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Case Report Open Access

Risperidone Induced Amenorrhea Resolved by Paliperidone

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Introduction

While amenorrhea can be caused by a various reasons, hormonal disbalance and hyperprolactinemia, in particular, are frequent causes. Hyperprolactinemia is often seen among schizophrenic patients due to a D2 receptor blockade caused by antipsychotics [1].

Risperidone is an atypical antipsychotic that has more pronounced serotonin antagonism compared to dopamine antagonism. However, risperidone has a high affinity for D2 receptor [2]. Due to its blockade in the tubero-infundibular system, risperidone can produce a rise in prolactin. Data suggests that compared to other atypical antipsychotic drugs, risperidone may cause more frequent increases in prolactine levels [3]. Interestingly, studies have shown that rates of hyperprolactinaemia are, in fact, also higher with risperidone than with FGA (50-100% compared to 40-90%) [4]. Finally, the relationship between doses of risperidone and prolactin levels has been demonstrated [5].

Paliperidone Extended Release (ER), a new oral atypical antipsychotic (R076477, Invega; Johnson & Johnson Pharmaceuticals, L.L.C., Titusville, NJ), is an atypical antipsychotic that belongs to the chemical class of benzisoxazole derivatives. It is the major and active metabolite of risperidone (9-hydroxyrisperidone) [6]. Paliperidone is a centrally active dopamine D2 and serotonergic 5-HT2A antagonist, as demonstrated in both in vitro and in vivo animal and human studies [7,8]. Since paliperidone is an active metabolite of risperidone, it would be reasonable to assume that paliperidone would have a similar side effect profile as risperidone since both raise prolactin levels [8].

This report describes an adult woman treated by risperidone which induced amenorrhea. The amenorrhoea was then successfully subsided after the introduction of paliperidone.

Case Report

The patient is a 31-year-old Caucasian female, single, without children, who was diagnosed with schizophrenia at the age of 22. The illness has had severe course, significantly affecting her ability to function independently. Despite the fact that she was treated by various antipsychotics in adequate dose and duration (i.e. haloperidol, flufenazine, chlorpromazine), her mental status had not improved. Moreover, the patient had shown low tolerance for olanzapine and clozapine induced somnolence and sedation. She was, therefore, switched to oral risperidone, with the dose titrated up to 8 mg per day, to which she responded (PANNS score decreased from 93 to 74). Her communication was better and her florid psychotic symptoms markedly decreased. Nevertheless, she still experienced significant delusional beliefs, conceptual disorganization, and remained socially withdrawn. Three months after she had been treated with risperidone, the patient developed amenorrhea. Before this patient had regular menstrual cycle (every 26 to 28 days). Patient had menarche when she was 13 years old. Due to amenorrhea, an ultrasound gynecological examination was performed, with normal findings; as well as an endocrinological evaluation, which revealed an elevated serum prolactin level (2730 uIU/mL). A brain CT scan also demonstrated normal findings, thereby excluding all known causes of amenorrhea (ie., prolactinomas, hypothalamic disease, hypothyroidism and renal insufficiency). Consequently, the diagnosis of risperidone induced amenorrhea was made. This was followed by an attempt to address amenorrhea with bromocriptine 5 mg per day, but without significant clinical effects (i.e. hyperprolactinemia was still significantly above the normal range- 2080 uIU/mL), and she still experienced amenorrhea one month after the treatment.

Due to the patient's good response to risperidone, she was switched to paliperidone ER 12 mg/day. One month later, her prolactin level decreased to 1390 uIU/mL, but amenorrhea was still present. Two months later, the amenorrhea subsided completely and a normal menstrual cycle was established. When the patients prolactin level fell to 830 uIU/mL, her bromocriptine treatment was stopped. While her prolactin level continued to decrease further, reaching the level of 690 uIU/mL, her menstrual cycle remained normal (normal values 102-496 uIU/mL). Moreover, a significant positive response to paliperidone ER treatment was noted and her psychotic symptoms subsided completely (PANNS score futher decreased to 42). The patient started to engage more with her family members, having meals with them as opposite to withdrawing to her room during meal times. In the following months, the patient began to work and started some friendships. Today, almost three years later, the patient is still on paliperidone ER 12 mg/day. She regularly attends the outpatient psychiatric follow up appointments, has a job, and now has a relationship. As a result her psychotic symptoms are in complete remission.

