

Methylphenidate, dexamphetamine and trismus

Introduction

Methylphenidate (Ritalin[®], Concerta[®], Equasym[®], Medikinet[®]) 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* [1-3]. It may also be prescribed for *narcolepsia*. In 1982, the drug was approved in the Netherlands under the brand name Ritalin[®] [1]. In 2011 more than 157,000 people used methylphenidate [17].

Dexamphetamine is used since the 1960's for the indications ADHD and narcolepsy. The drug is not officially registered by the Medicines Evaluation Board (MEB) in the Netherlands [4].

Methylphenidate and dexamphetamine are thought to block the reuptake of noradrenaline and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space [1,5].

Dystonia is defined as a syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures [6]. Trismus is a jaw-closing dystonia, a movement disorder consisting of dystonic contracture of jaw muscles, hampering the ability of the patient to open his/her mouth [7].

The current observation describes the association between trismus and the use of methylphenidate and dexamphetamine.

Reports

On July 24, 2012 the database of the Netherlands Pharmacovigilance Centre Lareb contained seven cases of jaw cramp/trismus associated with the use of methylphenidate. In addition to the cases about methylphenidate, Lareb also received two reports about trismus associated with the use of dexamphetamine.

Table 1. Reports of trismus associated with the use of methylphenidate

Patient, Sex, Age, Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 48844 M, 11-20 years physician NOS	methylphenidate 10mg 2dd		trismus, dizziness, blood pressure increased	1 week discontinued unknown
B 56752 M, 51-60 years pharmacist	methylphenidate 20 mg 2dd		teeth grinding, jaw spasm	not reported unknown unknown
C 86541 M, 31-40 years specialist doctor	methylphenidate 15mg 4dd attention deficit- hyperactivity disorder		jaw cramp	week no change not recovered
D 106332 F, 41-50 years pharmacist	methylphenidate (slow release) 18mg 1dd, fluvoxamine	simvastatin	trismus	10 months unknown not yet recovered

Patient, Sex, Age, Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
E 109632 F, 21-30 years physician	methylphenidate 20 mg 2dd attention deficit-hyperactivity disorder	ethinylestradiole/ levonorgestrel	trismus	2 days no change not yet recovered
F 122730 F, 31-40 years specialist doctor	methylphenidate 15mg 4dd attention deficit-hyperactivity disorder		trismus, extrapyramidal symptoms	30 minutes discontinued recovered positive rechallenge
G 130175 M, 21-30 years consumer	methylphenidate (slow release) 54mg attention deficit-hyperactivity disorder		jaw cramp, involuntary movement oral	4 months discontinued not recovered

Table 2. Reports of trismus associated with the use of dexamphetamine

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
AA 108867 M, 21-30 years physician	dexamphetamine attention deficit-hyperactivity disorder		trismus	34 days no change not yet recovered
BB 134541 F, 51-60 years consumer	dexamphetamine 5mg attention deficit disorder		trismus, pain tongue, taste loss, mouth dry	4 weeks discontinued not recovered

Some additional information about the cases is described below.

The reporting specialist doctor in case C saw another patient in addition to this case with trismus who was using methylphenidate 10 mg daily. The patient in case C recognized the jaw cramp from a friend, who had been using amphetamines as a recreational drug and suffered from similar complaints.

Patient D suffered from trismus following administration of methylphenidate with a latency of 10 months. Fluvoxamine was also used at this time. Extrapyramidal symptoms are described in the Dutch SmPc of fluvoxamine, although trismus isn't mentioned specifically [8]. Fluvoxamine was withdrawn and the patient did not recover from the trismus. Methylphenidate was not withdrawn at that time. It is unclear if methylphenidate was withdrawn at the time of reporting. The patient is recovering.

Patient E also suffered from trismus during an earlier use of methylphenidate. This time, she suffered from trismus 2 days after start of methylphenidate. The dose for methylphenidate is not changed. The patient is recovering.

