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Treatment of Polydipsia and Hyponatremia in Psychiatric Patients

Can Clozapine Be a New Option?

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Polydipsia occurs frequently in chronic schizophrenic patients, some of whom develop intermittent hyponatremia. Most therapeutic efforts have tried to control the hyponatremia. Four schizophrenic patients, followed for more than one year, showed improvement on clozapine. Case 1 was an outpatient without history of hyponatremia who improved from polydipsia and psychosis. The last three were inpatients with polydipsia, intermittent hyponatremia, and psychosis who showed minimal improvement of psychosis but significant decrease in polydipsia and water intoxication. Case 2 relapsed to polydipsia when clozapine was discontinued on two occasions. Case 3 demonstrated polyuria during 39% of days before clozapine and in 0% of days after two weeks of clozapine. In case 4, most baseline sodium levels were abnormal, but all became normal after clozapine. A time-series analysis for intervention effects showed a significant effect of clozapine (p = .017). The limited information provided by these case reports suggest the need for controlled studies of the clozapine effect on polydipsic patients. ***[Neuropsychopharmacology 12:133–138, 1995]***

KEY WORDS: *Water intoxication; Clozapine; Schizophrenia; Hyponatremia; Case report; Thirst*

Polydipsia, the excessive intake of liquids, is a frequent phenomenon in chronic psychiatric patients, particularly those with schizophrenia. It is a poorly understood and underdiagnosed disorder. Prevalence figures range from 3% to 39% of state hospital patients (de Leon et al. 1994).

From 25% to 86% of polydipsic patients, comprising 1% to 5% of chronic inpatients, develop a second phase with episodes of water intoxication (de Leon et al. 1994). These patients become unable to excrete all of the ingested fluids, leading to dilutional hyponatremia. Symptoms of hyponatremia can range from increased psychotic symptoms to seizures, coma, and even death. This state has been termed "Psychosis, Intermittent hyponatremia, and Polydipsia" (PIP syndrome) (Vieweg et al. 1988). In a third phase, some patients develop physical complications (osteopenia, and dilatation of the urinary and gastrointestinal tracts) secondary to the chronic polydipsia and polyuria.

The pathophysiology of these disturbances is not clearly understood, and the etiology of polydipsia is not known. Polydipsia is the primary problem and in many patients, the only problem. Polydipsia generally is not the result of drugs or other illnesses. It is believed that many of the patients who develop water intoxication have difficulty with free water excretion in the kidney because of inappropriate antidiuretic hormone secretion (SIADH). However, this is not identical to the syndrome referred to as SIADH in the medical literature. First, in SIADH, polydipsia is not a feature. Second, patients with polydipsia and hyponatremia suppress antidiuretic hormone (ADH) at very low osmolalities.

Most pharmacotherapeutic efforts in polydipsic pa-

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Received March 10, 1994; revised August 30, 1994; accepted September 8, 1994.

NEUROPSYCHOPHARMACOLOGY 1995—VOL. 12, NO. 2

Published by Elsevier Science Inc.
655 Avenue of the Americas, New York, NY 10010

0893-133X/95/$9.50
SSDI 0893-133X(94)00069-C

tients have been directed toward treating water intoxication by reducing the effect of ADH with lithium, lithium with diphenylhydantoin, and demeclocycline (Nixon et al. 1982; Khamnei 1984; Goldman and Luchins 1985; Vieweg et al. 1988; Vieweg et al. 1990; Alexander et al. 1991). Results have varied, and these medications have no effect on the polydipsia and only reduce the likelihood of developing hyponatremia by increasing free water excretion.

Polydipsia is the primary and enduring problem. Treatment has consisted of both pharmacotherapy and behavioral therapy and has been almost restricted to patients with both polydipsia and intermittent hyponatremia.

There is no consistent effective pharmacological treatment for polydipsia with hyponatremia. Most of the limited information about pharmacotherapy comes from case reports. Additionally, polydipsia is frequently episodic, making interpretation of findings from case reports even more difficult. Some drugs have been described as effective in case reports, but results were questioned or not replicated by different authors. The list of drugs includes: high doses of propranolol, captopril, enalapril, fluoxetine, and naloxone (Shevitz et al. 1980; Vieweg et al. 1985; Goldstein 1986; Kathol et al. 1986; Lawson et al. 1988; Goldstein and Folsom 1991; Sebastian and Bernardin 1990; Goldman and Janeck 1991; Deas-Nesmith and Brewerton 1992; Nishikawa et al. 1992).

