Brief Report

Fluoxetine-Induced SIADH: A Geriatric Occurrence?

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After major depression was diagnosed in an 83-year-old woman, fluoxetine was prescribed. Six days later she became delirious and weak, necessitating hospitalization. She was found to have hyponatremia secondary to fluoxetine-induced syndrome of inappropriate antidiuretic hormone secretion (SIADH). Recovery was complete after discontinuation of the medication.

Key words. Fluoxetine; antidepressive agents; inappropriate ADH syndrome; aged. *J Fam Pract 1993; 36:341-343.*

An increasing number of side effects and adverse reactions have been reported from the use of fluoxetine hydrochloride (Prozac). The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is one such adverse reaction to fluoxetine that is potentially life-threatening but readily reversible if recognized. Primary care physicians prescribe fluoxetine more often than psychiatrists (verbal communication, May 28, 1992, Eli Lilly and Co, Indianapolis, Ind). Yet primary care physicians may not be aware of this potential adverse reaction because reports of an association between fluoxetine and SIADH have appeared almost exclusively in the psychiatric literature, and the subject was not addressed in the *Physicians' Desk Reference* before 1992.

Case Report

An 83-year-old woman was seen in December 1991 for pain from old lumbar vertebral compression fractures secondary to osteoporosis. Pertinent serum chemistry levels were: sodium 137 mEq/L (137 mmol/L), chloride 98 mEq/L (98 mmol/L), blood urea nitrogen 28 mg/dL (10 mmol/L), and creatinine 1.6 mg/dL (140 μmol/L). She was treated with ibuprofen but showed minimal improvement, so it was discontinued. On follow-up examination in January 1992, she described urinary frequency without dysuria, urgency, fever, or flank pain. She was unable to produce a urine sample, and her physician empirically prescribed sulfamethoxazole/trimethoprim for a lower urinary tract infection. The patient reported "forgetfulness," decreasing energy, anhedonia, insomnia, and agitation for the past several months. No organic causes for depression, recent bereavement, or psychotic symptoms were identified. A diagnosis of major depression was made, and she was started on fluoxetine (20 mg/d). Six days later, the patient became confused and was unable to stand or feed herself. At that time, she was admitted to the hospital for evaluation of delirium and weakness.

The patient had no history of dementia or recent head trauma. She had been treated in the past for multiple urinary tract infections and elevated intraocular pressure after cataract removal. The family was unaware of any history of hypertension, diabetes mellitus, or vascular disease. Current medications included fluoxetine, sulfamethoxazole/trimethoprim, timolol ophthalmic solution, and calcium carbonate.

On physical examination, the patient was lethargic with intermittent incoherent speech, but she was responsive to verbal stimuli and oriented to person and time. Her blood pressure was 208/86 mm Hg. She had mild generalized muscle weakness. There was no peripheral edema.

Laboratory evaluation showed a serum sodium of 127 mEq/L (127 mmol/L), serum creatinine of 0.7 mg/dL (60 μmol/L), and BUN of 11 mg/dL (4 mmol/L). Serum and urine osmolality were 256 mOsm/kg (256 mmol/kg) and 573 mOsm/kg (573 mmol/kg), respectively, and urine sodium was 85 mEq/L (85 mmol/L). Thyroid function tests were within normal limits. A morning cortisol was 21.0 μg/dL (580 nmol/L). No indications of pneumonia were found on chest radiographs, and computerized tomography of the head re-

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Table 1. Case Reports of Hyponatremia and SIADH Associated with Fluoxetine

Cases Reported in The Literature	Age (y)	Daily Dose at Diagnosis (mg)	Serum Sodium (mEq/L) Lowest Reported	Start of Drug to Diagnosis of Hyponatremia (d)	Withdrawal of Drug to Resolution of Hyponatremia (d)
Case 1[5]	75	20	116	12	6
Case 2[6]	75	20	126	10	10
Case 3[7]	82	20	125	3	7
Case 4[7]	79	20	129	42	8
Case 5[7]	84	40	124	21	14
Case 6[7]	85	20	126	7	14
Case 7[8]	59	80	125	21	3
Case 8[9]	53	20	122	14	2

vealed no acute cerebrovascular accident. Her urine culture was negative.

