Priapism associated with methylphenidate: a case report

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Priapism is a persistent unwanted erection that is not associated with sexual desire or sexual stimulation. Immediate diagnosis and treatment are essential for priapism; otherwise, it causes ischemia of cavernous tissues, which will result in erectile dysfunction. In this paper, we report a 14-year-old male patient who presented with priapism after administration of immediate-release methylphenidate. When the usage of immediate-release methylphenidate was terminated, priapism spontaneously disappeared. To our knowledge, this is the first report in the literature of priapism associated with immediate-release methylphenidate use. This issue is significant because in the case of immediate-release methylphenidate prescription to adolescent male patients, the probability of the development of priapism should not be ignored.

Key words: priapism, immediate-release methylphenidate.

Priapism is a persistent painful erection of the penis unassociated with sexual stimulation or desire. It was named after Priapus, a mythical hero. Priapus, known as the god of fertility, was the son of Aphrodite and Dionysus. Because of his large erectile penis, he was used as the symbol of masculinity and power in mythical figures[1]. It is, however, a misnomer because impotence occurs in almost 50% of patients with priapism who require medical or surgical intervention for relief[2].

Priapism can be seen in many medical conditions or as a side effect of some drugs in all age groups. In children and adolescents, the most common cause of priapism is sickle-cell anemia and malignancy. Because priapism can cause permanent and irreversible erectile dysfunction, it is a serious medical condition[3-6]. Many drugs are known to cause priapism. It was reported that priapism may develop with the usage of anticoagulants, antihypertensives, antidepressants, antipsychotics, or intracavernous medicines or substances like cocaine[3-5].

The mechanism of priapism has been attributed to alpha-1-receptor blockade. Traditional alpha-1-receptor blockers such as prazosin have been known to cause priapism. Trazodone is the psychotropic medication most commonly associated with priapism, with an incidence of 1:6,000; however, patients taking either conventional or atypical antipsychotics may experience priapism[7].

According to our search in the current medical literature, there has been no report of priapism associated with immediate-release methylphenidate usage alone. To our knowledge, there are only six published cases of adolescents who developed priapism while taking psychotropic medications. Risperidone-paroxetine, risperidone-lithium, olanzapine-methylphenidate, risperidone, oxcarbazepine-aripiprazole-lithium and sustained-release methylphenidate have been implicated before as the cause of priapism in adolescents[2,8-11].

In this case report, a 14-year-old male who developed priapism after using methylphenidate is discussed.

Case Report

We report a 14-year-old male patient with a diagnosis of attention deficit hyperactivity disorder (ADHD) who presented with symptoms of intermittent priapism on methylphenidate

treatment. Methylphenidate was started as 10 mg/day initially, and after two months, the daily dose was escalated to 20 mg/day because of unsatisfactory clinical response. There was no drug holiday. Three days following dose escalation, the patient suffered from intermittent erections unassociated with sexual stimulation, lasting 40 to 45 minutes. There were approximately 3-4 erection episodes during a day, usually in the daytime, with a one-hour interval between each event. Although the episodes were not painful, the boy was very embarrassed and tried to remain quiet. The mother became aware of the erections after two months, thought that they may be associated with methylphenidate, and reported the problem to her son's psychiatrist. An extended check-up was done, and it was determined that the boy was not taking any illicit drug or any medical agent other than methylphenidate, and no medical condition that could be associated with priapism, such as hemoglobinopathies, sickle cell anemia or chronic myelocytic leukemia, was found. After the detailed medical examination, it was thought that the erection episodes could be associated with methylphenidate treatment and thus the drug was stopped. Three days later, the symptoms of priapism had disappeared. After the cessation of methylphenidate treatment, ADHD symptoms reappeared. Since it was considered that the priapism was a result of withdrawal of immediate-release methylphenidate with a half-life of 2-3 hours, sustained-release methylphenidate, which has a longer half-life, was started at a dosage of 36 mg/day. During the follow-up, ADHD symptoms were ameliorated, and no recurrence of priapism was reported.

Discussion

Priapism is an emergency condition that requires immediate attention as it can lead to long-term devastating consequences such as impotence, urinary retention and gangrene. Even with treatment, 40–50% of patients can become impotent due to ischemia and fibrosis of the corpus cavernosa[12,13]. Penile erection is a result of neural and vascular factors. An increased sacral parasympathetic tone that leads to an increased blood flow into the arterioles and sinusoids is found. The veins are compressed at this time. The detumescence occurs when the process is reversed with sympathetic stimulation. Priapism results from alpha-1-adrenergic blockade in the corpora cavernosa leading to a parasympathetic-mediated arteriodilation as well as inhibition of the sympathetic system that leads to detumescence. This leads to an intracavernosal stasis owing to inadequate venous outflow caused by the obstruction of subtunical venules, resulting in hypoxia, acidosis and pain. Alpha-2-blockade exacerbates the alpha-1-mediated priapism by stimulating the release of a nitric oxide-like substance, which is a potent muscle relaxant. The nitric oxide-like substance is released from the neurons innervating the afferent arterioles and corpora cavernosa and this stimulates erections[8].

The cause of priapism can be primary, secondary or idiopathic. Priapism with primary etiology is not accompanied by a disorder responsible for a prolonged erection, e.g. of physical or psychological origin[14]. Secondary priapism is induced by factors directly or indirectly affecting the penile erection, such as hematologic, traumatic, surgical, neoplastic, neurologic, infective, toxic, allergic, and pharmacologic problems[15]. Two kinds of priapism exist -- high-flow and low-flow. The high-flow priapism leads to the retention of well-oxygenated blood in the corpora. The etiology of arterial high-flow priapism remains unclear, although pharmacological, traumatic and neurological diseases have been proposed[16,17]. This is painless and does not cause ischemia, as opposed to the low-flow or veno-occlusive variety that results in hypoxia and tissue ischemia. If the blockage continues, it will lead to irreversible changes and permanent damage[8]. It is thought that the priapism caused by the immediate-release methylphenidate usage is the high-flow variety, since in the presented case the priapism was painless and did not cause ischemia.