Patient F suffered from extrapyramidal symptoms that consisted of involuntary movement of the tongue where the tongue is pushed against the teeth and palate and trismus. A positive rechallenge was reported. The patient recovered after withdrawal of methylphenidate. She is now treated with methylphenidate slow release and the complaints are less severe.

Patient G suffered from jaw cramp and oral involuntary movements that consisted of chewing on the inside of the cheeks.

Other sources of information

SmPC

The SmPCs of different methylphenidate products do not mention trismus or other forms of dystonia as a possible adverse drug reaction [1-3].

Muscle tension and muscle spasms are described as possible ADRs as well as dyskinesia and choreoathetotic movements [1-3].

Since dexamphetamine is not officially registered in the Netherlands, there is no SmPC. In the US SmPC trismus or dystonia are not mentioned. The SmPC does mention dyskinesia [5].

Literature

In the literature, no reports of trismus associated with the use of methylphenidate were found. However, other forms of dystonia are described in the literature for this drug.

Methylphenidate-induced dystonia is described in a 11-year-old boy, who was receiving aripiprazole monotherapy for bipolar disorder and attention-deficit hyperactivity disorder, and who had OROS methylphenidate extended-release tablets (18 mg once daily) added to his regimen to control his inattentiveness. He presented with acute dystonic symptoms after receiving his first dose of methylphenidate; physical examination showed rigidity in his extremities, torticollis and dysarthria. Methylphenidate was withdrawn and his dystonic symptoms resolved over two days [9].

Waugh [10] describes a case of dystonia consisting of transient torticollis and repetitive tongue thrusting and jaw opening in a previously-healthy toddler following accidental exposure to methylphenidate. His symptoms improved following a single dose of diphenhydramine, worsened again after several hours, and resolved completely when placed on a standing regimen of diphenhydramine. He had no pre-existing movement disorders, no recognized CNS injury, and was developmentally normal. His symptoms fully resolved within 24 hours, and he has remained normal for the subsequent seven months.

Husain *et al.* [11] describe a case study of a 2-yr-old hyperkinetic boy in whom the emergence of dystonia and dyskinesia was noted when the simultaneous use of methylphenidate and a phenothiazine was followed by withdrawal of the phenothiazine. It is postulated that the use of phenothiazine resulted in a postsynaptic supersensitivity that precipitated dystonia and dyskinesia when phenothiazine was withdrawn and methylphenidate reinstated.

Willemsen & van der Wal [12] describe the case of a seven-year-old boy who presented with a right-side mandibular luxation resulting from an acute unilateral dystonia of the masticatory muscles. In view of the rarity of jaw dislocation in someone so young it was assumed that it could have been caused by a dystonia possibly resulting from the patient's medication, which consisted of 1 mg risperidone daily for one year and 10 mg methylphenidate daily for two years for ADHD. Both drugs were withdrawn, the patient was treated with oxazepam and recovered. Methylphenidate was restarted however and the luxation has not recurred.

Anecdotal case reports of acute dystonia, including trismus, have been reported during the use of amphetamine or substances in the amphetamine-class like phenylpropanolamine [13-16].

Databases

On July 18, 2012, the database of the Netherlands Pharmacovigilance Centre Lareb contained 7 reports concerning trismus with the use of methylphenidate. The association was disproportionately present in the database with a Reporting Odds Ratio (ROR) of 17.2 (95% CI: 7.9-37.5).

Lareb received 2 reports of trismus associated with the use of dexamphetamine. Due to the limited number of reports, a reliable ROR could not be calculated for this drug.

The WHO database of the Uppsala Monitoring Centre contained 19 reports of trismus associated with methylphenidate and 9 for Lisdexamphetamine (a prodrug of dexamphetamine). The association was disproportionately present in the WHO database for both drugs.

Table 3. Reports of trismus associated with methylphenidate and dexamphetamine in the Lareb and WHO database.