The hyponatremia was believed to be secondary to fluoxetine-induced SIADH. Fluoxetine and sulfamethoxazole/trimethoprim were discontinued. Her systolic blood pressure was controlled with oral nifedipine. Fluids were restricted to 1000 mL/day. Her serum sodium reached a nadir of 124 mEq/L (124 mmol/L). It normalized at 139 mEq/L (139 mmol/L) 13 days after fluoxetine was discontinued. The mental status of the patient gradually returned to a normal baseline, paralleling the resolution of her hyponatremia. The fluid restriction was discontinued without recurrence of hyponatremia.

Discussion

Fluoxetine has been on the market in the United States since 1987. It has received unprecedented publicity and is now the most prescribed antidepressant medication in this country.[1] Fluoxetine has been promoted as being safer than tricyclic antidepressants because of its low cardiac toxicity and relative safety in overdoses.[2] This, in combination with its lack of orthostatic hypotension and anticholinergic effects, has made it an attractive antidepressant medication, especially for the elderly patient. The choice of an antidepressant agent is often made on the basis of a predominant side effect (such as sedation) that is either desired or unwanted.

In the elderly, however, there are risks associated with selecting fluoxetine to avoid the potential side effects of a tricyclic agent. This second-generation antidepressant agent has its own side effects of anxiety, agitation, insomnia, nausea, and weight loss, and it has potential drug interactions with benzodiazepines and tricyclic agents.[3] In addition, as with any new drug, adverse reactions unrecognized in preclinical trials are identified later with more extensive clinical exposure. Therefore, prescribing new medications for elderly patients, who in general may be more prone to side effects and adverse reactions,[4] may result in unexpected complications.

Eight cases of hyponatremia and SIADH associated with fluoxetine have been reported in the medical literature.[5–9] These are summarized in Table 1. Our patient's course had many features that were consistent with those cases: (1) the adverse reaction occurred in a geriatric patient, as did 6 of 8 of the previously reported cases; (2) her serum sodium level reached a low of 124 mEq/L (124 mmol/L), which was the average for the other cases; and (3) the serum sodium returned to normal 13 days after discontinuation of the fluoxetine, nearly an identical amount of time required by the two oldest patients. Therefore, based on the cases reported thus far, our patient's response to fluoxetine-induced SIADH was characteristic of her age group.

The age of the patient appears to be an important factor both in development of and response to fluoxetine-induced SIADH. Including our case, 7 of 9 patients were elderly. In the 63 cases of fluoxetine-induced SIADH reported to the Food and Drug Administration (FDA), the majority involved patients who were 70 years of age or older (verbal communication, May 27, 1992, FDA). The speed of recovery of the 9 patients was remarkably different at both extremes of age. The two youngest patients, aged 53 and 59 years, had the shortest recovery time (2 and 3 days, respectively), whereas the two oldest patients, aged 84 and 85 years, required the most time to recover (14 days each). Our patient's recovery followed the same course as that of the two oldest patients. These findings suggest that the geriatric patient is at higher risk for development of this adverse reaction and may be at risk for increased morbidity from prolonged recovery.

Further comparison of the nine cases does not identify any correlation between the severity of hyponatremia and age of the patient, dose of fluoxetine, or length of time on fluoxetine. The speed of resolution of hyponatremia after discontinuation of fluoxetine did not appear to be influenced by the severity of hyponatremia or the duration of its use.

In general, elderly patients are more susceptible to the adverse effects of drugs. The reason for this increased

vulnerability to fluoxetine-induced SIADH is a matter of speculation because (1) it is not known how fluoxetine causes SIADH in any age group, and (2) the metabolism of fluoxetine in the elderly has not been examined completely. Drug-induced SIADH typically is attributed to increased secretion of ADH, eg, carbamazepine, morphine[10,11]; increased renal responsiveness to ADH, eg, chlorpropamide, cyclophosphamide; or altered renal diluting capacity.[12] The mechanism by which tricyclic antidepressants, MAO inhibitors, antipsychotics, and clonidine cause SIADH has not been determined.[11,13] Elderly people do experience a decrease in total body water, renal blood flow, glomerular filtration rate, and renal tubular concentrating and diluting capacity.[14] These age-related alterations in water metabolism may render the elderly patient susceptible to this complication.

Summary

This case followed a pattern similar to that seen in previously reported cases linking fluoxetine and SIADH. The patient's only risk factor for fluoxetine-induced SIADH appeared to be her age, as she was not taking diuretics, nor was she volume-depleted. It may be that SIADH is a more common adverse reaction to fluoxetine in geriatric patients than in the general population and warrants further investigation.

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