Lareb
Nederlands Bijwerkingen Centrum
Netherlands Pharmacovigilance Centre

Loratadine, desloratadine and convulsions

Introduction

Loratadine is an antihistaminergic drug with a tricyclic structure and a selective peripheral H-1-receptor activity [1]. Desloratadine is its primary active metabolite and is a non-sedating, long-acting histamine antagonist. After oral administration, desloratadine selectively blocks peripheral histamine H1-receptors because the substance is excluded from entry to the central nervous system [2]. The antihistaminergic activity of desloratadine is 2.5 - 4 times as great as loratadine [3]. Loratadine and desloratadine have been approved for the Dutch market since 03-1989 and 01-2001, respectively [1]. Both drugs are indicated for *the relief of symptoms associated with allergic rhinitis and chronic idiopathic urticaria* [1,2]. Loratadine is marketed as an over-the-counter drug. Desloratadine is available on prescription.
The Dutch SmPC of desloratadine mentions seizures as an adverse reaction: in the Dutch SmPC this is incorrectly and confusingly mentioned as *"aanvallen"*. No further information is given about the severity or incidence of this reaction [2]. In the Dutch SmPC of loratadine convulsions or seizures are not mentioned.
The current observation describes the association between loratadine, desloratadine and convulsions.

Reports

Until May 19, 2008, the Netherlands Pharmacovigilance Centre Lareb received seven reports about convulsions or aggravated epilepsy in association with desloratadine and two reports of convulsions in association with loratadine.

Table 1. Reports of convulsions associated with the use of (des)loratadine.

Patient, Sex, age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, outcome
A 65968 M, 75	desloratadine 5 mg od allergic rhinitis	beclomethasone, salmeterol with fluticasone	grand mal seizure	1 month, recovered after drug cessation
B 44629 F, 48	desloratadine 5 mg Allergic rhinitis due to pollen		grand mal convulsion	8 hours, recovered after drug cessation
C 34259 M, 48	desloratadine 5 mg urticaria		grand mal convulsion	4 hours, recovered after drug cessation
D M, 35	desloratadine dosage unknown, allergy	valproic acid, clonazepam, carbamazepin, topiramate	aggravated epilepsy	unknown, recovered from the aggravation after drug cessation
E 57609 M, 48	desloratadine dosage unknown, hay fever also suspect phenytoin	valproic acid	aggravated epilepsy	10 hours after start of desloratadine, desloratadine

Patient, Sex, age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, outcome
				withdrawn, outcome unknown
F 36199 F, 34	desloratadine 5 mg od indication unknown		convulsions	One day, reaction lasted for seven minutes. Not known if desloratadine was withdrawn
G 33410 F, 31	desloratadine 5 mg od indication unknown		convulsions	3 days, recovered, not clear if desloratadine was withdrawn
H 33531 F, 2	loratadine 5 mg od Indication unknown		convulsions	3 days, unknown
I 24949 F, 11	loratadine 10 mg allergies salbutamol 200 MCG, asthma	cromoglicate	epileptiform fits	hours, unknown

In patient A, a CT scan and MRI scan performed after admission of the patient to hospital showed no abnormalities. The patient did not have a history of epilepsy.
Patient B was examined by a neurologist, EEG and CT showed no abnormalities. The patient did not have a history of epilepsy.
Patient C did not have a history of epilepsy. He was examined by a neurologist, no additional risk factors were found. An EEG and MRI showed no abnormalities.
Patient D had a medical history of epilepsy since he was 10 years old. In the week before the aggravated epilepsy, the settings of the patients' implanted Nervus Vagus Stimulator were altered. Desloratadine was withdrawn after three months and the patient recovered .The patient still has absences but this is related to his underlying condition (epilepsy).
Patient E had a medical history of epileptic seizures due to scar tissue in the brain as a result of an automobile accident, the patients epileptic seizures were under control with phenytoin.

Other sources of information

Literature

In 2003, the WHO published a report on convulsions with newer generation antihistamines, such as loratadine and desloratadine [4,5]. This report presented the following results on this association:

- Seizures or convulsions have been reported in the literature with some first-generation antihistamines (chlorpheniramine, diphenhydramine, pheniramine and pyribenzamine) as well as with some newer-generation antihistamines (astemizole, cetirizine, fexofenadine, loratadine and terfenadine).
- According to the US Food and Drug Administration Adverse Event Reporting System (July 1999), convulsions associated with cetirizine, fexofenadine and loratadine accounted for 2.5%, 3.1% and 2.1% respectively of the total adverse events reported with these drugs [6].

- From their respective dates of marketing in Canada to 19 September 2002, Health Canada received 20 reports of suspected convulsive disorders associated with the use of loratadine [9], cetirizine [7] and fexofenadine [4]. Fifteen of the 20 cases occurred in patients with a prior history of seizures or in those who used anticonvulsant drugs concomitantly. However, these data must be interpreted with caution, as causality has not been confirmed.
- Reports of seizures and convulsions accounted for 3.6%, 1.4% and 0.9% of the total number of adverse reactions (ARs) reported with loratadine, cetirizine and fexofenadine respectively. There have been no reports of suspected convulsive disorders associated with desloratadine at this time.
- It is unclear whether newer-generation antihistamines aggravate the medical condition of patients with a history of seizures or whether they interact with anticonvulsants. Further studies and continued monitoring of these agents regarding their role in causing seizures or convulsions, especially in patients predisposed to convulsive disorders, are required" [4,5].

