Antidepressant Induced Hyponatremia

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INTRODUCTION

Electrolyte imbalance is a very common cause as well as comorbidity of hospitalization, especially in elderly individuals. It also enhances the morbidity and mortality in this group of patients. Disorders of sodium balance are the most prevalent types of electrolyte disturbance in clinical settings. Among several etiological factors related to disturbed serum sodium concentration, iatrogenic causes are very common. Antidepressants are noteworthy contributors among the drugs causing reduced plasma sodium concentration and as these drugs are quite commonly used in elderly patients due to high prevalence of depression in this age group, here we discuss about antidepressant induced hyponatremia.

HYPONATREMIA

DEFINITION

Hyponatremia is defined as a plasma $[Na^+] < 135$ mEq/L

PREVALENCE

In a recent community study in subjects aged 55 years or more, hyponatremia was most prevalent (7.7%) electrolyte disturbance¹. While considering hospitalized patients, the prevalence shoots upto 22%.

CLASSIFICATION OF HYPONATREMIA BY CLINICAL CAUSE²

1. Syndrome of inappropriate antidiuretic hormone secretion. (SIADH), with no diuretic use, or 'possible SIADH', with diuretic use, when serum osmolality was <280 mOsmol/kg H₂O, urine sodium >30 mM, and urine osmolality >150 mOsmol/kg H₂O;

2. 'hypovolemia', when serum osmolality was <280 mOsmol/kg H₂O and urine sodium <25 mM;
3. 'out of defined range', when serum osmolality was >280 mOsmol/kg H₂O and urine sodium 25–30 mM;
4. 'other cause', i.e. the presence of hyperglycemia (defined as a serum glucose ≥ 15 mM).

COMMON ETIOLOGIES OF HYPONATREMIA

DISEASES ASSOCIATED WITH HYPONATREMIA³

Active heart failure
Active liver failure
Nephrotic syndrome
Pulmonary processes as infections and malignancy
Malignancy of pancreas or duodenum
Lymphoreticular malignancy
Thymoma
Psychosis
Idiopathic SIADH
Adrenal insufficiency with no sufficient therapy
Diabetes mellitus or glucose >10 mmol/L
Chronic obstructive pulmonary disease
Smoking of cigarettes
Hypertension defined as $>160/>90$ mmHg
Acquired immunodeficiency syndrome
Cerebral salt wasting syndrome

DRUGS ASSOCIATED WITH HYPONATREMIA⁴

Antipsychotic drugs : typical and atypical
Clofibrate
Antidepressants : SSRIs, SNRIs, TCAs

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Proton pump inhibitors
Benzodiazepines NSAIDs
Anti-epileptic drugs : carbamazepine,
oxcarbazepine, valproate,
Oral hypoglycemic drug : sulfonylureas,
biguanides
Anti-Parkinson drugs
Desmopressin, vasopressin, oxytocin
Rivastigmine
Ciprofloxacin, moxifloxacin, Voriconazole
Opioid analgesics, tramadol
Chemotherapeutics : cyclophosphamide,
vincristine, vinblastine
Thiazide diuretics, loop diuretics, aldosterone
antagonists
Beta Blockers, ACE inhibitors, nitrates, calcium
channel blockers

CLINICAL PRESENTATION

The clinical features of hyponatremia are related to the osmotic intracellular water shift leading to cerebral edema. Therefore, the symptoms are primarily neurologic, and their severity is dependent on both the magnitude of the fall in plasma $[Na^+]$ and the rapidity of the decrease. In acute hyponatremia (i.e., developing in <2 days), patients may complain of nausea and malaise with $[Na^+] \sim 125$ mEq/L. As the plasma $[Na^+]$ falls further, symptoms may progress to include headache, lethargy, confusion, and obtundation. Stupor, seizures, and coma do not usually occur unless the plasma $[Na^+]$ falls acutely below 115 mEq/L. In chronic hyponatremia (>3 days' duration), adaptive mechanisms designed to defend cell volume occur and tend to minimize the increase in ICF volume and its symptoms.

