Betahistine and hallucinations

Introduction

Betahistine (Betaserc®) is a histamine-like anti-vertigo drug with strong antagonist activity for the H_3 receptor and weak agonist activity for the H_1 receptor. The affinity for the H_2 receptor is negligible [1].

Betahistine was granted marketing authorization in the Netherlands in July 1970 and it is indicated for the treatment of *Meniere's syndrome*. Although the exact mechanism of action of betahistine in this indication is unknown, an increased blood flow to the inner ear and effects on vestibular compensation have been proposed [1].

Hallucinations are the perception of an external sensory stimulus where none exists. These can be somatosensory, visual, auditory, and olfactory.
Visual hallucinations are a clinical manifestation of neuroophthalmologic dysfunction resulting from a wide variety of underlying causes, such as epilepsy, migraine, and neurodegenerative disease. But also several drugs can cause visual hallucinations. Auditory hallucinations can arise from injury to any portion of the peripheral and central auditory pathways. Auditory hallucinations are most strongly linked to schizophrenia, but are also described in patients with Alzheimer disease and epilepsy. Several drugs are associated with auditory hallucinations [2].

Reports

In the period from June 1st 1995 until August 4th 2014, Lareb received five reports of hallucinations associated with the use of betahistine. The reports are listed in table 1.

Table 1. Reports of hallucinations associated with the use of betahistine

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 37238 M, 41-50 Pharmacist	betahistine 16 mg 3dd dizziness		hallucination	1 day no change unknown
B 87182 F, 71 years and older Physician with own pharmacy	betahistine 8 mg 3dd dizziness sotalol dose unknown atrial fibrillation zopliclone 3.75 mg 1dd sleep disorder	enalapril mesalazine omeprazole	hallucinations	1 day discontinued recovered
C 117820 F, 71 years and older Pharmacist	betahistine 16 mg 3dd meniere's syndrome	diltiazem metoclopramide	hallucination confusion insomnia head pressure	4 hours discontinued recovered
D 129891 M, 61-70 Pharmacist	betahistine 16 mg 3dd vertigo		auditory and visual hallucinations	1 hour discontinued recovered

E 162077 M, 71 years and older General practitioner	betahistine 16 mg 3dd vertigo	hallucinations	1 day discontinued recovered

Patient A had one episode of nocturnal and diurnal visual hallucinations respectively. The complaints consisted of seeing a person who was not really present.
Patient B previously experienced hallucinations during treatment with amitriptyline.
Patient C started metoclopramide, which is associated with hallucinations, on the same day as betahistine. However, the exact time of metoclopramide administration was not reported. It is therefore possible that the hallucinations started prior to the administration of metoclopramide.
In patient D the patient recovered from the complaints 5 hours after the last intake of betahistine.

In addition to the above mentioned cases, Lareb also received a report concerning a 70-year-old female who experienced tinnitus and auditory hallucinations, with a latency of 5 years after starting betahistine. The reporter suspected age-related tinnitus, but also reported auditory hallucinations. The causal relationship between betahistine and the auditory hallucinations is however unlikely. As a result, the report was not considered to be relevant for the association described here.

Other sources of information

SmPC

Hallucinations or related ADRs, are not mentioned in the Dutch SmPC of betahistine [1]. They are however mentioned in the Canadian and New Zealand SmPCs [3,4].

Literature

No previous cases of hallucination associated with betahistine were found in the literature. One case describing a 73-year-old male who experienced a delirium during betahistine treatment was published. The patient had been using betahistine for Meniere's disease for several years when the complaints arose. He recovered after withdrawal of betahistine and treatment with haloperidol. After restarting betahistine for dizziness, the symptoms returned, and a complete remission was seen after withdrawal. Although delirium can be accompanied by hallucinations, this was not reported in this patient [5].
A retrospective synopsis of safety data of betahistine, performed by the MAH, mentions the occurrence of 73 ADRs (7.3% of all ADRs) in the SOC Psychiatric disorders. Unfortunately, no details of the ADRs were reported [6].

Databases

Table 2. Number of reported cases of hallucinations associated with the use of betahistine in the databases of the Netherlands Pharmacovigilance Centre Lareb [7], WHO [8] and Eudravigilance (EMA) [9].

Database	Preferred Terms	Number of reports	ROR (95% CI)

Database	Preferred Terms	Number of reports	ROR (95% CI)
Lareb	Hallucinations	4	6.4 (2.4 – 17.4)
	Hallucination visual	0	-
	Hallucination mixed	1	-
	Hallucination auditory	0	-
	Total	**5**	**5.3 (2.2 – 13.0)**
WHO	Hallucinations	17	1.9 (1.2 – 3.1)
	Hallucination visual	4	2.9 (1.1 – 7.8)
	Hallucination mixed	1	-
	Hallucination auditory	0	-
	Total	**22**	**2.0 (1.3 – 3.0)**
Eudravigilance	Hallucinations	5	1.6 (0.6 – 3.7)
	Hallucination visual	3	3.0 (1.0 – 9.4)
	Hallucination mixed	2	-
	Hallucination auditory	0	-
	Total	**10**	**2.0 (1.0 – 3.8)**

Prescription data

Table 3. Number of patients using betahistine in the Netherlands between 2009 and 2013 [10].

