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Oral Therapy of Diabetes Insipidus With Chlorpropamide

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■ *Chlorpropamide was found to be an effective antidiuretic agent in vasopressin-sensitive diabetes insipidus. Full clinical use of this action is limited by the frequent occurrence of hypoglycemia on higher doses. This complication can be avoided, however, by restricting the dose and by employing combination therapy with hydrochlorothiazide.*

THE ANTIDIURETIC EFFECT of chlorpropamide was discovered, by serendipity, in Brazil when a patient with diabetes insipidus wrongly treated himself for diabetes mellitus with this drug.[1] The striking results were subsequently reproduced in other patients with true diabetes insipidus by investigators in several countries.[2,3,4] Detailed studies in some fifty patients have now been reported with overwhelmingly favorable conclusions.[5] It seems that most patients with diabetes insipidus can now be treated orally;[6] in only the most severe cases is injectable vasopressin required.

The purpose of this report is to call attention to these recent developments, to describe our own experience, and to point out the side effects which may occur.

Materials and Methods

Eight patients, including three children, with diabetes insipidus of various causes were studied (Table 1). Diagnosis was established by standard water deprivation tests[7,8] or the Hickey-Hare maneuver,[9] or both. Complete endocrine evaluation, including assessment of gonadal, thyroid and adrenocortical function, had previously been accomplished. Skull x-ray studies, carotid arteriograms and pneumoencephalograms were done in most cases, as indicated. All patients responded normally to parenteral vasopressin. This medication was then discontinued and 24-hour urine volumes were measured while the subjects were taking water, salt and food ad libitum. Essential hormone replacement therapy with thyroxine and hydrocortisone was continued throughout this investigation. After baseline urine volumes, urine and serum osmolality, serum electrolytes and creatinine clearances were obtained, treatment with oral chlorpropamide was begun. Doses between 125 and 1,000 mg were employed, using a once a day dosage schedule, and allowing at least three days at each dose level. Twenty-four hour urine volumes, urine and serum osmolality, electrolytes, creatinine clearance and fasting blood glucose levels were repeatedly determined during treatment. In most cases, water deprivation tests were performed during treatment to demonstrate maximal urine concentrating ability.

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TABLE 1.—*Data on Eight Patients Treated with Chlorpropamide by Mouth for Diabetes Insipidus*

Sex	Age	Height (Inches)	Weight (Pounds)	Illness Duration	Mean Daily Urine Volume (Liters/24 hr.)	Creatinine Clearance (ml/min.)	Etiology	Associated Endocrine Deficiency
M	40	72	225	2 Years	10.7	79	Suspected pinealoma	Hypogonadotropic hypogonadism
M	10	47	55	4 Years	5.4	110	Craniopharyngioma	Panhypopituitarism
M	18	67	164	5 Years	5.5	92	Craniopharyngioma	Panhypopituitarism
F	12	63	117	9 Years	5.8	125	Idiopathic	No other defects
M	13	62	117	5 Years	7.1	130	Histiocytosis X	No other defects
F	45	63	134	17 Years	10.0	69	Idiopathic	No other defects
M	20	72	172	6 Months	10.5	103	Idiopathic	No other defects
F	31	66	140	8 Months	8.6	144	Idiopathic	No other defects

Results

Untreated 24-hour urine volumes ranged from 5.4 to 10.7 liters. In five of six patients treated with chlorpropamide alone, daily urine volumes were reduced to less than 2 liters (Chart 1). In the sixth, urine excretion was reduced from an untreated volume above 10 liters, to less than 3 liters. In the seventh, treatment with chlorpropamide combined with hydrochlorothiazide decreased her daily urine volume from 10 to less than 2 liters (Chart 2). Although thiazide therapy produced remarkable antidiuresis, the addition of chlorpropamide to her regimen resulted in further reduction of her urine output to a completely satisfactory level. Only patient H, with an average daily urine volume of nearly 11 liters, was refractory to chlorpropamide therapy. His treated urine volume remained two-thirds of his untreated volume, in spite of hypoglycemic doses of chlorpropamide (Chart 3). Fortunately, hydrochlorothiazide was of considerable benefit in this case.

In most cases, there was a three to four day lag before maximal antidiuresis was achieved. Also, the antidiuretic effect seemed to be dose-related, as indicated in Chart 4.

