Psychiatry Research 217 (2014) 129–133

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Review article

A systematic review of the ability of urine concentration to distinguish antipsychotic- from psychosis-induced hyponatremia

Wanlop Atsariyasing [a], Morris B. Goldman [b,*]

[a] Department of Psychiatry, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand
[b] Department of Psychiatry and Behavioral Sciences, Feinberg School of Medicine, Northwestern University, 446 East Ontario, Suite 7-100Chicago, IL 60611, USA

ARTICLE INFO

Article history:
Received 24 October 2013
Received in revised form
31 January 2014
Accepted 20 March 2014
Available online 29 March 2014

Keywords:
Water intoxication
Schizophrenia
Vasopressin
Reset osmostat
SIADH

ABSTRACT

Life-threatening hyponatremia in psychotic patients is common and typically is attributable to either antipsychotic medication or to acute psychosis in those with the polydipsia-hyponatremia syndrome. The preferred treatment for one situation may worsen the hyponatremia if caused by the other situation. Hence it is critical to distinguish between these two possibilities. Case reports and series were identified through electronic databases. Fifty-four cases of hyponatremia without recognized causes in psychotic patients were divided into those with dilute (< plasma osmolality) or concentrated (> plasma osmolality) urine. The distribution of urine concentration and measures likely to be associated with psychotic illness and its treatment were compared in both groups. Naranjo's scale was utilized to determine the probability hyponatremia was drug-induced. Urine osmolality fit a bimodal distribution (intersection 219 mOsm/kg) better than a unimodal distribution. 'Probable' drug-induced cases occurred 6.8 (95%CI = 1.6–28.9) times more often in those with concentrated urine. Acute psychotic exacerbations occurred 4.5 (95%CI = 0.4–54.1) times more often in those with dilute urine. These findings, as well as several other trends in the data, indicate that measures of urine concentration can help distinguish between antipsychotic-induced and psychosis-induced hyponatremia.

Contents

1. Introduction

Life-threatening hyponatremia (water intoxication) is a relatively common condition in patients with psychotic illnesses (Renneboog et al., 2006; Hawken et al., 2009; Meulendijks et al., 2010; Williams and Kores, 2011). Often the electrolyte imbalance is attributable to prescribed medications, particularly diuretics or psychotropics such as anticonvulsant mood stabilizers, serotonin reuptake inhibitors, tricyclic antidepressants and antipsychotic medications (Liamis et al., 2008; Letmaier et al., 2012). In addition, nicotine as well as cigarette smoke per se can impair water balance (Robertson, 2006). This is especially apt to contribute to hyponatremia (Blum, 1984; Ismail

* Corresponding author. Tel.: +1 312 695 2089; fax: +1 708 383 6387.
E-mail address: m-goldman@northwestern.edu (M.B. Goldman).

http://dx.doi.org/10.1016/j.psychres.2014.03.021
0165-1781/

et al., 2010) because so many schizophrenic patients, particularly those at risk of hyponatremia (de Leon et al., 1996), smoke heavily. Hyponatremia typically resolves soon after the offending agent is stopped, but in the case of antipsychotics this may have a seemingly paradoxical effect if the hyponatremia is due to acute psychosis (Goldman et al., 1997; Meulendijks et al., 2010). This is because acute psychosis has also been associated with impaired water excretion (Targowla, 1923), primary polydipsia (Hoskins and Sleeper, 1933) and water intoxication (Barahal, 1938) well before antipsychotics were discovered. After their introduction, the literature is replete with reports indicating antipsychotic medication both contributes to (Meulendijks et al., 2010) and ameliorates (Dubovsky et al., 1973; Hariprasad et al., 1980; Canuso and Goldman, 1999; Liamis et al., 2008) hyponatremia. Currently perhaps 40% of psychotic patients admitted with unexplained hyponatremia are not taking antipsychotic medication (Williams and Kores, 2011).

Both antipsychotic medication and acute psychosis induce dilutional hyponatremia, which occurs when fluid intake overwhelms renal diluting capacity. The retained water swells all body tissues thus producing cerebral edema and ultimately cerebral compression by the skull (water intoxication). Under normal circumstances, hyponatremia can be prevented by varying urine dilution. Urine concentration is primarily regulated by the antidiuretic hormone, arginine vasopressin (AVP), which is secreted from the brain and then acts in the kidney. Decreases in plasma osmolality inhibit AVP secretion, in which case the normal kidney excretes huge amounts of water (~20 L/day).

