

Galactorrhea Probably Related with Switching from Osmotic-release Oral System Methylphenidate (MPH) to Modified-release MPH: An Adolescent Case

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Galactorrhea, as an adverse effect of psychotropic medications, usually develops due to high dose of antipsychotics. Selective serotonin reuptake inhibitors (SSRIs) have also been reported to be related to galactorrhea. To the best of our knowledge, no previous study reported galactorrhea with methylphenidate (MPH) use. Hereby, we report a case of an adolescent girl who developed galactorrhea after increasing his modified-release oral MPH to 50 mg/day while under treatment of sertraline and very low dose haloperidol.

KEY WORDS: Galactorrhea; Methylphenidate; Selective serotonin reuptake inhibitors; Adolescent.

INTRODUCTION

Endocrine adverse effects are very rare with methylphenidate (MPH) use. In the literature, only three case reports are available which reported gynecomastia in subjects who were treated with MPH for attention-deficit/hyperactivity disorder (ADHD).¹⁻³⁾ Galactorrhea, as an adverse effects of psychotropic medications, usually develops due to high dose of antipsychotics. Selective serotonin reuptake inhibitors (SSRIs) have also been reported to be related to galactorrhea.⁴⁾ To the best of our knowledge, no previous study reported galactorrhea with MPH use. Hereby, we report a case of a adolescent girl who developed galactorrhea after increasing his modified-release oral MPH from 40 to 50 mg/day while under treatment of sertraline and very low dose haloperidol.

CASE

A 15-year-old girl was diagnosed with adjustment disorder with depressive symptoms and trichotillomania. Family reported that the presenting symptoms have emerged after a perantial relationship problem. Her psy-

chiatric history revealed that she had been diagnosed with ADHD combined type when she was 9 years old and she was on osmotic-release oral system (OROS) MPH 54 mg/day for 2 years. She had a Children's Depression Inventory (CDI) total score of 24 at admission. Her body weight was 62 kg. To target the depressive and trichotillomania symptoms, sertraline was firstly initiated in the dose of 50 mg/day, and was gradually increased to 100 mg/day. Depressive symptoms greatly resolved however, trichotillomania was largely unchanged. As an addition to the sertraline treatment, risperidone 1mg/day was initiated. After 2 weeks, since risperidone induced increased appetite, risperidone was switched to haloperidol in the dose of 0.5 mg/day (5 drops). Haloperidol was used nightly since trichotillomania was evident only in the night time. During these treatments, OROS MPH treatment was kept unchanged. After 8 weeks of sertraline and haloperidol treatment, trichotillomania symptoms also greatly reduced. At the 12-week-follow-up, family reported that the patient had significant inattentiveness symptoms at school, especially in the early hours. OROS MPH was firstly increased to 72 mg/day; however, the patient could not tolerate this dose due to severe head ache. Thereafter, OROS MPH was switched to MPH-modified release, beginning with the dose of 30 mg/day. Patient tolerated the initial doses well and, in 2 weeks, MPH dose was planned to increase to 50 mg/day. Three days after MPH was increased to 50 mg/day, family communicated that the patient had spontaneous flow of milk from both of

Received: April 1, 2016 / **Revised:** May 6, 2016

Accepted: June 6, 2016

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her breasts. For the evaluation of galactorrhea, the patient was consulted to obstetrics and pediatric endocrinology clinics. Her physical examination and laboratory workup including liver, thyroid, and renal function tests; electrolytes; blood cell count; testosterone; estrogen; luteinizing hormone; follicle-stimulating hormone; and cortisol levels were all within normal range, while her prolactin level was found as 67.7 ng/ml (normal value, 6-29.9 ng/ml). No medical or surgical condition was detected to explain the galactorrhea. The evaluation of the Naranjo adverse drug reaction (ADR) probability scale was 7 (which indicates a probable ADR). Due to the suspect of an ADR, modified-release MPH and haloperidole was discontinued while continuing sertraline in the dose of 50 mg/day. One week later, galactorrhea symptoms resolved completely. Fifteen days after discontinuation, prolactin level of the patient was found as 19.4 ng/ml.