The therapeutic effects of methylphenidate are believed to be elicited primarily through inhibition of the presynaptic dopamine transporter, with a lesser effect on the norepinephrine transporter[18]. The immediate-release formulation of oral methylphenidate is rapidly and almost completely absorbed. Maximum plasma concentration occurs in 1 to 3 hours, with substantial intersubject

variation. Immediate-release methylphenidate is a short-acting stimulant, with a duration of action of 1 to 4 hours and a pharmacokinetic half-life of 2 to 3 hours[19]. The immediate-release methylphenidate is rapidly distributed and has low protein binding. These properties, combined with a high lipid solubility, result in rapid uptake of the immediate-release methylphenidate into the central nervous system. The immediate-release methylphenidate provides relief from ADHD symptoms for almost 4 hours; thus, multiple daily dosing is necessary to maintain improvements throughout the day[20].

Schwartz and Rushton[2] published a case report of an adolescent that had stuttering priapism associated with withdrawal from sustained-release methylphenidate. It was stated that priapism was observed on the drug holiday day after he used sustained-release methylphenidate for 6 days. However, in our case, priapism was associated with immediate-release formulation of oral methylphenidate, and developed while he was using the drug. This may be associated with the half-life of these drugs. The half-life of the immediate-release formulation of oral methylphenidate is 2-3 hours, which is shorter than the sustained-release methylphenidate[19]. As a result, the priapism occurred every day when the immediate-release formulation of oral methylphenidate was taken. The priapism with sustained-release methylphenidate occurred the day after the administration. Thus, priapism might be an adverse effect and a result of withdrawal of methylphenidate. Although it was the same active substance, the occurrence of priapism after immediate-release methylphenidate but not after sustained-release methylphenidate might be a result supporting this explanation.

Common adverse effects of methylphenidate have been reported as insomnia, decreased appetite, body weight loss, abdominal pain, headache, irritability, anxiety, and tendency to cry. Increases in heart rate and systolic and diastolic blood pressure have been reported, which may be dose-related[21].

Priapism may occur at any time during the course of treatment with psychotropic drugs and may occur without any change of dose. Priapism could be considered an idiosyncratic reaction because it is correlated neither with the dosage of a psychotropic drug nor with the duration of its use[8]. The mechanism of priapism associated with the immediate-release formulation of oral methylphenidate is not understood, but may be associated with its influence on multiple neurotransmitters. However, the effects of immediate-release methylphenidate on adrenergic regulation of cavernosal tissue and the potential role of sympathetic dysregulation in the development of priapism have not been studied.

It is unclear, but psychopharmacologic agents may affect the sexual life of humans in three steps, in either positive or negative directions. Dopaminergic agents show their effects especially in the first and second steps. In the first step, the libido is raised by amphetamine and methylphenidate, which cause dopamine discharge. It is also known that sexual stimulation, which is the second step, may be triggered by some dopaminergic agents[22]. The priapism observed in this case as a side effect of immediate-release methylphenidate may have been due to the psychostimulant effects of the drug on sexual functions.

Priapism, secondary to the use/abuse of vasodilators, is often encountered in the clinic. However, the use of sympathomimetics is not often associated with priapism[23]. Intracavernosal administration of sympathomimetics is becoming a mainstay in the management of priapism. Interestingly, the use of certain drugs that facilitate, potentiate or mimic the action of sympathetic nerves has been associated with priapism[23]. Several reports have associated priapism with the use of cocaine.[24-28] In addition, two cases of priapism occurred following the use of unprescribed weight-loss formulations containing high concentrations of ephedrine[23]. Because of its inhibitory effect on presynaptic norepinephrine reuptake, cocaine potentiates and prolongs the vasoconstrictor action of sympathetic nerves. Ephedrine is a nonspecific adrenergic receptor agonist and also stimulates the release of norepinephrine[23]. Methylphenidate is a sympathomimetic and psychostimulant drug and inhibits the presynaptic reuptake of catecolamines[29]. It shows its central effect through dopamine rather than norepinephrine[30]. However, vascular effects of the drug occur via the noradrenergic pathway through the sympathic

system[31]. Because vascular smooth muscle relaxation is necessary for penile tumescence, these mechanisms are in apparent contradiction to the association of sympathomimetics like methylphenidate, cocaine and ephedrine with priapism. Prolonged use or the withdrawal of immediate-release methylphenidate may produce local depletion of norepinephrine in adrenergic nerves caused by an increased exposure to catabolic enzymes at the presynaptic cleft. This may lead to impairment of the penile detumescence mechanism, which may result in the development of priapism.

In conclusion, the immediate-release methylphenidate, a commonly used anti-ADHD drug, may cause prolonged pathological erections. Priapism is often preceded by the onset of recurrent, prolonged and painless erections that are not associated with sexual activity. The lack of inquiry and reporting of this side effect can lead to potentially irreversible impotence. Thus, it is important that the clinician be aware of this side effect and counsel the children/adolescents and their families about its occurrence in order to improve the adaptation of methylphenidate treatment. Education of the patient and family about the risk of developing priapism would help increase the awareness of the side effect, promote early reporting and help reduce the long-term consequences like impotence and gangrene.

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