During treatment with various doses of chlorpropamide, serum osmolality was maintained within the normal range. Urine osmolality was consistently hypertonic with respect to serum whenever a satisfactory degree of antidiuresis was achieved. A decided increase in urine osmolality was demonstrated by water deprivation tests during therapy. More importantly, these treated patients were able to undergo 12-hour and 18-hour water deprivation tests without development of symptomatic dehydration. Excellent water conservation was demonstrated by the lack of significant weight loss and by the preservation of normal serum osmolality during water deprivation.

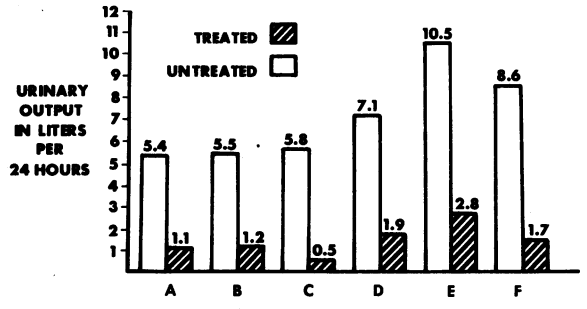

Chart 1.—Antidiuretic effect of chlorpropamide. These patients were treated with chlorpropamide, 500 mg daily. The resulting antidiuresis is shown by the shaded bars.

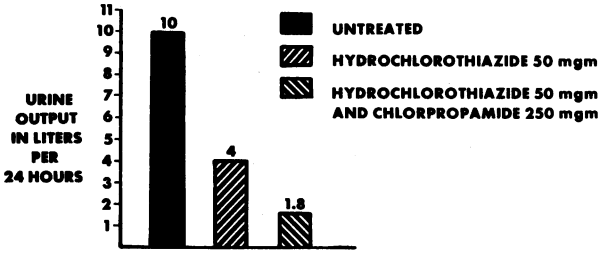

Chart 2.—Results of combined oral therapy with chlorpropamide and hydrochlorothiazide (Patient G).

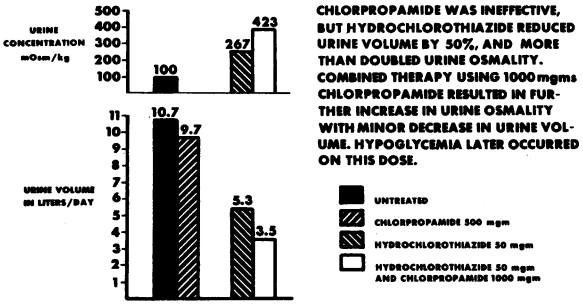

Chart 3.—Results of treatment with both chlorpropamide and hydrochlorothiazide (Patient H).

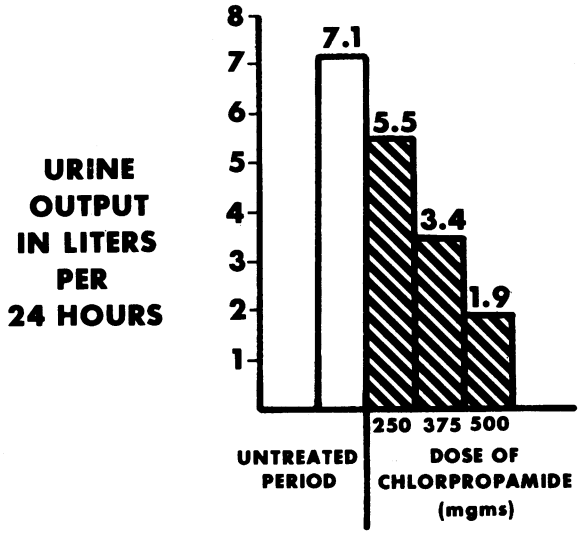

Chart 4.—Patient J was treated for three days at each of three dosage levels. Increasing antidiuresis resulted appeared to be dose-related.

