Absence of Changes in Antidiuretic Hormone, Angiotensin II, and Atrial Natriuretic Peptide With Clozapine Treatment of Polydipsia-Hyponatremia: 2 Case Reports

Cherian Verghese, M.D.; George Abraham, M.D.; Chand Nair, M.D.; Joseph K. Stanilla, M.D.; Jose de Leon, M.D.; M. Ian Phillips, Ph.D.; and George M. Simpson, M.D.

Background: Polydipsia-hyponatremia is a poorly understood disorder that causes considerable mortality and morbidity. Hyponatremia in polydipsia-hyponatremia has been attributed to disturbances in antidiuretic hormone (ADH) function. Improvements in polydipsia-hyponatremia during clozapine treatment offered the chance to see if levels of ADH and other hormones associated with osmoregulation changed with improvement in biochemical and clinical measures of polydipsia-hyponatremia.

Method: In this preliminary, longitudinal study, we studied 2 male schizophrenic patients (DSM-III-R) who had polydipsia-hyponatremia. Measures were (1) biochemical and clinical: serum sodium and osmolality, urine osmolality and specific gravity, normalized diurnal weight gain, and estimated urine volume and (2) endocrine: ADH, angiotensin II, atrial natriuretic peptide, and prolactin. Measures were collected during 2 months of baseline (typical neuroleptic) and 6 months of clozapine treatment.

Results: Single-case statistical procedures showed significant changes in sodium levels (a.m. and p.m.), estimated urine volume, and a.m. urine specific gravity in both patients and significantly decreased diurnal weight gain in 1 patient. Both serum and urine osmolality showed improvement, but values did not reach statistical significance. Low baseline ADH levels persisted through 6 months of clozapine treatment and showed no changes in the context of improvements in serum sodium and osmolality. No significant changes were seen in levels of angiotensin II and atrial natriuretic peptide.

Conclusion: Given the limitations of this study, there is some evidence to suggest that the improvements in serum sodium and osmolality during clozapine treatment of polydipsia-hyponatremia may not be related to serum levels of ADH, although altered ADH receptor function cannot be ruled out. These data need to be extended in larger samples.

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Received Feb 11, 1997; accepted Nov. 19, 1997. From the Albert Einstein Medical Center (Dr. Verghese); the Allegheny University of the Health Sciences, MCP♦Hahnemann School of Medicine, Philadelphia, Pa.; and Norristown State Hospital Clinical Research Center, Norristown, Pa., (Drs. Abraham, Nair, and Stanilla); University of Kentucky at Eastern State Hospital, Lexington, (Dr. de Leon); the Department of Physiology, University of Florida at Gainesville (Dr. Phillips); and the Department of Psychiatry and Behavioral Sciences, University of Southern California, Los Angeles (Dr. Simpson).

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Reprint requests to: Cherian Verghese, M.D., Albert Einstein Medical Center, Department of Psychiatry, 5501 Old York Road, Philadelphia, PA 19141.

Polydipsia-hyponatremia, a disorder of fluid regulation with complex forms and severity, is common among chronically psychotic patients. It causes considerable mortality and morbidity, and the pathophysiology is not well understood.[1] Polydipsia, or excess fluid consumption, is the primary and enduring feature accompanied by hyponatremia caused by intermittent water retention. The prevailing model of hyponatremia suggests abnormal functioning of antidiuretic hormone (ADH), generalized from the syndrome of inappropriate ADH secretion (SIADH) seen in medically ill patients with hyponatremia.[2,3] However, the standard treatments for SIADH did not improve the hyponatremia associated with polydipsia-hyponatremia,[4] and polydipsia-hyponatremia seems to differ from SIADH on several clinical and biochemical grounds.[5] A well-controlled study by Goldman and colleagues[6] found very low ADH levels among patients with polydipsia-hyponatremia, and these levels did not fully explain the observed hyponatremia and hypoosmolality. Thus, the role of ADH in this disorder remains ambiguous, and therefore an examination of ADH and other hormones associated with osmoregulation is needed.

Recent evidence showing that both polydipsia and hyponatremia may improve with clozapine treatment[7,8] offers

an opportunity to examine the functioning of hormones associated with osmoregulation in the context of improvement in polydipsia-hyponatremia. A correlation between changes in the levels of these hormones with improvements in polydipsia and/or hyponatremia would provide important hints as to the underlying pathophysiology of this complex condition. Therefore, this preliminary study was undertaken to study selected hormones associated with osmoregulation in patients with documented polydipsia-hyponatremia to see if there was any change in levels after the expected improvement with clozapine treatment.