In the absence of any standard, effective pharmacotherapy, limiting access to water has become the current standard treatment. Water restriction is not usually used for patients who have only polydipsia, but is reserved for patients exhibiting symptoms of water intoxication. Water restriction can be implemented most efficiently using the target weight approach (Goldman and Luchins 1987). Water drinking and retention causes diurnal weight gain, which is quantified as normalized diurnal weight (NDWG) expressed by the equation

$$\text{NDWG} = \frac{\text{4 P.M. weight} - \text{morning weight}}{\text{morning weight}} \times 100$$

A critical value of NDWG is established for each patient. When this value is reached, water restriction is instituted until the next day.

Lee and coworkers (1991) reported a case of a patient without history of hyponatremia who had a partial improvement in NDWG while on clozapine. Preliminary information from other cases has been published (Spears et al. 1993). In this article, we report our positive experience using clozapine on four patients (one with polydipsia and three with polydipsia and hyponatremia), over the past four years. This preliminary information merits additional investigation in controlled trials. If confirmed, it would provide another treatment option for polydipsia with water intoxication.

CASE REPORTS

Background

All patients had been followed for more than one year. The first case was an outpatient without documented history of hyponatremia, whereas the other three had histories of hyponatremia and were inpatients on research units in two state hospitals and managed by the same research team. These three patients were assessed using the NDWG for polydipsia and water retention, the Brief Psychiatric Rating Scale (BPRS) for the psychiatric symptoms and the Structured Clinical Interview for DSM-III-R Diagnosis (SCID). Total daily urine samples were collected for case 3 for 162 of 227 (73%) days. This includes 60 days when he was in restraints and urine collection was very difficult. Because of the difficulty in measuring total fluid intake, urine volumes were used as an indirect measure of polydipsia. The fourth patient finished a double-blind clozapine treatment protocol and weekly sodium levels were available.

Statistics

Because of the anecdotal nature of cases 1, 2, and 3, no statistical applications were attempted. In case 4, we had enough data to conduct a single-case statistical analysis. The percentage of abnormal values before and after clozapine were compared with the McNemar test. The classic t and F test could not be used because data was dependent and showed significant autocorrelation. The application of ARIMA models in case 4 resulted in a complex model that was difficult to interpret. Therefore, another time-series analysis, the C statistic, was used as a method of evaluating intervention effects. The C statistic assesses the variability in successive data points to evaluate relative changes in slope from one phase of treatment to another (Tryon 1982). Statistical analyses were performed with the computerized statistical program Systat (Wilkinson 1990).

Case 1

Case 1 is a 36-year-old white female with a history of schizophrenia from the age of 21 and multiple hospitalizations. She had been treated with various neuroleptics with only partial response. By her mother's report, the patient consumed 10 to 15 liters of water/day, and was nearly always in possession of a 1/2 gallon container of water. There was no documented history of water intoxication, but there was a history of urinary incontinence.

Because of her refractory psychotic symptoms, the patient was started on clozapine. Psychotic symptoms improved during the first three to four months of treatment. When urinary incontinence stopped after two

months of clozapine treatment, the patient's mother realized that polydipsia had also improved, although the patient still drank two to four liters/day. This first case brought our attention to the improvement in polydipsia and raised the possibility that clozapine may have had an unexpected therapeutic effect.

Case 2

Case 2 is a 39-year-old single white female patient with DSM-III-R diagnosis of schizophrenia. She had a 22-year history of psychosis with very severe formal thought disorder. The patient was admitted to a state psychiatric hospital at age 30 for unmanageable polydipsia and pica. At age 32, she developed enuresis and hyponatremia associated with vomiting. At age 34, the patient developed generalized seizures secondary to hyponatremia (sodium ranging between 115 and 129 mEq/l). Fluid intake measured during one 24-hour period was 15,210 ml, and urine output was 10,775 ml. She had been treated with various neuroleptics without significant effect on either the psychosis or polydipsia.

The patient was transferred to the research unit on loxapine 20 mg, lithium 900 mg, and phenytoin 400 mg per day. Propranolol up to 200 mg/day was added with no improvement in polydipsia. She had two hyponatremic seizures during the next year. She required continuous one-to-one supervision to restrict her water intake.

Clozapine was started in addition to the antiepileptic treatment. After a month and a half at dosages up to 400 mg of clozapine, she began to show improvement in the polydipsia and one-to-one supervision was discontinued. The psychosis showed a minimal improvement on the BPRS total score (45 to 41) and conceptual disorganization, the highest score, went from 7 to 6.

She remained stable without polydipsia for five months. She developed appendicitis, and clozapine was discontinued. Following surgery, she was medication free and remained stable without polydipsia. Eight weeks later, however, the staff observed that she had begun to drink excessively again and had to be placed on close supervision. In spite of adequate antiepileptic levels, the patient had hyponatremic seizures, and consequently clozapine was reinitiated. After two months on clozapine with dosages up to 300 mg, there was an improvement again in the drinking behavior. Four months after clozapine had been reinitiated the polydipsia had improved enough to discontinue one-to-one supervision.

