THE TREATMENT OF DIABETES INSIPIDUS WITH BENZYDROFLUMETHIAZIDE* AND POTASSIUM CHLORIDE IN ELEVEN PATIENTS

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REPORTS[1-5] of experimental treatment of diabetes insipidus with chlorothiazide and hydrochlorothiazide, and the more recent report[2] of the similar treatment of patients, prompted us to treat two patients, with this disease, with benzydroflumethiazide, a chlorothiazide-like drug.* Because hypokalemia was a problem reported by other investigators,[3,4] we used benzydroflumethiazide supplemented with potassium chloride. It was not our intention to make a detailed laboratory study to assess the results of treatment, but merely to assess its clinical effectiveness by means of pertinent simple laboratory tests that can be done on an outpatient basis.

The effects of the drug were ascertained in 11 patients with diabetes insipidus. In six of them there were definite favorable responses to the therapy. The 24-hour urinary volumes decreased from original values in the range of 4,000 to 10,000 ml. to between 2000 and 5000 ml. In two patients the urinary volumes decreased to approximately half the original values for a few days, and then increased again. In two other patients there were no responses at any time to the therapy. The results in the 11 patients are summarized in *Table 1.*

Illustrative Case Reports

Case 1. A 12-year-old white girl‡ was examined on August 20, 1960, because of symptoms of polydipsia and polyuria of 10 months' duration. Her birth, developmental, and family history were noncontributory. Her height was 60 inches and she weighed 109 pounds; blood pressure was 114/74 mm. of Hg; pulse rate, 84; the remainder of the physical examination disclosed no abnormality. The blood hemoglobin was 13.3 gm. per 100 ml.; cell volume was 42 per cent; leukocyte count, 8200 per cubic millimeter; fasting blood sugar, 68 mg. per 100 ml.; blood urea, 17 mg. per 100 ml. The serum electrolyte values were within normal limits. The 17-ketosteroids were 2.6 mg. per 24 hours; 17-hydroxycorticoids, 2.6 mg. per 24 hours; roentgenograms of the chest, skull, and sella turcica, normal; electroencephalogram, normal; visual fields and optic

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Table 1.—*Results of benzydroflumethiazide therapy in 11 patients with diabetes insipidus*

Cause of diabetes insipidus	Number of patients	Urinary volume, ml./24 hr.	
		Before therapy	After therapy
Chromophobe adenoma	2		
		5000	2500
		4000	2000
Hypophysectomy	3		
		4200	2000
		8000	2700
		5000	Same
Idiopathic diabetes insipidus	3		
		5500	3000
		10000	5000
		6300	2400 (failed later)
Sarcoidosis	1	8400	3200
Craniotomy	1	6500	2500 (failed later)
Craniopharyngioma	1	4000	Same
Total	11		

fundi, normal. Serial 24-hour urinary volumes were collected for seven days *(Fig. 1)* before treatment with benzydroflumethiazide, and ranged from 5500 to 6000 ml. with a specific gravity between 1.001 and 1.002. After three periods of fluid restriction for 12 hours, the specific gravity of the urine was 1.002 or less. A Carter-Robbins test was performed and was diagnostic of diabetes insipidus *(Fig. 2)*.

Case 2. A two and one-half year-old girl was first examined in December, 1958, because of a history of polydipsia and polyuria of 16 months' duration. At the onset of the symptoms, her family physician performed a therapeutic test with pitressin tannate. The patient received 1 ml. of pitressin tannate intramuscularly, and remained symptom-free for from four to seven days. Two weeks before examination here, she required one or two injections daily to maintain control of the polydipsia and polyuria. The birth, developmental, and family history were noncontributory. Her height was 38¼ inches and she weighed 31½ pounds; blood pressure was 90/60 mm. of Hg; pulse rate was 88. The physical examination disclosed no abnormality. The laboratory data were: blood hemoglobin, 12.9 gm. per 100 ml.; leukocyte count, 9000 per cubic millimeter; urinalysis, normal; roentgenograms of the chest, skull, and sella turcica, normal; serologic tests, normal; fasting blood sugar, 68 mg. per 100 ml.; serum electrolytes, normal; cerebrospinal fluid, 4 white blood cells, 19 mg. of protein; electroencephalogram, focal discharges originating from high brain stem area; pneumoencephalogram, normal; Carter-Robbins test, diagnostic of diabetes insipidus.

