

Low dosage carbasalate calcium and tinnitus

Introduction

Carbasalate calcium (600, 300 and 100 mg) is used for *the treatment of headache, fever and pain due to flu and other conditions like myalgia* [1,2,3].

Carbasalate calcium 100 mg is also used for *secondary prevention of a myocardial infarction and the treatment of unstable angina pectoris*. Carbasalate calcium 38 mg is used for *secondary prevention after a transient ischaemic attack and non-invalidating cerebral infarction* [4]. Recent recommendations in the NHG-standard include 80 and 100 mg dosages for the latter indication.

The SPCs of carbasalate calcium 600 mg and 300 mg mention reversible hearing loss and tinnitus as possible adverse effects [1,2]. The SPC of carbasalate calcium 38 mg only mentions tinnitus as sign of a moderate intoxication and not as an adverse reaction [4]. This is also the case for some of the SPCs of products that contain carbasalate calcium 100 mg [5,6]. The Netherlands Pharmacovigilance Centre Lareb received several reports of tinnitus in association with carbasalate calcium of 100 mg and 38 mg dosages and not the higher dosage-forms.

Reports

On 14 June 2006 the Lareb database contained 8 reports of tinnitus in association with carbasalate calcium 38 mg and 100 mg (patients A-I). Also ototoxicity was reported once for carbasalate calcium 38. In all the reports on carbasalate calcium 38 mg, the drug was used once daily.

Lareb received 1 report of a decreased hearing for the 300 mg dosage (patient J).

For carbasalate calcium 600 mg tinnitus was reported twice (patients K,L).

Although the SPCs mention that the hearing loss is reversible [1,2,3], in two of the cases reported to Lareb the patient did not recover after discontinuation of the suspected drug at the time of reporting.

Table 1. reports of tinnitus associated with the use of carbasalate calcium

Patient, Sex, age	Drug Indication for use	Concomitant medication	Adverse drug reaction	Time to onset, outcome
A M, 81	carbasalate calcium 38 mg od not specified	cimetidine	tinnitus	1 week, outcome not reported
B F, 78	carbasalate calcium 38 mg od prophylactic for aggregation of thrombocytes	estriol ovule, trimethoprim	tinnitus, hearing decreased	6 years, suspect drug not withdrawn, not recovered
C F, 61	carbasalate calcium 38 mg od not specified	furosemide, tolbutamide, isosorbide mononitrate, simvastatin, diltiazem, diclofenac, paracetamol with codeine	ototoxicity	5 years, outcome not reported

Patient, Sex, age	Drug Indication for use	Concomitant medication	Adverse drug reaction	Time to onset, outcome
D M, 56	carbasalate calcium 38 mg od angina pectoris	rosuvastatin	tinnitus	2 days, suspect drug withdrawn, recovered with sequel
E F, 63	carbasalate calcium 100 mg not specified	atenolol, oxazepam, phenprocoumon	tinnitus	2 weeks, outcome not reported
F F, 34	carbasalate calcium 100 mg not specified	ethinylestradiol with norgestrel, captopril, prednisone, azathioprine	tinnitus	2 months, outcome not reported
G M, 68	carbasalate calcium 100 mg od not specified	mesalamine	tinnitus, headache, sweating increased, hallucinations	17 months, outcome not reported
H F, 54	carbasalate calcium 100 mg myocardial infarction	atorvastatin	tinnitus	latency not reported, symptoms improved after discontinuation of suspect drug
I M, 73	carbasalate calcium 100 mg od prophylaxis of athero-thrombotic complications	simvastatin	tinnitus	2 weeks, suspect drug not withdrawn, not recovered
J M, 86	carbasalate calcium 300 mg od ischaemic attack	nifedipine	hearing decreased	year, not reported
K F, 57	carbasalate calcium 600 mg not specified	not reported	tinnitus, vision decreased	not reported
L F, 34	carbasalate calcium 600 mg acute pharyngitis	not reported	tinnitus	hours, suspect drug withdrawn, not recovered

Other sources of information

Literature

Carbasalate calcium is a 1:1 complex of calcium acetylsalicylate and urea. It is metabolized to acetylsalicylic acid following absorption. Salicylate, the active ingredient of acetylsalicylic acid is known to induce tinnitus [7]. An extensive review article by Cazals shows a variety of investigations and case-reports that describe auditory alterations induced by salicylate [7]. However, in this review the effects of moderate to large doses of salicylate are described and not the low dose of 38 or 100 mg daily. A Medline search yielded articles about hearing loss and tinnitus due to higher doses of salicylate [8,9] but the effects of low doses were not described.

Databases

On 14 June 2006 the Lareb database contained 8 reports of tinnitus in association with carbasalate calcium 38 mg and 100 mg, which is disproportional (ROR 10.8;

*Nederlands Bijwerkingen Centrum Lareb
Januari 2007*

95%CI 5.2 - 22.3). Ototoxicity was reported once for carbasalate calcium 38. In addition Lareb received 3 reports of hearing loss and tinnitus for the 300 and 600 mg dosage form. In the database of the Uppsala monitoring centre of the WHO it is not possible to make a distinction between acetylsalicylic acid and carbasalate calcium.

Discussion

The review article by Cazals mentions tinnitus, loss of absolute acoustic sensitivity and alterations of perceived sounds as the three auditory alterations described by human subjects after ingestion of salicylate in larger doses [7].

Most of the reports of tinnitus that Lareb received considered the lower dosages of 38 mg and 100 mg. There is a broad range in the time to onset.

The mechanism causing salicylate-induced ototoxicity is not entirely clear but may involve biochemical and consequent electrophysiological changes in the inner ear and a dysfunction of the auditory nerve [7,9,10].

Anatomical examinations revealed significant alterations at the outer hair cell lateral membrane of the cochlea [7]. It is suggested by Guitton *et al.* that activation of cochlear NMDA receptors might induce tinnitus [10,11].

Conclusion

In the Lareb database the association between the lower dosage forms (38 and 100 mg) and tinnitus is disproportional. Although no literature could be found about the effects of low dosed carbasalate calcium, our data suggest an association between low dosages and tinnitus.

References

1. Dutch SPC Ascal[®] 600. (version date 20-1-1997) <http://www.cbg-meb.nl/IB-teksten/08184.pdf>.
2. Dutch SPC Ascal[®] 300. (version date 20-1-1997) <http://www.cbg-meb.nl/IB-teksten/12915.pdf>.
3. Dutch SPC Ascal[®] 100. (version date 20-1-1997) <http://www.cbg-meb.nl/IB-teksten/14436.pdf>.
4. Dutch SPC Ascal[®] 38. (version date 14-11-2003) <http://www.cbg-meb.nl/IB-teksten/15199.pdf>.
5. Dutch SPC Ascal Cardio[®] 100. (version date 14-11-2003) <http://www.cbg-meb.nl/IB-teksten/16831.pdf>.
6. Carbasalaatcalcium Cardio 100 mg. (version date 29-5-2002) <http://www.cbg-meb.nl/IB-teksten/22716.pdf>.
7. Cazals Y. Auditory sensori-neural alterations induced by salicylate. *Prog. Neurobiol.* 2000;62(6):583-631.
8. Wecker H, Laubert A. Reversible hearing loss in acute salicylate intoxication. *HNO* 2004;52(4):347-51.
9. Seligmann H, Podoshin L, Ben David J, Fradis M, Goldsher M. Drug-induced tinnitus and other hearing disorders. *Drug Saf* 1996;14(3):198-212.
10. Guitton MJ, Wang J, Puel JL. New pharmacological strategies to restore hearing and treat tinnitus. *Acta Otolaryngol.* 2004;124(4):411-5.
11. Guitton MJ, Caston J, Ruel J, Johnson RM, Pujol R, Puel JL. Salicylate induces tinnitus through activation of cochlear NMDA receptors. *J Neurosci.* 2003;23(9):3944-52.