# Desloratadine and abnormal behaviour

## Introduction

Desloratadine is a histamine antagonist with selective $H_1$-receptor antagonist activity [1]. It is indicated *for the relief of symptoms associated with allergic rhinitis and urticaria*. Desloratadine has been granted marketing authorization in the Netherlands since 2001. Antihistamines can be divided into the first- and second-generation drugs. Desloratadine belongs to the second-generation. The first-generation antihistamines are effective $H_1$-receptor antagonists. Since they are highly lipophilic they easily cross the blood-brain barrier, causing considerable sedation. Second-generation agents are more lipophobic and possess different ionic charges than the first-generation antihistamines. As a result, they are far less likely to cross the blood-brain barrier and, for that reason, cause little if any sedation [2]. Abnormal behaviour, for example irritability is associated with the use of first-generation antihistamines [2,3]. For desloratadine irritability or other reactions leading to abnormal behaviour are not described in the Dutch SmPC [1].

## Reports

In the period from March 15th 2001 until June 20th 2014, 22 reports have been reported to the Netherlands Pharmacovigilance Centre Lareb of reactions related to abnormal behaviour associated with the use of desloratadine. Within the System Organ Class 'Psychiatric disorders', there are several MedDRA® Preferred Terms (PTs) that are related to abnormal behaviour. The following PTs were reported in association with the use of desloratadine: abnormal behaviour (3), aggression (5), agitation (3), anxiety (4), apathy (2), depressed mood (6), irritability (2), manic reaction (1), nervousness (1), panic attack (1), restlessness (1), unrest (1), violent thought (1).

The time to onset varied from hours to two weeks after start, median of 2 days. In one patient a depression started after years. In one patient the depressed mood started after desloratadine was withdrawn. A positive dechallenge was reported for sixteen patients, a positive rechallenge for four. There is no information on negative rechallenges. Further, there is no information on misuse of desloratadine.
There were 21 reports in which desloratadine was the only suspected drug. In one patient (woman, aged 74) xylometazoline 1,0 mg/ml nose drops was also suspected by the reporter. This patient experienced a depressed state, agitation, aggression and irritability. The complaints recovered after a few hours. Both drugs were withdrawn. In another patient risperidone 5mg was also suspected. The patient experienced violent thought, sedation, dystonia, difficulty standing, salivation and trismus.
There were eight reports in which the patient used concomitant drugs of which reactions related to abnormal behaviour are described in the SmPC as an adverse drug reaction: bisoprolol [4], budesonide [5], diclofenac [6], ethinylestradiol/levonorgestrel [7], lamotrigine [8], levonorgestrel IUD [9], ethinylestradiol/gestoden [10], terbutaline [11], naproxen [12], midazolam [13], salmetarol/fluticason [14]. For 4 reports the start date of the concomitant medication was reported. Bisoprolol was use for 6 months, diclofenac, naproxen, levonorgestrel and ethinylestradiol/levonorgestrel were used for more than 3 years.
There were 15 women and 7 men. There were nine reports from pharmacists, six from physicians and seven from patients. The ages varied between 4 and 73 years, average 32 years.
Of all reports, six concerned a child aged <12-years, average age 6-years. Time to onset varied from 1-3 days after start. In five patients the complaints recovered after withdrawal of desloratadine. A positive rechallenge was reported for one patient. This patient experienced anxiety after use of desloratadine. He was not known with anxiety. Desloratadine was used for 6 months and during the whole period he experienced anxiety. Since the allergy was recovered the drug desloratadine was withdrawn. The anxiety recovered after 2 days. The patient had a positive rechallenge.

# Other sources of information

## SmPC

Reactions related to abnormal behaviour are not described in the Dutch SmPC of desloratadine [1]. Hallucinations and sedation are mentioned as very rare adverse drug reaction. In the USA product information of desloratadine it is described that in clinical trials of 246 patients 6 months to 11 years of age irritability was reported in 12.1% subjects using desloratadine versus 11.3% using placebo [15].

Reactions related to abnormal behaviour are described in the SmPC of other second-generation antihistamines. For example, the Dutch SmPC of fexofenadine describes insomnia, nervousness and sleep disorders [16]. The Dutch SmPC of loratadine describes nervousness in the pediatric population with an incidence of 2.3% [17].

There is some inconsistency about the use of desloratadine in children. Desloratadine of the brand Aerius is not indicated for use in children below the age of 12 years [1]. Desloratadine of the brand Sandoz is indicated for the use in children of 2 to 11 years. It is described that the safety and efficacy in children below 1 year have not been established [18].

## Literature

Treatment with desloratadine is associated with minimal central nerve system (CNS) effects in symptomatic patients [19]. Desloratadine has been reported to increase drowsiness at higher than recommended doses (particularly 20 mg/day) when compared with placebo [20]. It has also been reported that there are subgroups of individuals who are slow metabolizers of desloratadine in whom the risk of drug accumulation and associated dose-related events cannot be ruled out [20].
*Layton et al.* explored the safety of desloratadine in a cohort of 11828 patients in England [18]. In total, 6189 patients experienced an adverse drug reaction. Of those, 4 experienced drowsiness, 2 sedation and 1 syncope.
*Conzalez et al.* conducted a Medline search to identify preclinical and clinical studies of desloratadine, focussing on its safety profile. They concluded that desloratadine had no central nervous system effects [21].

