

## Methylphenidate and hyperhidrosis

### Introduction

Methylphenidate is an indirect sympathicomimetic acting drug with effect on the central nervous system which has been approved for the Dutch market for the treatment of *Attention-Deficit/Hyperactivity Disorder (ADHD) in combination with psychotherapeutic and/or pedagogical treatment* and for treatment of *narcolepsy*. The recommended dose in children is 2 mg/kg/day [1].

Lareb received eight reports of hyperhidrosis in which methylphenidate was the suspect drug. In the SPC of methylphenidate hyperhidrosis is mentioned as one of the symptoms of methylphenidate overdose. It is not mentioned as an adverse drug reaction.

### Reports

Until December 21, 2006 the Netherlands Pharmacovigilance Centre Lareb received eight reports of hyperhidrosis in association with the use of methylphenidate. Report characteristics are listed in table 1.

Table 1. reports of hyperhidrosis associated with the use of methylphenidate

Patient, Sex, age	Drug Indication for use	Concomitant medication	ADR	Time to onset, outcome
A, M, 11	methylphenidate 10 mg 1 dd 15 mg indication not reported		anxiety, palpitation, hypertension, cramp, paraesthesia, peripheral coldness, nausea, sweating, for which hospitalization was necessary	20 minutes after start of 15 mg (patient used 7½ mg/day before), not reported
B, M, 7	methylphenidate 10 mg 2 dd ½ ADHD		flushing, sweating face/head/neck, abdominal cramp, crying abnormal, pulse 130/min	positive de- and rechallenge
C, M, 50	methylphenidate 10 mg 4 dd 1 indication not reported paroxetine 20 mg 1 dd 1 indication not reported	lithium carbonate 1 dd 1200 mg	sweating increased, emotional poverty	not reported, positive dechallenge
D, F, 49	methylphenidate 10 mg 2 dd 1 narcolepsy	clomipramine ritanserine	sweating, feeling cold, fatigue	2 months after start, not reported
E, M, 29	methylphenidate 10 mg 3 dd 20 mg ADHD		sweating, erythema	13 months after start, positive dechallenge
F, F, 24	methylphenidate 10 mg ADHD	metformin tolbutamide sumatriptan	sweating, anorexia	1 hour after start, sweating did not recover on ongoing therapy, anorexia did
G, F, 5	methylphenidate 10 mg 2 dd ½ ADHD amoxicillin 250 mg/5 ml 3 dd 4 ml Infective otitis externa with fever		sweating, crying abnormal, disorientation	not reported, recovered after end of amoxicillin

<b>Patient, Sex, age</b>	<b>Drug Indication for use</b>	<b>Concomitant medication</b>	<b>ADR</b>	<b>Time to onset, outcome</b>
H, F, 24	methylphenidate 10 mg 3 dd 1 hyperactivity co-trimoxazole 250 mg 3 dd 1 indication not reported		dizziness, sweating	not reported, recovered after withdrawal of methylphenidate

Patients G and H received an antibiotic drug next to the methylphenidate. Patient G recovered after withdrawal of the antibiotic drug, patient H recovered after withdrawal of methylphenidate.

## Other sources of information

### Literature

A Medline search based on the MeSH terms methylphenidate, central nervous system stimulants, hyperhidrosis and sweating did not yield any relevant publications.

### Databases

On December 21, 2006 the Lareb database contained eight reports of hyperhidrosis in association with methylphenidate. In total the database contains 837 reports of hyperhidrosis and 187 reports of methylphenidate. The association between hyperhidrosis and methylphenidate is disproportionally present in the Lareb database: ROR 3.11 (95% CI 1.53 - 6.33).

The database of the Uppsala Monitoring Centre of the WHO contained 36 reports of increased sweating in association with methylphenidate. In total the database contains 33,946 reports of increased sweating and 3,850 reports of methylphenidate. The association was not disproportionally present: ROR 0.87 (95% CI 0.63-1.21).

### Mechanism

Methylphenidate is a psychomotor stimulant with primary activation of the noradrenergic and dopaminergic systems [1]. It activates the noradrenergic pathway projecting from the locus coeruleus in the brainstem to the frontal cortex and the dopaminergic pathway projecting from the ventral tegmental area in the brainstem to mesocortical and dorsolateral prefrontal cortical areas. Overactivity of these noradrenergic neurons is associated with sweating [2].

## Discussion and conclusion

Lareb received eight reports of hyperhidrosis in patients using methylphenidate. Patient A, a male child aged 11 years, experienced hyperhidrosis in combination with anxiety, palpitation, hypertension, cramp, paraesthesia, peripheral coldness and nausea, shortly after dose increase from 7½ mg to 15 mg per day. The patient's weight was not reported. Clinically, these symptoms seem to fit in an overdose syndrome, while taking a, for his age, normal dosage. In cases G and H there might be confounding by the infection for which the antibiotic drug was prescribed. Latency in patient E, 13 months, was quite long according to the  $T_{max}$  of 1-2 hours [1]. On the other hand the positive dechallenge in cases B, C, E and positive rechallenge in patient B do support causality. Furthermore hyperhidrosis is a well known symptom of methylphenidate overdose. A possible mechanism supports the adverse drug reaction.

## References

1. Dutch SPC Ritalin®. (version date 13-9-2005) <http://www.cbg-meb.nl/IB-teksten/03957.pdf>.
2. Stahl SM. Essential Psychopharmacology. Second ed. Cambridge: Cambridge University Press; 2000.