Lareb
Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

Risperidone and epistaxis

Introduction

Risperidone (Risperdal®) was granted a marketing authorisation on 28 February 1994. It is indicated for treatment of schizophrenia. In addition it is also effective:
for maintenance therapy of the clinical improvement in patients in which a response was seen on initial treatment.
for treatment of severe aggressive behaviour in patients with progressed dementia [1].
for treatment of mild to severe manic episodes
Section 4.2 mentions that no experience in children below 15 years of age is available. Risperidone is an atypical antipsychotic agent that acts as a selective blocker of dopamine D2 and serotonin-5-HT2 receptors. Recently a 'drug point' in the BMJ was published concerning nose bleeds with use of risperidone [2]. Similar cases received by the Netherlands Pharmacovigilance Centre Lareb are presented below.

Reports

Until 25 augustus 2004 Lareb received 5 reports of patients perceiving epistaxis on risperidone use (table 1).

Table 1. reports of epistaxis associated with the use of risperidone reported to Lareb

Patient, Sex, age	Drug Indication for use	Concomitant medication	Time to onset, outcome	comments
A M, 8	0.25 mg 2 dd. ADHD	methylphenidate, clonidine, pipamperone	7 days, recovered after cessation	on average 2 nose bleedings per day, mainly in the evening and at night
B F, 13	3 mg	none	several days, recovered after cessation	on average 2 nose bleedings a day, mainly at night
C M, 11	1 mg 2 dd. pervasive development disorder	none	8 months, recovered	
D M, 11	0.5 mg 1 dd.	none	- recovered	
E F, 66	1 mg 1 dd. psychosis	carbasalate-calcium, bisoprolol, amiloride, amitriptyline, potassiumchloride, oxazepam	weeks -	3 nose bleedings, haematoma sclera

Other sources of information

SPC
The Dutch SPC mentions no epistaxis or relevant clotting related ADRs. The American SPC reports the occurrence of epistaxis in 0.1 to 1% of the patients in preclinical phase 2 and 3 studies [3].

Literature
Cases of nose bleeds associated with risperidone were described only by Harrison-Wooldrich and Clark [2]. In this report 2 patients with nose bleeds upon start of risperidone were presented together with an analysis of the reports in the WHO database.

Mechanism
Several pharmacological mechanisms might explain this ADR. Thrombocytopenia has been described for risperidone [4] and other antipsychotics [5].
Risperidone is also a potent 5-HT2A receptor antagonist. Antagonism of the 5-HT2A receptor is proposed to increase blood flow in coronary and cutanous microvasculature by reducing vasomotor tone, reduction of platelet aggregation, and vasoconstrictor release from platelets [6,7].

Databases
On 25 augustus 2004, the Lareb database contained 208 reports of epistaxis and 208 reports on risperidone. The association of epistaxis and risperidone is with 5 reports disproportionally present in the database (ROR 4.9, 95% CI 2.0-12).
In the Lareb database, 80% of the reports on epistaxis concernes the age group 0 to 17 years, probably to increased vulnerability of the Kiesselbach's plexus in children. This age distribution for this ADR is reflected in the reports on risperidone.

In the 1st quarter of 2004 the WHO database contained 60 reports concerning epistaxis and risperidone (ROR 1.5, CI95 1.1-1.9). The analysis of 54 of these case reports is published by Harrison-Wooldrich and Clark [2]. For other anti-psychotic drugs the association with epistaxis was not disproportional nor was the association risperiodone and thrombocytopenia (n=205, ROR 1.0, CI95 0.9-1.1).

Prescription data

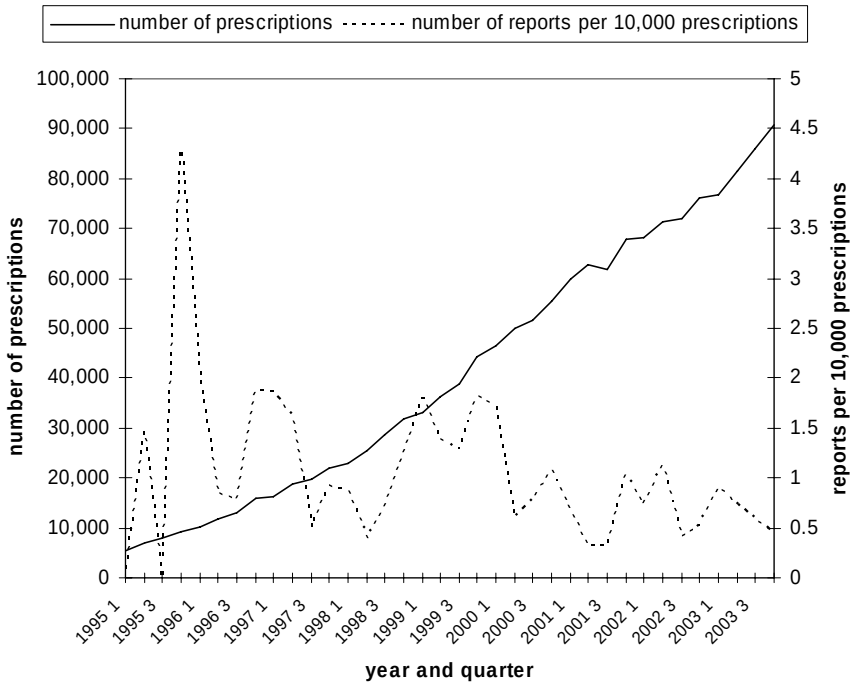

Figure 1.
Total number of prescriptions and all reports per prescriptions per quarter since 1995 (Source: GIP College voor Zorgverzekeringen, Diemen).

Conclusion

The association epistaxis and risperidone is well documented and disproportionally reported to Lareb and the WHO. Other cases were observed in pre-marketing studies, a case report was published in literature, and a plausible mechanism is proposed. Therefore epistaxis should be included in the SPC.

References

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6. Ootsuka Y, Nalivaiko E, Blessing WW. Spinal 5-HT2A receptors regulate cutaneous sympathetic vasomotor outflow in rabbits and rats; relevance for cutaneous vasoconstriction elicited by MDMA (3,4-methylenedioxymethamphetamine, "Ecstasy") and its reversal by clozapine. Brain Res 2004;1014(1-2):34-44.
7. Satomura K, Takase B, Hamabe A, Ashida K, Hosaka H, Ohsuzu F, Kurita A. Sarpogrelate, a specific 5HT2-receptor antagonist, improves the coronary microcirculation in coronary artery disease. Clin Cardiol. 2002;25(1):28-32.