## Databases

Reactions for which a Reporting Odds Ratio (ROR) can be calculated (>3 reports with the same PT) are shown in Table 2. For the database of the WHO and Eudravigilance the PTs are restricted to abnormal behaviour, aggression and irritability.

Table 2. Reports related to abnormal behaviour associated with the use of desloratadine in the database of Lareb, WHO and Eudravigilance [23-25]

| Database | MedDRA PT | Number of reports | ROR (95% CI) |
|---|---|---|---|
| Lareb | Abnormal behaviour | 3 | 7.0 (2.2-22.1) |
| | Aggression | 3 | 3.1 (1.0-9.6) |
| | Agitation | 3 | 2.5 (0.8-2.5) |
| | Anxiety | 3 | 1.8 (0.6-5.6) |
| | Depression | 3 | 1.2 (0.4-3.7) |
| WHO | Abnormal behaviour[#] | 7 | 1.4 (0.7-2.9) |
| | Aggression* | 13 | 1.3 (0.8-2.3) |
| | Irritability^ | 19 | 1.8 (1.2-2.8) |
| Eudravigilance | Abnormal behaviour | 11 | 2.8 (1.6 – 5.1) |
| | Aggression | 15 | 2.8 (1.7 – 4.6) |
| | Irritability | 12 | 2.5 (1.4 – 4.4) |

[#] 5 children aged <12, * 8 children ages <12, ^ 7 children aged <12

## Prescription data

Table 3. Number of patients using desloratadine in The Netherlands between 2009 and 2013 [26].

Delsoratadine is only available on prescription.

| Drug | 2009 | 2010 | 2011 | 2012 | 2013 |
|---|---|---|---|---|---|
| Desloratadine (Aerius®) | 509,280 | 536,610 | 590,710 | 576,750 | 593,900 |

## Mechanism

Since a histaminergic neuron system was demonstrated in the brain, it has been shown to be involved in many physiological functions through $H_{1-3}$-receptors. Based on accumulated data from neuropharmacological and behavioural studies, a role for histamine has long been thought to be involved in arousal, the sleep–wake cycle, appetite control, seizures, learning and memory, aggressive behaviour, and emotion [27]. *Yanai et al.* did a behaviour assessment of mutant mice lacking $H_1$-receptors to reveal its function in the behaviour of mice. They concluded that their results support the previous pharmacological findings that histamine modulates various neurophysiological functions such as locomotor activity, emotion, memory and learning, nociception and aggressive behaviour through $H_1$-receptors [27].
Since first-generation antihistamines are highly lipophilic they can easily cross the blood-brain barrier. Second-generation agents are more lipophobic and possess different ionic charges making them far less likely to cross the blood-brain barrier. Numerous studies have found desloratadine to be relatively free of sedative side effects or effects on performance, even at excessive doses.

CNS effects may also be related to the indication, histamine overload during allergic reaction, or due to nocturnal symptoms and sleep deprivation [28,29]. To the best of our knowledge there is no information on differences in effect of desloratadine between children and adults.

## Class effect

The database of Lareb also contains several reports of reactions related to abnormal behavior associated with other second-generation antihistamines. For example for loratadine: aggression (1), anxiety (2), apathy (1), depression (2), hallucinations (3), unrest (5), panic reaction (1), unrest (2), insomnia (3) and nervousness (1). Since these agents have a similar mechanism of action, a possible class effect cannot be excluded.

## Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 22 reports of reactions related to abnormal behaviour associated with the use of desloratadine. Of these reports, six concerned a child aged <12. Generally, the time to onset varied from hours to two weeks after start. Sixteen patients experienced a positive dechallenge. For the reports in children aged <12 the time to onset varied from 1-3 days after start. A positive dechallenge was reported five times. In our reports there is no evidence for confounding by indication. For some reports is was reported that the patient is not known with the kind of reactions reported.

Irritability is described in the USA product information of desloratadine [15]. Further, reactions related to abnormal behaviour are slightly described in the SmPC of other second-generation antihistamines. Some reactions (abnormal behaviour, irritability) are disproportionally present in the database of Lareb, the WHO.

The exact mechanism of reactions related to abnormal behaviour associated with the use of desloratadine is unknown. Histamine receptor blocking is associated with behaviour. Due to their characteristics, second-generation antihistamines are not likely to cross the blood-brain barrier. Although confounding by indication cannot completely be excluded, the positive dechallenge is sixteen of 22 patients indicates a possible relation between abnormal behaviour and the use of desloratadine.

Desloratadine is indicated for children aged 1 through 11 years however, there is limited clinical trial efficacy experience in this group. The SmPC of desloratadine of the brand Aerius® describes that the safety and efficacy in children below 12 years have not been established [1]. Since Lareb received 6 reports concerning children aged <12 years, of which two aged 4 years, it is advisable to further investigate this association also especially for this group.

- Further investigation of the information of the marketing authorization holders and other national centers is needed to confirm the signal.

References

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5. Dutch SmPC of Pulmicort® (budesonide). (version date: 29-3-2012, access date: 15-10-2014) http://db.cbg-meb.nl/IB-teksten/h13698.pdf.
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*This signal has been raised on March 2015. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbg-meb.nl*