Journal of Pharmaceutical Care
jpc.tums.ac.ir

Hyperprolactinemia and Galactorrhea Associated with Risperidone-Fluoxetine Combination Therapy: A Case Report

Nastaran Kordjazy[1,2], Kheirollah Gholami[1,2], Elliyeh Ghadrdan [1,3*]

[1]13-Aban Drug and Poison Information Center, Tehran University of Medical Sciences, Tehran, Iran.
[2]Department of Clinical Pharmacy, School of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.
[3]Department of Clinical Pharmacy, School of Pharmacy, Alborz University of Medical Sciences, Karaj, Iran.

Received: 2020-07-10, Revised: 2020-07-27, Accept: 2020-07-28, Published: 2020-09-30

A R T I C L E I N F O

Article type:
Case report

Keywords:
Hyperprolactinemi;
Galactorrhea;
Risperidone;
Fluoxetine;

A B S T R A C T

Prolactin is a polypeptide hormone secreted and released by lactotroph cells in the anterior pituitary gland in response to diverse physiological stimuli, principally via the inhibitory action of dopamine and serotonin. This paper describes a 44-year-old woman with depression and obsessive-compulsive disorder (OCD) who called the 13-Aban drug and poison information center (DPIC). She was being treated with fluoxetine (80 mg/day) for 10 months until risperidone was added to her regimen for augmentation therapy (0.5 mg/day). Her symptoms improved within less than 2 months without significant side effects until she experienced painful bilateral breast discharge along with spotting and menstrual irregularity, besides amenorrhea for the previous 2 cycles and serum prolactin level of 33.7 ng/mL, presenting hyperprolactinemia. After discontinuing risperidone, within two weeks, galactorrhea and breast pain disappeared and amenorrhea resolved. Further prolactin level measurement showed the significant reduction. This neuroendocrine effect observed with very low-dose risperidone plus fluoxetine is apparently exerted through both pharmacokinetic and pharmacodynamic augmentation of this combination therapy.

J Pharm Care 2020; 8(3): 154-156.

► Please cite this paper as:

Kordjazy N, Gholami K, Ghadrdan E.Hyperprolactinemia and Galactorrhea Associated with Risperidone-Fluoxetine Combination Therapy: A Case Report. J Pharm Care 2020;8(3): 154-156.

Introduction

Prolactin is a polypeptide hormone that is secreted and released by lactotroph cells in the anterior pituitary gland related to the circadian pattern. Prolactin is secreted in response to diverse physiological stimuli, but principally via the inhibitory action of dopamine. Also, serotonin modulates prolactin secretion. Auto-regulation of prolactin release also contributes to further control (1). Some symptoms associated with hyperprolactinemia include menstrual irregularities, sexual impairment, breast enlargement and galactorrhea, and mood alterations. The prevalence of prolactin elevation is more often than not underestimated. Hyperprolactinemia is most frequently occurred with neuroleptics and antidepressants, respectively (2). The main mechanisms by which various medications are presumed to exert this effect include decrease in dopamine, enhancing serotonin, and substantiation of neurotransmitters like vasoactive intestinal polypeptide (VIP) (1).

Case report

A patient called the 13 Aban drug and poison information center (DPIC) asking about the probability of increased prolactin level associated with fluoxetine use.
She was a 44-year-old married woman with 2 children living in Tehran, Iran, with a past medical history of childhood seizures, and a family history of breast cancer. Her menstrual cycles were previously irregular, then regular after fluoxetine initiation then after starting risperidone became irregular again. She denied any recent weight gain/loss, or any intense sports activities, conditions associated with hyperprolactinemia (such as celiac, rheumatoid arthritis, systemic lupus erythematosus). Her past drug

*Corresponding Author: Dr Elliyeh Ghadrdan
Address: 13 Aban drug and poison information center, Karimkhan St., 7 Tir Sq., Tehran, Iran.
Postal code: 158913115,Tel: +982188814158.
Email: EL.ghadrdan@gmail.com

history contained phenobarbital (discontinued 20 years ago) fluoxetine and risperidone. The patient was currently receiving fluoxetine (80 mg per day) cabergoline (0.5 mg twice weekly) and medroxyprogesterone (5 mg twice per day).

Due to depression and obsessive-compulsive disorder (OCD) she was being treated with fluoxetine for 10 months (dose fixed on 80 mg/day for more than 5 months) until her psychiatrist decided to add risperidone to her regimen for augmentation of therapy regarding obsessive thoughts mentioned by the patient, beginning with 0.25 mg daily, and titrating to 0.5 mg/day after one week. Her symptoms improved within less than 2 months without significant side effects from medications. Nevertheless, afterwards, visiting the gynecologic clinic, the patient declared she had noted painful bilateral breast discharge along with spotting and menstrual irregularity, besides amenorrhea for the previous 2 cycles. Her serum prolactin level was measured to be 33.7 ng/mL, presenting hyperprolactinemia. Other measured laboratory data were as follows: FBS, 92mg/dL; HDL, 76mg/dL; LDL, 140mg/dL; VLDL, 16mg/dL; TG, 79mg/dL; TSH, 2.22mcIU/mL; AST, 18U/L; ALT, 15U/L; BUN, 11 mg/dL; serum creatinine, 0.6 mg/dL. She was not aware of her baseline prolactin level before starting therapy.

