The Assessment and Treatment of Water Imbalance in Patients with Psychosis

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Abstract

Polydipsia and episodic life-threatening water intoxication remain important clinical problems for a significant portion of persons with schizophrenia. The disorders are associated with increased morbidity and mortality from a number of causes. With a basic understanding of the pathophysiology, one can easily diagnose and assess the clinical conditions. We review here the scope and pathophysiology of disordered water imbalance, including both primary and secondary polydipsia and hyponatremia. Reversible factors and possible interventions are reviewed. Treatment options for preventing water intoxication have expanded from discontinuation of offending agents, targeted fluid restriction, and clozapine therapy to the addition of oral vasopressin antagonists. The latter, however, are extremely potent and must be carefully monitored.

Key Words: Polydipsia, Water Intoxication, Hyponatremia, Vasopressin, Schizophrenia, Clozapine, Lithium, Thiazide Diuretics

Overview

Studies in the first half of the last century established disordered water balance as the most prominent and most significant metabolic abnormality in patients with severe mental illness. Thus, in 1923 it was shown that water excretion varied with severity of psychosis (1); in 1936, that excessive water intake was the most common (~25% of patients) metabolic abnormality in severe mental illness (2); and, in 1938, that life-threatening hyponatremia (i.e., water intoxication) occurs in psychotic patients (3). Five to fifteen percent of deaths in younger schizophrenic patients (i.e., <50 years old) have been attributed to acute water intoxication (4, 5). Polydipsic patients with or without water intoxication die, on average, almost ten years before closely matched persons with schizophrenia (age 58), who in turn die about ten years prior to those without mental disease (6). These abnormalities in water balance were described prior to the introduction of antipsychotic medications, cannot be attributed to these medications in current patients (7, 8), nor explained by known physiologic or pharmacologic factors (9).

Disordered water imbalance in psychiatric patients is most easily conceptualized as separate processes involving excess water intake (polydipsia) with or without diminished water excretion. Water intoxication in psychiatric patients rarely occurs unless both abnormalities are present: usually prominent polydipsia and subtly impaired water excretion. Different mechanisms underlie other types of life-threatening hyponatremia such as the syndrome of inappropriate antidiuretic hormone hypersecretion (SIADH) associated with lung cancer, hyponatremia seen in heart failure or that which occurs in elite athletes (10).

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Clinical Implications

Disordered water balance remains a clinically significant and potentially life-threatening problem for persons with schizophrenia. A basic understanding of normal water intake and excretion greatly simplifies the approach toward diagnosing primary polydipsia with and without hyponatremia, and distinguishing these disorders from each other and secondary causes of water imbalance. After confirming the nature of the water imbalance, removing possible offending agents, and optimizing treatment of concurrent disorders, a number of effective treatment options are available. Water restriction and some version of target weight monitoring should be considered in all cases where appropriate, though their efficacy is usually limited to inpatient settings. Clozapine is an important treatment option for "psychosis, intermittent hyponatremia, polydipsia" (PIP) and may be effective in the treatment of primary polydipsia as well. Vasopressin antagonists appear to be very effective in PIP, but more experience is needed to clarify their role and how to best initiate therapy.

After first defining the scope and nature of disordered water balance in psychiatric disorders, we will briefly review the underlying pathophysiology in order to build a conceptual framework which will underlie the subsequent discussion on assessment, differential diagnosis and therapeutic interventions.

Scope and Description of the Types of Water Imbalance

Primary Polydipsia

About 15 to 25% of persons with chronic mental illness, and smaller percentages of patients with other psychiatric diagnoses, have a "primary" polydipsia (oral intake>3 liters/day, normal<2.0 liters/day) (11, 12). That is, they exhibit increased intake without clinical evidence of impaired water excretion. The disorder is "primary" because there is no physiologic or pharmacologic explanation for the increased intake (see Table 1) (2). In the chronically mentally ill, genetic factors may contribute to this primary polydipsia (13, 14). These patients also consistently exhibit an increased incidence of alcoholism and smoking that appears to precede the mental illness and may further characterize the phenotype (6, 11, 15).

The excessive amounts of water flowing through the body may lead, over time, to systemic "plumbing" problems (i.e., dilated bowel, bladder and kidneys as well as associated disorders such as obstruction, incontinence, urinary infection, and renal failure) (11). Further, the increased intake and output seems to leech calcium from bones predisposing to osteoporosis and pathologic fractures (16).

