

Hyponatremia Associated with Selective Serotonin Reuptake Inhibitors

Key words: selective serotonin reuptake inhibitor (SSRI), serotonin and noradrenaline reuptake inhibitor (SNRI), hyponatremia, syndrome of inappropriate antidiuretic hormone secretion (SIADH)

Selective serotonin reuptake inhibitors (SSRIs) are among the most widely prescribed drugs in the world (1) and are the first choice for depression in older patients (2). On the other hand, there are numerous case reports accumulating that hyponatremia occurs more frequently with SSRIs than with antidepressants having no or a minor influence on the serotonergic system (3, 4). Liu et al (5) evaluated 706 cases of hyponatremia associated with SSRI use in unpublished reports obtained from pharmaceutical manufacturers and other sources, and reported that fluoxetine was the most common cause (75.3%), followed by paroxetine (12.4%), sertraline (11.7%), and fluvoxamine (1.5%). Recently Movig et al (6) conducted a matched case-control study using the PHARMO database (1990 to 1998) which includes information on drug exposure (serotonergic or nonserotonergic agents) and hospital admission due to hyponatremia for 320,000 inhabitants of 8 Dutch cities. Two hundred and three hyponatremic patients were compared with 608 community controls. They found that hyponatremia occurred during the first 2 weeks of treatment and the incidence of hyponatremia was higher in SSRIs than in non-serotonergic antidepressants.

In this issue of the journal, Wakita et al (7) describe a 78-year-old woman who developed encephalopathy secondary to severe hyponatremia after resumption of paroxetine but was successfully treated by discontinuation of paroxetine and oral fluid restriction together with intravenous saline infusion.

See also p 240.

Hyponatremia and impaired water excretion characterize the syndrome of inappropriate antidiuretic hormone secretion (SIADH). Symptoms of SIADH are nonspecific and range from mild lethargy, anorexia, insomnia, fatigue, nausea, muscle cramps, headache and confusion to coma. The diagnosis is supported by hyponatremia and hyperosmolar urine without the development of edema or features of intravascular volume depletion such as tachycardia, orthostatic hypo-

tension or hypokalemia. The mechanism of SSRI-induced SIADH remains unknown. However experimental studies using conscious rats indicated that serotonin might have a stimulatory effect on antidiuretic hormone secretion and 5-HT_{2/1} C receptors seemed to be implicated (8).

In addition to SSRIs (fluoxetine, sertraline, paroxetine, fluvoxamine and citalopram), serotonin and noradrenaline reuptake inhibitors (SNRIs), such as venlafaxine, duloxetine and milnacipran have also been reported to be a potential cause of hyponatremia (9). In Japan, fluvoxamine, paroxetine and milnacipran are currently available, while sertraline, venlafaxine, duloxetine and some others are expected to come on the market in the near future.

It has been said that hyponatremia may be a relatively common early asymptomatic side effect of SSRIs, especially in older women (10). According to a descriptive and case control study for people aged 65 years and over (11), about 1 in 200 elderly people treated per year with fluoxetine or paroxetine developed complicating hyponatremia, and most cases occurred within 3 weeks of treatment. Low body weight was pointed out as a particular risk factor.

Physicians, therefore, have to be aware of the possible development of hyponatremia and SIADH when patients are placed on SSRIs or SNRIs, and serum sodium concentrations should be monitored not only in the first few weeks of therapy, but also during the entire course for early detection and treatment of hyponatremia.

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