1. Dexamphetamine and Raynaud's phenomenon

Introduction

Dexamphetamine is indicated as part of an extensive treatment program for *attention deficit/hyperactivity Disorder (ADHD) in children and adolescents from 6 until 17 years,* after methylphenidate appeared to have insufficient effect.
Dexamphetamine belongs to the group of amphetamines and is a sympathomimetic amine with a stimulatory effect on the central nervous system stimulants, and with anorectic activity [1].
Dexamphetamine was granted market authorization in the Netherlands in 2014, but has been used off-label before 2014 [2].

Lisdexamphetamine is a prodrug of dexamphetamine. Similarly to dexamphetamine, lisdexamphetamine increases dopamine and noradrenalin release in the CNS, causing psychostimulant effects [1]. This drug is registered in the US for AHDH, but not in the Netherlands [3].

Raynaud's phenomenon (RP) is a syndrome characterized by episodes of digital vasospasm triggered by exposure to physical, chemical, or emotional stress. It typically manifests with 'triple' or 'double' color changes (pallor, cyanosis, and erythema). It can be classified as primary or secondary, depending on whether it occurs as an isolated condition or because of an underlying disease. The exact pathogenesis of RP has not been entirely clarified. Multiple mechanisms such as endothelial function and regulation of nerve fibers play a role in the regulation of the vascular tone [4].

Reports

From 21 February 2008 until 26 September 2016 the Netherlands Pharmacovigilance Centre Lareb received 2 reports of Raynaud's phenomenon associated with the use of dexamphetamine (case A and B). Furthermore Lareb received 2 reports with symptoms which might indicate RP, that is 1 report of peripheral coldness (case C) and 1 report of blue hands with painful skin bumps (case D).

Case A (report number 75032)
This non-serious spontaneous report from a general practitioner concerned a female aged 21-30 years, with RP following administration of dexamphetamine 5mg 4dd1 for ADHD with a latency of half a year after start. It is unknown in which month the reaction occurred. The action taken and patient outcome were unknown. Concomitant medication was salbutamol (for asthma).

Case B (report number 196811)
This non-serious spontaneous report from a physician concerned a male aged 11-20 years, with RP following administration of dexamphetamine 5mg 2dd2 for ADHD with a latency of 1 day after start. The reaction occurred in March. The dose was lowered (dosage unknown) after which the patient started recovering. The physician reports that increase of the dosage led to worsening of RP. No concomitant medication was reported.

Case C (report number 171541)
This non-serious spontaneous report from a specialist doctor concerned a male aged 31-40 years, with peripheral coldness following administration of dexamphetamine for attention deficit/hyperactivity disorder with a latency of one month after start. The reaction occurred in March. No concomitant medication was reported. The reporter mentioned that another cause or circumstance that might have caused or aggravated the reaction was elevated blood pressure, possibly related to previously used methylphenidate.

Case D (report number 215040)
This non-serious spontaneous report from a specialist doctor concerned a male aged 11-20 years, with blue hands with painful skin bumps following administration of dexamphetamine for ADHD with a latency of 2 days after start. The reaction occurred in February. The dose for dexamphetamine was increased (dosage unknown) and the patient has not recovered. The reporter mentions that the patient had a positive family history for Raynaud's phenomenon (grandfather). Concomitant medication was not reported.

Other sources of information

SmPC

The Dutch SmPC of dexamphetamine does not mention RP as an adverse drug reaction [1].

In US SmPC of dexamphetamine Dexedrine® peripheral vasculopathy, including RP, is described as an adverse drug reaction. The SmPC describes that RP as adverse drug reaction was reported with post marketing use of stimulants including dexamphetamine, at therapeutic doses, and reducing the dose or discontinuing therapy may improve signs and symptoms [5].

Literature

A retrospective case-control study investigated whether medications used for the treatment of ADHD were associated with the development of RP. Sixty-four children were enrolled in the study, 32 patients with RP and 32 age and sex matched control patients without RP. A significant association between the presence of RP and past or current use of ADHD stimulants (methylphenidate and dexamphetamine) was found. [6]

Syed *et al* described two case reports of dexamphetamine-induced peripheral vasculopathy. The first case concerned a 10 year girl without relevant medical history who presented with cold, cyanotic, bruised and painful toes 1 month after using 30mg dexamphetamine. After withdrawal of dexamphetamine the patient recovered. The second case concerns a 20 year old female with generalized arthralgia's for the last seven years and livedo reticularis with delayed capillary refill. The patient had started methylphenidate 11 years ago and switched to dexamphetamine 5 years ago. Concomitant medication was loratadine, contraceptive pills and ibuprofen. Ibuprofen was switched to naproxen, followed by disappearance of the musculoskeletal symptoms, but the skin changes remained constant [7].