As far as we know, no further case-studies nor epidemiological findings of the association between (des)loraratidine and convulsions have been published.

Databases

In May 2008, the database of the Netherlands Pharmacovigilance Centre Lareb contained three reports of grand mal convulsions in association with the use of desloratadine. The reporting odds ratio (ROR) is 20.7 (95%CI 6.4 - 66.5).
The database of the World Health Organization contained 8 reports of grand mal convulsions for desloratadine (ROR=1.4; 95%CI 0.7 – 2.8).
For loratadine there were two reports of 'seizure disorders' in the Lareb database. In the WHO database there were 121 reports of convulsions in association with loratadine (ROR=1.4; 95%CI 1.2 – 1.8). In addition there were 11 reports of aggravated convulsions (ROR 2.7; 95%CI 1.5 – 5.0) and 29 reports of grand mal convulsions (ROR 1.3; 95%CI 0.9 – 2.0).
On June 8, 2008, the Eudravigilance database contained 11 reports of epileptic conditions associated with loratadine or desloratadine. Loratadine was involved three times, desloratadine eight times. Two reactions concerned an aggravation of a pre-existing epileptic disorder. Age was not specified once and ranged in the remaining cases from fourteen to sixty-one years. In one case epilepsy was reported together with a pulmonary embolism, cardiac arrest and death: in this case epilepsy due to a postanoxic state cannot be ruled out.

Mechanism

Experimental and epidemiological studies [7] have indicated that the central histaminergic neuron system plays an important role in inhibition of convulsive disorders through histamine H1-receptors, especially in children [7]. Clinical experiences to support this hypothesis are described in the review article by Yokoyama [7].

Pharmacokinetic properties

After oral administration loratadine is absorbed fast and undergoes its most important first-pass metabolism via CYP3A4 en CYP2D6. The most important metabolite desloratadine is pharmacologically active and responsible for a large

part of the clinical effect. Loratadine and desloratadine reach their maximum plasma concentration (T_{max}) between 1-1.5 hours and 1.5- 3.7 hours respectively. The average elimination-halftime for adults is 8.4 hours (interval 3-20 hours) for loratadine and 28 hours (interval 8.8 – 92 hours) for desloratadine [1,2].
The SmPC of desloratadine mentions that plasma concentrations can be detected within 30 minutes of administration.
The relatively short latencies of hours in almost all reports match the time for reaching T_{max} for these drugs.

Users in the Netherlands

The number of users has decreased from 81,994 in 2003 to 24,937 users in 2007 for loratadine (Claritine®). The number of users for desloratadine (Aerius®) has risen from 217,940 in 2003 to 453,570 users in 2007. Loratadine is available as over-the-counter medication; a prescription is needed for desloratadine.

Discussion and Conclusion

Older antagonists of histamine H1-receptors are commonly classified as first-generation or new generation antihistamines based on their frequent sedating effect at therapeutic doses. The “newer generation” antihistamines, also known as second- or third-generation antihistamines, includes astemizole, cetirizine, desloratadine, fexofenadine, loratadine and terfenadine, and were developed as non-sedating alternatives to the first-generation compounds [4,5].
Lareb has received reports of convulsions in patients with- and without a history of epilepsy, in association with the use of desloratadine and loratadine. In the two reports of patients who had a history of epilepsy, epilepsy was well controlled when the patient started to use (des)loratadine. The association is supported by a possible mechanism of action through the central histaminergic neuron system. Seizures should be mentioned in the Dutch SmPC of loratadine and be more explicitly mentioned in the SmPC of desloratadine. Instead of the Dutch word “aanvallen” it should state “convulsies” or “epileptische aanvallen.”
Lareb is vigilant of reports of convulsions in association with other antihistaminergic drugs. For example the Dutch SmPC of cetirizine does not mention convulsions [8]. Lareb has received one report of a grand mal convulsion, and one of aggravated convulsions in patients with epilepsy treated with cetirizine.
It is unclear if the incidence of convulsions is higher compared to the other new-generation antihistamines. Additional studies should be carried out to make a correct estimation of this ADR.

References

1. Dutch SmPC Claritine®. (version date: 7-1-2008, access date: 19-5-2008) http://db.cbg-meb.nl/IB-teksten/h13388.pdf.
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4. World Health Organisation (WHO). WHO Drug Information - Convulsions with newer generation antihistamines. (version date: 2003, access date: http://www.who.int/medicinedocs/collect/edmweb/pdf/s4955e/s4955e.pdf.
5. Health Canada. Canadian Adverse Reaction Newsletter - Reports of convulsions with newer-generation antihistamines. (version date: 6-1-2003, access date: http://www.hc-sc.gc.ca/dhp-mps/medeff/bulletin/carn-bcei_v13n1_e.html#antihistamines.
6. Ten Eick AP, Blumer JL, Reed MD. Safety of antihistamines in children. Drug Saf 2001;24(2):119-47.

7. Yokoyama H. The role of central histaminergic neuron system as an anticonvulsive mechanism in developing brain. Brain Dev 2001;23(7):542-7.
8. GIP College voor Zorgverzekeringen, Diemen
9. Dutch SmPC Zyrtec®. (version date: 4-4-2005, access date: 19-5-2008) http://db.cbg-meb.nl/IB-teksten/h13010.pdf.

This signal has been raised on July 2008. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbg-meb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).