Lareb
Nederlands Bijwerkingen Centrum
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Risperidone and pipamperon in association with epistaxis

Introduction

Risperidone (Risperdal®) is an atypical antipsychotic drug with strong antiserotonergic and antidopaminergic activity. It was granted a marketing authorization in 1994. It is indicated for *treatment of schizophrenia, treatment of severe aggression in patients with advanced stage of dementia and for the treatment of moderate to severe manic episodes*. Risperidone is not registered for use in children [1].
Pipamperon (Dipiperon®) is a butyrophenone derivative with antidopaminergic, antihistaminergic and anticholinergic activity, which was approved for the Dutch market in 1968. It is indicated for *treatment of psychoses and for the symptomatic treatment of severe forms of excitement and agitation*. Pipamperon is registered for use in children [2].

Epistaxis, or nose bleed, is classified into anterior and posterior bleeds. Anterior bleeds are responsible for about 80% of epistaxis. They occur at the Kiesselbach's plexus, an anastomosis on the lower part of the anterior septum. Posterior bleeding derives primarily from the posterior septal nasal artery, which forms part of the Woodruff plexus [3]. Epistaxis can be severe, requiring medical intervention.
The aetiology of epistaxis can be divided into local and general causes; however the vast majority nose bleeds (80-90%) is actually idiopathic. Nasal sprays, anticoagulants and anti-platelet drugs (aspirin, clopidogrel) are known causes of epistaxis [3].

The Netherlands Pharmacovigilance Centre Lareb reported in September 2004 to the Medicines Evaluation Board that it had received five reports of epistaxis in association with risperidone [4]. In July 2007 the number of reports on risperidone and epistaxis has increased to twelve. In addition, Lareb received eleven reports of epistaxis in association with pipamperon.
Since risperidone and pipamperon are by far the most frequently prescribed antipsychotic drugs to children and both are associated with epistaxis in the Lareb database, they are combined in this report.

Reports

Up to August 30, 2007 the Netherlands Pharmacovigilance Centre Lareb received 12 reports of epistaxis in association with risperidone and 11 reports in association with pipamperon. Sixteen reports concern males, seven concern females. The majority of reports concern children: 17 of them are aged 5 to 14 years.
Patient C was prescribed pipamperon 120 mg/day according to the reporter.
In two patients (E and F) additional laboratory findings were reported. Thrombocyte count, APTT (activated partial thromboplastin time), and PT (prothrombin time) were all within normal ranges.
Patient L used risperidone and pipamperon, but only risperidone was reported as the suspect drug.

Table 1. reports of epistaxis associated with the use of pipamperon

Patient, Sex, age	Drug Indication for use	Concomitant medication	Time to onset	Comments
A M, 6	pipamperon 20 mg BID not reported	pimozide	23 days	positive dechallenge
B M, 8	pipamperon 12 mg/day behavioural problems	not reported	23 days	after start and after dose increase epistaxis
C M, 10	pipamperon 120 mg/day behavioural problems	not reported	unknown	positive dechallenge
D M, 6	pipamperon 28 mg/day behavioural problems	not reported	unknown	recovered after dose reduction
E F, 12	pipamperon 20 mg/day behavioural problems	methylphenidate	some days	positive de- and rechallenge
F M, 8	pipamperon 20 mg/day contact disorder	not reported	1 week	epistaxis on regular basis
G F, 8	pipamperon 10 mg TID aggressiveness	not reported	3 months	epistaxis during the night
H F, 32	pipamperon 20 mg/day impulse control disorder	not reported	3 days	positive dechallenge
I, M, 8	pipamperon 20 mg/day oppositional defiant disorder	not reported	14 days	positive dechallenge
J F, 10	pipamperon 10 mg/day obsessive 'voices' in head	not reported	16 hours	epistaxis four times in first two days
K M, 9	pipamperon 20 mg BID not reported	methylphenidate	2 days	other reactions: abdominal pain, headache, anorexia, pallor, several haematomas

Table 2. reports of epistaxis associated with the use of risperidone

Patient, Sex, age	Drug Indication for use	Concomitant medication	Time to onset	Comments
L M, 8	risperidone ¼ mg BID not reported	methylphenidate, clonidine, pipamperon	7 days	other reaction: nasal congestion epistaxis did not reappear after cessation of clonidine and pipamperon
M F, 13	risperidone 1 mg TID not reported	not reported	unknown	epistaxis twice daily, especially during the night, did not reappear after start of xylomethazoline nose spray
N M, 11	risperidone 1 mg BID pervasive development disorder	not reported	8 months	
O M, 11	risperidone ½ mg/day not reported	not reported	unknown	
P F, 66	risperidone 1 mg/day not reported carbasalate calcium 100 mg/day	bisoprolol, amiloride, amitriptyline, kalium chloride,	several weeks after start of risperidone, years after start of	3 times epistaxis haematoma sclera right eye

