Methylphenidate and epistaxis

Introduction

Methylphenidate (Ritalin®, Concerta®, Equasym®, Medikinet®) is a sympathicomimetic acting drug. It is indicated *for 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® [1-3]. In 2011 more than 157,000 people used methylphenidate [4].
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].

Epistaxis, or nose bleed, is estimated to occur in 60% of persons during their lifetime with a higher incidence during the winter months. The prevalence is increased for children less than 10 years of age, is lower for adolescents and young adults and then rises again after the age of 35 years. Nose bleeds are more common in older patients; a mean age of 64 is mentioned [5]. Among hospitalized patient with nose bleeds, male patient are more presented in the age of 20 - 49 years. From the age of 50, no sex differences were found [6]. Approximately 6% of the patients with nosebleeds seek medical treatment. More than 90% of episodes of epistaxis occur along the anterior nasal septum, at a site called Kiesselbach's area [5].

In the SmPC of methylphenidate epistaxis is not described [1-3]. This report describes epistaxis associated with the use of methylphenidate.

Reports

On August 8 2012, the database of the Netherlands Pharmacovigilance Centre Lareb contained seven reports of epistaxis associated with the use of methylphenidate. The reports are listed in table 1.

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

Patient, Sex, Age, Reporter	Drug, dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 30221 M, 11-20 years general practitioner	methylphenidate 15mg 1dd attention deficit/hyperactivity disorder		epistaxis	not reported no change recovering
B 76957 F, 31-40 years consumer	methylphenidate 36mg 1dd attention deficit-hyperactivity disorder	cyproterone/ ethinylestradiol	epistaxis, haematoma	1 month no change recovered
C 82584 M, 8-10 years pharmacist	methylphenidate 5mg 2dd concentration impaired		epistaxis	6 months discontinued recovered
D 102962 F, 8-10 years pharmacist	methylphenidate 10mg 1dd fluoxetine risperidon	melatonin	loss of eyelashes, growth retardation, epistaxis	not reported dose decreased unknown

Patient, Sex, Age, Reporter	Drug, dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
E 107429 M, 5-7 years pharmacist	methylphenidate 30mg 1dd attention deficit-hyperactivity disorder		epistaxis, eructation	3 days discontinued recovered
F 120423 M, 11-20 years pharmacist	methylphenidate 18mg 1dd ADHD	citalopram	fainting, facial rash, bleeding nose	6 hours discontinued recovered
G 136968 M, 8-10 years pharmacist	methylphenidate 7.5mg 2dd;2.5mg 1dd ADHD		epistaxis	17 month no change recovered

In the seven reports of epistaxis in association with methylphenidate that Lareb received, positive dechallenges were reported in three cases and in one case (patient C) a positive rechallenge was reported. Some of the characteristics of the reports are described below.

Patient A
Bleeding time, clotting time and thrombocytes were reported as normal, and no allergy or aspecific hyperreactivity was mentioned.
Patient B
The dose of methylphenidate was increased from 18 to 36 mg and
the patient reported normal coagulation factors and leukocyte count by means of a blood test. Although the latency was reported as one month, the complaints occurred approximately ten days after increasing the dose to 36 mg per day.
Patient C
the dose of methylphenidate was increased from 10 to 15 mg. A positive de- and re- challenge was reported: after decrease of the dose to 10 mg the patient recovered, and when 15mg was used for a second period, the patient experienced epistaxis again. Although the latency was reported as six months, the complaints occurred days to weeks after increasing the dose to 15 mg per day.
Patient F
The patient had used methylphenidate previously and used to experience nosebleeds previously as well. It was not mentioned whether these events were considered to be related to the use of methylphenidate.
Patient G
The patient experienced nosebleeds previously, approximately 5-6 months after starting methylphenidate. One month after dose increase they reappeared. According to the reporter, the patient's sister also experienced epistaxis approximately 6 months after starting methylphenidate.

Other sources of information

SPC

Epistaxis is not mentioned in the SmPC's of methylphenidate containing products [1-3].

Literature

In some widely used Dutch guidelines epistaxis in association with methylphenidate is mentioned. However these sources are not referring to original case reports or studies [7]. Rare cases of thrombocytopenia and/or easy

bruisability, epistaxis, and gingival bleeding are reported in association with the use of methylphenidate [8,9]. Also, leukopenia; anemia; and eosinophilia have been reported in patients receiving methylphenidate, and several haematological adverse drug reactions are described in the SmPC of methylphenidate [1-3]. It is described that inhaled methylphenidate can be very harmful to tissues, and can lead to epistaxis [10].

Databases

On June 6th 2012 the database of the Netherlands Pharmacovigilance Centre Lareb contained seven reports of epistaxis associated with the use of methylphenidate, which was reported disproportionally (ROR = 2.16, 95% CI 1.02 – 4.57).
On June 6th 2012, the WHO database of the Uppsala Monitoring Centre contained 61 reports of epistaxis associated with the use of methylphenidate and this was reported disproportionally (ROR = 1.33, 95% CI 1.04 – 1.71).

Table 2. Reports of epistaxis with methylphenidate in the databases of the Netherlands Pharmacovigilance Centre Lareb and the WHO.

Drug	Number of reports	ROR (95% CI)
Methylphenidate	Lareb: 7 WHO: 61	2.2 (1.0 – 4.6) 1.3 (1.0 – 1.7)

On June 6th 2012, the Eudravigilance database contained 36 reports of epistaxis in association with methylphenidate, which was not reported disproportionally (ROR = 1.3, 95% CI: 0.9 – 1.8). It should be noted that it is not possible to stratify data in the Eudravigilance database and the results of the disproportionality analysis could be influenced by the presence of older patients using oral anticoagulants in the comparator group. It concerned seven females and twenty-eight males and the median age was 12.5 years (range 6 – 37 years). In two cases, age was not reported and in one case, sex was not reported. A total of 29 reports were classified as serious. The criteria for seriousness were mainly “hospitalisation” and “other”.

Prescription data

The number of patients using methylphenidate in the Netherlands is shown in table 3 [4].

Table 3. Number of patients using methylphenidate in the Netherlands between 2007 and 2011 [4].

Drug	2007	2008	2009	2010	2011
Methylphenidate	86,976	99,383	117,760	140,660	157,970

Mechanism

Several factors may contribute to epistaxis. Dehumidification of the nasal mucosa probably underlies the increased incidence of nosebleeds noted during the winter months [11]. In one of our reports (report B) this could be a confounding factor. Also coagulopathies should be considered as underlying factor [11]. For patient A and B, laboratory tests showed no abnormalities. Methylphenidate administration is associated with a significantly increased heart rate, systolic and diastolic blood pressures [12]. Also digital trauma (nose picking), dry mucosa, rhinosinusitis, septal perforations, and neoplasms can lead to epistaxis [8]. Moreover, young age can be a confounding factor as epistaxis is a common paediatric complaint [13]. Hypertension may contribute to epistaxis, but this theory is controversial [11].

Methylphenidate activates the alfa-2-adrenoceptor, which can lead to contraction of smooth muscles [14,15].

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received seven reports of epistaxis associated with the use of methylphenidate. Latencies were not very consistent and varied between several hours and six months. In three cases a positive dechallenge was reported and in one of them a positive rechallenge. Since the majority of the patients were children, and the incidence of epistaxis in this group is increased compared to the general population, age should be considered as a possible confounder.
The association between methylphenidate and epistaxis is statistically supported by the database of the Netherlands Pharmacovigilance Centre Lareb and the WHO.
The described association is a new signal of epistaxis with the use of methylphenidate.

- 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).