DISCUSSION

In the present case, all of the three psychotropic agents may be related with development of galactorrhea, while haloperidol is a widely known cause of medication-induced galactorrhea.⁵⁾ Haloperidol, which is a potent dopamine receptor antagonist, may be considered a potential candidate to cause hyperprolactinemic galactorrhea. However, the 3-month use of very low dose haloperidol may unlikely cause hyperprolactinemia symptoms in an adolescent. The concomitant use of sertraline may also be related with the adverse reaction. SSRIs have been previously linked with normoprolactinemic and hyperprolactinemic galactorrhea.^{4,6)} Galactorrhea has been reported to develop either acutely or months after the initiation of SSRIs.⁴⁾ In the available literature, three adult case reports exist for sertraline-induced galactorrhea.^{4,7,8)} It has been suggested that the inhibition of dopaminergic neurotransmission by SSRIs can be related to adverse effects such as hyperprolactinemia.⁹⁾ There is also evidence from animal studies that sertraline may increase extracellular dopamine levels in the nucleus accumbens and striatum.¹⁰⁾

It should be noted that our case developed galactorrhea shortly after the switching from OROS MPH to modified-release MPH. Therefore, this switching might have increased the vulnerability of the patient to extrapyramidal symptoms. The exact pathophysiological mechanisms through which the switching of MPH can cause galactorrhea are unknown. Although not previously shown, the differential effects of OROS MPH and modified-release

MPH on dopaminergic activation may be a candidate mechanism. Equivalent daily doses modified-release MPH and OROS MPH have been shown to result in different levels of action throughout the day. Modified-release MPH may be considered to have almost twice as higher dopaminergic activity than OROS MPH (50% vs. 22%) in the first hours of treatment.¹¹⁾ In our case, the high dose of modified-release MPH, especially in a more strict duration, may have resulted in an overdopaminergic state. One explanation may be that the higher dopaminergic concentration with modified-release MPH may have led to a higher degree of dopaminergic blockade by haloperidol. In an earlier case report, it has been postulated that the dopamine-blocking actions of typical antipsychotics may necessitate the use of larger quantities of stimulants.¹²⁾ In the present case, the higher availability of dopamine by modified-release MPH may have potentiated the dopaminergic blockade of haloperidol and, in turn, may have resulted in galactorrhea.

Galactorrhea can be related with numerous drugs including antidepressants, antipsychotics, anxiolytics, antihypertensives, antihistamines, antiepileptics and hormones.¹³⁾ In the comprehensive review by Peña and Rosenfeld,¹³⁾ amphetamines have also been mentioned among the medications that cause galactorrhea. Since amphetamines are a class of potent dopamine and noradrenaline reuptake blockers,¹⁴⁾ it can be postulated that monoamine reuptake blockade may be a rare mechanism of medication-induced galactorrhea. In line with this assumption, serotonin norepinephrine reuptake inhibitor (SNRI) group antidepressants have been reported to cause galactorrhea.¹⁵⁾ Although MPH's main mechanism of action is the inhibition of dopamine reuptake, it also has an affinity on noradrenaline transporter.¹⁶⁾ To the best of our knowledge, the present report is the first to link MPH use with galactorrhea.

Serotonin may have an important role in regulating human prolactin.¹³⁾ In the present case, serotonergic activation may also be responsible for the development of galactorrhea. The effects of MPH on serotonin system is largely unknown. However, some animal studies have shown that MPH may act on serotonergic receptors and increase serotonin levels.^{17,18)} In the present case, the serotonergic activity of sertraline may be potentiated by high dose MPH and galactorrhea may have developed through this mechanism.

In the present case, before the resolution of galactorrhea, the patient was discontinued from both MPH and haloperidol. Therefore, it is difficult to arrive a clear conclusion about the real cause of galactorrhea. Clinicians

should be aware of rare adverse effects when using polypharmacy in children and adolescents, especially when antipsychotics are present in the medication regimen. Given the high risk of extrapyramidal adverse effects in youth, extra caution must be given when changing the medication regimens. The possible drug–interactions and receptor regulations may be related with rare adverse reactions including galactorrhea. Concomitant use of medications that are reported to be associated with galactorrhea may increase the likelihood of this adverse reaction.

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