Primary Polydipsia Plus Hyponatremia

About one fourth of these polydipsic patients fail to match urine output to oral intake because of impaired water excretion (see Table 1) (8, 9). The impairment is often relatively mild and transient. This is the "psychosis, intermittent hyponatremia, polydipsia" (PIP) syndrome systematically characterized by Vieweg in the 1980s and 90s (17). While primary polydipsia occurs across psychiatric disorders and occasionally in normals (i.e., dipsogenic polydipsia), this previously unexplained hyponatremia is seen almost exclusively in psychotic patients (11, 12). Furthermore, most of these patients have a severe and unrelenting form of schizophrenia (18, 19).

Water intoxication, when it occurs, is primarily attributable to acute cerebral edema (i.e., a water-saturated brain encountering a rigid cranium). Patients with chronic

Table 1 Common Types of Water Imbalance in Psychiatric Patients

Problem	Mechanism	Thirst	Vasopressin/Aquaporin-2
Primary polydipsia	Increased intake with appropriate output	Suppressed	Appropriately suppressed
Primary polydipsia plus hyponatremia	Increased intake with diminished output	Suppressed	Suppressed but transiently elevated
Secondary polydipsia	Increased output with appropriate intake	Elevated	Elevated* or suppressed
Secondary hyponatremia	Diminished output	Normal or suppressed	Elevated

* Nephrogenic diabetes insipidus

hyponatremia (e.g., plasma sodium 125 mEq/L) adapt to the excess brain water by excreting organic osmolytes (i.e., idiogenic osmoles) and may appear to exhibit few, if any, symptoms. They, too, can experience water intoxication, however, if their sodium levels drop even further (e.g., 110 mEq/L). Furthermore, even mild degrees of chronic hyponatremia (plasma sodium of 130 mEq/L) can impair cognition (20) and promote falls, particularly in the elderly (21, 22). Symptoms of acute severe hyponatremia include nausea, ataxia, confusion, lethargy, seizures and coma. It may, however, appear as a psychotic exacerbation (e.g., increased paranoia) or an idiopathic seizure disorder (11). These patients are also at risk for the sequalae experienced by those with primary polydipsia (above). Furthermore, severe morbidity may occur because of rhabdomyolysis due to changes in muscle solute composition following recovery from hyponatremia (23). Similar factors likely account for central pontine myelinolysis, which is linked to overly rapid correction of hyponatremia (particularly chronic hyponatremia). This syndrome may cause irreversible changes in the myelin sheath of long tract fibers, causing profound quadriplegia and occasionally death (24).

Secondary Polydipsia and Hyponatremia

Beyond these "primary" disorders in water imbalance, secondary polydipsia is commonly seen with lithium treatment (about 30%) and may be a prelude to lithium-induced renal failure (25). In addition, several drugs (e.g., carbamazepine and agents commonly prescribed to treat hypertension and diabetes mellitus) produce secondary hyponatremia in patients with or without primary polydipsia (see Table 1) (26). Finally, psychiatric patients are not immune to other causes of hyponatremia, particularly those associated with smoking (e.g., SIADH from small cell carcinoma of the lung). In most or all of the cases of secondary hyponatremia, the impairment in water excretion is severe and sustained in contrast to the mild, transient defect seen in PIP patients.

Pathophysiology

Normal Water Intake and Excretion

While regulation of water balance may appear to be a complicated physiologic process, a grasp of only a few basic principles permits a solid understanding of the mechanism of these problems (see Table 2). It is easiest to conceptualize water balance as separate processes of oral intake and urine output, with the amount of solute in the body remaining constant (due to intake matching excretion). The amount of water relative to solute is the same throughout the body

Table 2 Key Principles of Normal Water Balance

• amount of water relative to solute in body (tonicity) is tightly regulated by brain
• dehydration increases vasopressin release from brain leading to reabsorption by kidney
• if above is inadequate, thirst is perceived leading to water-seeking behavior
• overhydration leads to suppression of vasopressin and diuresis (≥1 liter/hour)

(because water flows freely across all membranes) and is tightly regulated by the brain so as to not vary more than about one percent from the mean. Even slight dehydration leads to secretion of the antidiuretic hormone, arginine vasopressin, from the hypothalamus into the peripheral circulation (see Figure 1A). Vasopressin then binds to the kidney and increases the density of aquaporin-2 channels in the inner medulla, permitting water to flow from the collecting ducts back into the renal parenchyma. Indeed, most factors known to cause secondary polydipsia and hyponatremia also ultimately influence the density or function of aquaporin-2 channels (27). For instance, lithium produces secondary polydipsia (nephrogenic diabetes insipidus) by decreasing, and hydrochlorthiazide produces secondary hyponatremia by increasing, the density of aquaporin-2 channels (28).

