

Hyperprolactinemia and bleeding following use of sertraline but not use of citalopram and paroxetine: a case report

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Summary

Aim. The authors present the first reported case of simultaneous hyperprolactinemia, loss of menstruation, painful breast enlargement and genital tract bleeding in female following use of sertraline and shortly review these side effects.

Case report. A 36-year old female with moderate depressive symptoms had poor effect and no side effects while treated with paroxetine. After change to sertraline satisfactory reduction of symptoms was observed, however the treatment was followed by severe hormonal side effects and bleeding. After next drug – citalopram – the ailments ceased and the symptom reduction remained stable.

Results. The case report suggests significant differences in efficacy and tolerability between the SSRIs. In the case described treatment with paroxetine and citalopram was well tolerated while only citalopram was effective. Sertraline treatment in this case was followed by serious side effects.

Conclusion. We observed serious hormonal and hemorrhagic side effects during sertraline treatment. The case report provides support for essential differences in efficacy and safety between SSRIs and also reminds rare risks accompanying using drugs with serotonergic and dopaminergic properties.

hyperprolactinemia / bleeding / sertraline / citalopram / paroxetine

INTRODUCTION

Hyperprolactinemia as the side effect of selective serotonin reuptake inhibitors (SSRIs)

The increase of prolactin levels during SS-RI treatment is fairly rare, the literature on this topic includes several case studies [1, 2, 3, 4, 5]. Moreover, usually in most patients with increased prolactin (PRL) levels recorded concentrations slightly exceed the reference values. The mechanism of these changes is not entire-

ly clear. An increasing level of serotonin which stimulates the pituitary cells to produce PRL by increasing concentrations of oxytocin and/or vasoactive intestinal peptide (VIP) putatively plays the principal role [6, 7]. The role of dopamine concentration changes (by inhibiting the production and release of PRL) is probably less important in this mechanism. It is particularly important in the case of sertraline, which, as it is generally known, affects dopaminergic transmission more than other SSRI and interestingly is described as most frequent cause of hyperprolactinemia [8] or rarely the safest option [9].

Hemorrhagic complications during use of antidepressants with SSRIs

The risk of bleeding (petechiae, purpura, epistaxis, gastrointestinal, genital and urinary tract haemorrhagias, intra- and postoperative complications) is increased approximately 2.5-

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fold during SSRIs treatment. In addition, simultaneous treatment with serotonergic antidepressants and NSAIDs (non-steroid anti-inflammatory drugs) increases the risk up to 6-fold [10, 11, 12]. Drugs which taken in combination with SSRIs may increase risk of bleeding include steroids, cytostatics, second-generation antipsychotics and valproic acid [13]. The risk of bleeding is also increased in patients with liver failure [14].

Serotonin has a crucial role in the clotting process since it is necessary in the actin polymerization, leading to the change of platelet shape and the increase of its aggregation potential [15]. Serotonin is not produced by the platelets but actively transported from the extracellular space. Inhibition of the serotonin transporter by SSRIs leads to changes of the serotonin penetration into the platelets and thus impairment of aggregation.

As mentioned, both complications are relatively rare, their coexistence has not been described in the available literature yet.

CASE REPORT

A 36-year old woman, without any chronic somatic disease and previous central nervous system dysfunction (eg. epilepsy, Parkinson disease) and alcohol or substance abuse, previously psychiatrically not treated, without any concomitant antidopaminergic or serotonergic treatment was admitted as an outpatient with depressive symptoms. Depressed mood, anxiety, tearfulness and lack of energy occurred along with the difficulties at work. Severity of symptoms was assessed on 25 points in Hamilton Depression Rating Scale (HDRS, 21-item version). Apart from the recommended psychological intervention treatment with paroxetine at a dose of 20 mg/day was started because the symptoms significantly impaired normal performance. After 6 weeks of the treatment due to the lack of significant improvement (in the absence of serious side effects) we decided to discontinue paroxetine and started sertraline treatment, reaching 50 mg/day after a few days. After the first 3 weeks mental state improved and no significant side effects occurred. Over successive weeks progressive improvement in mood, drive, reduction of anxiety and inner tension were observed.

After 6 weeks of therapy severity of depressive symptoms was 9 points in HDRS scale and the improvement of mood was assessed as good by the patient. After about 8 weeks of treatment with sertraline the patient noted breast enlargement. Over the next 10 days swelling reached extreme severity, however galactorrhea was not observed. During this period there was also loss of menstruation (absence of menstrual bleeding in two consecutive cycles). However, 6-day long profuse uterine bleeding occurred beyond the expected date of the menstruation. The consulting gynecologist ordered hormonal testing (Tab. 1), linking the symptoms with the antide-

Table 1. Results of laboratory tests. Sertraline treatment period, after the occurrence of side effects:

PRL-prolactin, TSH-stimulating hormone, fT₃-fraction of free triiodothyronine, fT₄-free thyroxine fraction, INR-international normalized ratio. Shorter prothrombin time, pregnancy was excluded

Parameter	Value	Standard Values
PRL	26.8	1.9-25.0 [ng/mL]
TSH	0.32	0.4-4.0 [μIU/mL]
fT ₃	3.21	1.2-4.1 [ng/L]
fT ₄	12	8-20 [ng/L]
INR	1.0	0.8-1.2
Prothrombin index	100	90-120 [%]
Prothrombin time	11.9	13-17 [s]
Pregnancy test (β-hCG)	Negative	+/-

pressant treatment. Because of these symptoms and laboratory-confirmed hyperprolactinemia (of slight degree), change of the treatment was necessary. Shortly after discontinuation of sertraline the symptoms disappeared - there was no bleeding between periods, breast swelling reduced within one week, the pain disappeared, menstruation returned normal. After a two-week period without antidepressant a small dose of the third SSRI, with potentially the most favorable safety profile and good efficacy - citalopram (at a initial dose of 10, then 20 mg/day) was administered. After a few follow-up visits the patient's mental state improved and the intensity of depressive symptoms was assessed on 8 scores using HDRS. Consecutive prolactin level (Tab. 2) showed no abnormalities. During observation period patient have no other medication than SSRI. Blood cell count was stable and normal.

The patient continued the medication (GP) and psychotherapy.

Table 2. Results of laboratory tests. Citalopram treatment period, six weeks after discontinuation of sertraline: PRL-prolactin, anti-TPO-antiperoxidase antibodies, Anti-TG-antithyroglobulin antibodies. Autoimmune thyroiditis was initially excluded.

Parameter	Value	Standard Values
PRL	21.1	1.9-25.0 [ng/mL]
Anty-TPO	<10	<35 [IU/mL]
Anty-TG	<20	<40 [IU/mL]

DISCUSSION

SSRIs are commonly used; therefore patients who develop side effects (also severe) represent a potentially large group. Loss of menstruation, painful breast enlargement and bleeding observed in a patient must be considered as severe symptoms, requiring change in the antidepressive treatment. Pregnancy test was necessary for obvious reasons in such a situation. Among other causes of increased PRL levels, besides influence of sertraline, subclinical hyperthyroidism (normal thyroid hormone levels with a decreased level of TSH) should be considered. Hypothalamic TRH (thyroid releasing hormone) and serotonin promote production and release of PRL [16, 17], therefore, reduced levels of TSH may also indirectly show changes (elevation) in TRH release. Both issues were not crucial in this case - before sertraline treatment and after paroxetine and citalopram medication no clinical symptoms associated with hyperprolactinemia occurred, but possibly both factors: sertraline with serotonergic and dopaminergic properties and also decreased levels of TSH were of importance here [18, 19].

Interestingly, the efficacy of potentially similar drugs from one group – SSRI – was different (paroxetine < citalopram = sertraline), also safety profile was different – paroxetine and citalopram safer than sertraline – what is not consistent with the observations of Trenque et al. [9]. The case is possibly important in the context of the recommendations: according to meta-analysis by Cipriani, sertraline was reported as an effective drug (4th place among the evaluated antidepressants) and well tolerated (second place) [20], having favorable reputation

among clinicians. It can, therefore, be assumed that the population of patients treated with this substance will be growing, even at the expense of other antidepressants. Other drugs used in the patient, particularly paroxetine, are characterized by slightly poorer tolerance and clinical efficacy.

However, citalopram treatment in this case combined efficacy and safety; hence the results of its use should be considered the best. According to recent recommendations, in the absence of treatment effect or poor tolerability drug from another group should be used. Our experience indicates that we can use the essential differences between substances within one pharmacological group.

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