The patient continued to do well until clozapine was discontinued for a tubal ligation eight months later. Within five days of discontinuation, she had to be restarted again on one-to-one supervision to control polydipsia. The polydipsia persisted until clozapine was restarted.

Case 3

Case 3 is a 31-year-old single white male with DSM-IIIR diagnosis of schizophrenia. He had a 13-year history of psychosis and had been continuously hospitalized for seven years. At age 28, he was noted to have polydipsia with episodes of hyponatremia resulting in delirium, dysarthria, and occasional severe self-mutilatory behavior. When transferred to the research unit, he was taking 10 mg of pimozide per day. Propranolol was started for akathisia and polydipsia, and was increased to 290 mg/day with no improvement in polydipsia. Staff tried to observe the patient closely and discourage water intake as much as possible. Episodes of water intoxication with confusion and self-mutilatory behavior requiring physical restraints were occurring in 26% of 158 days.

Clozapine was started and increased to 500 mg/day. After two months, episodes of water intoxication, self-mutilatory behavior and need for restraints had ceased. Close supervision was discontinued. There was no significant improvement in psychosis as measured by the total score BPRS (43 v 43), but the global clinical impression showed a mild improvement.

Before clozapine, polyuria was present in 39% of 121 days with volume as high as 8 liters/24 hours. Polyuria is defined as a daily volume greater than 3 liters. During the first two weeks of clozapine treatment, the frequency of polyuria dropped to 20% of days and after two weeks to 0%. Mean daily volumes of urine before and after clozapine also suggest a positive effect of clozapine, 3.0 liters/day before clozapine and 1.5 liters/day after.

Normalized diurnal weight showed significant improvement after two weeks on clozapine. Abnormal NDWGs (> 1.2%) were present in 43% of 103 days before clozapine and 14% of 55 days afterwards. The mean NDWG dropped from 0.92% to 0.36%.

Prior to clozapine, the patient had been placed on restraints because of excessive polydipsia and water intoxication in almost one third of the days (26% of 158). While on restraints, it was difficult to measure weight changes or polyuria and it is possible that days with maximum weight changes and polyuria were missed.

The dose of clozapine was reduced to 450 mg per day after five months of treatment. The patient was followed for another six months, during which time restraints were needed in only 4% of days to control the behavior related to psychosis and not to water intoxication. Only one episode requiring restraints appeared to be related to water intoxication with a corresponding NDWG of 4% on that day. This suggests that after several months of treatment, clozapine did not com-

pletely prevent the episodes of water intoxication, but they became rather infrequent in spite of the patient having free access to water.

Case 4

Case 4 is a 33-year-old white male with chronic paranoid schizophrenia that started in his early twenties. The patient was stabilized on haloperidol until he was 26 years old. At that time he began to deteriorate with hostile, assaultive, impulsive outbursts associated with delusional behavior and excessive water drinking. He was hospitalized repeatedly without significant change in behavior. At age 29, he had an episode of grand mal seizure secondary to hyponatremia (serum sodium 110) caused by excessive water drinking. He was transferred to the research unit for evaluation for a double-blind, dose response study of clozapine in patients with treatment resistant schizophrenia, where he received three trials of three typical neuroleptics. His psychotic symptoms remained unchanged during these trials, and he entered the clozapine protocol.

He ultimately underwent three four-month trials of clozapine at 100, 300, and 600 mg/day. The total BPRS score was 40 at baseline, 57 at the end of the first clozapine trial, 61 at the end of the second trial, and 47 at the end of the third trial. Although his psychotic symptoms did not improve significantly with clozapine, it became evident that his polydipsia improved with clozapine. It is interesting to note that he was occasionally noncompliant with clozapine for a few days, which was evident by a prompt relapse in polydipsia.

Data on NDWG for 181 days on typical neuroleptics and 336 days on clozapine were available. The number of days that the patient needed water restriction changed significantly from 34% before clozapine to 5% after clozapine (McNemar test 177.0, df = 1, $p < .001$). Mean sodium levels, before and after clozapine, were 132 and 142 mEq/1, respectively. Nine of 11 sodium levels prior to clozapine were abnormally low, whereas all 40 weekly serum sodium levels after clozapine were normal. The mean NDWG on clozapine was 2.69 prior to clozapine and 1.57 on clozapine. These data all suggest that clozapine reduces polydipsia in a clinically significant way that was underscored by normal weekly morning sodium levels. Although polydipsic episodes were less frequent, they were not completely eradicated on clozapine.