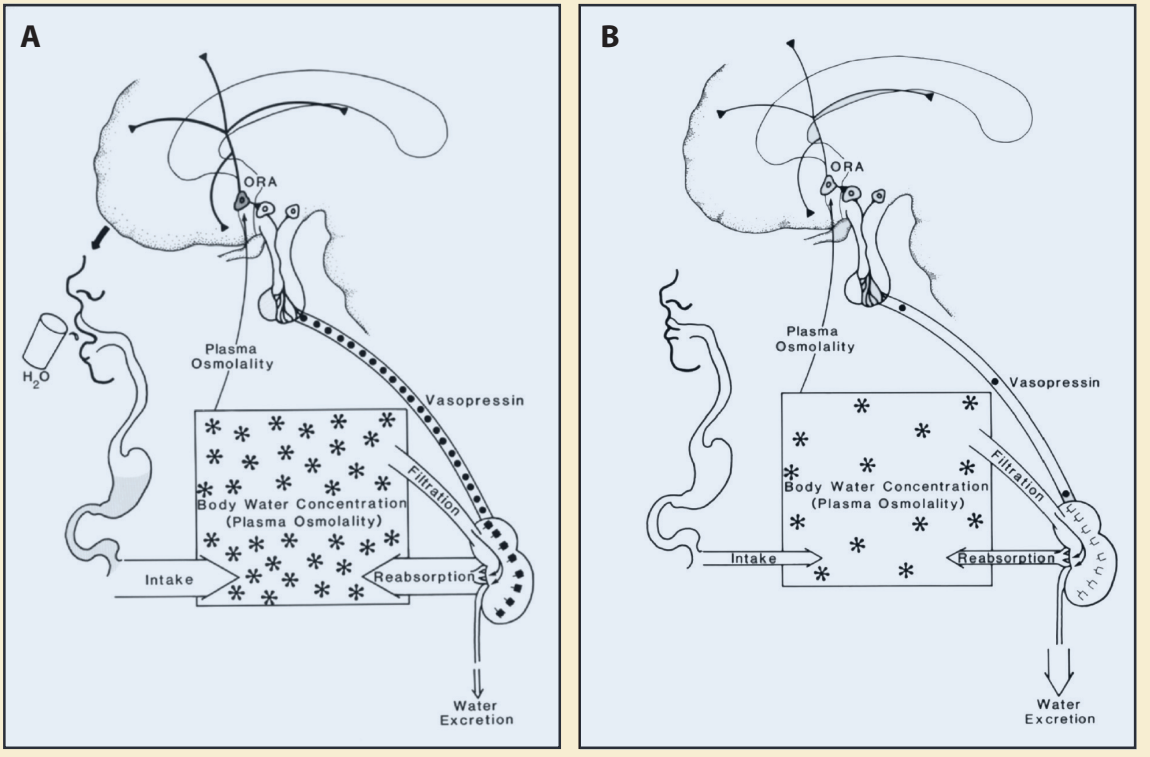
If dehydration becomes more severe and cannot be corrected by water retention alone, thirst is initiated (see Figure 1A). True thirst rarely plays a role in daily water regulation, as normal drinking revolves around food intake, social mores or physical stimuli (e.g., dry mouth). Thus, thirst normally serves to backup the vasopressin system. Overhydration, in contrast, suppresses arginine vasopressin (and suppresses thirst) (see Figure 1B). When maximally suppressed, the kidney is able to excrete about one liter of water per hour (i.e., 24 liters/day). While patients not infrequently exceed their excretory capacity over the short term, this is rarely, if ever, responsible for symptomatic hyponatremia (as evidenced by the efficacy of vasopressin antagonists summarized below).

Nature of Water Imbalance in Psychiatric Patients

Disorders of water balance in psychiatric patients can be conceptualized as one of four distinct phenomena (see Table 1):

- increased intake with appropriately increased output
- increased intake with inadequately increased output
- increased output with appropriately increased intake
- diminished output with inadequately diminished intake.

