

(Es)omeprazole and tinnitus

Introduction

Omeprazole (Losec[®]), a substituted benzimidazole, and esomeprazole (Nexium[®]), the S-enantiomer of omeprazole belong to the class of proton pump inhibitors (PPIs) which strongly reduce gastric acid secretion by the parietal cell [1]. PPIs are acid-activated prodrugs that require gastric acid secretion to be converted to the active sulfenic acids or sulfonamides [2]. The pharmacological mechanism of action is based on irreversible inhibition of the H⁺/K⁺-ATP-ase enzyme (the so-called proton pump) in the parietal cell of the stomach mucosa. Both the basal and the stimulated gastric acid secretion are dose dependently inhibited [1-3].

Omeprazole has been registered since November 1988 and esomeprazole has been registered since August 2000. *(Es)omeprazole is indicated for use in gastroduodenal ulcer disease, acid relate dyspepsia, reflux-oesophagitis or reflux symptoms and in Zollinger-Ellison's syndrome* [4]

The pharmacodynamic activity of omeprazole and esomeprazole is comparable. Other PPIs available on the Dutch market are lansoprazole, pantoprazole and rabeprazole [3].

Tinnitus is a sensation of hearing in the absence of external sounds. The cause of tinnitus is unknown in most cases. Tinnitus may occur together with changes in the cochlea, in the central nervous system, with intracranial hypertension, and other conditions. In some cases tinnitus can be psychosomatic. Tinnitus can also be an adverse drug reaction (ADR) of different types of drugs [5].

The current observation describes the association between (es)omeprazole and tinnitus.

Reports

On April 3rd 2013, the database of the Netherlands Pharmacovigilance Centre Lareb contained six reports of tinnitus or an aggravation of tinnitus associated with the use of omeprazole and four reports associated with the use of esomeprazole. The reports are listed in Table 1.

Table 1. Reports of (aggravated) tinnitus associated with the use of (es)omeprazole

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 61566 F, 51-60 Consumer	omeprazole od 20mg prophylaxis against drug- induced ulcer, piroxicam od 20mg arthralgia		tinnitus	3 days discontinued recovered
B 121361 F, 31-40 General Practitioner	omeprazole od 40mg upper abdominal pain	ethinylestradiol/nor ethisterone, mebeverine, mometasone	tinnitus	2 days discontinued recovered restarted (positive rechallenge) final outcome unknown
C 128546	omeprazole od	ibuprofen	tinnitus, diarrhoea,	2 weeks

F, 31-40 Consumer	20mg prophylaxis against drug- induced ulcer		flatulence, maculo- papular rash, pruritus, dizziness, blurred vision, dry mouth.	discontinued recovered
D 138643 F, 51-60 Pharmacist	omeprazole bid 20mg Helicobacter pylori infection		tinnitus, blurred vision, depressed mood	20 days discontinued recovered restarted unknown
E 149269 F, 71 or older Pharmacist	omeprazole od 20mg prophylaxis against drug- induced ulcer, teriparatide oam 600mcg osteoporosis prophylaxis, meloxicam od 15mg	budesonide, calcium carbonate/colecalc iferol	tinnitus, unilateral hearing loss	2 years unknown unknown
F 92296 M, 31-40 Consumer	omeprazole 20mg	venlafaxine	aggravated tinnitus	hours discontinued recovered
G 82062 F, 41-50 General Practitioner	esomeprazole od 20mg, valaciclovir bid 500mg retinitis/uveitis, prednisolone od 40mg retinitis/uveitis	alendronic acid, zopiclone	tinnitus	1 day unknown unknown
H 118096 F, 61-70 Pharmacist	esomeprazole od 20mg		tinnitus after switching from brand to generic product	4 days discontinued recovered
I 31738 M, 31-40 Pharmacist	esomeprazole bid 20mg dyspepsia		aggravated tinnitus	1 day discontinued recovered
J 143598 F, 41-50 Consumer	esomeprazole od 40mg oesophageal reflux		aggravated tinnitus, urinary retention	1 week no change not recovered

od = once a day
bid = twice a day
oam = once a month

In three cases (A,E,G) other drugs were also reported as suspect drugs. In four cases the patient used other drugs that have been associated with tinnitus (A piroxicam, C ibuprofen, E meloxicam, F venlafaxine) [6-9]. Omeprazole was started in 1994 for dyspepsia in case C and the reaction occurred with a latency of two weeks. Ibuprofen which is listed as concomitant medication was only started in 2009. The dosage of omeprazole was increased when ibuprofen was started (dosage not further specified). In three cases (F,I,J) aggravation of pre-existing tinnitus was reported. In four cases (C,D,E,J) other ADRs were reported beside (aggravation of) tinnitus. The time to onset varied from hours to weeks and was up to 2 years in case E. Unfortunately there was no response to follow-up questions for case E. In six cases (A,B,D,F,H,I) the patient recovered after withdrawal of the drug. In case C the patient recovered, but it is unknown if she recovered during treatment or after withdrawal of the drug. In two cases (E,G) the action taken for the drug and the outcome was not reported or unknown. In case J the drug was continued and the patient was not recovered at the time of notification.