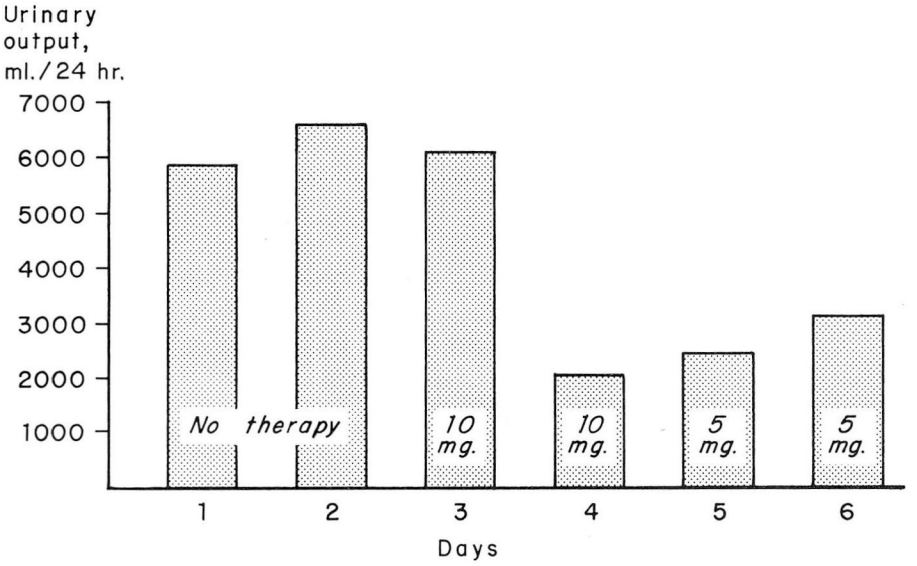

Fig. 1. Case 1. Graph showing the daily urinary volumes before and after treatment with benzydroflumethiazide in a 12-year-old girl.

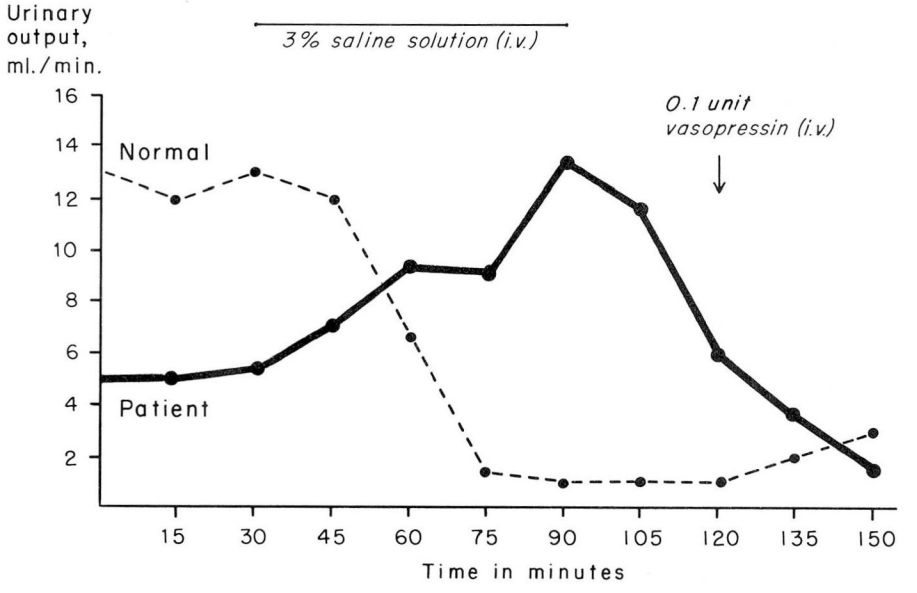

Fig 2. Case 1. Graph showing the minute-urinary volumes in a 12-year-old patient with diabetes insipidus, as compared with the normal volumes after intravenous injection of 3 per cent saline solution and vasopressin in a Carter-Robbins test in the patient.

Treatment consisted of injections of 1 ml. of pitressin tannate as required. She was maintained on this dosage for three months, requiring an injection every three or four days. The polydipsia and polyuria increased, and the dose was increased to 2 ml. of pitressin tannate. She remained asymptomatic on this treament for approximately six months, when the symptoms again became so severe as to require two injections daily for control. At that time a preliminary course of benzydroflumethiazide was begun, 5 mg. orally daily, and 1 ml. of pitressin tannate intramuscularly as required. On this regimen she required an injection every three or four days. She was readmitted to the hospital for re-evaluation and a trial on benzydroflumethiazide therapy alone. On admission her height was 43½ inches and she weighed 36 pounds. Blood pressure was 100/50 mm. of Hg; pulse rate, 80; the physical examination disclosed no abnormality. Laboratory data were: blood hemoglobin, 14 gm. per 100 ml.; white blood cells, 7500 per cubic millimeter; urine specific gravity, 1.003; blood urea, 15 mg. per 100 ml.; 17-ketosteroids, 5.6 mg. per 24 hours; 17-hydroxycorticoids, 2.1 mg. per 24 hours; serum electrolyte, urinary electrolyte, urea clearance values are listed in *Table 2.* Roentgeno-

Table 2.—*Laboratory data (case 2) obtained before and after treatment with benzydroflumethiazide*

Test	Treatment with benzydroflumethiazide			During Carter-Robbins test	Day of discharge from hospital
	Before	2 days after	5 days after		
Serum carbon dioxide, mEq./l.	22.3	25.3	23.7	—	28
Serum chloride, mEq./l.	1.2	99	103	—	102
Serum potassium, mEq./l.	4.8	5.0	3.5	—	3.3
Serum sodium, mEq./l.	143	140	145	—	138
Urinary potassium, mEq./l.	9.5	10.6	9.5	3.7	—
Urinary sodium, mEq./l.	4.5	30	10.0	10.5	—
Urinary chloride, mEq./l.	9.0	—	13.0	14	—
Urea clearance, ml./min.	98	—	109	—	—
Urine urea, mg./100 ml.	120	480	300	190	—

grams of chest, skull, and sella turcica were normal; electroencephalogram, paroxysmal slow dysrhythmia of subcortical origin, but improved in comparison to previous record; result of Carter-Robbins test shown in *Figure 3;* daily urinary output is graphed in *Figure 4.* There was an immediate response to 10 mg. daily of benzydroflumethiazide. Two weeks after discharge from the hospital the therapy became ineffective. Doses were increased to 15 mg. daily and produced some improvement, but the urinary output soon increased to 5000 ml. or more daily. Therapy now consisting of 5 mg. of benzydroflumethiazide orally daily, and 1 ml. of pitressin tannate intramuscularly every three or four days, adequately controls the polyuria.

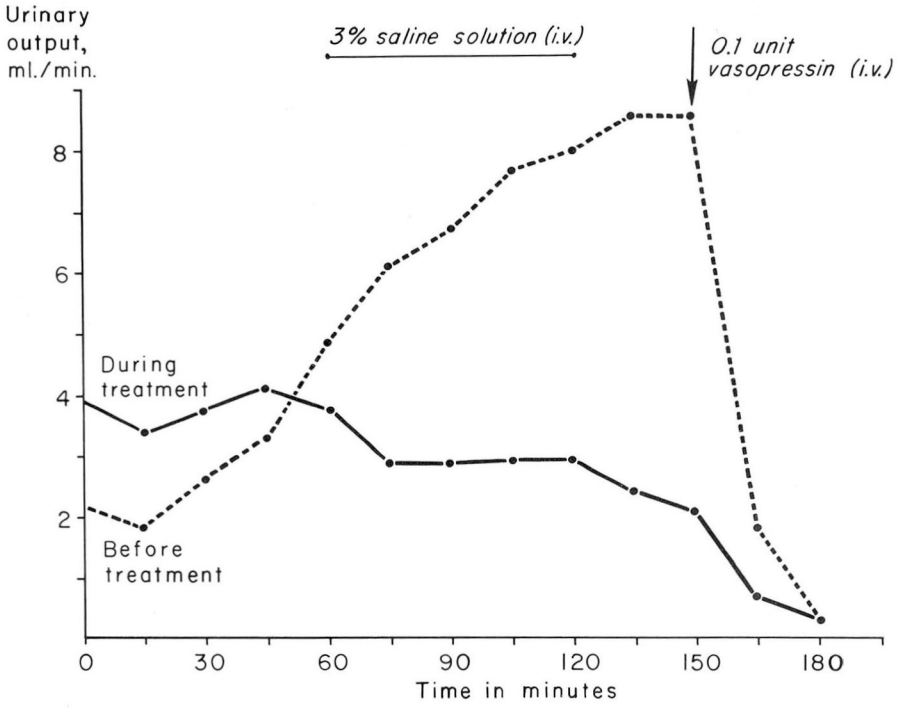

Fig 3. Case 2. Graph showing minute-urinary volumes in two Carter-Robbins tests before and during treatment with benzydroflumethiazide.

Carter-Robbins Test

The Carter-Robbins test is made after the patient has fasted for eight hours, and consists of hydrating the patient with 20 ml. of water per kilogram of body weight. If hydration is adequate, the urinary output rises to 5 ml. per minute. Then 3 per cent saline solution is injected intravenously, 0.25 ml. per kilogram of body weight per minute for 45 minutes. The urinary output is measured. Vasopressin,* 0.1 unit, is injected intravenously and the urinary volume is measured. The results of this test in our patients are shown in *Figures 2 and 3.*

In a normal person the hypertonic saline solution results in an output of vasopressin and a prompt decrease in urinary flow. In a person with diabetes insipidus there will be no decrease in urinary flow per minute following the injection of hypertonic saline solution. After the intravenous administration of vasopressin a notable decrease in the minute-volume of urine excludes the presence of renal diabetes insipidus. Because urinary output increased in our patients, after administration of 3 per cent saline solution, and a prompt decrease occurred after intravenous administration of vasopressin, the diagnosis of diabetes insipidus was proved.

**Pitressin, Parke, Davis & Company.*

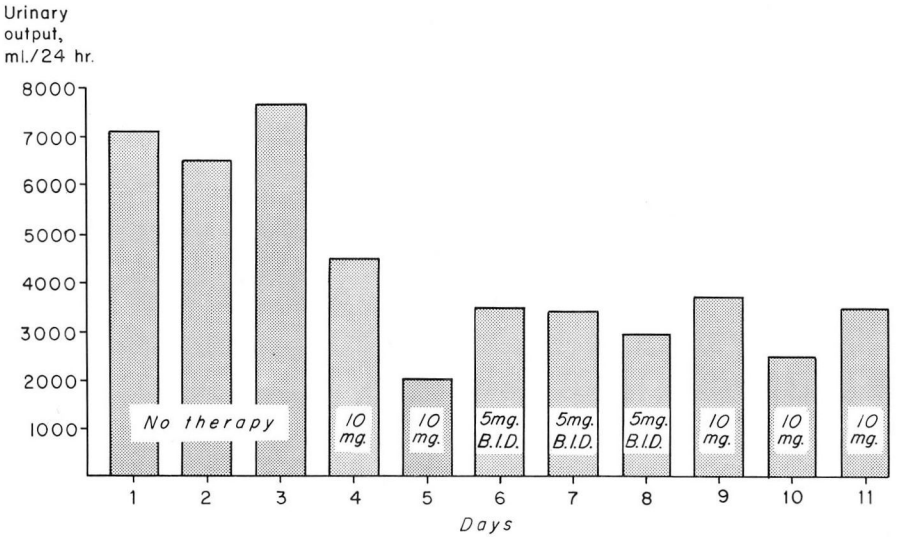

Fig. 4. Case 2. Graph showing the daily urinary volumes before and after treatment with benzydroflumethiazide in a four-year-old girl.

Comment

The responses of the 11 patients to benzydroflumethiazide therapy are similar to those reported by others[1-4] using chlorothiazide and hydrochlorothiazide. In our patients the daily urinary outputs decreased from an average of 7400 ml. to about 2000 ml., and became stabilized at about 2900 ml. The mechanism of decrease is not understood. In one patient *(case 2)* the Carter-Robbins test was performed while the patient was receiving 10 mg. of benzydroflumethiazide daily. The curve of the urinary output in *Figure 3* closely approximates the normal curve in *Figure 2*. The urinary potassium excretion, during the test, decreased to 3.7 mEq. per liter from previous values of 10.6 mEq. per liter obtained before the test. The concentrations of urinary sodium and chloride remained essentially the same as before the test.

The first-mentioned patient has been receiving 10 mg. of benzydroflumethiazide daily for six months. Although the urinary output (average, 3500 ml.) has not decreased to normal, it has been sufficiently controlled so that the patient remains comfortable. These patients have bladder capacities up to 500 ml., and seem well able to tolerate the large urinary output. On subsequent examinations the hemoglobin, leukocyte count, and serum electrolyte values have remained within normal limits. The urinary specific gravity has increased to 1.006.

The authors[1-4] who have demonstrated the effectiveness of chlorothiazide-like drugs in some patients with diabetes insipidus have recommended that the drug not be used routinely in clinical practice. We believe that the drug may be clin-

ically effective as long as it is used under close medical supervision.

Patients who receive posterior pituitary powder, as a "snuff," may acquire a local sensitivity in the nose with severe nasal stuffiness and even asthma. Occasionally the medication used intranasally will become ineffective and the patient must resort to intramuscular injections. Serious side-reactions to a sulfonylurialike drug may occur when it is used as an antibiotic, an antihypertensive, an oral hypoglycemic agent, or as a diuretic. Under close supervision, however, it is used for these purposes without much hesitation.

Although diabetes insipidus rarely is harmful insofar as the patient's physical well-being is concerned, the symptoms certainly interfere with his living a normal life. Chlorothiazide-like drugs might well be useful in the clinical management of this problem. There has been no evidence of serious reactions to benzydroflumethiazide in our patients. The addition of the potassium chloride helps to prevent the development of severe hypokalemia, one of the major potential side-effects. The use of the drug has not changed the patients' sense of well-being nor has postural hypotension developed.

Many patients, particularly children, are extremely loathe to use either the nasal medication or the intramuscular preparation. Our patients were well satisfied with the form of medication as well as the clinical effects of benzydroflumethiazide, even though the urinary output did not decrease to normal.

Summary

A chlorothiazide-like drug, benzydroflumethiazide, was used in treating 11 patients who have diabetes insipidus. In seven, a definite decrease in the polyuria and polydipsia occurred; in four patients the drug was not effective.

It is our impression that the drug is useful in the clinical management of diabetes insipidus if the treatment of the patient can be closely supervised.

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