Discussion

Medications are the most frequent cause of nontumoral hyperprolactinemia, with antipsychotics as the most common cause. Hyperprolactinemia is known to be caused by both typical and atypical antipsychotics. It is believed that antipsychotics block endogenous dopamine receptors in the hypothalamic tubero-infundibular system and on the lactotrophs, in turn causing prolactin secretion to increase [9].

Treatment with conventional antipsychotics in patients with schizophrenia has been shown to increase serum prolactin concentrations 5-10 times above that of healthy control subjects [5]. Some cross-sectional studies in the USA and UK have estimated hyperprolactinaemia prevalence rates of up to 42% in men and 75% in

women with schizophrenia who were receiving conventional antipsychotics [10,11].

In contrast to classical antipsychotics, atypical antipsychotics are known to cause less hyperprolactinemia [12]. There are several hypotheses to explain this: regional limbic selectivity, preferential binding to D3 and D4 receptors, peculiar binding dynamics at the D2 receptors or differences in affinity to D2 receptors, combined antagonism of dopamine and serotonin receptors [13]. However, risperidone and paliperidone are the second generation antipsychotics which cause marked elevation in serum prolactin levels [10].

Paliperidone ER elevates prolactin levels in a fashion similar to risperidone. In clinical trials with paliperidone the median increase in serum prolactin was observed in 67% of subjects, although symptomatic hyperprolactinaemia (including amenorrhea) was low. In the acute trials, potential prolactin related adverse events were reported in 1%-2% of subjects receiving paliperidone ER (3-12 mg/day) [14-16].

There is evidence that prolactin elevation is more closely related to paliperidone concentration, rather than with risperidone concentration [14-17]. Conversely, other authors have not demonstrated a correlation between serum prolactin levels and plasma concentrations of risperidone, 9-OH risperidone, or the active moiety, following oral administration of risperidone [18]. However, in contrast to risperidone, paliperidone is available in an oral extended-release formulation, using a patented technology called osmotic controlled-release oral delivery system [19]. It is thought that by reducing the variation in plasma concentrations, which are seen with immediate-release oral therapies in general, the risk of adverse effects may be reduced. Sheehan et al have shown that paliperidone exibit the lowest (1.47 paliperidone extended-release, once daily) and risperidone the highest (3.30 active-moiety risperidone, once daily) variation in the steady-state, peak-to-trough, plasma-concentration ratio [20].

In agreement with this is the finding that variations in peak plasma concentrations of serum prolactin are lower in patients treated with paliperidone ER as compared to those treated with risperidone (for paliperidone ER fluctuation index was 38%, compared with 125% for risperidone IR) [21]. Moreover, there is evidence that paliperidone binds to D2 receptors less tightly, suggesting that paliperidone might cause fewer extrapyramidal and prolactine-related side effects [22].

However, Skopek et al described paliperidone induced hyperprolactinemia in four female patients. The levels were significantly raised above the normal upper limit of 500 mIU/L, ranging between 1500 and 3996 mIU/L, and returned to within the normal range after cessation of the medication (82–381 mIU/L) [23].

While many patients tolerate an increased level of prolactine with no symptoms at all, hyperprolactinemia can cause menstrual abnormalities, decreased libido, breast engorgement, galactorrhea, and sexual dysfunction in women24. There are also reports of an increased risk of bone loss in women with antipsychotic-induced hyperprolactinemia. In men, the most common symptoms of hyperprolactinemia are loss of interest in sex, erectile dysfunction, infertility, and gynecomastia. Osteoporosis has also been associated with chronic elevation of prolactin levels [24].