In addition to ADH, we examined some other hormones associated with osmoregulation: angiotensin II (AII), atrial natriuretic peptide (ANP), and prolactin. Although they originate in different organ systems, they all have a potential role in polydipsia-hyponatremia. AII is a potent inducer of drinking behavior in animals,[9] in normal human subjects at higher doses,[10] and in medical illnesses associated with abnormal thirst.[11] Even though AII levels have not yet been studied in patients with polydipsia-hyponatremia, the role of AII in this disorder was indirectly addressed by using angiotensin-converting enzyme inhibitors to treat the disorder. The results of these studies were inconclusive.[12,13] In an earlier paper, we had proposed an AII model of polydipsia-hyponatremia, on the basis of a number of animal studies that showed evidence of dopamine-AII interaction in the hypothalamus.[5] In this study, we sought to examine baseline levels of AII and changes, if any, during clozapine treatment. ANP function has been studied in patients with polydipsia-hyponatremia by Vieweg and colleagues.[14] They reported that ANP levels were elevated in the afternoon, coinciding with the worsening of hyponatremia. We sought to confirm this in our study and to see if improvements in sodium levels were related to changes in ANP. We also studied prolactin levels because it has been shown to have a role in mammalian fluid regulation,[15] and the lack of prolactin elevation is an important aspect of clozapine, the only drug known to improve polydipsia and hyponatremia. We hoped that this preliminary study would help us to focus on particular hormones in later studies on clozapine treatment of polydipsia-hyponatremia.

METHOD

Subjects

Subjects were 2 male schizophrenic patients (DSM-III-R) with primary polydipsia and hyponatremia for over 10 years recruited from the Norristown State Hospital Clinical Research Center. They were part of a National Institute of Mental Health–sponsored study on dose-response to clozapine treatment in which patients were randomly assigned to 100, 300, or 600 mg/day of clozapine.[16] Weekly Brief Psychiatric Rating Scale (BPRS) ratings were done on both patients as part of this larger study.

Table 1. Clinical Characteristics for 2 Patients With Schizophrenia and Polydipsia-Hyponatremia

Characteristic	Patient 1	Patient 2
Age, y	55	34
Sex	Male	Male
Race	White	White
Age at onset, y	22	20
Duration of illness, y	33	14
Serum clozapine level, ng/mL[a]	115	64
Brief Psychiatric Rating Scale score		
Baseline	36	46
Clozapine	39	56
Blood pressure, mm/Hg		
Baseline	109/72	104/75
Clozapine	105/72	107/77

[a]Clozapine values were measured after 16 weeks of treatment.

Table 1 shows demographic information and treatment parameters. Patients went through a pre-clozapine baseline when they were treated with a typical neuroleptic. Haloperidol was administered for a month at a mean dose of 3 mg for patient 1 and 7 mg for patient 2. During this phase, mean estimated daily urine volumes were 3998 and 8033 mL, respectively. Mean p.m. sodium levels were 131 and 130 mEq/mL, respectively (see Figure 1). Patient 2 had documented hyponatremic seizures. Clozapine doses were as follows: patient 1 took 300 mg for 16 weeks and 100 mg for 8 weeks; patient 2 took 100 mg for 16 weeks and 600 mg for 8 weeks. Both patients gave informed consent to the study procedures.