Figure 1 Physiologic Regulation of Water Balance



A. Dehydration: the osmoreceptor apparatus (ORA) in the anterior part of the third ventricle senses a fall in body water concentration (dehydration), and stimulates release of plasma vasopressin from the posterior pituitary into the peripheral circulation. Vasopressin then binds to the kidney, increasing the reabsorption of filtered water. If inadequate, the ORA activates various cortical sites producing thirst and water-seeking behavior (32). **B.** Excess hydration: increased body water suppresses vasopressin and thirst leading to excretion of nearly all filtered water.

In the first instance (primary polydipsia), output is increased to keep up with enhanced input. In the second (PIP), output is increased but not enough to keep up with input. In the third (secondary polydipsia), input is increased to keep up with enhanced output. In the last (secondary hyponatremia), input is decreased but not enough to prevent water retention due to diminished output.

Pathophysiology of Water Balance in Primary Polydipsia and PIP

The excess drinking in primary polydipsia does not appear to be due to excess thirst (29). Instead, patients with primary polydipsia report hydrophilic delusions, boredom or a general sense of discomfort as the primary stimulus to drink which, in turn, may be related to hippocampal pathology (30). The hormonal defect(s) associated with the PIP syndrome appear to be specific to psychological stress in that neuroendocrine regulation is otherwise normal, including responses to physical stressors. The osmotic regulatory system controlling vasopressin and thirst are generally intact in these patients (9). Indeed, the water imbalance may be closely connected to the pathophysiology of the underlying psychiatric disorder. Specifically, converging data suggests that anterior hippocampal pathology contributes to both polydipsia and to the PIP syndrome, as well as schizophrenic symptoms, by disrupting the normal hippocampal-mediated constraint of neuroendocrine and behavioral responses to psychological stress (31). Of interest is that schizophrenic patients without water imbalance exhibit the opposite pattern (i.e., their neuroendocrine and other responses to psychological stress are blunted).

Assessment, Etiology and Interventions

Diagnosis of Polydipsia

Polydipsia of any origin presents as nocturia, incontinence or simply with the observation that the patient is always seen with a cup in his hand. In general, such reports are not reliable, but two or three spot measures of urine specific gravity or urine osmolality can confirm or exclude the diagnosis. Alternatively, the diagnosis may be suggested by findings of hyposthenuria (low urine specific gravity) on a routine urinalysis. Since urine output normally matches up well with oral intake and the rate of solute excretion in the urine is fairly constant, urine tonicity provides a fair index

Table 3 Diagnosis of Primary Polydipsia and PIP Syndrome

Presenting Problem	Diagnostic Approach	Differential Diagnosis
Polydipsia	Two or three urine specific gravities ≤1.008 or urine osmolalities ≤150 mOsm/Kg	Diabetes mellitus, lithium treatment, diabetes insipidus
Hyponatremia	Diurnal weights for one week or afternoon sodium levels	Thiazide diuretics, SSRIs, carbamazepine, lung cancer

of oral intake (32). Hence, polydipsia can be diagnosed by demonstrating dilute urine (urine specific gravity<1.008 [normal 1.015–1.030]; osmolality<150 mOsm/Kg [normal 700–1400 mOsm/Kg]) on two of three spot urine samples spread out over a week or more (see Table 3).

Differential Diagnosis of Polydipsia

Once the diagnosis is made, the next step is to look for *reversible causes*, particularly diabetes mellitus given the predisposition of antipsychotics to cause a metabolic syndrome. In the chronically mentally ill, anticholinergic-induced dry mouth likely plays a measurable, but clinically insignificant, role in the disorder. Patients with primary polydipsia are frequently *misdiagnosed* as having diabetes insipidus (i.e., deficient vasopressin secretion or action), since polydipsia itself reduces renal response to vasopressin by downregulating aquaporin-2 channels (27). Treatment of these patients with vasopressin can be disastrous as their water intake is rarely driven by thirst, so they will just keep drinking as they retain more and more water.