Databases

Table 1. Reports of the PT "Raynaud's phenomenon" associated with dexamphetamine and lisdexamphetamine, in the Lareb [8], WHO [9] and Eudravigilance database [10].

Database	MedDRA PT	Number of reports	ROR (95% CI)
Lareb	Raynaud's phenomenon - dexamphetamine	2	
	Raynaud's phenomenon - lisdexamphetamine	0	
WHO	Raynaud's phenomenon - dexamphetamine	3	9.2(3.0-28.7)
	Raynaud's phenomenon - lisdexamphetamine	53	57.0(43.4-74.9)
Eudravigilance	Raynaud's phenomenon - dexamphetamine	3	21.8(7.0-67.8)
	Raynaud's phenomenon - lisdexamphetamine	12	20.7(11.7-36.6)

Eudravigilance

On 23 September 2016 the Eudravigilance database contained 1 case of dexamphetamine associated with RP in addition to the 2 Lareb cases, and 12 cases of lisdexamphetamine associated with RP. The ages varied between 9 and 62 years. Of the 13 patients, 7 were aged 17 years or younger (mean = 25.7 years, median = 16 years). The indication for dexamphetamine was attention deficit disorder (ADD). The indications for lisdexamphetamine were ADD in 3 cases, and ADHD in 7 cases, and in two cases the indications were unknown. The time to onset varied between approximately 1 month to approximately 2 years; in 5 cases RP occurred within the first few months after start. In the dexamphetamine report the latency was 3 to 4 months. In 3 patients other factors might have caused RP, namely lupus and scleroderma in 2 cases. In 2 cases amphetamine/dexamphetamine Adderall® was a suspect as well, besides lisdexamphetamine. In 2 other cases the patient did not develop RP on amphetamine/dexamphetamine Adderall® , but did so on lisdexamphetamine. There were 3 positive dechallenges described (including 1 patient who switched from dexamphetamine to amphetamine/dexamphetamine), with in 1 case also a positive rechallange. Furthermore, one patient recovered by warming her hands whilst continuing lisdexamphetamine. One patient did not recover after dexamphetamine was withdrawn and switched to methylphenidate. In the other 8 patients the outcome is unknown.

Prescription data

Table 2. Number of patients using dexamphetamine in the Netherlands between 2010 and 2014 [11].

Drug	2010	2011	2012	2013	2014
Dexamphetamine	4,297	5,804	7,653	10,785	20,789

Mechanism

Raynaud's phenomenon is characterized by transient ischaemia of the extremities, which manifests as pallor (vasospasm and decreased blood flow), cyanosis (deoxygenation of static venous blood), and rubor (reperfusion), often accompanied by pain. Abnormalities of the cutaneous microcirculation are primarily involved in the pathophysiology of RP [12]. Drugs that enhance vasoconstriction possibly influence the development RP. Stimulation of the central nervous system through the dopaminergic and noradrenergic systems causes a release of peripheral cathecolamines. This, in turn, might lead to vasoconstriction by stimulation of the alpha-1 adrenergic receptors, and affect the digital microcirculation [6,13].

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 2 cases of RP and 2 cases of symptoms which might indicate RP, associated with the use of dexamphetamine. There was only one case with a positive dechallenge, and in 2 cases other possible causes for the reaction were described.
The Eudravigilance database contains another report of RP associated with dexamphetamine. There were 12 cases available of RP associated with lisdexamphetamine. In 6 of these cases the latency was comparable (within a few months after start) and there were 3 positive dechallenges and 1 positive rechallenge.
The literature provides a possible mechanism for both dexamphetamin and lisdexamphetamin [13]. Furthermore RP is labeled in the Dutch SmPC of methylphenidate, which also belongs to the group of amphetamines [1,14].
RP associated with dexamphetamine and RP associated with lisdexamphetamine are disproportionally present in both the Eudravigilance database and the WHO database.

Although the association RP and dexamphetamine is supported by only a limited number of reports, the described cases in the literature, the labeling of RP in the US SmPC of dexamphetamine Dexedrine® and the number of reports concerning lisdexamphetamine in the WHO-, and Eudravigilance databases, suggest a possible causal relationship between RP and dexamphetamine.

References

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This signal has been raised on January 2017. 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