Management of iatrogenic hyperprolactinemia includes discontinuation of the medication. With drug-induced hyperprolactinemia it usually takes 3 days for levels to return to normal after drug discontinuation [25]. If the drug cannot be discontinued, it should be replaced with another that acts in a similar manner but does not cause hyperprolactinemia (i.e. prolactin sparing antipsychotics like quetiapine, aripiprazole or clozapine). In the case that this is infeasible, cautious administration of a dopamine agonist (i.e bromocriptine, cabergoline, quinagolide and amantadine) is recommended [26]. Special attention in a case of dopamine agonists needs to be paid because they can aggravated acute psychotic episodes.

Treatment of patients with asymptomatic medication-induced hyperprolactinemia is not recommended. Interestingly, aripiprazole is considered to be a prolactin-sparing agent due to its partial D2 receptor agonist activity, and therefore suppression of prolactin release [27]. In a randomized controlled trial, aripiprazole had a lower rate of prolactin elevation compared with placebo [28]. Aripiprazole's ability to reduce an elevated prolactin level caused by other antipsychotics has been demonstrated in several studies with haloperidol, olanzapine, and risperidone [29-32]. Moreover, aripiprazole has been used to decrease the prolactin level in patients with paliperidone induced hyperprolactinemia [33]. The prolactin-sparing effect of aripiprazole may be explained by aripiprazoles partial agonism at D2 receptors, in contrast to the D2 antagonism of other second-generation agents and specially first generation antipsychotics. Aripiprazole has been shown to act as an agonist in pituitary cells at the molecular level and thus, lactotroph cells do not become blocked by aripiprazole treatment [34].

After carefull consideration, we concluded not to stop risperidone in the patient because it was the only medication to which she showed significant improvement in psychotic symptoms. Moreover, because aripiprazole is not registered in Serbia, it could not be used in her treatment, and therefore dopamine agonist - bromocriptine was included, as it is recommended. However, as there was no significant decline in her prolactine level, we switched risperidone to paliperidone in the hope that the therapeutic efficacy of risperidone could be kept, and subsequently, that a decline in the prolactine level could be achieved.

One important issue of the current case is in regards to doses of paliperidone and risperidone. Although Arakawa et al. [35] indicate that the equivalent ratio of a daily dose between risperidone and paliperidone ER appears to be about 1:2, there are also different equivalent ratios [36,37] which correspond to doses mentioned in our case. While exact equivalent doses between risperidone and paliperidone are unknown, this indicates that the dose of paliperidone in our case may not have been adjusted according to dose equivalents (i.e. 12mg of paliperidone ER may be slightly lower then 8mg of risperidone daily). Further, because we could not detect serum concentrations of risperidone (risperidone + 9-OH-risperidone) and paliperidone (9-OH-risperidone), the exact concentration of active moiety after the switch to paliperidone could not be determined, and the relationship with drug dosage remains unclear.

Hence, the finding of a better profile of side effects to paliperidone compared with risperidone has been confirmed with the metabolic profile of these drugs. Based on United States Product Inserts one can calculate that the potential of risperidone to induce significant weight gain (incidence of ≥ 7% increase in body weight in short-term trials) is 18% while for paliperidone is 7.9%. It is tempting to consider similar results considering other side effects i.e. hyperprolactinemia.

Finally, as the threshold of hyperprolactinemia is estimated at about 73% of striatal dopamine D2 receptor occupancy various attempts to avoid these thresholds in development of new antipsychotics have been made. Of special importance is partial agonism at D2 receptor

that is associated with a prolactine-sparing properties. The most obvious examples include brexipiprazole and cariprazine.

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Conflict of Interest

All authors declare that there are no conflicts of interest.

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