Approach to Lithium-Induced (Secondary) Polydipsia

Lithium downregulates aquaporin-2 channels to an even greater degree than polydipsia (28), thereby producing a nephrogenic diabetes insipidus and secondary polydipsia. Interestingly, this appears to be more prominent in patients receiving serotonergic antidepressants despite the fact that such drugs normally diminish water excretion (25). While the benefit of lowering the lithium dose/level or changing to a single daily dose are in doubt (25, 33), they may be worth trying. Irreversible nephrogenic diabetes insipidus and impaired glomerular filtration (e.g., elevated plasma creatinine) normally take years of lithium treatment to develop. Recent findings indicate the lithium-induced tubulointerstitial nephritis which underlies the chronic polyuria may be directly responsible for the progressive renal failure (35). At present, polyuria should be considered a risk factor for renal failure with lithium therapy, and physicians should consider treating it or switching medications.

Addition of a thiazide (e.g., 25 mg hydrochlorthiazide) or potassium-sparing diuretic (5 mg amiloride [Midamor]) is generally effective in diminishing secondary polydipsia from lithium (36). The lithium dose, however, should first be reduced by about one third as more lithium will be retained once diuretic treatment is initiated. Lithium levels should initially be followed at more frequent intervals to be certain they remain therapeutic and safe. It is important to realize that these agents place patients at an increased risk of lithium intoxication, which is also a risk factor for renal failure (33, 34). Theoretically, amiloride, which blocks lithium uptake into renal tubule cells, should lower the risk of nephrotoxicity (34). In any case, patients need to maintain fluid and salt intake during heat spells or periods of intense exercise. Also, if the polyuria is instead due to primary polydipsia (e.g., preceded lithium treatment), beginning a thiazide diuretic will predispose the patient to water intoxication.

Treatment of Primary Polydipsia

Primary polydipsia is a diagnosis of exclusion. Group (36) and behavioral therapies (37) have been reported to be effective, but may have to be maintained indefinitely and, to date, have been applied only in inpatient settings. Water restriction should also be advised (but is rarely effective). Many therapeutic agents (e.g., beta-blockers, clonidine, ACE inhibitors, naltrexone) have been tried, but their efficacy remains uncertain (38). Primary polydipsia generally appears resistant to antipsychotics except perhaps for clozapine (Clozaril). This agent has been reported to be effective for hyponatremia by many investigators, and the mechanism may involve reduction of fluid intake (39). Clozapine also reduces alcohol intake in the severe mentally ill, which, as previously noted, occurs more commonly in polydipsic patients (15). Indeed, it has been reported to reduce polydipsia in an alcoholic patient who did not have schizophrenia (40). While it has not been clearly established, the efficacy of clozapine likely accounts for the clinical impression that the incidence of polydipsia and water intoxication have diminished over the past decade.

The clinician, however, may decide not to treat primary polydipsia in the absence of hyponatremia. This is not an unreasonable action given the side effect profile of clozapine, the absence of other effective outpatient pharmacologic or other treatments, and that serious sequelae rarely follow long-standing increases in fluid intake alone.

Diagnosis of Hyponatremia

As noted above, transient hyponatremia may occasionally arise from acute ingestion of large amounts of water.

Even small amounts of plasma vasopressin, however, markedly diminish maximal water excretion (i.e., free water clearance) to levels below the intake of many with primary polydipsia (range 3 to 15 liters/day). These patients still produce relatively dilute urine (e.g., 100 mOsm/L), but it is well above the minimum levels (i.e., 40 mOsm/L) they could otherwise generate. This unexcreted water "backs up" inside the body, producing marked increases in body weight (e.g., recall 60% of body is normally water, so a 10% increase in a 70 kg adult would be >4 kg) (17). During the day, this retained water produces a dilutional hyponatremia (plasma sodium<130 mEq/L [normal 135–150 mEq/L]), placing patients at risk for life-threatening water intoxication. At night, when fluid intake ceases and the impaired excretion normalizes, the excess water is excreted and plasma sodium returns toward normal.

Unlike polydipsia, hyponatremia may or may not be detected with spot measures of tonicity, as sodium and plasma osmolality are typically near normal in the morning (when routine blood samples are obtained) and severe hyponatremia often occurs episodically (17). Afternoon measures of serum or plasma sodium or osmolality are more sensitive, but simply measuring diurnal weight change from morning to afternoon for a week provides a very good screening tool (see Table 3). While a certain amount of body water is normally retained during the day due to postural stimulation of sodium (and, hence, water) retention, this rarely exceeds one kilogram. People with episodic hyponatremia, on the other hand, typically retain 3 to 6 kg between arising and mid-afternoon and this can be easily detected with any scale (17).

