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TREATMENT OF CONGESTIVE HEART FAILURE WITH 3-BENZYL DIHYDROFLUMETHIAZIDE: PRELIMINARY REPORT

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Since the introduction of chlorothiazide in 1957,¹ several analogues of the benzothiadiazine series have been made available for the treatment of edematous states, and most widely applied in the treatment of congestive heart failure. Hydrochlorothiazide, flumethiazide and hydroflumethiazide, in addition to the former, have all been reported to be potent oral diuretic agents.^{2,4}

Toxicity to this group of drugs has been low, despite their wide clinical use. The most serious side effects are related to depletion of electrolytes, particularly of potassium and chloride. Efforts to develop more potent agents with fewer side effects, however, will undoubtedly continue.

A new substituted benzothiadiazine derivative, 3-benzyl dihydroflumethiazide, has recently been made available for clinical trial (Figure 1). Preliminary animal studies and clinical tests indicated that its diuretic activity was significantly greater than that of chlorothiazide and dihydroflumethiazide.⁵

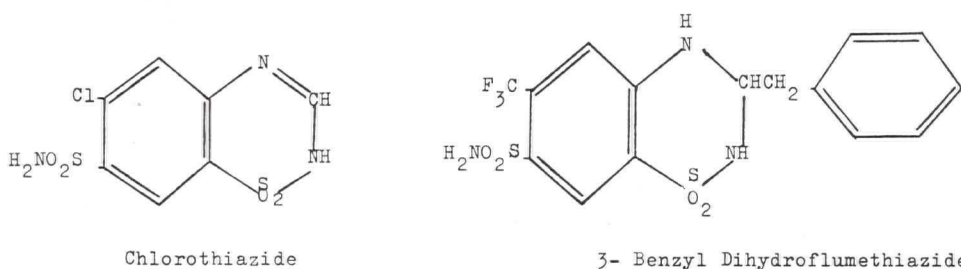


Figure 1 Structural Formulae

METHOD

3-benzyl dihydroflumethiazide was administered to a group of 21 patients with congestive heart failure. The subjects were divided into three groups as determined by the severity of the congestive failure and response to previous diuretic therapy (Table 1). Grade I patients had mild to moderate degrees of congestive heart failure,

Table 1
Type of congestive heart failure of 21 patients

Etiology	Grade I	Grade II	Grade III	Total
Arteriosclerotic	2	9	2	13
Rheumatic	0	6	0	6
Congenital	1	1	0	2
TOTAL	3	16	2	21

manifested by dyspnea, moist basilar rales and hepatic congestion. Grade II patients

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Drug material for this study was supplied by E. R. Squibb & Sons, Division of Olin Mathieson Chemical Corp., New Brunswick, N. J.

had severe degrees of heart failure with edema and/or ascites, while Grade III patients consisted of those who had become resistant or refractive to previous diuretic therapy.

Thirteen patients had arteriosclerotic heart disease, 6 had rheumatic heart disease and there were 2 cases of congenital heart disease. All patients were digitalized and maintained on 400 to 1600 mgm. sodium diets as indicated. The majority had received previous diuretic therapy, mercurials and/or one of the benzothiadiazine derivatives.

Seventeen patients were hospitalized and actively treated because of their de-compensated status. A daily weight was obtained as well as regular blood counts, urinalyses and blood urea nitrogen determinations. Serum electrolytes were determined prior to and immediately after each period of diuretic administration. In 4 cases the drug was substituted for a previous diuretic agent as maintenance therapy in the out-patient clinic.

The drug was administered in a dosage of one 5 mgm. tablet two to three times daily for a period of two to three days, followed by a rest period of the same duration. In a few instances of severe congestive heart failure, the drug was given for a longer consecutive period. Patients previously treated with chlorothiazide or hydrochlorothiazide were given 5 mgm. of the new agent in place of 500 mgm. of the former or 50 mgm. of the latter. Ammonium chloride was given concurrently in about one-half of the cases while supplemental potassium salts were used in only a few instances.

RESULTS

Grade I. Two patients with arteriosclerotic heart disease and one with congenital heart disease (aortic stenosis) had early congestive heart failure. One had received no previous diuretic therapy. All had a good response with a weight loss of 2 to 7 pounds. No marked change in serum electrolytes was noted. One patient continued to have diuresis on the third day after the drug was discontinued, a phenomenon we have previously noted with hydrochlorothiazide, and described again in Case 2 below.

Grade II. Sixteen patients were classified as having Grade II congestive heart failure, 9 with arteriosclerotic heart disease, 6 with rheumatic heart disease and 1 with congenital heart disease (atrial septal defect). Of 12 hospitalized patients, all had a good diuresis with weight losses ranging from 4 to 25 pounds. Ten of these 12 had received prior therapy with mercurial or the benzothiadiazine diuretics and all responded equally well or better to 3-benzyl dihydroflumethiazide. No toxicity was noted and no severe electrolyte depletion occurred. All showed evidence of a mild hypochloremic alkalosis as noted with the prior thiazide derivatives.

Case 1. W. G. was a 48 year old man who had known rheumatic heart disease with aortic incompetency since the age of 18. Nine months prior to admission he developed atrial fibrillation and signs of congestive heart failure. Despite conversion of the arrhythmia on two occasions a sinus rhythm could not be maintained. He did well for a time on digitalis, a low sodium diet and intermittent administration of chlorothiazide and occasional injections of a mercurial diuretic.

Congestive Heart Failure

He was admitted to the hospital on Sept. 2, 1959, because of increasingly severe exertional dyspnea, nocturnal dyspnea and orthopnea. The blood pressure was 132/62. There was atrial fibrillation at a rate of 84 per minute and aortic systolic and diastolic murmurs with an absent A2. There were medium moist rales in both lung bases and the liver edge was palpable 5 cm. below the costal margin and was tender.

He was continued on digitoxin 0.1 mgm. daily and a 400 mgm. sodium diet. On the first day of administration of 3-benzyl dihydroflumethiazide he lost 10 pounds and felt much improved. He lost a total of 20 pounds during the 8 days of intermittent administration of the drug (Figure 2), and the congestive failure was completely controlled. Slight hypochloremic alkalosis was the only change in electrolytes noted despite the fact that no supplementary chloride or potassium was given.

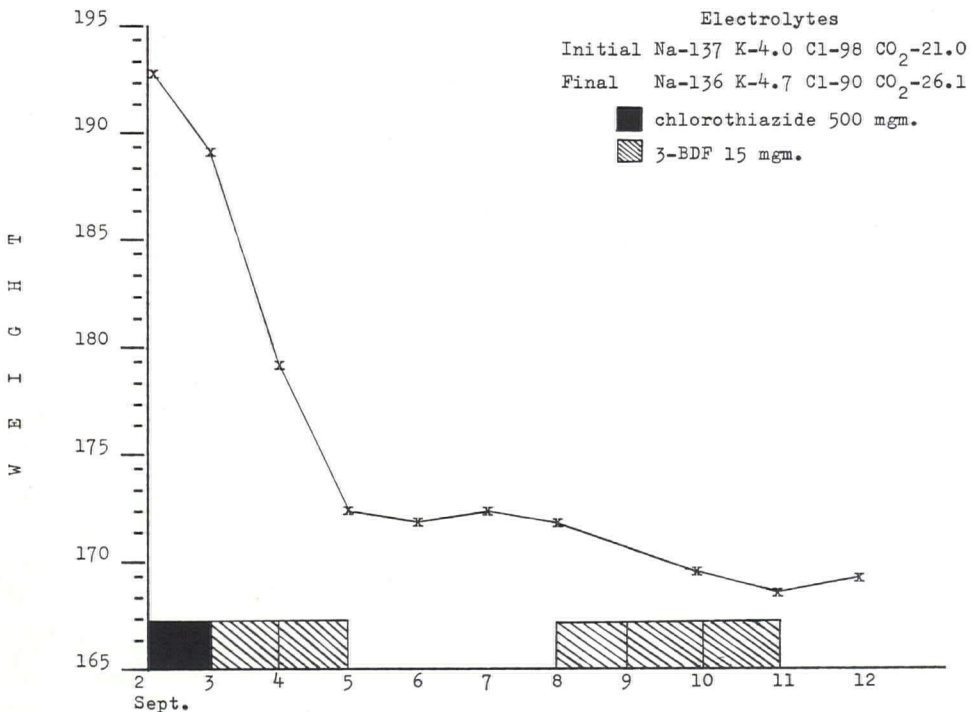


Figure II. Weight loss and electrolyte change in W. G. (Case 1) on 3-benzyl dihydroflumethiazide. Complete control of congestive failure in 10 days.

One Grade II patient showed the continued diuresis following cessation of drug administration referred to above and warrants a brief case report.

Case 2. C. F. was a 54 year old Negro male who had been treated at this hospital in 1953 for an acute anterior myocardial infarction. In January 1956 he first developed congestive heart failure and in the ensuing years was hospitalized on several occasions for the treatment of exacerbations of chronic congestive heart failure. He was unable to work since October 1957.

He was re-admitted on July 5, 1959, because of an increase in dyspnea, ankle

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edema and loss of appetite. The heart was grossly enlarged and there was a gallop rhythm with frequent premature systoles. The liver edge was palpable 6 cm. below the costal margin and tender. There were bilateral moist basilar rales and 3+ pretibial pitting edema.

Digitalis and a 400 mgm. sodium diet were continued. After four days of stable weight, 3-benzyl dihydroflumethiazide was given in a dosage of 5 mgm. three times daily. A prompt diuresis resulted. (Figure 3) After 7 consecutive days of drug administration it was discontinued, but diuresis continued and he lost an additional 11 pounds of weight in the next 6 days without any other change in therapy.

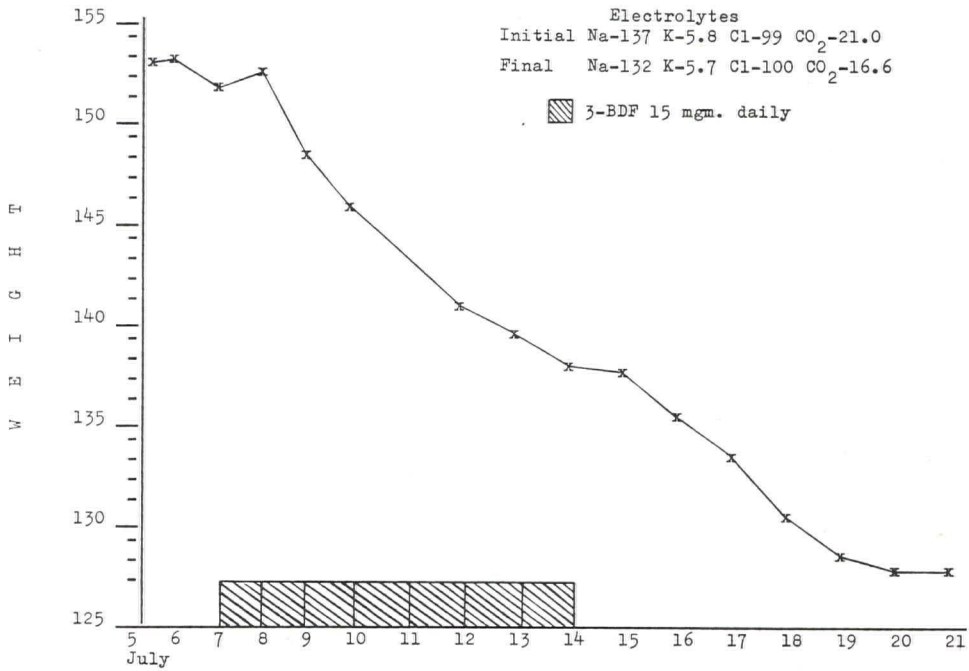


Figure III. Weight loss and electrolyte change in C. E. (Case 2) with 3-benzyl dihydroflumethiazide. Note continued diuresis following cessation of drug. Congestive failure completely controlled.

Four patients with Grade II congestive heart failure were treated in the out-patient department. Two patients with rheumatic heart disease were well controlled on chlorothiazide and continued to do equally well when given the new maintenance diuretic. Two patients with arteriosclerotic heart disease and near the terminal stage of their disease were poorly controlled on a maintenance dose of chlorothiazide and intermittent injections of mercurial diuretics. No improvement was noted when 3-benzyl dihydroflumethiazide was substituted for the chlorothiazide.

Grade III. Two patients with arteriosclerotic heart disease and severe advanced congestive heart failure had become refractive to mercurial diuretics, chlorothiazide and hydrochlorothiazide. The serum electrolyte patterns were within the normal range. Neither showed any response to 3-benzyl dihydroflumethiazide.

Congestive Heart Failure

COMMENT

The thiazide derivatives produce diuresis as a result of blockage of the tubular transport mechanisms involved in the reabsorption of sodium, chloride, and, to a lesser degree, of potassium and bicarbonate. The electrolyte excretion patterns are basically similar, though definite differences have been noted.⁴ Beyer and Baer are of the opinion that this does not necessarily indicate a difference in pharmacologic action, but is more likely related to differences in the back diffusion of chloride and bicarbonate secondary to differences in distribution of the drug.⁶

3-benzyl dihydroflumethiazide would seem to share this same mechanism of action. On a milligram for milligram basis, however, it is a more potent agent than chlorothiazide or hydrochlorothiazide, being approximately 100 times more potent than the former and 10 times more potent than the latter.

Mild hypochloremia was noted in all cases in which diuretic responses were obtained. This was easily corrected by the administration of ammonium chloride. No significant reduction in the levels of serum sodium or potassium was observed. No change was noted in the blood count, urinalysis or BUN of any case.

3-benzyl dihydroflumethiazide was well tolerated by all patients in this series. No side effects were noted. A low incidence of nausea, vomiting and weakness has been reported previously with chlorothiazide and hydrochlorothiazide.

These results indicate that 3-benzyl dihydroflumethiazide is a potent oral diuretic agent. A decreased incidence of side effects, if substantiated by further study, would be a decided advantage over previous thiazide derivatives. Further investigation may also indicate that there is less of a tendency to depletion of sodium and potassium, though these should be watched for in long continued use of this agent as with the other thiazide derivatives. This is particularly true of the patient with advanced cardiac or hepatic disease.

SUMMARY

A new benzothiadiazine derivative, 3-benzyl dihydroflumethiazide, was administered to a group of 21 patients with varying degrees of congestive heart failure. Results of this preliminary study indicate that it is an active diuretic agent approximately 100 times more potent than chlorothiazide. No toxicity or serious electrolyte disturbances were noted.

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