Her gynecologist after ruling out pregnancy soon prescribed cabergoline 0.5 mg for her. In spite of the fact that her psychiatrist proposed in case the adverse effects are tolerable, she'd better continue her medications, the patient discontinued risperidone after a week. Within two weeks, galactorrhea and breast pain disappeared and amenorrhea resolved. Further prolactin level measurement showed remarkable reduction i.e. dropped to 0.6 ng/mL. During 1 month of follow-up, there was no re-emergence of galactorrhea and based on patient's reluctance, the psychiatrist intended not to restart risperidone, hence continuing treatment with fluoxetine monotherapy.

Discussion

Although pharmacotherapy of OCD is preferably recommended with selective serotonin reuptake inhibitors (SSRIs) which are currently considered the drug of choice in these patients (3), near half OCD patients do not respond desirably to monotherapy with these agents, yet even after switching to another drug in the family. Previous findings indicate that adding an antipsychotic to the regimen exerts improved response to SSRI therapy in patients (4). This observation was most significant with risperidone (5). Several studies demonstrated that risperidone might be associated with increased serum prolactin level and related symptoms. However, this effect was mainly experienced when using higher doses of risperidone (i.e. more than 2 mg/day). Risperidone was shown to more frequent hyperprolactinemia compared to most other second-generation antipsychotics, but less than first generation ones. Notwithstanding, the serum prolactin levels induced by risperidone therapy was significantly higher than that associated with conventional antipsychotic medications (6-8).

All conventional antipsychotics block dopaminergic D2 receptors located on lactotroph cells, therefore removing the principal inhibitory component on prolactin secretion. Generally, newer antipsychotics are less frequently assumed to induce this effect. Tricyclic antidepressants and SSRIs are less prevalent causes. Most SSRIs are able to cause hyperprolactinemia through presynaptic mechanisms indirectly via serotonin-mediated inhibition of tuberoinfundibular dopaminergic neurons. Presumably, prolactin release is regulated by serotonin either by elevating oxytocin level through direct stimulation of VIP or indirectly via stimulation of gamma- aminobutyric acidergic neurons (9).

There have been just a few reports of adverse drug reactions from pharmacovigilance centers and papers describing hyperprolactinemia-related conditions in fluoxetine-treated patients, mostly during the first few months of drug initiation (10). In these reports, symptoms promptly subsided after discontinuation of fluoxetine. In our case, she was taking a dose of 80 mg/day of fluoxetine for more than 10 months, but she did not show any adverse effects. Also, symptoms began following risperidone use and resolved after antipsychotic discontinuation while the patient continued to take fluoxetine.

On the other hand, fluoxetine, as a cytochrome P450 2D6 inhibitor seems to enhance the plasma level and also the area under the curve of risperidone (11) and probably 9-OH-risperidone, its active moiety, in simultaneous administration. This effect is more prominently seen in extensive metabolizers (12). It is well-known that CYP 2D6 is essential in risperidone exposure, clinical effect, and also adverse effects (13). The mean effect on risperidone plasma concentration was a 4-fold increase, but could exhibit as large a 10-fold elevation (11).

There are some case reports which presented hyperprolactinemia associated with risperidone fluoxetine combination therapy.

A patient suffering bipolar disorder who was taking a regimen containing risperidone (1 mg/day), started fluoxetine 5 mg daily for controlling depressive phases until a few weeks later when she experienced bilateral breast enlargement along with pain. After risperidone discontinuation, pain vanished in less than a week, and re-appeared when risperidone (0.5 mg/day) restarted. Although the prolactin level was not investigated in the patient, it can be assumed to have contributed to observed symptoms (14).

A 44-year-old woman with a history of schizophrenia was being treated with risperidone 4.5 mg/day and fluoxetine 20 mg/day. She complained of amenorrhea for 1 year and the measured prolactin level was 377 ng/mL. Gynecologists decided to initiate cabergoline, which led to exacerbation of psychotic features (15).

In another study, concomitant treatment with low doses of risperidone and a few SSRIs (not fluoxetine) with the aim of augmentation therapy resulted in hyperprolactinemia in men and women. Bothersome adverse effects included amenorrhea, galactorrhea, and muscle rigidity, all of which improved after discontinuing risperidone and proceeding with another antipsychotic (16).

Conclusion

In this case reported, we mentioned a woman who experienced galactorrhea and menstrual irregularities with an increase in serum prolactin level following psychotropics administration. Regarding our patient, co-medication with very low-dose risperidone and fluoxetine established increased level of prolactin besides bilateral breast discharge and pain. This neuroendocrine effect was reversed following risperidone withdrawal and cabergoline treatment. Apparently, this effect was exerted through both pharmacokinetic and pharmacodynamic augmentation of this combination therapy. Although galactorrhea associated with antidepressants and antipsychotics is not consistently related to elevated prolactin levels, still unexplained mechanisms of the induced galactorrhea may be suggested.

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