The C statistic of NDWG clearly supported the efficacy of clozapine. The pre-clozapine baseline did not show any significant trend (C = .087, z = 1.08, $p = .28$), but there was a difference when compared to the clozapine period (C = .120, z = 2.38, $p = .017$). This time-series-analysis suggested that the dose of clozapine (100, 300, or 600 mg) was not a significant factor, and a similar response occurred at all three doses (C = .003, z = .05, $p = .65$).

DISCUSSION

Our first patient showed an improvement in both psychosis and polydipsia on clozapine. She had no documented history of hyponatremia. Most previously described cases of treatment of polydipsia have been in the context of polydipsia, intermittent hyponatremia, and psychosis. There are several documented cases in the literature of a parallel improvement of psychosis, polydipsia, and hyponatremia on typical neuroleptic treatment. The first case suggests that clozapine may improve polydipsia in patients without hyponatremia.

In the last three patients who had polydipsia with hyponatremia, both appeared to improve in parallel. We do not know if clozapine improves the excretion of free water, but the clinical observation suggests that the polydipsia improves in these patients, and in case 3 collected urine samples attested to this fact.

The last three patients demonstrated improvement of polydipsia and hyponatremia, with little or no improvement of psychosis. Several factors suggest that the improvement of polydipsia and hyponatremia was not the result of placebo response or spontaneous variations. Patients 2 and 3 were treated with high doses of propranolol without response, suggesting the lack of placebo effect. The measure of change in cases 3 and 4 were objective measures—NDWG, volume of urine, and sodium levels. Case 2 follows a naturalistic design A-B-A-B-A-B with a consistent relapse after discontinuation. Case 4 clearly got worse whenever the patient was noncomplaint with clozapine.

The degree of response seemed to vary between cases. In case 2, polydipsia and hyponatremia seemed to disappear with clozapine treatment. However, in case 3 the polydipsia and hyponatremia initially disappeared on clozapine but reappeared with mild polydipsia and very infrequent hyponatremic symptoms. In case 4 clozapine did not completely stop polydipsia because water restrictions were needed in 4% of days. It did, however, stabilize sodium levels and significantly reduced the need for water restriction.

The patient described by Lee and coworkers (1991) showed a partial clinical improvement in NDWG while on clozapine for one month. The improvement continued when he was switched to loxapine, but follow-up lasted only two weeks. The psychosis improved mildly on clozapine and became worse than baseline level on loxapine.

Prospective controlled studies of clozapine in polydipsia-hyponatremia are required before its efficacy and dosing guidelines are established. Our patients tended

to improve in the first and second weeks of treatment with low doses of clozapine (100 to 200 mg/day). Clozapine needed to be continued to maintain the improvement of polydipsia. Case 3 relapsed after two to three weeks of discontinuing clozapine, whereas case 4 tended to get worse when he missed a few doses. Lee and coworkers (1991) discontinued their patient's clozapine and substituted it with loxitane; there was no relapse at two weeks follow-up.

There may be interesting clues to the pathophysiology of polydipsia if larger, well-controlled studies replicate this improvement of polydipsia on clozapine. We have hypothesized that polydipsia may be related to disturbances in angiotensin II secondary to D2 supersensitivity, and that clozapine improves polydipsia because it does not induce supersensitivity in these receptors (Verghese et al. 1993). An alternative explanation is that polydipsia may be associated with dysfunction of the D4 receptors for which clozapine has high affinity. The distribution of D4 receptors in the hypothalamus follows a completely different pattern from D2 receptors (Watson 1992).

Our reduced experience may suggest that polydipsia with hyponatremia could be a new indication for clozapine treatment in chronic patients. The value of these improvements on clozapine should be seen in the context of current available treatments. The target weight approach only decreases the risk of water intoxication associated with polydipsia but does not resolve polydipsia. The behavioral treatment modality looks promising but appears to be expensive and time-consuming.

In conclusion, these case reports suggest the need for controlled studies to assess the effect of clozapine on polydipsic patients with and without hyponatremia. We hope that these cases do not suggest that clozapine is a "magic bullet," but they should prompt systematic investigation of its beneficial effects on polydipsia. This is a common and serious disorder for which appropriate treatments are lacking. Long-term follow up is needed to demonstrate that these effects are not just spontaneous variations of the disorder. The benefits to patients, in terms of decreased mortality and morbidity, and to health care systems, in terms of decreased staffing ratios, make this a worthwhile proposition.

ACKNOWLEDGMENTS

The authors are grateful to Marion Wilson, R.N., Sudhir Stokes, M.D., and to the staff of Haverford and Norristown State Hospital Research Units for their help with the patients. Ken H. Gilman and Robert Blake, medical students, were recipients of the Stanley Foundation Fellowship when they were working on this project. This study was partially supported by a PAL NIMH grant (MH 45190). Cherian Verghese, M.D. had additional support from a NARSAD grant.

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