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Clinical Experience with a New Diuretic, Triamterene, in Congestive Heart Failure

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ABSTRACT

Triamterene therapy was evaluated in 35 patients with congestive heart failure over a period of two and one-half years. The parameters used were: clinical assessment; daily 24-hour urine sodium, potassium, chloride, and total volume; bi-weekly serum sodium, potassium, chloride, uric acid, and SGOT; hemogram, and BUN.

Triamterene is a moderately potent diuretic and natriuretic, with the added desirable property of potassium conservation. It acts synergistically with spironolactone and not only potentiates the effects of hydrochlorothiazide but greatly minimizes its kaluretic effect.

It is particularly useful in patients in whom cardiac arrhythmias are associated with digitalis intoxication or with inadvertently induced hypokalemia. Its main therapeutic value, used either alone or in combination with other diuretics, is in the long-term management of chronic edema, especially in certain patients refractory to the currently used diuretics.

No significant undesirable side effects were noted.

SOMMAIRE

Le triamterene a été essayé chez 35 insuffisants cardiaques pendant deux ans et demi. Les critères de l'essai ont été: bilan clinique, dosage quotidien du sodium, du potassium et du chlorure dans l'urine des 24 heures et volume total de celle-ci; dosage bi-hebdomadaire dans le sérum du sodium, du potassium, du chlorure, de l'acide urique et de la transaminase glutamo-oxalacétique; hémogramme et azotémie.

Le triamterene est un diurétique et un natriurétique modérément actif et qui a l'heureuse propriété de conserver le potassium. Il agit en synergie avec la spironolactone et, non seulement potentialise l'action de l'hydrochlorothiazide, mais réduit considérablement son effet sur la kaliémie.

Le produit est surtout utile chez les malades dont les arythmies relèvent d'une intoxication digitalique ou d'une hypokaliémie provoquée accidentellement. Sa principale indication thérapeutique, qu'il soit employé seul ou associé à d'autres diurétiques, est le traitement à long terme de l'œdème chronique, mais surtout chez certains malades qui sont rebelles aux diurétiques classiques.

On n'a noté aucune réaction secondaire fâcheuse.

OVER the last few years, great advances have been made in the synthesis and clinical application of diuretic agents, but the search for an ideal one continues. Since the first published work on triamterene (2,4,7-triamino-6-phenylpteridine, SK & F 8542) by Laragh *et al.*[1] and Wiebelhaus *et al.*,[2] many papers[3-9] have appeared in the literature describing its capacity to effect natriuresis with conservation of potassium. It has been shown to potentiate the effects of other diuretics[6-9] (it probably acts on the sodium/potassium exchange mechanism in the distal renal tubule) and, though it has anti-aldosterone-like effects, its mechanism of action seems different from that of spironolactone.[3, 5, 9]

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Given orally, its appearance in the urine is manifested as a blue fluorescence within the first hour, appears to exert its effects within two hours, and has a peak effect at from four to eight hours.[3, 5]

We have been interested in the effect of triamterene in patients with congestive heart failure (CHF) since December 1961. This paper recounts some of our experiences with the drug over a period of two years. During this time we have treated over 35 patients, and have followed up some for over 18 months.

SUBJECTS AND METHOD OF STUDY

Patients who were admitted to the medical wards of the Halifax Infirmary with clinical features of CHF were started on the following therapeutic regimen: diet containing approximately 30 mEq. sodium and 80 mEq. potassium; bed-rest except for bathroom privileges, daily weight as indicated, and digitalis.

Whenever possible, a period of one to three days was allowed for observation of the effect of bed-rest alone on diuresis (natriuresis) and on the clinical features of the patient's illness. Following this, triamterene was given for a period of two to five days. Initially, a starting dosage of 50 mg./day increasing to a maximum of 200 mg./day was used; however, we soon found that the optimum dosage was 150 mg./day, given in three divided doses. Subsequently, other diuretics (especially hydrochlorothiazide and spironolactone) were added, for assessment of their potency separately, but specifically in combination with triamterene. At the same time, the following laboratory investigations were performed: 24-hour (daily) urinary excretion of sodium, potassium, and chloride;[10] and at least two times a week serum sodium, chloride, potassium, and uric acid,* serum glutamic oxaloacetic transaminase (SGOT),† a blood urea nitrogen (BUN),* and a hemogram.

After discharge from hospital, the majority of patients were followed up by one of us (S.T.L.), during which time triamterene was given in combination with one or more other diuretics as indicated.

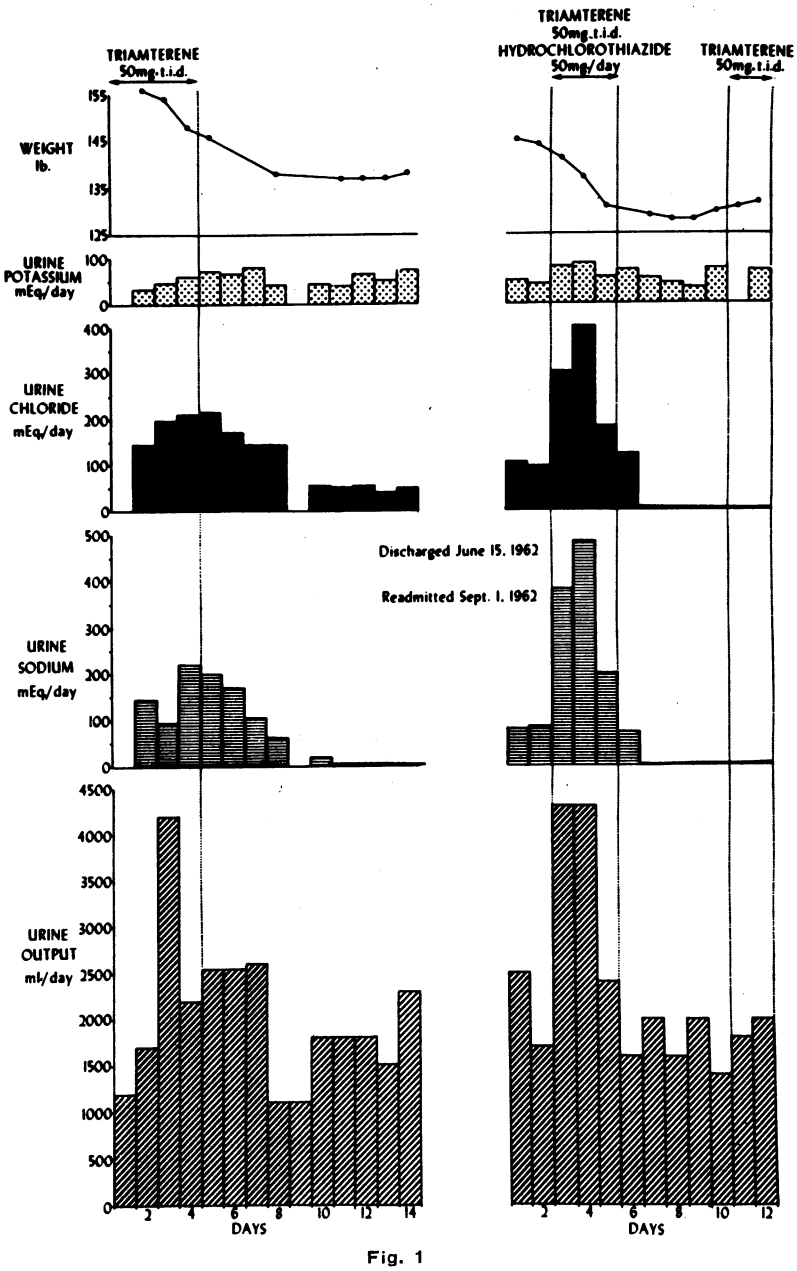

Fig. 1

RESULTS

In all there were 55 separate trials of triamterene treatment during the hospital admissions and readmissions of the 35 patients with CHF who were studied. However, because of some differences in treatment approach, the drug's therapeutic effects during this time are best demonstrated by dividing the patients into three groups, even though a patient from one group may have several features in common with those of another.

Group I

Thirteen patients (16 admissions) presented with clinical features of acute CHF. Fig. 1 depicts the pertinent data of one such patient, who was followed up for over seven months. The patient was admitted to hospital on three occasions for the

*Autoanalyzer, Technicon Company, Chauncey, New York.
†Dade Reagents, Inc., Miami, Florida.

same illness, and the results of two of these admissions are shown.

It is apparent that triamterene alone produced significant diuresis and natriuresis, weight loss was favourable, and there was marked clinical improvement. Note, however, that potassium excretion was not greater than on control days. On the second admission, a combination of triamterene with hydrochlorothiazide produced brisker and more abundant diuresis and natriuresis, a faster weight loss, and an earlier clinical improvement, yet there still was no significant increase in potassium excretion. The patient's mean urine sodium/potassium ratio while on triamterene was 3.4, while on triamterene plus hydrochlorothiazide it was 4.6, and on control days, 1.7.

Group II

Eight patients (12 admissions) who were unresponsive to a regimen of various diuretic combinations (especially the thiazides and the mercurials) were admitted with features of digitalis intoxication — extrasystoles, fibrillation — most probably related to potassium deficiency. Fig. 2 represents one such case.

The arrhythmias could be reproduced with hydrochlorothiazide, but they disappeared following institution of triamterene therapy. The natriuretic and diuretic effects were less prominent than those shown in Fig. 1, yet again potassium conservation was demonstrated. However, there was a prominent increase in potassium excretion when the patient received hydrochlorothiazide alone. The patient's mean urine sodium/potassium ratio was 4.1 while on triamterene therapy, compared to 1.4 on hydrochlorothiazide alone.

Group 3

Fourteen patients (27 admissions) were cases of chronic CHF. They showed an improved response with prolonged use of triamterene at a daily dosage of 150 to 200 mg., given four days each week or once every two days. Occasionally, a thiazide diuretic or chlorthalidone was added, as indicated by the clinical features of each individual case.

Discussion

Triamterene has been shown to be a moderately potent natriuretic and diuretic agent. When combined with hydrochlorothiazide, it has proved to be very effective in prolonged therapy of chronic CHF, both in our own series and in others.[6] It is also effective in patients with cirrhosis and ascites.[7] Although it is not as potent a diuretic as a thiazide, it has the added desirable property of conserving potassium,[6-8] as shown in Figs. 1 and 2.

If regular determinations of blood potassium levels are not done during diuretic therapy, the physician runs the danger of being lulled into a false sense of security about the patient's electrolyte balance. (Note, however, that serum potassium levels do not necessarily reflect the level of total body potassium.) Furthermore, the depletion of body potassium by diuretic agents—especially the thiazides—is a real problem; one which is seldom easily solved. Therefore, triamterene's property of preventing potassium depletion assumes great importance in the safe and effective treatment of patients with edema.

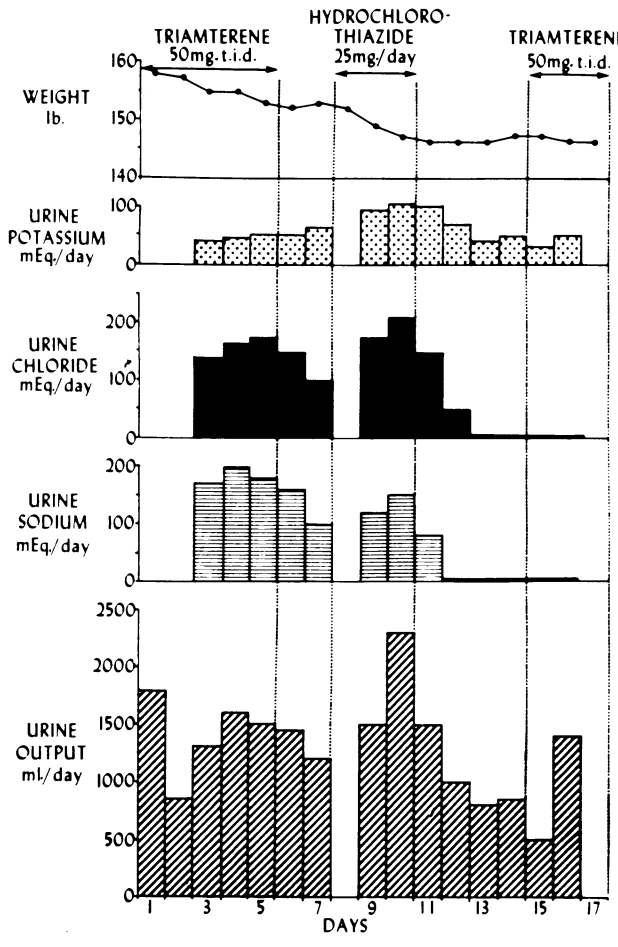

Fig. 2

This property of potassium conservation is again extremely important in the management of patients with chronic CHF who are receiving digitalis therapy, since potassium deficiency secondary to diuretic therapy may precipitate digitalis intoxication (manifested as abnormalities of atrioventricular conduction), and the administration of potassium in an effort to correct this condition may just further aggravate it.[11] Moreover, Friedberg *et al.*[12] have recently shown that bradycardia can inhibit natriuresis.

As shown in Figs. 1 and 2, when sodium excretion in urine is minimal (less than 5 mEq./24 hours), triamterene has virtually no natriuretic effect. However, if hydrochlorothiazide is added at this stage, natriuresis occurs and the patient loses weight as shown in Fig. 3.