Patient, Sex, age	Drug Indication for use	Concomitant medication	Time to onset	Comments
	not reported	oxazepam	carbasalate calcium	
Q M, 12	risperidone 1½ mg BID not reported	not reported	unknown	spontaneous epistaxis
R M, 8	risperidone dose > 1mg agitation	not reported	unknown	epistaxis after dose increase
S F, 58	risperidone 1 mg BID not reported	not reported	unknown	
T M, 2	risperidone ½ mg/day autism	not reported	unknown	epistaxis on regular basis
U M, 37	risperidone 5 mg/day not reported	oxazepam	5 years	
V M, 19	risperidone 2 mg BID paranoid psychosis	diazepam, midazolam, promethazine, methylphenidate	4 months	epistaxis on daily basis, positive dechallenge
W M, 9	risperidone ¼ mg/day not reported	atomoxetine	3 days and 1 day respectively	other reaction: excessive bronchial secretion

Other sources of information

SPC

Neither the Dutch SPC of risperidone nor the Dutch SPC of pipamperon mentions epistaxis. The American SPC of risperidone mentions epistaxis as an infrequent ADR (incidence 0.1 to 1%) [5]. There is no American SPC concerning pipamperon available.

Literature

Cases of nose bleeds associated with risperidone were described only by Harrison-Woolrych and Clark [6]. In this report two patients with epistaxis upon start of risperidone were presented together with an analysis of the reports in the WHO database.

Databases

On September 4, 2007 the Lareb database contained 308 reports of epistaxis, 249 reports on risperidone and 74 on pipamperon. Epistaxis in association with antipsychotic drugs (ATC N05A) has been reported 24 times to the Netherlands Pharmacovigilance Centre Lareb: 12 reports of risperidone, 11 of pipamperon and one of olanzapine.
In the WHO database other antipsychotic drugs with ATC code N05A than risperidone and pipamperon were not disproportionally associated with epistaxis.

Table 3. reports of epistaxis associated with the use of pipamperon and risperidone in the Lareb database and the WHO database (2nd quarter of 2007)

	drug	reports	ROR (95%CI)
Lareb database			
	pipamperon	11	37.0 (19.3-71.0)
	risperidone	12	10.8 (6.0-19.5)
WHO database			
	pipamperon	9	6.3 (3.3-12.2)
	risperidone	74	1.4 (1.1-1.8)

Mechanism

Several pharmacologic mechanisms might explain this adverse drug reaction. Thrombocytopenia is a recognised adverse effect of antipsychotic drugs and has been described with risperidone [7]. In addition, risperidone is a potent serotonin receptor antagonist. Antagonism of the serotonin receptor is proposed to increase blood flow in coronary and cutaneous microvasculature by reducing vasomotor tone, reduction of platelet aggregation, and vasoconstrictor release from platelets [8].
The anticholinergic effects of pipamperon could cause additional mucosal dryness. Epistaxis has been described before in other anticholinergic agents [9]. In this case study a dose relation was suggested. Nose-picking was not a plausible explanation in the two described cases. Dryness of the nasal mucosa was seen in one of the patients. One patient experienced also facial flushing, making vessel dilation a possible mechanism.

Prescription data

Total number of prescriptions of risperidone and pipamperon per age is shown in table 4.

Table 4. total number of prescriptions of risperidone and pipamperon per age in 2005 (Source: GIP College voor Zorgverzekeringen, Diemen)

	0-4	5-14	15-24	25-44	45-64	65-74	75+
pipamperon	513	11,218	12,386	61,381	62,994	12,239	58,811
risperidone	185	30,032	31,368	148,352	125,295	25,158	61,073

Discussion

The reports Lareb received predominantly concern children aged 5 to 14 years. In literature the incidence of epistaxis appears to vary with age. There seems to be a

bimodal distribution with peaks in children and young adults and in the older adults (45-65 years) [3].
Epistaxis occurred in six cases during winter, in two during spring, in three during summer and in seven during autumn. The seasonal pattern could be explained by the finding that a non-traumatic epistaxis seems to occur more commonly in winter [10]. Central heating and low humidity could play a role.
Striking points, however, are that in some of the reported cases epistaxis occurred during the night. In seven patients epistaxis did not reoccur after cessation or after dose decrease of the suspect drug. Patient E experienced also a positive rechallenge.

Conclusion

Twenty-three case reports of epistaxis in the Lareb database are associated with the use of risperidone and pipamperon. In the Lareb database and the WHO database the association was disproportionally reported. Literature supports the relation and probable mechanisms are proposed.

References

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