The Effect of Chlorpropamide Hyponatremia on Mental Status in a Nursing Home Population

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Fifty-nine nursing home patients (average age, 79.9 ± .9 years) receiving chlorpropamide were screened with a serum sodium determination. Nine patients (15.3 percent) had a serum sodium concentration less than 135 mEq/L; six of these patients (10.2 percent) had a serum sodium equal to or less than 130 mEq/L; none of the patients had a serum sodium less than 125 mEq/L. Five hyponatremic patients (Na ≤ 130 mEq/L) and nine normonatremic patients (Na ≥ 135 mEq/L) were screened with a standardized mental status examination and additional laboratory studies. The hyponatremic patients were switched to tolazamide after a one-week wash-out period, and the mental status examination and laboratory studies were repeated in both groups four weeks later. One patient in the hyponatremic group died during the course of the study; the other four became normonatremic on tolazamide. Mental status scores increased significantly in the hyponatremic group, 16.0 ± 3.6 to 20 ± 4.6 (a 37.3 ± 21.5 percent increase), compared with the normonatremic group, 14.5 ± 2.6 to 15.8 ± 2.9 (a 7.8 ± 3.2 percent increase). There were no significant differences in serum glucose, creatinine, chlorpropamide, or antidiuretic hormone concentrations between the two groups. It is recommended that periodic serum sodium determinations be obtained in geriatric patients receiving chlorpropamide.

Chlorpropamide (Diabinese) is an oral hypoglycemic agent of the sulfonylurea group that has been in clinical use for more than 20 years. In 1969 Hagen and Frawley[1] implicated chlorpropamide as a cause of the syndrome of inappropriate secretion of antidiuretic hormone (SIADH). Since that time a number of additional reports have confirmed this observation.[2-6] The drug appears to potentiate the action of antidiuretic hormone at the renal tubule by sensitizing the enzyme adenyl cyclase to activation by antidiuretic hormone. This effect has been useful therapeutically in treating patients with partial diabetes insipidus.

The incidence of hyponatremia in patients treated with chlorpropamide has varied from 5 percent to 16 percent. Elderly patients may be

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somewhat more susceptible to this complication. Symptoms of hyponatremia are myriad and include nausea, vomiting, headache, abdominal pain, weight loss, and a wide spectrum of central nervous system dysfunction. Central nervous system symptoms may vary from mental confusion, impaired memory, and disorientation to lethargy, stupor, and coma. All reported cases have been reversible after stopping the drug.

Although no study has confined itself to an elderly population, most cases have occurred in the elderly. This population may be at significant risk because of an impaired ability to excrete chlorpropamide. Chlorpropamide has a half-life of 36 hours (assuming normal renal function) and is not metabolized to an inactive form but is rather slowly excreted unchanged in the urine. In patients with normal renal function, 80 to 90 percent of a single oral dose will be excreted in the urine in 96 hours. Thus, elderly patients with age-related decrements in renal function are likely to accumulate the drug. Serum sodium determinations are not routinely done in patients receiving chlorpropamide. Severe hyponatremia causing dramatic symptoms such as seizures or coma frequently results in hospitalization and proper diagnois. However, mild hyponatremia may cause more subtle changes in mental status, such as confusion or impaired memory, that may be diagnosed in the elderly patient as senile dementia or as "cerebral vascular disease" when, in fact, they represent a metabolic encephalopathy that is drug induced and totally reversible.

The objectives of this study were to determine the prevalence of chlorpropamide-induced hyponatremia in an elderly nursing home population, to determine associated risk factors, to determine whether mild hyponatremia is a cause of impaired mental function in this population, and to determine whether chlorpropamide hyponatremia can be related to the plasma levels of this drug. In addition it was hoped to determine whether substituting tolazamide (an oral hypoglycemic agent not reported to produce hyponatremia) for chlorpropamide corrected the hyponatremia.

Methods

Twelve nursing homes agreed to participate in this study. From these homes, 74 patients receiving chlorpropamide (Diabinese) were identified. Fifty-nine patients agreed to participate in the study, and written informed consent was obtained. For those individuals deemed incompetent to sign for themselves, the signature of the legal guardian was obtained. The protocol had been approved by the Clinical Investigation Committee of the Milton S. Hershey Medical Center.

The study was divided into three phases. During phase 1, serum sodium concentration and fasting blood sugars were obtained in all 59 patients, and age, sex, clinical diagnoses, and medications other than chlorpropamide were recorded. It was found that 39 of the 59 patients were on diuretics, which can also be a cause of hyponatremia. Patients were then classified according to serum sodium concentration (serum sodium concentrations from 135 mEq/L to 145 mEq/L were considered normal).

In phase 2 nine patients from the normonatremic group and five patients from the hyponatremic group were chosen to be studied in greater detail as the control and experimental groups, respectively. Seven patients in the normonatremic group and three patients in the hyponatremic group were taking diuretics. The following laboratory tests were performed in each group of patients: serum and urine osmolalities, fasting blood sugar, serum lipids, blood urea nitrogen, serum creatinine, electrolytes, chlorpropamide level (trough), and antidiuretic hormone concentration. These tests were performed by one laboratory (MDS, Reading, Pa), except for the serum and urine osmolalities, which were performed in the Clinical Laboratories of the Milton S. Hershey Medical Center. An investigator administered a standard mental status examination[7] of 30 objective questions, checked for edema, and measured supine and standing blood pressures.

In phase 3 of the study chlorpropamide was discontinued in the experimental group and tolazamide (Tolinase) was substituted at an equivalent dosage (milligram for milligram) after a one-week wash-out period. The patient's personal physician followed the patient clinically and measured urine glucose concentration to assess the adequacy of diabetic control during the switch-over. Four weeks after the tolazamide was started, the tests performed in phase 2 (with the exception of serum lipids) were repeated. A double-blind mental status examination was administered.

Table 1. Prevalence of Hyponatremia in 59 Nursing Home Patients Treated with Chlorpropamide

Serum Sodium (mEq/L)	No. (%)
<135	9 (15.3)
≤130	6 (10.2)
≤125	0 (0)

Table 2. Serum Sodium Concentrations (mEq/L)

	Experimental Group Patient No.					Control Group Patient No.								
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Phase 1	126	130	130	127	129	136	142	144	138	139	135	143	141	144
Phase 2	127	127	133	136	127	138	140	142	139	131				
Phase 3	—	136	139	139	135	137	141	138	139	128	136	143	135	146

Results

The prevalence of hyponatremia in the 59 patients screened is shown in Table 1. The exact serum sodium concentration obtained in the experimental and control groups during the three phases of the study is depicted in Table 2. It should be noted that patient 1 died between phases 2 and 3 of the study. The exact cause of death was not determined.

Using the unpaired *t* test, the experimental and control groups were compared (during phase 2) according to several important clinical parameters (Table 3). The age of the patients in the experimental group was significantly greater than the age of the patients in the control group. In addition, the serum sodium concentration, serum chloride concentration, and serum osmolality were significantly different between the two groups. Analysis of other important laboratory data, such as serum creatinine, chlorpropamide level, and antidiuretic hormone concentration, failed to reveal any significant difference between the two groups.

Four of the five hyponatremic patients became normonatremic after being switched to tolazamide (phase 3); the fifth patient died before the completion of the study. A repeat statistical analysis comparing the two groups after the experimental group was switched to tolazamide (phase 3) no longer showed a significant difference between serum sodium and chloride concentrations or serum osmolality. Although eight of the nine control patients remained normonatremic during phase 3, one patient became hyponatremic.