Database	Drug	Number of reports	ROR (95% CI)
Lareb	Methylphenidate	7	17.2 (7.9- 37.5)
	Dexamphetamine	2	-
WHO	Methylphenidate	19	4.8 (3.1- 7.6)
	Lisdexamphetamine	9	10.5 (5.5-20.3)

On August 8 2012, the Eudravigilance database contained twelve reports of trismus in association with methylphenidate and one in association with dexamphetamine. It concerned five females and eight males and the median age was 24 years (range 7 – 55 years. Seven reports were classified as serious, and the criteria for seriousness were “hospitalization”, and “other”. The reporting odds ratio (ROR) was 3.5 (95% CI: 2.0-6.2). In addition, there was one report of trismus associated with the use of dexamphetamine. The combined ROR for methylphenidate and dexamphetamine (n=13) was 3.7 (95% CI: 2.1-6.4).

Prescription data

The number of patients using methylphenidate in the Netherlands is shown in table 4.

Table 4. Number of patients using methylphenidate in the Netherlands between 2007 and 2011 [17].

Drug	2007	2008	2009	2010	2011
Methylphenidate	86,976	99,383	117,760	140,660	157,970
Dexamphetamine	788	1,708	2,760	4,297	5,799

Mechanism

The exact mechanism through which methylphenidate and dexamphetamine cause trismus remains unknown. Acute dystonic reactions are a long-recognized complication of medications that alter dopamine signalling. The great majority of these reactions occur following exposure to agents that block dopamine receptors (e.g., antipsychotics, anti-emetics) [6]. In addition serotonin-induced stimulation of dopaminergic pathways has also been a suggested mechanism for movement disorders, such as dystonia and tardive dyskinesias. SSRI's and bupropion may induce dystonia in this manner [18].

According to Waugh [10], agents that increase dopaminergic tone (including stimulants such as methylphenidate) can also trigger acute movement disorders, although acute movement disorders have been reported mostly in patients also taking dopamine receptor blockers [19].

Class-effects

This observation describes trismus as a class-effect for the central nervous system stimulants methylphenidate and dexamphetamine. Lareb did not receive any reports of trismus for modafinil, another amphetamine-related drug available on the Dutch market.

Discussion and conclusion

Lareb received seven cases of jaw cramp/trismus associated with the use of methylphenidate. In one case a positive de- and rechallenge was reported. In addition to the cases about methylphenidate, Lareb also received two reports of trismus associated with the use of dexamphetamine. The reported latencies in the cases vary from days to months. Dyskinesias associated with methylphenidate treatment for attention-deficit/hyperactivity disorder (ADHD) were described as arising several weeks after starting stimulant treatment, and developing as acute symptoms within hours of methylphenidate administration [19]. Possibly similar latencies could be seen for dystonia induced by methylphenidate.

Patient B also suffered from teeth grinding (bruxism) in addition to the trismus. Bruxism may be an unusual manifestation of dyskinesia and is described in the literature for methylphenidate [20] and amphetamine [21].

The association between trismus and methylphenidate is supported by a disproportional number of reports in the Lareb database as well the WHO- and the Eudravigilance database. For (lis)dexamphetamine, the association is also disproportionately present in the WHO database.

Some cases of dystonia and dyskinesia induced by methylphenidate in the literature describe the concomitant use of antipsychotics [9,12]. Alterations in dopamine receptor sensitivity could play a role when a combination of a psychostimulant and dopamine-receptor blocker is used [19]. In the cases reported to Lareb no antipsychotics were reported as concomitant medication.

This observation describes a signal of trismus associated with the use of methylphenidate and dexamphetamine. Further investigation of the information of the marketing authorization holders is advisable.

- New signal of trismus associated with the use of methylphenidate and dexamphetamine
- Further investigation of the information of the marketing authorization holders is advisable

References

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This signal has been raised on November 2012. 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).