This latter phenomenon is most likely due to hydrochlorothiazide's effect in promoting an in-

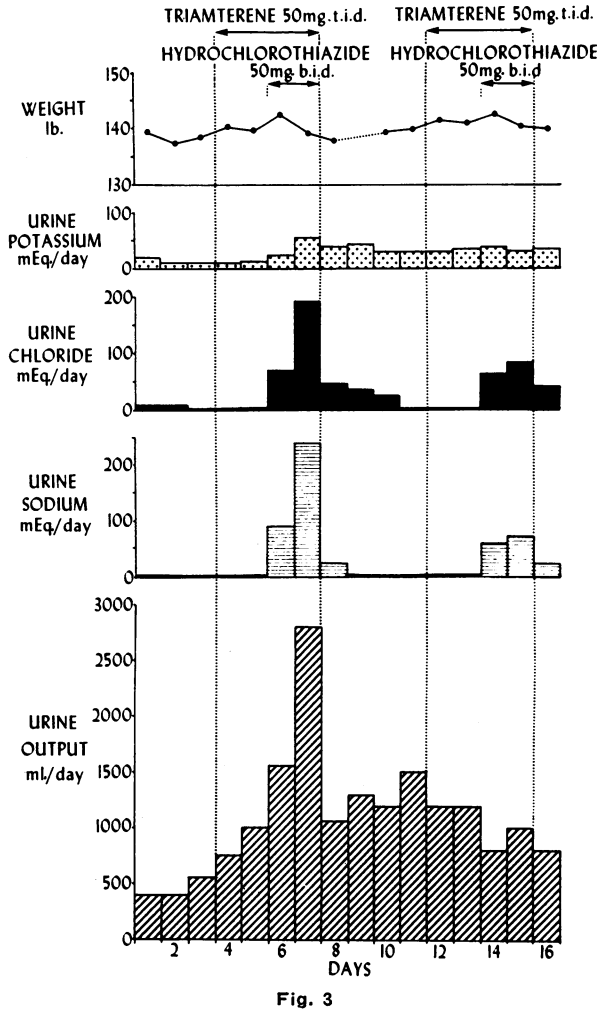

Fig. 3

creased delivery of sodium to the distal renal tubules, where triamterene probably interferes with the sodium/potassium exchange mechanism, causing a natriuresis.

The mechanism of action of triamterene is not yet fully settled. However, it most probably does not inhibit the carbonic anhydrase enzyme,[5, 8, 9] nor is it an aldosterone antagonist, for, although it has some antialdosterone-like properties,[5, 9] it acts in adrenalectomized rats[5] and potentiates the effects of spironolactone. This was seen in our patients and in other series.[8, 9] As stated above, it most probably acts at a distal tubular level on the sodium/potassium exchange mechanism.

Figs. 1 to 3 show the occasional separation of the chloruretic from the natriuretic effect, as seen by Crosley *et al.*[3] The mechanism involved remains unexplained, but it is reasonable to assume that a dual mechanism (passive and active) for chloride transport exists in the distal renal tubule, as proposed by Rector and Clapp.[13]

In five of our patients there was a slight increase in BUN. The highest recorded was 25 mg. %, but this decreased promptly on discontinuation of triamterene. Others[6, 8] have found more marked elevations of BUN. These are most likely due to a combination of factors: a decrease in cardiac output,[14] a decrease in glomerular filtration,[3, 7] and a decrease in the renal plasma flow.[3]

We have not observed any increase in serum uric acid, but Cattell and Havard[8] have reported increased urinary excretion of uric acid with this drug. If this fact is borne out by further studies, it may prove to be an added advantage in the use of triamterene. Serum potassium increased in some of our patients but no values were seen above 5.5 mEq./l. There were no significant changes in SGOT, white blood count, hemoglobin, serum sodium, serum chloride or blood pressure.

We have outlined our clinical experience with this new diuretic compound without resorting to a statistical analysis of the data. We make no apologies for this because we feel that, in a study of this type, statistical analysis can become misleading.

SUMMARY

In a series of 35 patients with congestive heart failure (CHF), triamterene demonstrated a significant natriuretic and diuretic property. In combination with hydrochlorothiazide, natriuresis was markedly potentiated without potassium wasting, and natriuresis occurred even though urinary excretion of sodium was previously very small. The drug also potentiated the natriuretic effects of spironolactone.

Combined with other diuretics, triamterene was very effective in the long-term management of CHF.

No significant side effects were observed.

ADDENDUM

Figs. 1 to 3 indicate that when a patient's urine sodium output is 5 mEq. or less per day, the addition of triamterene to the therapeutic regimen does not cause an increase in excreted sodium. However, we have since been able to show, several times, that if the drug therapy is continued for several days, there is a minimal natriuretic effect which occurs on the third or fourth day. It lasts, however, for only a few days.

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