ANTIDEPRESSANT HYPONATREMIA ASSOCIATION

Prevalence and risk factors of hyponatremia as Adverse Reaction to Antidepressants (AR-AD) :

In one recent study involving elderly patients aged 60 yrs or more, who are using antidepressants, prevalence of hyponatremia as an AR-AD was 9.3%. For TCA users this prevalence was 11.5%, for SSRIs 10.2%, for venlafaxine 8.6% and for

mirtazapine 5.6%. Risk factors were a history of hyponatremia (adjusted Odds Ratio 11.17), weight < 60 kg (adjusted OR 3.47), and psychosis (adjusted OR 3.62). Hyponatremia was not associated with gender, age, class of antidepressant, or duration of antidepressant use according to this study³.

In another study⁵ involving patients aged >18 yrs admitted in hospital with primary or secondary diagnosis of hyponatremia, compared with non-recipients of antidepressants the adjusted OR for hyponatraemia associated with current use of antidepressants was 3.96 for serotonergic antidepressants and 1.87 for non-serotonergic antidepressants. The overall adjusted OR for antidepressant use was 2.75 compared with non-use of antidepressants. This study also concludes that the risk for hyponatraemia after initiation of a serotonergic antidepressant is highest during the first 2 weeks of drug therapy, although it can range from 4 days to 28 days (average 12.5 days).

Another recent review⁶ concluded that as far the risk of hyponatremia is concerned, odds ratios for SSRIs (1.5–21.6) were consistently higher than for TCAs (1.1–4.9). The risks associated with monoamine oxidase inhibitors, reboxetine and bupropion could not be established owing to insufficient information. Patient risk factors included older age (odds ratios 6.3) and concomitant use of (thiazide) diuretics (odds ratios 11.2–13.5).

As published in WHO drug information⁷, The Australian Adverse Reactions Advisory Committee (ADRAC) received a total of 311 reports of hyponatraemia involving SSRIs and venlafaxine. As a group, the SSRIs account for about one-quarter of all reports of hyponatraemia received by ADRAC, and are second only to diuretics as the group most commonly associated with hyponatraemia. In more than two-thirds of the 311 reports, the SSRI was the only suspected drug and three quarters of the reports involved females, implicating female sex to be an at risk group. A small proportion (14%) identified concurrent use of a diuretic. The median patient age was 77 years (range 13 to 99); about 85%

were older than 60 years. Onset was usually within the first month of treatment. In about two-thirds of cases, full recovery followed withdrawal of the SSRI and fluid restriction. Three cases had a fatal outcome related to hyponatraemia.

The largest review of reported cases of hyponatremia⁸ involved 736 cases of hyponatremia and SIADH associated with SSRI use. Fluoxetine was involved in 554 (75.3%) of the cases, paroxetine in 91 (12.4%), sertraline in 86 (11.7%) and fluvoxamine in 11 (1.5%). Median time to onset of hyponatremia was 13 days (range 3 to 120 days).

MECHANISM OF HYPONATREMIA BY ANTIDEPRESSANTS

There are three possible ways drugs can affect water homeostasis⁸:

- They can increase ADH secretion centrally
- Potentiate the effect of endogenous ADH at the renal medulla
- Reset the osmostat, thus lowering the threshold for ADH secretion.

ADH secretion from the posterior lobe of the pituitary gland is thought to be affected by such nonosmolar factors as angiotensin II, noradrenaline, acetylcholine and endorphin levels. Dopamine antagonists such as haloperidol and domperidone have been shown in animal models to facilitate ADH secretion and increase thirst by increasing angiotensin II levels. Noradrenaline induces the release of ADH via α_1 adrenergic receptors; stimulation of α_2 -adrenergic and beta-adrenergic receptors may, however, inhibit ADH release. Serotonin-mediated effects on 5-HT₂ and 5-HT_{1C} receptors have been shown to induce release of ADH. Although the SSRIs are believed to be highly selective in their effect on serotonin reuptake, animal studies have shown that the SSRIs have some inhibitory effects on the reuptake of dopamine and noradrenaline. As a result, antidepressants cause a syndrome of inappropriate antidiuretic hormone (ADH) secretion (SIADH) leading to increased water retention and hyponatremia.