Dilutional hyponatremia typically occurs due to either a relatively fixed impairment in the ability to produce dilute urine, or a variable impairment which lessens as the hyponatremia worsens. Depending on the plasma osmolality at which urine begins to be concentrated (osmotic set point), the patient may either present with symptomatic or asymptomatic hyponatremia (Robertson, 2006). Hyponatremia with other psychotropics has been associated with both fixed and variable impairments (Meulendijks et al., 2010), while acute psychosis has been consistently associated with the variable impairment (Hariprasad et al., 1980; Vieweg et al., 1986; Goldman et al., 1988; Kishimoto et al., 1989; Delva et al., 1990; Ohsawa et al., 1993). The mechanism appears to be attributable to psychosis lowering the osmotic set point for AVP secretion (Goldman et al., 1997) perhaps due to a stress diathesis that is associated with the underlying psychiatric illness (Goldman et al., 2007, 2011; Goldman, 2009). The contribution of the elevated AVP to the hyponatremia is demonstrated by its rapid reversal with AVP antagonists (Josiassen et al., 2008, 2012). All classes of antipsychotic drugs are associated with hyponatremia (Mannesse et al., 2010), and currently there are no published guidelines to aid clinicians whether to increase or decrease antipsychotic medication. In the absence of controlled studies, we conducted a systematic review of published cases of medicated psychotic patients with unexplained hyponatremia who had concurrent measures of urine dilution.

2. Methods

2.1. Data sources and study selection

One hundred and thirty-six articles were identified from the MEDLINE database from 1960 to September 2012 using the following MeSH terms: hyponatremia, inappropriate ADH syndrome, antipsychotic agents and English language (see Flow Diagram Fig. 1). Ninety-one more were drawn from a recent comprehensive review of antipsychotic-induced hyponatremia authored by Meulendijks et al. (2010). Forty-one duplicates were identified, leaving 186 to be screened. None were controlled studies, and all were either single or a series of case reports. Eighty-one of these articles were excluded on the basis of the abstract because they did not describe psychotic patients.

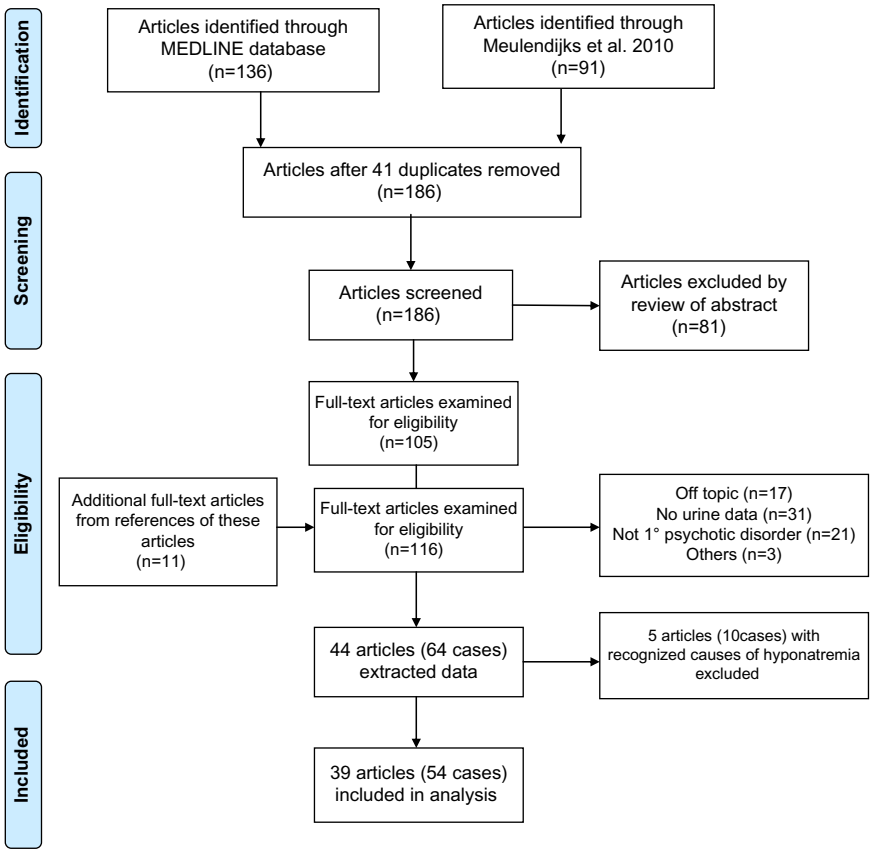

Fig. 1. Flow Diagram.
Source: Adapted from the PRISMA 2009 Flow Diagram (Moher et al., 2009).