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Duloxetine Associated Galactorrhea and Hyperprolactinemia: A Case Report

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SUMMARY

Duloxetine is a serotonin-noradrenaline reuptake inhibitor (SNRI). The noradrenergic effects contribute to the treatment of painful physical symptoms. Hyperprolactinaemia and galactorrhea are recognized side effects of psychotropic drugs used in the treatment of psychiatric diseases.

Although hyperprolactinaemia is a known side effect of the tricyclic antidepressants, evidence on hyperprolactinaemia and galactorrhoea induced by the selective serotonin reuptake inhibitors (SSRIs) and the SNRIs is limited. Hyperprolactinaemia due to SSRI or SNRI therapy is usually asymptomatic and is diagnosed after a detailed examination of the patient following the emergence of galactorrhea.

In this report, a case who developed amenorrhea, galactorrhea, and hyper-prolactinaemia identified at the 5th month of duloxetine for major depression will be discussed. After a month of drug-free period and cabergoline treatment, the prolactin levels returned to normal.

Keywords: Duloxetine, galactorrhea, prolactin

INTRODUCTION

Hyperprolactinemia is observed in the most common endocrine diseases of the hypothalamic-pituitary axis after drug therapy as well as the physiological, pathological and etiological factors. Whereas hyperprolactinemia is a physiological outcome of pregnancy and lactation; it is a pathological manifestation of the prolactinomas (Ajmal et al. 2014, Molitch 2008, Voicu et al. 2013, Wattegama and Siyambalapitiya 2017). In women, hyperprolactinemia can cause pathological changes including galactorrhea, sexual dysfunction, oligomenorrhea, amenorrhea, infertility, and osteoporosis; as well as leading to behavioural and mood changes such as hostility, depression, and anxiety (Schlechte 2003, Molitch 2008). In men, hyperprolactinemia results in decreased libido, erectile and ejaculatory dysfunction, gynecomastia, galactorrhea, priapism, and reduced semen volume (Voicu et al. 2013).

Physiological galactorrhea develops during pregnancy and breastfeeding and it can also occur with nipple stimulation, during sleep, and under stress (Schlechte 2003). Serum prolactin can reach ≥ 10 times the normal levels during pregnancy and lactation and can rarely increase up to 40 mg/l with physical exercise and psychological stress (Wattegama and Siyambalapitiya 2017).

The medication-induced elevations of prolactin levels are observed with antipsychotics, antidepressants, antihypertensives, drugs that increase gastrointestinal motility, estrogen preparations, and cocaine and opiates may elevate prolactin levels (Wattegama and Siyambalapitiya 2017). Typical antipsychotics that are associated with elevated prolactin levels include phenothiazine, butyrophenone, and thioxanthenes, while atypical antipsychotics include risperidone, molindone, olanzapine, and quetiapine. The antidepressants associated with elevated prolactin levels include the tricyclic antidepressants, SSRIs, and SNRIs (Ashton and Longdon 2007, Coker and Taylor 2010, Voicu et al. 2013).

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Table 1. Prolactin Levels in Periods with and without Antidepressant Use

Depression episode	Antidepressant (AD)	Galactorrhea	MRI	Prolactin level (ng/ml)	Prolactin level (ng/ml) One month later Without AD +Cabergoline
First episode	Fluoxetine	Negative (-)	-	-	-
Second episode	Duloxetine	Positive (+)	Normal	56.00	5.25

CASE

The 37-year old female patient, a working university graduate, married with one child and medical history of depression with fluoxetine use (20 mg/day) for 6-months 9 years previously, consulted us with complaints of unhappiness, anhedonia, forgetfulness, difficulties of maintaining concentration, burn-out, and intolerance. The patient was diagnosed with major depression based on the DSM IV-R diagnostic criteria. Her Beck Depression Inventory (BDI) score was 27. The laboratory test results were normal for serum ALT, AST, urea, creatinine, thyroid hormones (free T3, T4, and TSH), ferritin, complete blood count, and vitamin D. Vitamin B12 was 103 pg/ml (normal limits: 180-1200 pc/ml). The patient was started on duloxetine (30 mg/day) along with an intramuscular injection of cyanocobalamin (1000 mcg/week). One month later, the dose of duloxetine was increased to 60 mg/day. Cyanocobalamin treatment was discontinued after four injections. At the beginning of the fifth month of treatment, the patient presented to the obstetrician with the complaints of amenorrhea and lactation. At that time, her prolactin level was 56 ng/ml (normal limits: 4.79-23.3 ng/ml) and space-occupying lesions were not identified in the cranial magnetic resonance imaging (MRI) and the results were interpreted to be within normal limits. The patients were started on cabergoline (0.5 mg, 2 tablets/week) and was referred to the psychiatry clinic for consultation and revision of the antidepressant therapy. Duloxetine treatment is terminated when the serum prolactin level dropped to 5.25 ng/ml one month later. The psychiatric examination of the patient and her BDI score of 8 indicated significant improvement in her complaints noted at admission. The patient was switched to fluoxetine therapy (20 mg/day), planned to be continued for 1 year with regular follow up visits.

DISCUSSION

Hyperprolactinaemia is a generally observed adverse effect of psychotropic drug therapy (Alosami et al. 2018), reported more frequently with typical antipsychotics (Madhusoodanan et al. 2010), especially with risperidone, olanzapine, and quetiapine use (Ajmal et al. 2014, Reeves et al. 2016). The atypical characteristics of antipsychotics are often attributed to their concurrent D2-receptor a 5-HT2A antagonism (Stahl 2015). In drug-induced hyperprolactinemia, prolactin levels are usually less than 100 ng/ml; but have been reported to be over 100 ng/ml with typical antipsychotics (Molitch 2008, Voicu et al. 2013, Spina and Leon 2014)and to exceed 200 ng/ml during treatment with risperidone and phenothiazine (Wattegama and Siyambalapitiya 2017). Raised prolactin levels due to treatment with psychotropic agents return to normal within 48-96 hours upon discontinuation of drug therapy (Wattegama and Siyambalapitiya 2017).

Hyperprolactinaemia reported in association with tricyclic antidepressants is manifested by modest increases in prolactin levels. There are a few case reports in the literature on hyperprolactinaemia and galactorrhea associated with using the SNRI venlafaxine and with the SSRIs sertraline, fluvoxamine, fluoxetine, escitalopram, and paroxetine (Reeves et al. 2016, Wattegama and Siyambalapitiya 2017, Coker and Taylor 2010). It is believed that the raised prolactin levels during antidepressant use are asymptomatic in comparison to antipsychotic therapy(Spina and Leon 2014, Coker and Taylor 2010).

Duloxetine belongs in the SNRI type antidepressants which not only increase serotonin and noradrenaline levels in the brain but also specifically raise the dopamine levels in the prefrontal cortex (Stahl 2015). Although the mechanism of increasing prolactin levels by raised serotonin levels has not yet been completely explained, it hs been considered that serotonin stimulated GABAergic neurons may be modulating the release of prolactin (Coker and Taylor 2010). Antidepressants are suggested to cause galactorrhea via two mechanisms including the blockade of tuberoinfundibular dopaminergic neurons as the first mechanism and the direct stimulation of the postsynaptic serotonergic receptors in the hypothalamus as the second one (Voicu et al. 2013, Belli et al. 2013, Korkmaz et al. 2011).

In our patient, prolactin levels were tested and cranial MRI was performed to investigate the complaints of amenorrhea and lactation in the 5th month after duloxetine treatment was started in the second episode of depression. The high prolactin level was normalised after starting cabergoline treatment and discontinuing duloxetine treatment. In the literature, there are a limited number of case reports on the emergence of hyperprolactinemia during duloxetine treatment with results resembling those reported here (Luo et al. 2019, Belli et al. 2013, Korkmaz et al. 2011, Ashton and Longdon 2007).

In conclusion, asymptomatic hyperprolactinemia may develop during antidepressant treatment. However, serum prolactin levels are not routinely tested in clinical practice unless clinical symptoms such as galactorrhea and amenorrhea occur. Therefore, potential aetiological factors should be investigated in patients presenting with amenorrhea and galactorrhea by determining the prolactin level and by cranial MRI. For treatment, it may be considered to use 0.5mg cabergoline tablets twice per week and to discontinue the ongoing antidepressant therapy or switch to another antidepressant agent.

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