Differential Diagnosis of Hyponatremia and Treatment of Secondary Hyponatremia

Hyponatremia in psychiatric patients usually occurs in the presence of a marked primary polydipsia. If polydipsia is not apparent (e.g., urine osmolality>300 mOsm/Kg), then other medical causes (e.g., lung cancer, hypothyroidism) should be vigorously pursued (see Table 3). Many psychiatric patients who are hyponatremic are taking thiazide diuretics, oral sulphonylurea antidiabetic agents, carbamazepine or antidepressants (26, 41, 42). These drugs likely act by increasing the density of aquaporin-2 channels in the renal tubular membrane (28). Simply stopping the offending agent will usually lead to rapid resolution of the hyponatremia, though polydipsia, if present, will remain. Finding alternative medications is usually not a problem. Thus, there are many different classes of antihypertensive agents outside of the thiazide diuretics (Diuril, Microzide, Hydrodiuril); among oral hypoglycemic agents, hyponatremia appears to be limited to clorpropamide (Diabanase), with a few cases reported with tolbutamide (Orinase); and, while there have been several reports of hyponatremia with oxycarbazine (Trileptal) (and many with carbamazepine [Tegretol]), other mood stabilizers (e.g., lithium) are safe.

The risk of hyponatremia appears to be about four times higher with serotonin reuptake inhibitors than with other antidepressants, occurring most commonly in elderly women during the first few weeks of therapy (41). It appears likely that any antidepressant which enhances serotonin activity (e.g., trazodone, chlomipramine) may be associated with hyponatremia, though reports appear to have occurred with all agents including mirtazapine and buproprion (26). Other serotinergic agents, including street drugs such as methylenedioxymethamphetamine (MDMA: ecstacy), have also been associated with hyponatremia, perhaps by directly enhancing vasopressin secretion (43).

Role of Antipsychotics in Hyponatremia

Outside of clozapine (see below), the role of antipsychotics in hyponatremia remains unclear. It appears these drugs may modestly impair water excretion in a dose-related manner (8). The likely mechanism is related to direct dopamine effects on renal sodium rather than water balance (44). It is unclear whether second-generation antipsychotics (SGAs) are any less likely to have an adverse effect on water balance than first-generation agents (FGAs). While most FGAs have been reported to both protect and predispose to hyponatremia, the only systematic dose reduction study has shown no clear effect (45).

Prevention and Treatment of PIP

Most of the early interventions to prevent water intoxication were restricted to inpatient settings. Prior to the mid-1980s, the main therapeutic intervention was fluid restriction, which almost invariably failed due primarily to patients finding alternative sources of unhealthy water (e.g., toilets). When environments were arranged so that access to water was successfully restricted, patients were usually unable to move outside of these settings.

In the mid-1980s, targeted fluid restrictions were introduced and instituted at the times the patient appeared to be at increased risk of water intoxication (17). As noted above, water retention leads to easily detected gains in body weight. This procedure relies on this fact and, specifically, the identification of a "target weight" at which the patient's dilutional hyponatremia is likely to be approaching levels associated with water intoxication. The procedure requires weighing patients twice a day (morning and afternoon) and whenever early signs of water intoxication are suspected. If body weight is substantially above the normal day-to-day variation (e.g., 7 kg), the patient is restricted from drinking

water for a brief period (e.g., 2 to 6 hours), over which time the excess water is usually excreted (remember the defect in water excretion is usually mild and/or transient). Care is taken to end the fluid restriction when the patient returns to his basal body weight. Addition of salt tablets during the fluid restriction may quicken restoration of fluid balance, but is contraindicated in some patients (e.g., hypertensives, congestive heart failure) and could theoretically predispose to central pontine myelinolysis. The target weight procedure is best suited to inpatient settings but may rarely be adapted to less restrictive settings, depending on the diligence of the caretakers and the cooperation of the patient.

Many agents have been tested for the treatment of hyponatremia (e.g., demeclocyline, sports beverages, urea), but their efficacy is in doubt. Thus, for many years, there were no effective outpatient treatments for hyponatremia. In the 1990s, it became apparent that clozapine reduces the risk of hyponatremia and water intoxication (39). As noted above, it is unclear whether clozapine improves water excretion or diminishes fluid intake. In any event, unless otherwise indicated, it is currently the treatment of choice for patients with severe PIP. The drug often normalizes sodium levels and enables patients to leave restricted settings and participate more completely in therapeutic programming. Clozapine may be effective in very low doses (~100 mg/day), and there is not much evidence that going above 300 mg/day will improve water imbalance (39).