Drug	2009	2010	2011	2012	2013
betahistine	112,580	112,390	110,520	105,860	100,170

Mechanism

Although the exact neurophysiology of hallucinations has not been elucidated yet, several drug related mechanisms have been proposed. Rolland et al. review three pharmacological models of hallucination: the dopamine model, which is associated with the use of psychostimulants (e.g. amphetamine), the glutamate model, associated with dissociative anesthetics (e.g. ketamine), and the serotonin model which is associated with the use of psychedelics (e.g. LSD) [11].
Since H_3 agonism inhibits the synthesis and secretion of, among others, dopamine and serotonin, the antagonistic effects of betahistine on the H_3 receptor could result in increased amounts of these monoamines, and subsequently hallucinations. However, although betahistine does cross the blood-brain-barrier [12], it should be noted that in animal studies, ADRs of the CNS only occurred after iv doses much higher than achieved in the clinical setting [1].

Conclusion

Lareb received five reports of hallucinations associated with the use of betahistine, with positive dechallenges reported in four of them. Latencies were up to one day in most cases which is to be expected based on the pharmacokinetics of betahistine ($t_{max} \approx 1$ hour). In another case (B) zopiclone was considered to be suspected since it is known to cause hallucinations [14]. However, since the patient recovered after withdrawal of betahistine and continuation of zopiclone, and zopiclone had been used for several years, a causal relationship with betahistine is

more plausible. In general, hallucinations are difficult to diagnose and can be a symptom of delirium. Although delirium was not reported for any of the described cases, it should not be ruled out. Additionally, delirium can be caused by drugs with anticholinergic properties. However, for betahistine, no anticholinergic properties have been described and no anticholinergic drugs were reported for any of the patients. In all databases the association was disproportionally present.
Although no cases of hallucination associated with betahistine could be found in the literature, the ADRs are present in the Canadian and New Zealand SPC of betahistine, and the association can be pharmacologically explained by increased levels of dopamine and serotonin due to betahistine's H3 antagonistic properties. Additionally, this association needs attention based on the large number of users (see also table 3) and the lack of evidence of efficacy of betahistine in Meniere's syndrome [15].

- Further investigation of the information of the marketing authorization holders and other national centres is needed to strenghten the signal

References

1. Dutch SPC betahistine (Betaserc®). (version date: 12-3-2013, access date: 7-8-2014) http://db.cbg-meb.nl/IB-teksten/h05852.pdf.
2. Nguyen, T. T. and Kaplan, P. W. Nonepileptic paroxysmal disorders in adolescents and adults. (version date: 1-8-2014, access date: 30-9-2014) UpToDate®.
3. New Zealand SPC betahistine (Serc®). (version date: 2-11-2012, access date: 7-8-2014) http://www.medsafe.govt.nz/profs/datasheet/s/Serctab.pdf.
4. Canadian Product monograph betahistine (Serc®). (version date: 8-4-2013, access date: http://www.abbott.ca/docs/SERC-PM-E.pdf.
5. Hoenders HJ, Wilterdink J. [Delirium in a 73-year-old man after many years of unwise use of betahistine]. Ned.Tijdschr.Geneeskd. 2004;148(47):2338-41.
6. Jeck-Thole S, Wagner W. Betahistine: a retrospective synopsis of safety data. Drug Saf 2006;29(11):1049-59.
7. Lareb database. (version date: 2014, access date: 4-8-2014) http://www.lareb.nl/Bijwerkingen/Zoek-op-geneesmiddel.
8. WHO Global Individual Case Safety Reports database (Vigibase). (version date: 2014, access date: 4-8-2014) https://tools.who-umc.org/webroot/ (access restricted).
9. Eudravigilance database. (version date: 2014, access date: 23-4-2014) http://bi.eudra.org (access restricted).
10. College for Health Insurances. GIP database. (version date: 9-6-2009, access date: 16-3-2011) http://www.gipdatabank.nl/index.asp?scherm=tabellenFrameSet&infoType=g&tabel=01-basis&item=J01FF.
11. Rolland B, Jardri R, Amad A, Thomas P, Cottencin O, Bordet R. Pharmacology of Hallucinations: Several Mechanisms for One Single Symptom? Biomed Res.Int. 2014;2014:307106
12. Arrang JM, Garbarg M, Quach TT, Dam TT, Yeramian E, Schwartz JC. Actions of betahistine at histamine receptors in the brain. Eur.J Pharmacol. 1985;111(1):73-84.
13. Simoes S, Mesquita J, Marcal N, Santos M. Musical hallucinations: case report and review of the literature. J Neuropsychiatry Clin.Neurosci. 2012;24(2):E8
14. Dutch SPC Immovane® (zopiclon). (version date: 22-6-2012, access date: 12-8-2014) http://db.cbg-meb.nl/IB-teksten/h11063.pdf.
15. Farmacotherapeutisch Kompas. Farmacotherapeutisch Kompas. (version date: 30-3-2011, access date: 30-3-2011) http://www.fk.cvz.nl/.

This signal has been raised on November 2014. 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.cbgmeb.nl