with a long history of previous admissions, failed to improve after a week on digoxin, anti-biotics and 'Dytide'; he died after a further week on other intensive diuretic therapy. Another patient, aged 70 with a nephrotic syndrome due to amyloidosis secondary to chronic rheumatoid arthritis, gave an initial favourable response to 'Dytide' with a 5 lb. loss of weight in the first week; however, this improvement was not maintained and she made a weight gain of 8 lb. in the second week. 'Dytide' was discontinued and diuresis was eventually effected by a combination of mersalyl, chlorothiazide and spironolactone. A patient with mild left ventricular failure (No. 21) failed to respond and 'Dytide' was withdrawn because there was a considerable rise in the blood urea (from 39 to 72 mg./100 ml.) which settled on withdrawal of the drug. A fifth patient (22) with chronic bronchitis and cor pulmonale who was being treated with digoxin, antibiotics and three capsules of 'Dytide' daily developed anorexia and weakness. Although there was a loss of 8 lbs. in weight her blood urea rose from 42 to 103 mg./100 ml. On withdrawal of 'Dytide' she felt better and her blood urea returned to pre-treatment levels.

Results of Biochemical Investigations

Serum Potassium Levels

Potassium levels were maintained for the most part within the normal range (Table 2). Patients 2, 4 and 5 showed, on one occasion each, serum potassium of just below 3.5 mEq./l. during the course of treatment; these low figures were seen in the early stages during the maximum diuresis and they reverted to normal values without a further change in treatment. In the five patients who were given mersalyl as additional therapy there was also a transitory fall in the serum potassium, and a rise in the blood urea after starting the injections but in the next two or three weeks they returned to their previous levels. In one patient (17) the serum potassium rose to 5.85 mEq./l. on one occasion. No instance of hyperkalaemia occurred.

Urinary Electrolytes

The urinary electrolyte excretion on the 7th day of treatment with 'Dytide' was compared with the pattern of electrolyte excretion in the first 24 hours of hospital admission, before 'Dytide' was exhibited. At the end of the 1st. week of treatment, such changes towards improvement as are brought about by general therapy (e.g. bed rest, control of infection, reduction in pulse rate, etc.), might reasonably be supposed to have exerted their maximum effect, and the urinary electrolyte pattern on the 7th day can be assumed to be influenced mainly by the diuretic agent.

The mean changes in the 24-hour urinary sodium and potassium levels and the mean weight changes, after one week's treatment, are shown in Table 3. Patients who responded to 'Dytide' clinically had higher values for 24-hour sodium

TABLE 3

	Mean wt. loss (lbs) after 7 days on 'Dytide'	Mean change in 24 hour Na output (mEq.)*	Mean change in 24 hour K output (mEq)*
Satisfactory Response Group (Cases 1-11)	—10	+74.1	+2.7
Partial Success Group (Cases 12-17)	—5.5	+55.0	+9.2
Poor Response Group (Cases 18-22)	—3.5	—13.3	+2.2

* These figures express the mean difference between the 24 hour urine collection before treatment, and on the 7th day of 'Dytide'.

excretion on the 7th day of treatment as compared with pre-treatment. Patients who failed to respond had, with the exception of Case 19, lower values for 24-hour sodium excretion on the 7th day of treatment as compared with pre-treatment values. The mean potassium excretion, on the other hand, was increased to a much less extent in all groups. The potassium excretion was unchanged in one patient, decreased by amounts from 3 to 43 mEq. in eight patients and increased by amounts from 6 to 26 mEq. in 12 patients. The remaining patient (Case 2) appeared fairly insensitive, at the start of treatment, to the potassium retaining properties of triamterene. His 24-hour urinary potassium after seven days on 'Dytide' rose from 13 to 74 mEq. with a serum potassium of 3.3 mEq./l. However without change of therapy, his serum potassium returned to normal levels and has remained so after 10 weeks of two capsules of 'Dytide' daily.

Blood Urea

Table 4 shows the blood urea levels for the 17 patients who showed a satisfactory or fairly satisfactory response to 'Dytide' therapy. Those patients in whom blood urea was elevated on admission usually showed a reduction in the subsequent weeks of treatment, which was associated with an improvement in the clinical state. In some patients who were kept on 'Dytide' daily for several weeks there was an increase in the blood urea level from the lowest value obtained. This elevation was unaccompanied by symptoms except in Case 10, where the patient was discharged in error on three capsules of 'Dytide' daily. She had been on three capsules daily for a fortnight with a satisfactory response but after being discharged, she failed to appear for her first follow-up appointment and was re-admitted three-and-a-half weeks later with a minor cerebrovascular accident, from which she completely recovered. The blood urea after six weeks on three capsules of 'Dytide' daily was 84 mg./100 ml. but on stopping the drug rapidly fell to 31 mg./100 ml.

In four patients of the partial success group, there was a rise of blood urea after starting mersalyl therapy. In one (14) who was receiving two capsules 'Dytide' daily and once weekly injection of mersalyl, which was continued for 28 weeks, the blood urea rose to 80 mg./100 ml.

In Case 21 of the poor response group, the drug was withdrawn, as although there was a loss of weight of 8 lb. in the first week, the blood urea rose from 42 to 103 mg./100 ml.

