

1.1. Methylphenidate and priapism

Introduction

Methylphenidate (Ritalin®) is indicated as part of a comprehensive treatment programme for *Attention Deficit Hyperactivity Disorder (ADHD) in children from the age of six years and older when remedial measures alone are insufficient*. Furthermore it is indicated for the treatment of *narcolepsy*.

Methylphenidate is an indirect centrally acting sympathomimetic and has a stimulating effect on the central nervous system. The pharmacological properties resemble those of amphetamines. It is a racemic mixture consisting of d-methylphenidate and l-methylphenidate in the ratio 1: 1, where it is assumed that the L-enantiomer is pharmacologically inactive.

Methylphenidate was granted marketing authorization in the Netherlands in 1982 [1].

Priapism is defined as persistence of an erection of the penis or clitoris independent of sexual arousal. It is generally defined as the erection lasting for at least four hours, but studies differ as to the duration defining priapism. It is a rare disorder with different causes. In children the most common cause is sickle cell disease. In adults the most common cause is medication use, especially intracavernosal injections. Other causes include thalassemia, multiple myeloma, thrombocytopenic purpura, metastatic cancer, malaria and several metabolic disorders like gout and amyloidosis, or cases may be idiopathic. Priapism can be ischaemic (veno-occlusive, low flow) which occurs most frequently, or nonischaemic (arterial, high flow) which is usually the result of a fistula e.g. due to trauma. Ischaemic priapism is an urgent medical condition and requires prompt evaluation. Rapid detumescence is needed to avoid long-term sequelae like erectile dysfunction [2].

Reports

From 18 August 2014 until 16 February 2016 the Netherlands Pharmacovigilance Centre Lareb received two reports concerning priapism associated with the use of methylphenidate. Lareb received no reports of priapism in association with dexamphetamine.

Case A (report number 180245)

This non-serious spontaneous report from a specialist doctor (paediatrician) concerns a male aged 8-10 years, with priapism following administration of methylphenidate tablet 15 mg, 2 tablets twice daily, for attention deficit disorder (ADD) with a latency of 1 year after start. The drug methylphenidate was withdrawn 1 year after the occurrence of the priapism. The outcome is unknown. Concomitant medication was not reported.

The medical history indicates attention deficit disorder. The patient used methylphenidate in the past without experiencing priapism.

Case B (report number 208045)

This non-serious spontaneous report from a specialist doctor (paediatrician) concerns a male aged 11-20 years, with genital swelling and priapism for hours following administration of methylphenidate Concerta® prolonged-release tablets for attention deficit / hyperactivity disorder with an unknown latency after a dose increase from 36 to 54 mg. Afterwards the patient had a lot of local pain. The dose for methylphenidate is not changed. The symptoms recurred (less severe) upon readministration of this dose. The patient is recovering. Information on treatment is not specified, Concomitant medication was not reported.

The past drug therapy indicates that the patient had similar symptoms following a previous dose increase from 18 to 36 mg of methylphenidate. Follow-up information confirmed the patient did not have sickle cell disease.

Other sources of information

SmPC

The Dutch SmPC of methylphenidate does not mention priapism as an adverse drug reaction [1]. The US SmPC of methylphenidate Ritalin® contains the following text under "warning": "Priapism. Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products in both pediatric and adult patients. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or during

discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.” [3].

The US SmPC of methylphenidate Concerta® contains a similar text [4].

Literature

In 2013 the FDA published a safety announcement warning for the risk of long-lasting erections in males taking methylphenidate, as a result of 15 case reports. Of the 14 cases in which an age was reported the range was 8 to 33 years, median 12.5 years. 12 cases concerned patients under the age of 18 years. The announcement reports that in a few patients, priapism occurred after an increase in the dosage of methylphenidate, but that priapism has also occurred under other conditions, such as during short periods of time when the drug was stopped temporarily, when there was a longer than typical time between doses, or after stopping the drug permanently. In some of these patients, priapism resolved after the drug was restarted. The announcement reports that it is possible that priapism may be more likely to occur with the use of immediate-release methylphenidate, which has a shorter half-life [5].