Side Effects

Hypoglycemia of varying degrees was observed in almost all cases at some time during investigation of the drug, and it was used as the end point to judge dose-effect relationships. This was generally the limiting factor, as further antidiuresis could usually be achieved at the expense of hypoglycemia. For example, patient C felt well on 250 mg with a 1.6 liter average urine output. On 500 mg her urine volume further decreased to 0.5 liter but intolerable hypoglycemia soon developed. Patient G was symptomatically hypoglycemic on 500 mg of chlorpropamide, but felt well on 250 mg plus 50 mg of hydrochlorothiazide daily. The latter drug not only reduced her urine volume, but was thought to be beneficial in protecting her from chlorpropamide-induced hypoglycemia.

In most cases, however, the antidiuretic dose was substantially less than the hypoglycemic dose, thus allowing general acceptance of the drug as an antidiuretic agent. The doses used to achieve maximal antidiuresis (Chart 1) tended to cause hypoglycemia after the patient had been discharged from the hospital, and for that reason were subsequently reduced with slight sacrifice in water conservation. However, the values given do serve to demonstrate the profound antidiuretic action of this drug.

Hyponatremia with symptoms of water intoxication (inappropriate antidiuretic hormone [ADH] effect) was not observed during this study and is mentioned only because it has recently been reported as a complication of chlorpropamide therapy.[10]

Discussion

Treatment of diabetes insipidus with vasopressin in various forms (parenteral, snuff, nasal spray) is not infrequently attended by unpleasant allergic or idiosyncratic local reactions. Although true refractoriness to vasopressin is uncommon, it was encountered in the present series with use of both vasopressin tannate injection and lysine-8-vasopressin nasal spray and served as motivation to attempt other forms of therapy. Despite its effectiveness in most cases, vasopressin is generally a nuisance, at best. However, patients with severe deficiency of vasopressin, as manifest by high grades of polyuria and polydipsia, are obligated to accept this nuisance if they are to live normally.

The first* oral form of treatment was reported in 1959 by Crawford and Kennedy who used chlorothiazide[11] and hydrochlorothiazide.[12] These drugs increased the osmolality of urine and reduced the daily excreted volume by about 50 percent. Since that time, thiazides have become a widely used adjunct in the management of diabetes insipidus and the mainstay of treatment of nephrogenic diabetes insipidus.[13] The mechanism of action has been disputed.[14] It is unlikely that significantly increased permeability to water of the distal nephron results (ADH-like effect) since the resulting urine never becomes hypertonic.

In contrast, consistently hypertonic urine is achieved during treatment with chlorpropamide. This finding is consistent with reduction of free water clearance as demonstrated by Hocken and Longson[15] in their patient on treatment with chlorpropamide. The elaboration of urine which is hypertonic to plasma is uniquely characteristic of the action of vasopressin. This suggests that chlorpropamide may act by enhancing the neurohypophyseal secretion of vasopressin, much as it enhances pancreatic islet-cell secretion of insulin. Pharmacologic stimulation of vasopressin release in man, independent of plasma osmolality, by means of nicotine, provides a physiologic precedent for this possibility.[16] Moreover, this theory is in keeping with chlorpropamide's lack of effect in nephrogenic diabetes insipidus,[1,5] wherein vaso-

*The antidiuretic action of aminopyrine was reported by B. S. Kahn in 1933 (JAMA 100:1593) but the drug received scant clinical application because of its potential hematologic toxicity.

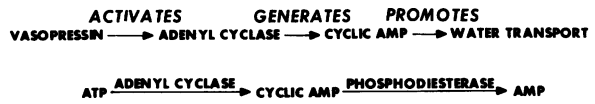

Chart 5.—Generally accepted sequence of vasopressin-induced water transport. (Possible role of chlorpropamide is discussed in text.)

pressin resistance, but not deficiency, is the problem. Augmentation of endogenous vasopressin levels would be of no benefit here since exogenous vasopressin is without effect. Therefore, if chlorpropamide acts by increasing endogenous hormone secretion, it should be effective only in vasopressin-deficient diabetes insipidus and not in the vasopressin-resistant form. Indeed, this seems to be the case.[1] Substantiation of this theory requires direct measurement of plasma vasopressin which has not yet been reported in this setting.