The mental status scores are shown in Table 4. All four hyponatremic patients improved their scores significantly compared with the control group (average increase was 37.3 ± 21.5 percent) after becoming normonatremic on tolazamide; however, there was also improvement in the control group scores (7.8 ± 3.2 percent). Although the most dramatic increase in mental status score occurred in patient 4, the serum sodium concentration of this patient appeared to be correcting before tolazamide was instituted. One member of the control group, patient 10, became hyponatremic

Table 3. Comparison of Experimental and Control Groups During Phase 3

Clinical Parameter	Experimental Group (n = 5)	Control Group (n = 5)	Statistical Significance Nonpaired *t* test
Age (yr)	87.2 ± 3.5	78.4 ± 2.4	Significant $P < .05$
Chlorpropamide base (mg)	195 ± 33.9	190 ± 36.7	NS
Sodium (mEq/L)	129.2 ± 1.0	138.9 ± 1.4	Significant $P < .005$
Potassium (mEq/L)	4.3 ± 0.1	4.3 ± 0.1	NS
Chloride (mEq/L)	77.8 ± 18.5	102.0 ± 1.3	Significant $P < .01$
Bicarbonate (mEq/L)	26.2 ± 0.9	24.8 ± 1.3	NS
Glucose (mg/100 mL)	110.4 ± 11.8	132.9 ± 13.7	NS
Blood urea nitrogen	15.6 ± 4.9	24.4 ± 2.6	NS
Creatinine (mg/100 mL)	1.0 ± 0.1	1.3 ± 0.2	NS
Serum osmolality (mosm/kg)	274 ± 6.4	295.6 ± 5.1	Significant $P < .025$
Urine osmolality (mosm/kg)	479.8 ± 98.0	624.4 ± 54.9	NS
Total serum lipids (mg/100 mL)	452 ± 31.5	518.8 ± 63.7	NS
Chlorpropamide serum level (μg/mL)	86.0 ± 25.8	68.0 ± 25.6	NS
ADH (pg/mL)	1.1 ± 0.1	4.4 ± 1.7	NS

NS = Not statistically significant

during the course of the study but showed no deterioration in mental status score.

Discussion

The prevalence of hyponatremia in chlorpropamide-treated patients reported in this study (15.3 percent) is in the upper portion of the previously reported range (5 to 16 percent). The average age of the five hyponatremic patients in the experimental group was 87 ± 3.5 years, compared with 78.4 ± 2.4 years for the control group, suggesting that age alone may be a risk factor. Even though there was no statistical difference in serum creatinine between the two groups, suggesting that renal function was not a risk factor in this study, it is tempting to postulate that the experimental group had a significantly lower creatinine clearance. Because of a dilutional effect, the serum creatinine in the experimental group may have been falsely reduced. Even if one assumes the serum creatinine was correct, it is known that patients in this age range (85 to 90 years) can have a creatinine clearance of 50 cc/min or less with a normal serum creatinine. In spite of these possibilities, the study did not demonstrate significant chlorpropamide accumulation (drug toxicity) in the experimental group.

All cases of hyponatremia were mild; the lowest serum sodium concentration detected was 126 mEq/L. Although this study does not prove unequivocally that chlorpropamide caused hyponatremia in each patient, four of the patients reverted to normal serum sodium concentrations when

Table 4. Mental Status

Patient	Score		
	Phase 2	Phase 3	Percent Change
Experimental*			
1	6	—	—
2	10	13	+30
3	28	30	+7
4	9	18	+100
5	17	19	+12
Mean	16.0 ± 3.6	20.0 ± 4.6	37.3 ± 21.5**
Control†			
6	19	20	+5
7	23	25	+9
8	7	8	+14
9	18	22	+22
10	19	19	0
11	23	25	+9
12	8	10	+25
13	14	12	−14
14	4	4	0
Mean	14.5 ± 2.6	15.8 ± 2.9	7.8 ± 3.2

*These patients were hyponatremic in phase 2 and normonatremic in phase 3
**$P < .05$ compared with controls
†These patients were normonatremic in both phase 2 and phase 3, except for patient 10, who became hyponatremic in phase 3

switched to tolazamide. The common causes of pseudohyponatremia (elevated lipids and hyperglycemia) were eliminated in this group of patients.