In the literature a case was reported concerning a prepubertal 12-year old male patient who experienced prolonged unwanted painful erections after start of a response-adjusted dosing regimen of sustained release methylphenidate [6].

Furthermore a case was reported concerning a 14-year old male with priapism after administration of immediate-release methylphenidate. After withdrawal of the drug, priapism spontaneously disappeared [7].

Another article in Czech describes, based on the English abstract, a 14-year old boy with priapism after olanzapine and methylphenidate. After conservative treatment detumescence appeared [8].

Finally, one case of stuttering priapism, that is intermittent, prolonged, painful, pathologic erections with intervening periods of detumescence, was reported in a 15-year old male patient after withdrawal from sustained-release methylphenidate [9].

Databases

Table 1. Reports of priapism associated with methylphenidate, in the Lareb [10], WHO [11] and Eudravigilance database [12]. For the Lareb database no reliable ROR can be calculated because of the small number of reports.

Database	MedDRA PT	Number of reports	ROR (95% CI)
Lareb	Priapism	2	
WHO	Priapism	30*	3.0 (2.1-4.3)
Eudravigilance	Priapism	26	4.8 (3.2-7.0)

* Of the 30 reports in the WHO database, 24 reports concerned patients under the age of 18 years.

Prescription data

Table 2. Number of patients using methylphenidate in the Netherlands between 2009 and 2013 [13].

Drug	2010	2011	2012	2013	2014
Methylphenidate	140,660	157,310	170,460	180,310	189,990

Mechanism

The mechanism might be a dopamin mediated process, methylphenidate causing release of dopamin from presynaptic vesicles in dopamergic nerves, while dopamine agonists are believed to mediate penile erection [6,15,16].

A less likely mechanism might be through alpha-1 or 2 blockade. It had been hypothesized that priapism is associated with blockade of alpha 1 receptors in the corpora cavernosa, leading to a parasympathetic-mediated arteriodilatation and inhibition of the sympathetic system that leads to detumescence. Alpha-2-blockade exacerbates the alpha-1-mediated priapism by stimulating the release of nitric oxide-like substance, a potent muscle relaxant [7,14]. This does not match with the centrally acting sympathomimetic methylphenidate though.

Discussion and conclusion

The complete database with all the reports on all drugs received by the Netherlands Pharmacovigilance Centre Lareb only contains 5 reports of priapism in patients under the age of 18. Two of these reports concern the two reports of priapism associated with the use of methylphenidate. The other 3 reports concern sertraline, pipamperon and testosterondecanoaat Andriol®, wherein in all of these drugs priapism is a listed adverse drug reaction [17-19].

In the reports of priapism and methylphenidate, one of the reports the latency of one year after start of methylphenidate was reported, without further details. In the other report priapism occurred at dose increase from 36 to 54 mg. After the second administration the same reaction occurred, but less severe. This patient had also experienced priapism in the past after dose increase from 18 to 36 mg. This patient experience a lot of local pain, suggesting ischaemic priapism [2]. Both cases concerned children, of 8 and 14 years old, and both concerned male patients. Lareb did not receive cases concerning female patients. In the cases received by Lareb other possible causes of the priapism are very unlikely, because of the young age of the patients which makes involvement of other causes like gout or multiple myeloma unlikely. Furthermore the reporters being both specialist doctors (paediatricians), mentioned that there were no other possible causes for the reaction, which makes causes like for instance sickle cell disease very unlikely. In the WHO database there are 30 cases present of priapism associated with methylphenidate, of which 24 reports concern patients under the age of 18 years. In both the WHO and Eudravigilance databases the association is disproportionately present. The ROR in the Lareb database can't be reliably calculated because of the small number of reports.

Because of the two cases in children received by Lareb, the high ROR in the WHO and Eudravigilance database, and the supporting literature including the FDA safety announcement concerning the subject, it is suggested that methylphenidate might have a causative role in the occurrence of priapism. It could be considered to mention priapism as an adverse drug reaction, and to formulate warnings and actions to be taken concerning priapism in the section "Special warnings and precautions for use".