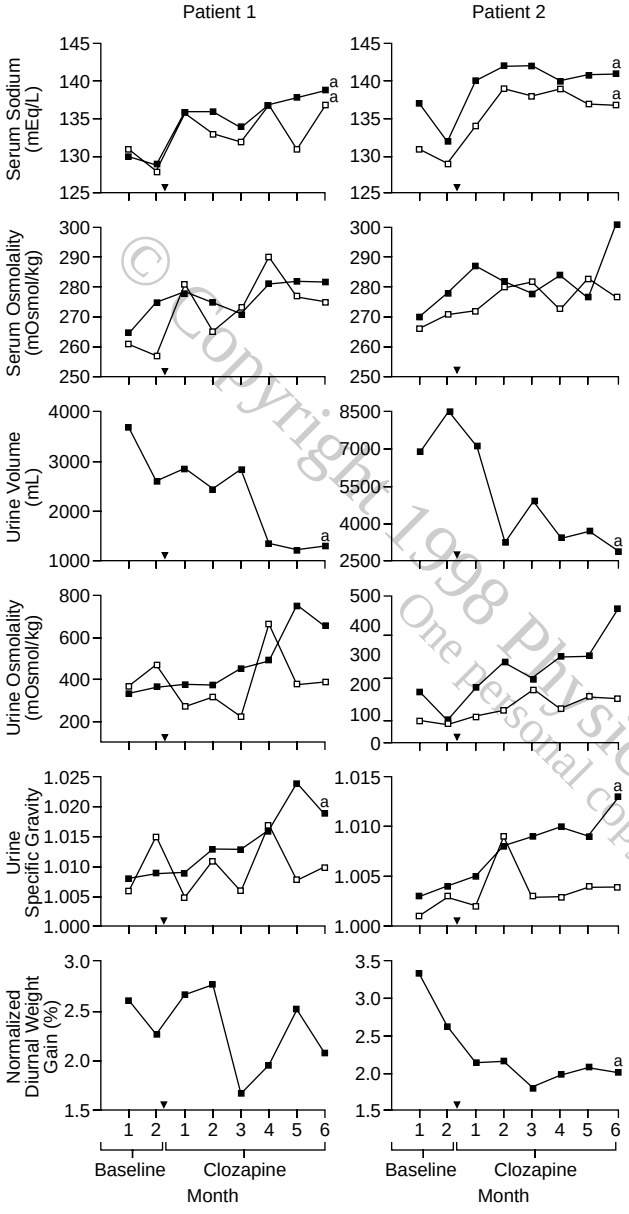
Measures

Presence and severity of polydipsia-hyponatremia were quantified using biochemical and clinical measures: (1) the daily clinical measure used was normalized diurnal weight gain, calculated by using the formula [(p.m. weight – a.m. weight)/a.m. weight] × 100 and (2) weekly biochemical measures were serum sodium and osmolality, urine osmolality, urine specific gravity, and urine creatinine concentration to estimate daily urine volumes.

Hormonal samples were collected every 2 weeks in chilled syringes; collection tubes with enzyme inhibitors were kept on ice and cold centrifuged, and plasma was stored in plastic microvials at –80°C for assay. Angiotensin II levels are very sensitive to changes in dietary sodium[17]; hence, patients were on a fixed-sodium diet (3 g/day) for 3 days prior to hormonal sampling. Since postural changes[18] and nicotine[3] influence ADH levels, patients were recumbent and did not smoke for an hour prior to collection. Briefly, the assay procedures for AII and ANP were as described by Hoffman and colleagues,[19] and, for ADH, the methods described by Hogarty and colleagues[20] were used. Prolactin was assayed by an immunoradiometric assay using the ImmuChem Prolactin-CT IRMA kit (ICN Biomedicals, Calif.).

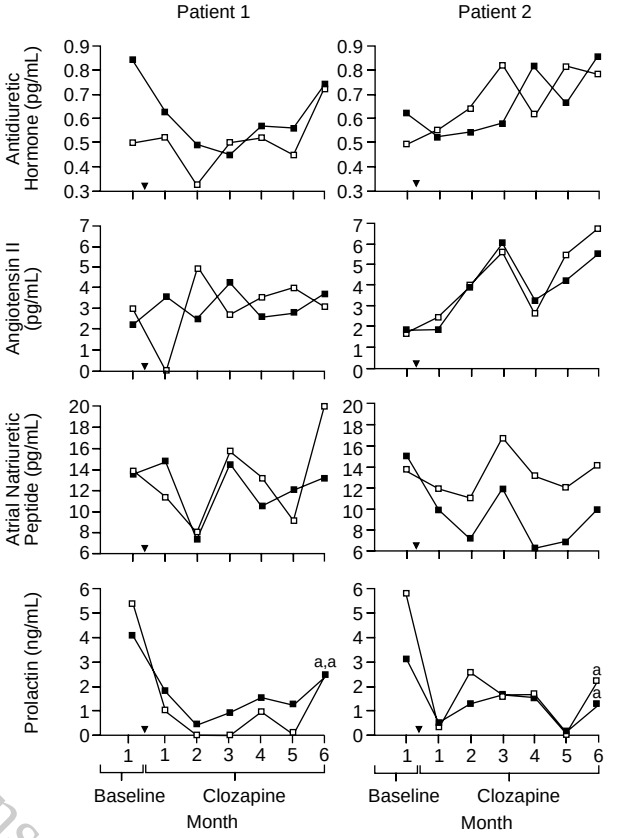
All measures were taken at 7:30 a.m. and 3:30 p.m. In the baseline phase (typical neuroleptic), biochemical and

Figure 1. Biochemical and Clinical Data Across 8 Months of the Study, Shown as Monthly Means*



*Symbols: triangles show the beginning of the clozapine phase; ■ = a.m.; □ = p.m.
[a]p < .01.

Figure 2. Endocrine Data Across 7 Months of the Study, Shown as Monthly Means*



*Symbols: triangles show the beginning of the clozapine phase; ■ = a.m.; □ = p.m.
[a]p < .01.

clinical measures were collected over 2 months, while endocrine measures were collected for 1 month. All measures were then repeated over 6 months of clozapine treatment.