Hyponatremia associated with SSRI use may be a manifestation of a drug interaction. SSRIs are known to inhibit a number of cytochrome P450 isoenzymes⁹. In several of the cases the patients concurrently receive a drug known to cause SIADH. By inhibiting the metabolism of concomitant drugs such as neuroleptics, adverse effects on sodium metabolism may be augmented.

CLINICAL RELEVANCE

SSRIs are usually considered safer than older antidepressant agents and therefore are often recommended as first-choice drugs in the treatment of depression and anxiety disorders. However, the documented relatively higher hyponatremia risk profiles of SSRIs imply that this recommendation might not necessarily be appropriate for specific patients. As the potential for specific adverse events varies for the different antidepressant classes, class- or drug-specific side-effect profiles should be considered together with patient-specific risk factors when deciding on the optimal treatment for individual patients. Clinicians' awareness of the higher risk and signs of hyponatremia associated with certain antidepressants should be raised, as particularly in psychiatric populations, clinical symptoms of hyponatremia can be misinterpreted as a worsening of the primary illness. Sodium levels should be checked in all elderly patients exhibiting abrupt or unexplained changes in mental status (e.g., lethargy or confusion) at any time during treatment with an antidepressant, especially SSRI or venlafaxine. Some authors recommend a routine serum sodium analysis within the first 2 weeks after initiating such treatment in patients with additional risk factors for hyponatremia, such as older age, female sex, diuretic use, low BMI, and a baseline plasma sodium level <138 mmol/L^{10,11,12}. A thorough cost-benefit analysis seems warranted to validate the latter recommendation.

TREATMENT¹³

Management requires one to determine :

- ❑ The rate of correction
- ❑ The appropriate intervention
- ❑ The presence of other underlying disorders

ACUTE SYMPTOMATIC HYPONATREMIA

Severe symptomatic hyponatremia, with evidence of neurologic dysfunction, should generally be treated promptly with hypertonic saline. The risks of correcting hyponatremia too rapidly are volume overload and the development of central pontine myelinolysis (CPM). CPM is thought to result from damage to neurons resulting from rapid osmotic shifts. In its most overt form, it is characterized by flaccid paralysis, dysarthria, and dysphagia, and in more subtle presentations, it can be confirmed by computed tomography (CT) scan or magnetic resonance imaging (MRI) of the brain. The risk of precipitating CPM is increased with correction of the $[Na^+]$ by $> 12 \text{ mEq/L}$ in a 24-hour period. In addition to overaggressive correction, other risk factors for developing CPM include preexisting hypokalemia, malnutrition, and alcoholism.

MEDICATIONS

- Loop diuretics promote urinary excretion of water by reducing the concentration gradient necessary to reabsorb water in the distal nephron and impair the ability to excrete concentrated urine.
- Lithium and demeclocycline interfere with the collecting tubule's ability to respond to ADH, but are rarely used because of significant side effects. They should only be considered in severe hyponatremia that is unresponsive to more conservative measures.
- Vasopressin antagonists promote a water diuresis and may be useful in the therapy of SIADH. As of yet, the only formulation approved in the United States is conivaptan, which is an IV preparation and thus not applicable to

chronic outpatient management of euvolemic hyponatremia.

LIFESTYLE/RISK MODIFICATION

- Oral fluid intake should be less than daily urine output.
- SIADH should first be distinguished from the conditions, which stimulate vasopressin secretion. The standard first-line therapy is water restriction and correction of any contributing factors (nausea, pneumonia, drugs, etc.).
- Water restriction. The amount of fluid restriction necessary depends on the extent of water elimination. A useful guide to the necessary degree of fluid restriction is as follows:
 - ✧ If $(\text{Urine Na} + \text{Urine K})/\text{Serum Na} < 0.5$, restrict to 1 L/d.
 - ✧ If $(\text{Urine Na} + \text{Urine K})/\text{Serum Na}$ is 0.5 to 1.0, restrict to 500 mL/d.

CONCLUSION

Hyponatremia is a potentially dangerous and hazardous side effect of antidepressants, which at instances can be proved fatal. Though it's most commonly associated with SSRIs, but other antidepressants can also cause it in rare instances. The risk of developing it is mainly during the first few weeks of drug treatment and in certain high risk groups such as elderly females. Physicians should be aware of this side effect, should be able to recognize the symptoms and if need arises, should be able to manage it properly.

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