- Priapism should be mentioned in the SmPC of methylphenidate

References

1. Dutch SmPC Ritalin® 10 tabletten. (version date: 27-10-2014, access date: 16-2-2016) <http://db.cbg-meb.nl/IB-teksten/h03957.pdf>.
2. UpToDate. Priapism. (version date: 2016, access date: 16-2-2016) http://www.uptodate.com/contents/priapism?source=search_result&search=priapism&selectedTitle=1%7E57.
3. FDA label Ritalin®. (version date: 2015, access date: 16-2-2016) [http://www.accessdata.fda.gov/spl/data/44555803-7377-4acd-a3f7-1d65d8660b2d.xml](http://www.accessdata.fda.gov/spl/data/44555803-7377-4acd-a3f7-1d65d8660b2d/44555803-7377-4acd-a3f7-1d65d8660b2d.xml).
4. FDA label Concerta®. (version date: 2015, access date: 16-2-2016) <http://www.accessdata.fda.gov/spl/data/3ce4251f-a23b-41cd-9227-5d6da4db7c5d/3ce4251f-a23b-41cd-9227-5d6da4db7c5d.xml>.
5. FDA Drug Safety Communication: FDA warns of rare risk of long-lasting erections in males taking methylphenidate ADHD medications and has approved label changes. (version date: 17-12-2013, access date: 17-2-2016) <http://www.fda.gov/Drugs/DrugSafety/ucm375796.htm#>.
6. Kelly BD, Landon DJ, McGuinness D, Brady CM. Methylphenidate-induced erections in a prepubertal child. J Pediatr Urol. 2016;213 Feb(9(1)):e1-2.
7. Cakin-Memik N, Yildiz O, Sismanlar SG, Agaoglu B. Priapism associated with methylphenidate: a case report. Turk J Pediatr. 2010;Jul-Aug; 52(4):430-4.
8. Husar M, Zerhau P. [Priapism in childhood--case report of 14-year-old boy]. [Article in Czech]. Rozhl Chir. 2006;Jul;85(7):329-30.
9. Schwartz RH, Rushton HG. Stuttering priapism associated with withdrawal from sustained-release methylphenidate. J Pediatr. 2004;May; 144(5):675-6.
10. Lareb database. (version date: 2016, access date: 17-2-2016) <http://www.lareb.nl/Bijwerkingen/Zoek-op-geneesmiddel>.
11. WHO Global Individual Case Safety Reports database (Vigibase). (version date: 2016, access date: 17-2-2016) <https://tools.who-umc.org/webroot/> (access restricted).
12. Eudravigilance database. (version date: 2016, access date: 17-2-2016) <http://bi.eudra.org> (access restricted).
13. College for Health Insurances. GIP database. (version date: 2016, access date: 17-2-2016) <http://www.gipdatabank.nl/>.

14. Sood S, James W, Bailon MJ. Priapism associated with atypical antipsychotic medication: a review. Int Clin Psychopharmacol. 2008;Jan;23(1):9-17.
15. Viggiano D, Vallone D, Sadile A. Dysfunctions in dopamine systems and ADHD: evidence from animal modeling. Neural Plast. 2004;11(1-2):97-114.
16. Mulhall JP, Bukofzer S, Edmonds AL, George M. An open-label, uncontrolled dose-optimization study of sublingual apomorphine in erectile dysfunction. Clin Ther. 2001;Aug;23(8):1260-71.
17. Dutch SmPC Zolof® 25/50/100 mg tablets. (version date: 19-11-2014, access date: 2-3-2016) <http://db.cbg-meb.nl/IB-teksten/h16292.pdf>.
18. Dutch SmPC dipiperon 40 mg tabletten, 40 mg/ml druppels. (version date: 8-2-2016, access date: 2-3-2016) <http://db.cbg-meb.nl/IB-teksten/h00183.pdf>.
19. Dutch SmPC Andriol® 40 mg capsules. (version date: 28-8-2015, access date: 2-3-2016) <http://db.cbg-meb.nl/IB-teksten/h07531.pdf>.

This signal has been raised on June 2016. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl