1.1. Methylphenidate and erectile dysfunction

Introduction

Methylphenidate is a mild central nervous system stimulant which is indicated *as part of a comprehensive treatment programme for Attention Deficit Hyperactivity Disorder (ADHD) in children six years of age and over when remedial measures alone prove insufficient*. It may also be prescribed for off-label use in obesity, other psychiatric disorders or as psychostimulant in adults. The pharmacological mechanism of therapeutic action in ADHD is not known. Methylphenidate is thought to block the reuptake of noradrenaline and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space [1,2]. In 1982, the drug was approved in the Netherlands under the brand name Ritalin® [2].
Erectile dysfunction is the inability to sustain an erection satisfactory for sexual intercourse. This could be the result of vascular, neurologic, psychologic, hormonal disorders and certain drugs [3]. The SmPCs of different methylphenidate products do mention libido disorder as rare adverse drug reaction, but do not mention erectile dysfunction [1,2].
The reports received by the Netherlands Pharmacovigilance Centre Lareb concerning erectile dysfunction associated with the use of methylphenidate will be discussed.

Reports

On April 7th, 2010, the database of the Netherlands Pharmacovigilance Centre Lareb contained five reports of erectile dysfunction associated with the use of methylphenidate (Table 1).

Table 1. Reports of erectile dysfunction associated with the use of methylphenidate

Patient, Number, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 98118 M, 31	methylphenidate (Ritalin®) 15-20 mg/day attention deficit-hyperactivity disorder		erectile dysfunction	not reported no change recovered a couple of hours after every drug administration
B 80726 M, 17	methylphenidate (Concerta®) 18 mg/day attention deficit-hyperactivity disorder		erectile disturbance	couple of hours discontinued recovered
C 63527= 63721 M, 14	methylphenidate (Ritalin®) 10-15 mg/day attention deficit-hyperactivity disorder		impotence	30 minutes dose reduction recovered a couple of hours after every drug administration
D 41940 M, 51	methylphenidate (generic) 40 mg/day attention deficit/hyperactivity disorder moclobemide depressive episode	melatonin l-tryptophan	erection decreased	one week no change unknown

Patient, Number, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
E 91254 M, 34	methylphenidate (generic) 200 mg/day attention deficit-hyperactivity disorder		erectile disturbance	not reported no change not recovered

A dose-dependent relationship was reported in two patients (A and C). Patient C reported erectile dysfunction which started 30 minutes after administration of each dose (Ritalin®) and recovered again after a couple of hours. Psychological causes were excluded for this patient according to the reporters (the parents of the patient and the treating psychiatrist). The complaints aggravated when the dose was increased from 10 to 15 mg per day. Patient A also suffered from erectile dysfunction after each dose (Ritalin®) and also recovered after a couple of hours. This time period corresponds with the pharmacokinetic profile of Ritalin®; the preparation used by patients A and C, the maximum plasma concentration is achieved after one to two hours and the elimination half life is two hours [2].
A positive de- and rechallenge was reported in patient B. One patient (D) was not recovered at time of reporting. He also used an antidepressant which has been associated with impotence before [4] and has a medical history of alcoholism. Patient E has a medical history of alcoholism and cocaine addiction. The methylphenidate dose in this patient, 200 mg per day, was more than three times the maximum recommended dose, 60 mg per day, in the SmPC [1,2].

Other sources of information

SmPC

The Dutch SmPCs of methylphenidate do not mention erectile dysfunction as a possible adverse drug reaction [1,2].

Literature

The literature on the possible sexual effects of methylphenidate is inconclusive. The USA SmPC of Concerta® mentions erectile dysfunction as an adverse drug reaction seen during clinical trials with an incidence of less than 1% [5]. In contrast, a recent case report describes two cases of hypersexual behaviour with increased erections during methylphenidate treatment [6]. Methylphenidate has also been suggested for the treatment of SSRI-induced sexual dysfunction [7]. Priapism has been associated with the use [8] and with the withdrawal of methylphenidate [9]. As far as we are aware, no case reports concerning a possible association between methylphenidate and erectile dysfunction have been published. However, erectile dysfunction has been described for amphetamine users [10]. This compound is structurally related to methylphenidate.

Databases

On April 7, 2010, a case non-case comparison showed that reports of methylphenidate and erectile dysfunction were disproportionally present in the database of Lareb. The reporting odds ratio (ROR) is 4.2 (95%CI 1.7-10.1). To correct for the large number of methylphenidate reports in the database among children under the age of thirteen, the ROR was calculated excluding this age group.

The database of the World Health Organization (WHO) contained 22 reports of erectile dysfunction in association with methylphenidate. The ROR is not statistically disproportional: 0.92 (95%CI 0.6-1.4).

On April 12, the Eudravigilance database contained eight reports of erectile dysfunction associated with methylphenidate use. Reactions occurred in patients ranging in age from fifteen to 52 years. All cases were considered serious. In one case erectile dysfunction was reported together with a wide range of other adverse events, such as suicide attempt, tiredness, rash, anxiety, nightmares and addiction, which led to hospital admission. Besides methylphenidate the following drugs were also considered as suspect drugs in this patient: methixene, chlorprothixene and carbamazepine. In the remaining cases no specific reason for seriousness was indicated. In one case drug overdose was mentioned; in another case, erectile dysfunction occurred secondary to priapism.

Prescription data

The increasing number of patients using methylphenidate in the Netherlands is shown in table 2.

Table 2. Number of methylphenidate users between 2004 and 2008 [11].

Drug	2004	2005	2006	2007	2008
Methylphenidate	55,120	60,980	75,601	85,918	103,730

Mechanism

Penile erection is the result of a complex interaction of psychological, neural, vascular and endocrine factors [3]. Erection is mediated by cholinergic parasympathetic pathways, and nonadrenergic, noncholinergic pathways, which release nitric oxide. Endothelial cells also release nitric oxide, which causes vasodilatation of vascular smooth muscle cells. This enhances blood flow into the erectile chambers. As blood flow accelerates, the pressure within the chambers increases and chokes off venous outflow. The combination of increased intracavernosal blood flow and decreased venous outflow causes and maintains an erection [3,12].
Erectile dysfunction can have a vascular, neurologic, psychologic or hormonal of origin and can also be caused by certain drugs [3].
Methylphenidate is a mild central nervous system stimulant. It is thought to block the reuptake of noradrenaline and dopamine into the presynaptic neurone and increase the release of these monoamines into the extraneuronal space [1,2]. The increased noradrenaline concentration causes an increase in sympathetic nervous system effects, like an increased heart rate, blood pressure and also detumescence [12,13]. Stimulation of the postsynaptic α_1- and α_2-receptors by noradrenaline causes vasoconstriction of vascular smooth muscle cells. This vasoconstriction could lead to insufficient intracavernosal blood flow to achieve and maintain an erection [12]. It can be expected that this is a dose-dependent relationship.

Discussion

The five reported cases to the Netherlands Pharmacovigilance Centre Lareb suggest methylphenidate can induce erectile dysfunction. A plausible pharmacological mechanism that could explain this phenomenon is the indirect increased stimulation of the alpha-receptors in the penile vascular smooth muscle cells caused by methylphenidate, which inhibits adequate blood flow into the erectile chambers. This also explains the observed dose-dependent relationship in patients A and C. As erectile dysfunction has multiple possible causes, confounding in the reported cases cannot be excluded. Especially in patient D and E, the influence of age, concomitant medication and alcohol and/or drug misuse could also have caused or attributed to the sexual dysfunction.
No cases reported in literature support this association. However, erectile dysfunction has previously been described for amphetamines [10].
The association is statistically disproportional in the Lareb database, but not in the database of the WHO.

Conclusion

This report describes a possible new signal of erectile dysfunction associated with the use of methylphenidate. It should be considered to mention erectile dysfunction as a possible adverse drug reaction in the SmPC of methylphenidate containing products.

- It should be considered to mention erectile dysfunction the SmPC of methylphenidate containing products.

References

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This signal has been raised on September 2010. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).