ORIGINAL INVESTIGATION

Efficacy of Indapamide in Central Diabetes Insipidus

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Background: Central diabetes insipidus (CDI) results from deficient vasopressin (antidiuretic hormone) secretion and causes polydipsia and polyuria. Desmopressin, a synthetic analog of vasopressin, is the drug of choice in the treatment of CDI, but in mild cases, there are alternative drugs that can be used, including chlorpropamide, carbamazepine, and thiazides.

Methods: In this study, we investigated the efficacy of treatment with indapamide, which is an antihypertensive diuretic oral agent, in 20 consecutive patients with CDI. The diagnosis of CDI was established by water-deprivation and vasopressin tests. Before the study, serum and urinary osmolality, daily urinary volume, and serum electrolyte levels were measured in all 20 patients. Indapamide (2.5 mg/d) was administered for 10 days, and then the investigations were performed again; for purposes of comparison, 250 mg/d of chlorpropamide was also administered to 11 of the 20 patients who had been given indapamide.

Results: Indapamide revealed a 40.56% ± 9.70% (mean ± SD) (range, 19.6%-55.0%) reduction in 24-hour urinary volume and an increase in urinary osmolality, as well as a decrease in serum osmolality, and was as effective as chlorpropamide ($P<.05$) in the treatment of CDI.

Conclusion: Because of its low cost and lack of significant adverse effects, indapamide may be a suitable, easy-to-use alternative oral agent for some patients with CDI.

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CENTRAL DIABETES insipidus (CDI) is a disorder that results from deficient vasopressin (antidiuretic hormone) action and is characterized by the passage of copious amounts of very dilute urine. The drug of choice for patients with CDI is desmopressin acetate, a synthetic, long-acting vasopressin analog with minimal pressor activity and twice the antidiuretic potency of arginine vasopressin. Patients with mild forms of CDI, who have a circulating arginine vasopressin concentration, can also be treated with a variety of oral agents, such as thiazides,[1] carbamazepine,[2] clofibrate,[3] and chlorpropamide.[4] Chlorpropamide, which is the agent that has most frequently been used in patients with mild CDI, appears to potentiate the antidiuretic action of circulating arginine vasopressin, reducing urinary output by 50%. However, the use of these oral agents can induce adverse reactions, such as hypoglycemia, hyponatremia, hyperlipidemia, hyperuricemia, hypercalcemia, hyperglycemia, hypokalemia, metabolic alkalosis, and myopathy. We previously reported the antidiuretic effect of indapamide in 3 patients with CDI.[5] In a review of the literature, we were unable to find another study on the use of indapamide in patients with CDI.

In this study, the antidiuretic effect of indapamide was investigated in 20 patients with CDI, and in 11 of these patients, the efficacy of indapamide was also compared with that of chlorpropamide.

RESULTS

The causative factors of CDI in our study included pituitary surgery (6 patients), head trauma (2 patients), and unknown (idiopathic) pathogenesis (12 patients) (Table). The mean ± SD reduction in the 24-hour urinary output in the patients who received indapamide was 40.56% ± 9.70% (range, 19.6%-55.0%) (**Figure**). After indapamide therapy, 9 subjects demonstrated an increase in urinary osmolality, and 4 subjects revealed a statistically significant decrease in serum osmolality ($P<.05$) (Figure). The biochemical parameters, which were measured before and during indapamide therapy, did not show any significant change. There were no adverse effects from indapamide therapy during the study. The patients in whom indapamide therapy was discontinued and

PATIENTS AND METHODS

Six men (mean ± SD age, 28.0 ± 5.6 years; age range, 26-36 years) and 14 women (aged 32.7 ± 9.9 years; age range, 16-55 years) with CDI were included in the study. The diagnosis of CDI was established by water-deprivation and vasopressin tests. None of the patients had undergone any previous treatment for CDI. Six patients whose disease resulted from pituitary surgery also received L-thyroxine and glucocorticoid replacement therapy for secondary thyroid and adrenal failure during the study. The characteristics of the patients are summarized in the **Table**. All the patients were informed about the study, and their permissions were obtained. Before and during the study, blood pressure levels, pulse rates, 24-hour urinary output, and fasting blood glucose, serum urea nitrogen, creatinine, serum electrolyte, and uric acid levels, as well as serum and urinary osmolality, were measured in each patient. An autoanalyzer (Olympus AU 5200; Melville, NY) was used to measure serum electrolyte levels, and a micro-osmometer (Advanced TM Micro-Osmometer Model 3300; Advanced Instruments Inc, Norwood, Mass) was used to determine serum and urine osmolality. Indapamide (2.5 mg) was administered daily at 8 AM to every subject, and the patients were observed for 10 days. Administration of indapamide to 11 patients was discontinued on day 10; then, after a 5-day washout period, serum and urinary osmolality and 24-hour urinary volume (at 8 AM) were measured before the administration of chlorpropamide (250 mg/d at 8 AM) for the next 10 days, after which the same investigations were performed. The results of indapamide therapy were also compared with those of chlorpropamide therapy. The data were evaluated with a commercially available statistical program (Version 6.1 for Windows; SPSS Inc, Chicago, Ill). A *t* test and a Mann-Whitney *U* test were used to analyze the data.

Clinical Data of the 20 Patients With Central Diabetes Insipidus (CDI)

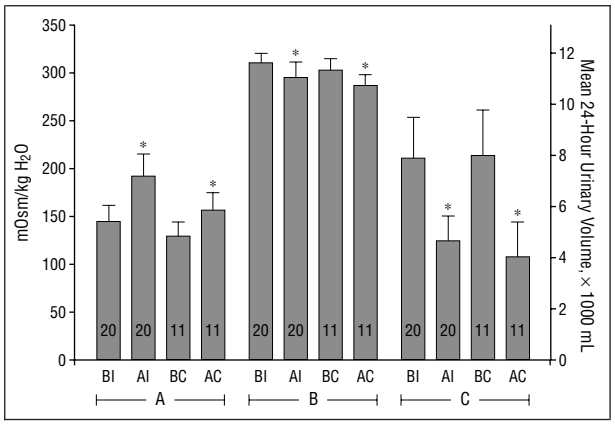
Patient No./ Sex/Age, y	Causative Factor	Onset of CDI, mo	Urinary Volume, mL/d	Urinary Osmolality, mOsm/kg H_2O	Serum Osmolality, mOsm/kg H_2O
1/F/35	Idiopathic	1	10 500	121	304
2/F/32	Idiopathic	8	5650	167	295
3*/F/46	Idiopathic	96	7160	155	329
4*/M/33	Idiopathic	12	11 300	170	312
5*/F/43	Idiopathic	3	10 460	146	307
6/M/28	Head trauma	3	6470	164	300
7*/F/34	Idiopathic	3	7900	136	324
8/M/36	Idiopathic	2	12 700	162	321
9/M/21	Idiopathic	3	15 900	163	310
10*/F/26	Pituitary surgery	3	4700	115	313
11*/F/26	Idiopathic	12	11 875	107	292
12/M/24	Head trauma	20	4900	303	343
13*/F/55	Pituitary surgery	2	8900	157	312
14*/F/24	Idiopathic	180	5300	168	304
15/F/16	Pituitary surgery	4	4850	177	331
16*/F/28	Idiopathic	36	12 500	83	310
17*/F/31	Pituitary surgery	4	5000	146	323
18/F/28	Pituitary surgery	2	5400	134	300
19*/F/35	Idiopathic	3	10 900	120	325
20/M/26	Pituitary surgery	3	6000	136	342

** The patients who also received chlorpropamide.*

who then received chlorpropamide showed a reduction in 24-hour urinary volume of 48.49% ± 10.69% (range, 35.8%-71.7%). However, chlorpropamide therapy had to be discontinued in 2 patients because of severe hypoglycemic symptoms. After chlorpropamide therapy, the urinary osmolality increased in 7 patients and the serum osmolality decreased significantly in 7 patients ($P<.05$) (Figure). The maximum antidiuretic effect of both drugs was seen on on the third to fifth days of therapy and persisted during the entire study. When the antidiuretic effect of indapamide was compared with that of chlorpropamide, chlorpropamide was clinically revealed to be slightly more efficient, but the difference was statistically nonsignificant ($P>.05$).

COMMENT

Indapamide is an antihypertensive diuretic oral agent whose molecular structure is similar to that of hydrochlorothiazides and chlorpropamide. When the molecular structures of these 3 drugs are compared, they are seen to have a common "chlorosulfamoyl benzamide" moiety: their antidiuretic effects are probably attributable to this structural similarity. In a previous study, it was suggested that the antidiuretic effect of chlorpropamide causes a potentiating action of residual antidiuretic hormone on collecting tubules and stimulates its release from the neurohypophysis.[6,7] Similarly, in our study, indapamide and chlorpropamide not only increased urinary osmolality but



A, Mean urinary osmolality of the patients with central diabetes insipidus (CDI) before and after therapy with indapamide and chlorpropamide. B, Mean serum osmolality of the patients with CDI before and after indapamide and chlorpropamide therapy. C, Mean 24-hour urinary volume of the patients with CDI. BI indicates before indapamide therapy; AI, after indapamide therapy; BC, before chlorpropamide therapy; AC, after chlorpropamide therapy; and asterisks, P<.05. The numbers at the bottom of the bars represent the number of patients included for each group. Values are means and error bars indicate SEM.

they also decreased serum osmolality, which may indicate that there is similar activity on collecting tubules. However, since there is a structural relationship between indapamide and thiazides, the antidiuretic effect of indapamide may take place by inducing proximal tubular water absorption, as occurred by thiazides. Chlorpropamide is the most commonly prescribed alternative drug for patients with CDI. In the present study, none of the patients who received indapamide experienced any adverse effects, but 2 patients who received chlorpropamide had to stop taking the drug because of severe hypoglycemic symptoms. The cause of CDI in these 2 patients was idiopathic, and they did not have pituitary failure.

In conclusion, indapamide is well tolerated and can be a useful alternative low-cost treatment for patients with CDI.

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