1.1. Ropinirole, pramipexole and nasal congestion

Introduction

Ropinirole (Adatrel®, Requip®, generic brand) and pramipexole (Mirapexin®, Sifrol®, generic brand) are dopaminergic agonists and are indicated for Parkinson disease and restless legs syndrome [1,2]. Nasal congestion is not described in the SmPC's of ropinirole or pramipexole [1,2].
In the Netherlands ropinirole was used by almost 14,000 people, pramipexole was used by almost 31,000 people in 2008 [3].

Reports

On February 8, 2010, the database of the Netherlands Pharmacovigilance Centre Lareb contained three reports of nasal congestion associated with ropinirole and two reports of nasal congestion with pramipexole.
The reporter of report A (82217) states the nasal congestion occurred every 30 minutes after administration, and the adverse reaction initially continued for two hours, later it lasted during the night (tablet was taken once a day in the evening). Report C states that the patient experienced nasal congestion shortly after administration at night, and recovered in the course of the night. With the following dose the reaction reoccurred (positive rechallenge). In report B (63663) and C (60686) the reaction occurred after dosage increase. In report A the reaction started in October, the reaction in reports B started in February. The reactions of reports C, D and E started in July and August.

Table 1. Reports of rhinitis associated with the use of ropinirole and pramipexole.

Patient, Number, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A, 82217 F, 51 – 60 years	ropinirole 0,5 mg restless legs	hydrochlorothiazide 12,5 mg	nasal congestion, tearing eyes	1 month, discontinued recovered
F, 63663 F, 51 – 60 years	ropinirole 1 mg sleep disorder	melatonin 5 mg	nasal congestion	1 day after dose increase no change unknown
C, 60686 F, 61 – 70 years	pramipexole 0,125 mg restless legs	macrogol/electrolytes	nasal congestion	2 months, after dose increase, no change, recovered
D, 59756 F, 51 – 60 years	pramipexole 0,125 mg restless legs	macrogol/electrolytes	nasal congestion	1 month, discontinued, treated with xylometazolin recovering
E, 26407 F, 51 – 60 years	ropinirole 5 mg parkinson's disease	trihexyphenidyl 2 mg domperidone 10 mg	nasal congestion somnolence insomnia	3 months no change not recovered yet

The onset of the nasal congestion is within 30 minutes in report A and within hours in report C (after increase of dose). Ropinirole and pramipexole reach their maximum plasma concentrations

at 1.5 and respectively 1 to 3 hours. Their terminal half-life is 3.5 to 10 hours for ropinirole and 8 to 12 hours pramipexole [1,2].

Other sources of information

Literature

To the best of our knowledge, no case reports are published in peer-reviewed medical journals about ropinirole or pramipexole in association with nasal congestion.
In the US SmPC of ropinirole and pramipexole nasal congestion is mentioned with an incidence of respectively 2% and 3 to 6% [4,5]. In addition to nasal congestion rhinitis is also mentioned in the US SmPC [4,5].
Nasal congestion is a known adverse drug reaction for other dopamine agonists as bromocriptine and pergolide. Bromocriptine is a D2-dopaminereceptor-agonist with a D1-receptor-antagonistic action. Pergolide is a dopamine agonist which stimulates the D2 receptor and, to a lesser extent, the D1 receptor. The Dutch SmPC of pergolide stated an incidence of 10% of nasal congestion, in the US SmPC only rhinitis is reported with an incidence of 12.2% but not nasal congestion [6,7].
Nasal congestion is mentioned in the SmPC of bromocriptine with an incidence of 1 to 10%. The US SmPC states an incidence of 10.7 to 13.8% of rhinitis of patients who were treated with bromocriptine but does not mention nasal congestion [8,9].

Databases

On February 8 2010, the database of the Netherlands Pharmacovigilance Centre Lareb contained three cases of nasal congestion associated with ropinirole, with a reporting odds ratio (ROR) of 38.8 (95% CI 12.3–128.7).
On February 8 2010, nasal congestion associated with pramipexole was reported twice in the database of Lareb. Given the limited number of reports in the database of the Netherlands Pharmacovigilance Centre Lareb, disproportionality could not be assessed.

The database of the World Health Organization (WHO) does not contain “nasal congestion” as a Preferred Term that can be used to search the database. The WHO database contained 14 reports of rhinitis associated with ropinirole (ROR=0.7, 95% CI = 0.4 – 1.1) and 13 reports of rhinitis associated with pramipexol (ROR=0.7, 95% CI = 0.4 - 1.2).The number of cases does not result in disproportionality.

On February 3 2010, the Eudravigilance database contained no cases of ropinirole associated nasal congestion.
Because of the nature of the ADRs they will probably be reported as non-serious, which may explain why there are no reports of nasal congestion present in the the Eudravigilance database.

Mechanism

Ropinirole has a high selectivity for D2-like receptors and shows no affinity for the D1-like receptors. In addition, it has insignificant affinity for central adrenoceptors, 5-hydroxytryptamine (5-HT) receptors, gamma aminobutyric acid receptors, benzodiazepine receptors, or muscarinic acetylcholine receptor. In contrast, bromocriptine and pergolide have shown affinity to nondopaminergic receptors, particularly 5-HT1, 5-HT and alpha-2 adrenoceptors [10]. Beyond the dopamine D2 receptor subfamily, pramipexole has a low affinity only for alpha-2-adrenoceptors, its affinity for other dopaminergic, adrenergic, histaminergic. scrotonergic, cholinergic, glutaminergic, histaminergic, adenosine, and benzodiazepine receptors being negligible or undetectable [11].
The mechanism for nasal congestion associated with ropinirole and pergolide is still unclear. *Bende et al*. give the following hypothesis about nasal congestion in association with the dopamine agonist bromocriptine; Bromocriptine can release vasoactive intestinal polypeptide

(VIP) via a postsynaptic DA_2 receptor mechanism outside the blood-brain barrier. VIP greatly dilates blood vessels, which could be a plausible explanation of the nasal congestion seen after bromocriptine ingestion [12].

Discussion and conclusion

The relation between nasal congestion and pramipexol or ropinirole use is supported by the reports in the Lareb database and a possible mechanism. However, we cannot exclude that other factors, such as the underlying disease or allergy, may have played a role in the occurrence of the reactions. In the SmPC's of bromocriptine and pergolide nasal congestion is described.

- It should be considered to mention nasal congestion in the SmPC of ropinirole and pramipexole

References

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4. US SmPC Requip®. (version date: 31-12-2008, access date: 8-2-2010). http://www.accessdata.fda.gov/drugsatfda_docs/label/2008/020658s018s020s021lbl.pdf
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This signal has been raised on June 2010. 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).

07-10-2010: Information from the Marketing Authorisation Holders (MAH's):

GSK, MAH of ropinirole, informed Lareb that nasal congestion has not been identified as a safety signal for ropinirole to date from review of post-marketing data and from the ropinirole clinical trials data.
GSK does not agree with the Lareb recommendation to include nasal congestion in the SmPC for ropinirole. GSK will however continue to monitor all safety data received for ropinirole including reports of nasal congestion to determine whether or not this adverse drug reaction needs to be added to the SmPC for ropinirole.

Boehringer Ingelheim, the MAH of pramifexole, informed Lareb that at present there is no significant information identified that would indicate a change of the pramipexole safety profile and, thus, would warrant the inclusion of nasal congestion as a side effect in the Boehringer Ingelheim Company Core Data Sheet for Mirapexin®/Sifrol®.