RESULTS

Figures 1 and 2 show biochemical and clinical and hormonal data across the study (monthly means) for both cases. The White test[21] was used as a single-case statistical procedure to test for significance of change between baseline and clozapine conditions for each measure. Weekly measures were used to create celeration lines rather than monthly means shown in figures. Statistically significant changes ($p < .01$) between conditions were seen in both patients for serum sodium levels (both a.m. and p.m.), daily urine volume, urine specific gravity (a.m. only), normalized diurnal weight gain (patient 2 only), and prolactin (both a.m. and p.m.). No other comparisons reached statistical significance.

The actual levels of the hormones associated with osmoregulation were well below normal values. ADH levels stayed less than 1 pg/mL (normal ADH = 1–10 pg/mL) at baseline and after clozapine, even when osmolality normalized. Angiotensin II levels were considerably lower than normal (normal AII = 15-40 pg/mL), with a modest increase with clozapine treatment. ANP levels were also suppressed below normal (normal ANP = 15–30 pg/mL) and showed no consistent change with clozapine treatment. Blood pressure remained within normal ranges in both phases and could not be an intervening factor (Table 1). Only prolactin levels showed a sharp and persistent drop between conditions.

DISCUSSION

The purpose of this exploratory study was to examine baseline levels of selected hormones associated with osmoregulation and to study the behavior of these hormones when polydipsia and hyponatremia improved during treatment with clozapine.

Notably, levels of all hormones associated with osmoregulation were below normal. Low ADH levels are in keeping with previous studies that actually measured ADH.[3,6,22] Disturbed ADH function has been cited as the cause of water retention, hyponatremia, and hypo-osmolality.[3] The persistence of abnormally low baseline ADH levels over 20 weeks suggests a close relationship of ADH to the pathophysiology of polydipsia-hyponatremia. This result is in keeping with the conclusions from the well-controlled study by Goldman and colleagues, which stated that "the abnormalities in vasopressin secretion and action are inadequate to explain the patients' episodes of more severe hyponatremia and hypo-osmolemia."[6(p402)] However, the absence of change in ADH levels when there were improvements in water retention, hyponatremia, and hypo-osmolality would argue against a direct relationship. It is possible that these patients have altered renal ADH receptor function, which is influenced by clozapine. This could be tested in future studies with challenge tests before and after successful clozapine treatment.

The improvement in serum sodium, which occurred very early during clozapine treatment, may be a direct effect of clozapine on renal D_1 receptors. Clozapine is a strong D_1 blocker, and renal D_1 blockade is known to result in sodium retention.[23]

The low baseline levels of AII increased during clozapine treatment, probably because of decreased water retention and volume expansion in this phase. This also suggests that peripheral AII levels may not have much to do with polydipsia, since one would have expected the effect in quite the opposite direction. ANP levels were also low and showed no consistent change after clozapine treatment. The role of these hormones needs further exploration.

Prolactin is considered an index of central D_2 blockade. The decrease in prolactin levels in the first few weeks of clozapine corresponded with improvement in hyponatremia and delayed improvement in polydipsia, which may support our earlier hypothesis that chronic D_2 blockade may exacerbate osmoregulatory abnormalities.[5] However, these may be completely unrelated events, representing differing clozapine effects.

The patients were in a fixed-dose study of dose-response to clozapine, were randomly assigned to low doses of clozapine, and had low clozapine levels. They showed no improvement in psychosis (Table 1), suggesting that improvement in polydipsia and hyponatremia is not consequent to an improvement in psychosis. It has also been suggested that hyponatremia could be due to massive polydipsia overwhelming the kidneys' water excretion capacity, leading to hemodilution.[24] This explanation for hyponatremia seems unlikely since sodium improved in the first few weeks, while polydipsia took 12 weeks to improve.

Our study has its clear limitations in that these are 2 case studies and the baseline period of observations was rather short. These findings need to be replicated in larger samples. However, this is a longitudinal study that showed that levels of hormones associated with osmoregulation were suppressed below normal levels over extended periods in patients with polydipsia-hyponatremia. ADH, implicated in water retention and hyponatremia, showed very low and fixed levels that did not change when there were considerable changes in water retention, osmolality, and sodium levels. ANP and AII levels showed no significant changes associated with the improvement in polydipsia-hyponatremia. These data need to be confirmed in larger studies. The question of the effect of clozapine on renal sensitivity to ADH appears to be quite important. Studies also need to address the etiology of polydipsia—the primary and enduring feature of this disorder.

Drug names: clozapine (Clozaril), haloperidol (Haldol and others).

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