Water intoxication and other sequelae of polydipsia have, however, occurred in schizophrenic patients on clozapine (23). Clozapine requires monitoring that is not available to all physicians, and clozapine can cause an impressive array of life-threatening adverse effects. Furthermore, cognitive impairments are apparent even when sodium levels are within normal limits in these patients, drawing into question the benefits of normalizing plasma sodium if water intoxication is not a problem (19).

Over the past several years, there have been a series of trials with vasopressin antagonists in the treatment of hyponatremia. Most of the subjects have had heart failure, liver disease or medical explanations for SIADH, but some have had the PIP syndrome. Conivaptan (Vaprisol), approved only in an intravenous formulation, has been administered orally during Phase 3 trials to a number of patients with PIP, but the effects on these specific subjects were never reported.

A recent study documents the marked efficacy of an orally administered agent, tolvaptan (Samsca), in PIP (46). Nineteen PIP subjects were randomly assigned to receive placebo (n=12) or tolvaptan (n=7) once daily for 30 days at a dose of 15 to 60 mg, based on serum sodium changes. Basal levels were 130 mEq/L in both groups, and normalized (>135 mEq/L) within 24 hours of treatment in those receiving tolvaptan but did not change in those on placebo. The salutary effects were apparent throughout the 30-day treatment period, and subjects on tolvaptan returned to previous hyponatremic levels after the treatment was stopped. Two subjects receiving active drug (28.6%) became dehydrated and experienced hypotension, and five subjects receiving placebo (41.7%) experienced symptoms associated with dilutional hyponatremia. The study also included an open label extension arm in which the salutary effects appeared to be maintained (Goldman, Josiassen; unpublished data). The drug has just recently been approved by the FDA and time is needed to further clarify its role and administration in the treatment of PIP. It has a very rapid onset and must be started in the hospital at the lowest dose since it can potentially cause dehydration and associated problems such as demyelination, orthostasis and renal insufficiency. In particular, patients must be monitored in order to be certain their serum sodium does not increase more than 12 mEq/L over the first 24 hours, or with any further change in dosage. Because the onset of action is very fast, one should be able to judge over a 24-hour period if the drug causes a marked diuresis.

Treatment of Water Intoxicaton

Seizures and clouded consciousness (i.e., frank water intoxication), if it occurs, can be treated with fluid restriction alone as long as consciousness is rapidly regained. Otherwise, the patient should be transferred to an acute care setting where more rapid correction of hyponatremia can be considered. Evidence suggests that rapid correction of acute hyponatremia with hypertonic saline is almost always safe in psychotic patients (47), though fluid restriction and normal saline alone have been rarely associated with fatal central pontine myelinolysis (CPM) (24). The risks of CPM are probably confined to those with chronic hyponatremia, or patients with severe acute hyponatremia and concurrent alcoholism and poor nutrition. Thus, unless one is certain that the hyponatremia is acute and these other risk factors are absent, one should probably be content to increase sodium levels no more than 10 to 12 mEq/L/day, though correction can be initiated at a rate of 1 to 2 mEq/L/hour for several hours (48). Hence, persons with profound hyponatremia (i.e., <110 mEq/L) may still be severely hyponatremic (e.g., 120 mEq/L) the day following admission but on the road to recovery.

Conclusions

In summary, disordered water balance remains a clinically significant and potentially life-threatening problem for persons with schizophrenia. A basic understanding of normal water intake and excretion greatly simplifies the

approach toward diagnosing primary polydipsia with and without hyponatremia, and distinguishing these disorders from each other and secondary causes of water imbalance. After confirming the nature of the water imbalance, removing possible offending agents, and optimizing treatment of concurrent disorders, a number of effective treatment options are available. Water restriction and some version of target weight monitoring should be considered in all cases where appropriate, though their efficacy is usually limited to inpatient settings. Clozapine is an important treatment option for PIP and may be effective in the treatment of primary polydipsia as well. Vasopressin antagonists appear to be very effective in PIP, but more experience is needed to clarify their role and how to best initiate therapy.

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