

Reversible Galactorrhea and Prolactin Elevation Related to Fluoxetine Use

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Fluoxetine, an antidepressant of the selective serotonin reuptake inhibitor class, may stimulate prolactin release by pituitary lactotrophs. A 71-year-old woman taking estrogen replacement therapy developed galactorrhea after initiation of fluoxetine for depression and was found to

have an elevated prolactin level. Fluoxetine was discontinued with resolution of the patient's galactorrhea and normalization of her prolactin level.

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Fluoxetine is a commonly used antidepressant of the selective serotonin reuptake inhibitor class. Both serotonin and its precursor 5-hydroxytryptamine (5-HT) are recognized as stimuli for prolactin release by pituitary lactotrophs. In rats^{1,2} and in humans,³⁻⁵ fluoxetine may potentiate elevation of prolactin levels from other stimuli, including insulin, fenfluramine, and 5-HT. Other antidepressants, including paroxetine⁶ and dothiepin,⁷ also may cause galactorrhea, sometimes with prolactin elevation. The following report describes a patient who developed reversible hyperprolactinemia and galactorrhea that were associated with fluoxetine use.

REPORT OF A CASE

A 71-year-old woman was seen in consultation for unilateral galactorrhea of approximately 2 months' duration. Prior to referral, her evaluation had included a breast examination and mammogram, which were normal; her prolactin level was elevated at 37.4 ng/mL (reference range, 1.2-24.2 ng/mL); and a computed tomographic scan of the pituitary was normal. The prolactin analysis was repeated, and the elevated level confirmed.

The patient reported that she had been taking fluoxetine because of symptoms of depression somewhat longer than a week before her galactorrhea began though she was uncertain about the exact time course. Her medical history included hypertension, a cholecystectomy, and a hysterectomy. Thyroid function as assessed by serum thyroid-stimulating hormone level was normal. Her other medications included conjugated estrogens (Premarin), benazapril, and alprazolam, which the patient had taken only rarely since it did not improve her symptoms. Other than initiation of

fluoxetine, the patient's medications had not been altered recently.

The patient was instructed to stop taking fluoxetine. Her galactorrhea discontinued within 10 days of her visit, and 8 weeks later her prolactin level was 6.1 ng/mL (within normal limits).

DISCUSSION

Prolactin release has been studied extensively but is not yet completely understood. Factors involved in its control include dopamine, which is a potent inhibitor of prolactin release, and thyrotropin releasing hormone, serotonin, and a serotonin precursor 5-HT, all of which promote prolactin release. Elevation of prolactin occurs with a number of medications used to treat psychiatric disorders. These include neuroleptics, such as perphenazine, chlorpromazine, and haloperidol, and several antidepressants, including imipramine, amitriptyline, paroxetine,⁶ and dothiepin.⁷ Fluoxetine is known to potentiate the 5-HT-induced elevation of prolactin in rats.^{1,2} Meltzer and colleagues⁵ reported an increase in the 5-HT-mediated rise in prolactin in human subjects treated with fluoxetine. Fluoxetine also may potentiate prolactin release associated with administration of insulin³ and of fenfluramine⁴ in humans.

Several short series of patients suggest no effect on prolactin level by fluoxetine alone in humans, including 2 series of 5 patients^{3,8} and another series of 7 patients.⁹ A female adolescent has been reported with galactorrhea and hyperprolactinemia after treatment with fluoxetine.¹⁰ Another patient has been reported with prolactin elevation due to fluoxetine use,¹¹ and a series of 7 postmenopausal women had at least short-term increase in prolactin secretion after administration of fluoxetine,¹² although long-term measurements showing prolactin elevation over time were not reported.

Estrogen has positive effects on prolactin release at several levels. Estrogen increases the number of prolactin-secreting cells in the pituitary as evidenced by autopsy

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studies¹³; it leads to increased levels of prolactin messenger RNA by increasing prolactin gene transcription¹⁴; and it also modifies the pituitary's response to some of the factors known to affect prolactin release. Estrogen lessens the inhibitory effect of dopamine and heightens the releasing response to thyrotropin-releasing hormone.¹⁵

The fact that estrogen modulates pituitary responsiveness to factors that affect prolactin release may have bearing on this case. It would seem plausible that estrogen would potentiate the release of prolactin in response to fluoxetine similar to the interactions noted between fluoxetine and 5-HT, fluoxetine and insulin, and fluoxetine and fenfluramine. In ovariectomized rats, estrogen has been shown to increase dramatically the prolactin release due to serotonin administration.¹⁶ In rhesus monkeys, progesterone treatment significantly increased the prolactin release seen in ovariectomized, estrogen-treated animals given fluoxetine vs such animals not given progesterone.¹⁷ The authors of the article comment on the interesting question of why fluoxetine has not been shown consistently to exert greater effect on prolactin secretion in estrogen-dominant animals.

In summary, this article describes a patient with reversible galactorrhea and prolactin elevation associated with fluoxetine that occurred in the context of estrogen use. Both animal and human data show that fluoxetine can potentiate prolactin rise from other stimuli. Estrogens are known to promote prolactin elevation, and in this case, the patient's galactorrhea and prolactin elevation did not persist when she continued to use conjugated estrogens without fluoxetine. It seems likely that the modest elevation in prolactin level and galactorrhea were due to the patient's use of fluoxetine in the presence of estrogenic tone. The relationship between fluoxetine and estrogen on prolactin release deserves further study. Clinicians should be aware of the possibility of prolactin elevation and galactorrhea with fluoxetine use particularly in patients who have other factors that might stimulate prolactin release.

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