Comparison of other case reports of chlorpropamide hyponatremia with the patients in the experimental group reveals several interesting points. The average age of 24 cases reported in the literature[2-4,6,8-15] was 64 ± 10.3 years, including 21 women and 3 men, whereas the average age reported in this study was 87.2 ± 3.5 years (4 women and 1 man). The average dose of chlorpropamide in the previous case reports was 460.9 ± 33.3 mg/d compared with 195 ± 33.9 mg/d in the experimental group of this study. Thus, since older female patients may be more likely to develop the SIADH, even at relatively low chlorpropamide doses, being female may be a risk factor.

Patients 1 and 5 in the experimental group and patient 10 in the control group (during phase 3) were the most likely candidates to have SIADH. Serum osmolalities in these three patients were 264, 266, and 262 mosm/kg(H_2O), respectively, whereas urine osmolalities were 677, 403, and 529 mosm/kg(H_2O). In each case the urine was inappropriately concentrated in relation to the serum osmolality. Each of these patients was clinically normovolemic and had normal electrolyte and renal profiles. These patients were on relatively low doses of chlorpropamide, 250 mg, 125 mg, and 100 mg, respectively. Interestingly, the antidiuretic hormone concentrations were not elevated, supporting the assumption that chlorpropamide does not increase the release of antidiuretic hormone from the neurohypophysis but rather sensitizes the renal tubule to the effects of the hormone.[16]

Patient 10 developed SIADH during the course of the study, indicating that hyponatremia can develop even after months of chronic therapy and several normal electrolyte determinations. It is in-

teresting to note that although this patient's serum creatinine and dose of chlorpropamide remained unchanged, the serum chlorpropamide level (trough) increased from 140 to 275 μg/mL as the SIADH developed.

Mental status scores increased significantly ($P < .05$) in the experimental group compared with the control group, but both groups did show improvement in mental status. Some of the improvement in mental status scores may have been related to familiarity with the test and the examiner. All four patients in the experimental group showed clinical improvement, which was measured in this study by increased scores on the mental status examination, and one patient (patient 4) showed marked improvement. Patient 4 appeared more alert and talkative after taking tolazamide for four weeks. This patient's serum sodium concentration, however, appeared to be correcting spontaneously during the laboratory testing obtained approximately one week following the administration of the mental status test. Unfortunately, the patient's serum sodium concentration on the exact day of the mental status test is not known. The mental status score in patient 10 remained unchanged, even though this patient's serum sodium concentration changed from 139 to 128 mEq/L during the course of the study.

It is quite likely that not only the absolute value of the serum sodium concentration in hyponatremic individuals, but also the rate of change from the normonatremic to the hyponatremic state, affects mental status. It is impossible to determine the rapidity of serum sodium changes from the data available, except in patient 10, in whom the change appeared gradually over a several-month period.

The switch from chlorpropamide to tolazamide in the four patients in the experimental group was accomplished uneventfully on a milligram-for-milligram basis after a one-week wash-out period. There was no statistical difference in serum glucose concentration before and after the switch (110.4 ± 11.8 mg/100 mL and 141.3 ± 63.2 mg/100 mL).

Conclusions

The prevalence of hyponatremia in geriatric patients receiving chlorpropamide is high, 15.3 percent. Although the hyponatremia is usually mild, it may adversely affect the mental status of the patient. Risk factors associated with an increased prevalence of chlorpropamide-induced hyponatremia appear to be advancing age and female sex. Chlorpropamide serum levels and renal function did not seem to be valid predictors of patients who would develop SIADH. Serum sodium concentrations should be monitored periodically in patients receiving chlorpropamide, and the drug should be discontinued if hyponatremia occurs. Tolazamide is a safe and effective alternative to chlorpropamide and has the advantage of not being associated with SIADH.

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