Alternatively, chlorpropamide may have a direct vasopressin-like effect or may potentiate the effect of minute amounts of vasopressin which persist in diabetes insipidus. These possibilities were investigated by Ingelfinger and Hays,[17,18] using the toad bladder. They found that although chlorpropamide alone had no effect on water movement, it did potentiate vasopressin-induced water transport. This could result either from activation of renal tubular adenyl cyclase which generates cyclic adenosine monophosphate (AMP) from adenosine triphosphate (ATP) or from inhibition of the phosphodiesterase which degrades cyclic AMP (Chart 5). Cyclic AMP has been shown to be the chemical mediator of vasopressin's water transporting effect. Since chlorpropamide did not enhance cyclic AMP-induced water transport, the authors reasoned that it must act by increasing the sensitivity of renal tubular adenyl cyclase to vasopressin.[17]

Our data is consistent with this explanation. Milder cases of diabetes insipidus were more sensitive to chlorpropamide and responded better to this form of treatment than the more severe cases. In other words, those with low levels of circulating vasopressin (partial diabetes insipidus[19]) were more likely to respond than those without any hormone at all. Webster and Bain[5] made similar observations. As for patients with nephrogenic diabetes insipidus, the lack of antidiuretic effect would imply that they lack the chlorpropamide-sensitive reaction involving adenyl cyclase. We are unaware of any data bearing on this point, however.

The long-term safety of chlorpropamide has been demonstrated by its use for over a decade in the treatment of diabetes mellitus. Physicians are familiar with its infrequent adverse reactions. Initial fears that it might worsen diabetes mellitus by causing premature islet-cell exhaustion have been dispelled by the finding that after long-term treatment serum insulin levels actually become lower in concert with lower glucose levels.[20]

In our experience to date, the only hazard associated with chlorpropamide therapy of diabetes insipidus has been hypoglycemia. Some degree of hypoglycemia developed sooner or later in almost all of our patients on the potent 500 mg dosage. This is in contrast to the experience of Arduino et al[1] and Reforzo Membrives et al,[3] whose patients seemed to resist the drug's hypoglycemic effect. In our patients, chlorpropamide was of practical value as an antidiuretic agent only in cases in which it was effective in the 125 to 375 mg dose range. Higher doses almost invariably caused hypoglycemia. This may be attributed partially to the fact that three of our patients were small children, and three had other associated endocrine deficiencies. Patients with pan-hypopituitarism, including corticotrophin and growth hormone deficiency, were particularly susceptible to this complication.

Hypoglycemia could usually be avoided, however, by restricting the dose to around 250 mg and when necessary by adding hydrochlorothiazide to the regimen. The effects of these two drugs were found to be additive (Charts 2 and 3). Hydrochlorothiazide, by virtue of its own antidiuretic action, reduces the need for large doses of chlorpropamide and also protects against hypoglycemia, probably by inhibiting insulin secretion.[21] Fortunately, significant hypokalemia is not usually encountered with doses of only 50 mg of hydrochlorothiazide. Hence, the two in combination yield a highly desirable therapeutic result.

Addendum

Since this manuscript was submitted for publication, Robertson and Mahr have shown (program of the Fifty-third Meeting of the Endocrine Society, 1971) by means of a highly sensitive radioimmunoassay that in patients with diabetes insipidus chlorpropamide does not increase plasma vasopressin levels. Their data indicates that the

antidiuresis results from augmentation of the antidiuretic effects of suboptimal amounts of vasopressin measurable in their patients.

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ADVANCES IN PLACENTAL FUNCTION TESTS

"The last five years have seen tremendous advances in the development of placental function tests. With the aid of several new procedures, the obstetrician is now able to assess the health of the unborn child. Anderson, in a report from the University of Southern California, delineates his experience with the determination of urinary estriol in the diabetic pregnancy. Although use of the quantitative chemical assay of the 24-hour urine specimen has been controversial and opinion divided as to its value, Anderson showed that he could reduce the perinatal mortality in the insulin-dependent diabetic from 17 percent when the estriol was not employed to 8 percent if it were employed to manage the time of delivery in these pregnancies. . . .

"Another significant report on placental function tests was that of Spellacy and associate from the University of Miami who have developed a test for human placental lactogen and employ this to assess the righ-risk pregnancy. The greatest value of this test has been in the hypertensive complications of pregnancy. There is a 95 percent reduction in the human placental lactogen in the serum when the fetus is dying or in impending jeopardy. So this is a very important advance. As this test is developed, I am sure we will see almost routine employment of this material in the high-risk pregnancy."

—JOHN W. GREENE, JR., M.D., Lexington
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