Serum Uric Acid Levels

Serum uric acid was estimated in 14 patients who had been treated with 'Dytide' for 10 weeks or more. In only two was the level above the normal of 3 to 6 mg./100 ml. In one patient (7) believed to be suffering from myelomatosis, the value, after ten weeks on 'Dytide', was 8.4 mg./100 ml. After a further four weeks treatment it was 7.9 mg./100 ml. In another patient (13) the serum uric acid rose from 4.9 mg./100 ml. in the twelfth week of treatment to 8.4 mg./100 ml. in the sixteenth week. This was coincident with a rise in the blood urea after adding mersalyl and both the serum uric acid and blood urea returned to near previous levels without changing treatment.

Side Effects

Side effects, other than those associated with a rise in the blood urea, were a mild gastric intolerance in one patient and a transitory erythema in the legs in a second. Another patient, after five months on the drug, complained of falling hair but this improved although treatment was continued. No changes in blood pressure were recorded in patients not on hypotensive drugs.

Discussion

This triamterene-benzthiazide combination (triamterene 50 mg.; benzthiazide 25 mg.) is an effective diuretic. Some practitioners object to the use of fixed dose combinations of drug. Although no evidence was obtained of its superiority over

TABLE 4
BLOOD UREA RESPONSES AT VARIOUS TREATMENT LEVELS

PATIENTS CASE NUMBER	BLOOD UREA pre-treatment	TOTAL NUMBER OF WEEKS ON 'DYTIDE' ALONE	NO. OF WEEKS ON 'DYTIDE' CAPS. 3 DAILY	BLOOD UREA at end of this period.	NO. OF WEEKS ON 'DYTIDE' Caps. 2 daily	BLOOD UREA at end of this period.	NO. OF WEEKS ON 'DYTIDE' caps. 2 alternate days.	BLOOD UREA at end of this period.	NO. OF WEEKS ON mersalyl and 'Dytide' caps. 2 daily.	BLOOD UREA at end of this period.	Lowest blood urea after commencing treatment	Week occurring.
1	58	25	2	54	11	40	12	44	—	—	40	25
2	30	10	1	34	9	46	—	—	—	—	34	1
3	64	14	1	51	7	59	6	56	—	—	40	2
4	58	14	2	46	12	27	—	—	—	—	26	4
5	94	27	4	60	19	60	4	54	—	—	20	2
6	90	23	1	40	4	65	18	48	—	—	40	1
7	39	16	2	36	14	40	—	—	—	—	28	1
8	51	24	1	55	5	56	18	38	—	—	42	3
9	50	16	3	52	—	—	13	51	—	—	38	1
10	34	6	6	82	—	—	—	—	—	—	44	1
11	70	5	—	—	5	44	—	—	—	—	32	1
12	46	10	1	72	9	47	—	—	—	—	47	6
13	33	10	10	52	—	—	—	—	4	64	47	6
14	48	16	2	54	14	49	—	—	7	53	40	8
15	48	0	—	—	—	—	—	—	2	63	38	8
16	46	2	2	41	—	—	—	—	28	80	50	1
17	52	6	1	50	5	59	—	—	2	49	41	2
											42	2

"No response" patients not included. Blood ureas expressed as mg./100 ml.

other diuretic agents this series of cases shows that it is possible for patients on 'Dytide' to maintain normal serum potassium levels without the requirement for potassium supplements. This permits electrolyte investigations in out-patients to be kept to a minimum in long term patients which might not be the case when the proportions of triamterene and thiazides were being varied. As an example one patient (5) had a tendency to a low normal serum potassium levels (3.5 to 4.0 mEq./l.) and it is reasonable to suppose that increasing the daily dose of benzthiazide would further depress her potassium levels.

The patients studied in this trial were, for the most part, well over middle age when the glomerular filtration rate is lower than in the young and blood urea levels of 50-60 mg./100 ml. may be considered normal. The continued use of 'Dytide' is, however, sometimes associated with a rise in the level of the blood urea, especially when given

daily. This had been noted during the original trials with triamterene (Crosley and others, 1962; Donnelly and others, 1962; Shaldon and Ryder, 1962), and can usually be avoided if for routine use a daily dose of 3 or 4 capsules is not exceeded. This dosage should not be continued for longer than a week and if no response is being obtained, an alternative diuretic should be tried. If a diuresis has commenced and the patient is well, then the dose should be reduced to 2 capsules daily for another week or two, by which time the maximum diuresis will have been effected. If further maintenance therapy is required, it can usually be achieved by giving 'Dytide' on alternate days. Should the drug be used daily for more than a few weeks, then periodic estimations of the blood urea and serum potassium should be undertaken. In patients with evidence of renal impairment, 'Dytide' like other diuretics, should be used with caution, if at all.

Summary

A clinical trial has been carried out to evaluate the effect of a triamterene-benzthiazide combination ('Dytide') on the serum potassium levels of oedematous patients when used over prolonged periods without potassium supplement.

Twenty-two cases were treated of whom 17 had a satisfactory clinical response over periods from 5-28 weeks with maintenance of the serum potassium levels within normal limits. Four patients failed to achieve a satisfactory diuresis and one patient had to stop therapy because of an excessive rise in the blood urea.

An increase in the blood urea in patients taking 'Dytide' daily was not uncommon, especially if mersalyl was also given. It was usually not of clinical significance, and was always reversible on withdrawing the drug. It is recommended that patients on long term treatment with 'Dytide' should receive the drug on alternate days. If daily dosage is necessary, then periodic estimations of the blood urea and serum potassium should be made.

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