Patient A was recovering two weeks after the withdrawal of both omeprazole and piroxicam. Case B describes a positive de- and rechallenge. It is unknown if omeprazole was withdrawn after the second administration. Patient D had an eardrum transplant, but

didn't suffer from tinnitus in the period prior to the administration of omeprazole. The outcome after the re-administration is unknown. Patient H was using the brand medication Nexium[®] for a period of eight years with no ADRs. After generic substitution tinnitus occurred. After withdrawal of generic esomeprazole the patient recovered. The two products are bioequivalent and it seems unlikely that tinnitus is caused by one of the pharmaceutical excipients. The patient switched back to the brand Nexium[®]. Patient I was using pantoprazole prior to the administration of esomeprazole. During treatment with pantoprazole the patient suffered from tinnitus. After the conversion to esomeprazole tinnitus aggravated. Within one week after withdrawal of esomeprazole tinnitus decreased to the earlier level.

Other sources of information

SmPC

None of the Dutch SmPCs of the PPIs, including omeprazole, esomeprazole, lansoprazole, rabeprazole, and pantoprazole mention tinnitus as a possible ADR [10-14]. However, the US product monographs of Prevacid[®] (lansoprazole) and Panto[®] (pantoprazole) describe tinnitus as a possible ADR [15,16]. In the US SmPCs of Nexium[®] and Prilosec[®] (omeprazole) tinnitus is listed as an ADR [17,18].

Literature

An association between omeprazole and rare auditory adverse reactions has been previously reported briefly in literature. An overview article on drug-induced tinnitus mentions omeprazole as a possible causative drug, based on a short communication in the Lancet where visual and auditory adverse drug reactions are described for omeprazole [19,20]. The German regulatory authority suspended the licenses for two intravenous preparations of omeprazole in 1995, and ordered the manufacturer to undertake studies. It insisted on labelling changes to alert the physician to rare visual and auditory adverse reactions even with the oral form.

Several studies have been conducted to investigate the role of gastric-type H⁺/K⁺-ATP-ase in inner ear function [21-23]. See the section *Mechanism* for a further description of these studies.

Databases

On April 5th 2013, the database of the Netherlands Pharmacovigilance Centre Lareb contained 10 reports of (aggravated) tinnitus in association with (es)omeprazole. The reporting odds ratio (ROR) was 0.9 (95% CI: 0.5-1.8), which is not disproportional, see Table 2.

Table 2 Reports of (es)omeprazole associated with (aggravated) tinnitus in the Lareb database

Drug	Number of reports	ROR (95% CI)
(es)omeprazole	10	0.9 (CI 0.5-1.8)

On April 5th, the WHO database of the Uppsala Monitoring Centre contained 171 reports of (aggravated) tinnitus associated with omeprazole and 75 reports of (aggravated) tinnitus associated with esomeprazole. The reporting odds ratio (ROR) was respectively 1.4 (95% CI: 1.2-1.6) and 0.7 (95% CI: 0.6-0.9), which is disproportional, only the ROR seems to suggest a protective effect for esomeprazole. The WHO database contained 349 reports of (aggravated) tinnitus associated with the use of the total group of PPIs. The reporting odds ratio (ROR) was 1.13 (95% CI: 1.02-1.26), which is disproportional. Table 3 shows the number of the reported cases of tinnitus (aggravated) by PPIs with the corresponding ROR in the WHO database. Table 4 shows the number of the reported cases of tinnitus (aggravated) by PPIs with the corresponding ROR in the Eudravigilance database.

Table 3. Reports of (aggravated) tinnitus with PPIs associated in the WHO database

Drug	Number of reports	ROR (95% CI)
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omeprazole	171	1.4 (1.2-1.6)
esomeprazole	75	0.7 (0.6-0.9)
pantoprazole	44	1.3 (1.0-1.8)
lansoprazole	41	1.2 (0.9-1.6)
rabeprazole	18	1.2 (0.8-2.0)
PPIs total	349	1.1 (1.02-1.3)

Table 4. Reports of (aggravated) tinnitus with PPIs associated in the Eudravigilance database

Drug	Number of reports	ROR (95% CI)
omeprazole	42	1.6 (1.2-2.1)
esomeprazole	28	1.2 (0.9-1.8)
pantoprazole	24	1.2 (0.8-1.9)
lansoprazole	16	0.9 (0.6-1.5)
rabeprazole	2	N.A.
PPIs total	112	1.2 (1.02-1.5)

Prescription data

The number of patients using omeprazole and esomeprazole in the Netherlands is shown in Table 5 [24].

Table 5 Number of patients using omeprazole and esomeprazole in the Netherlands between 2007 and 2011

	2007	2008	2009	2010	2011
omeprazole	1,039,000	1,220,000	1,376,000	1,596,000	1,700,000
esomeprazole	284,320	310,670	344,730	340,750	338,020

Mechanism

The exact mechanism by which PPIs can cause or aggravate tinnitus is unknown.

It is well known that the acid base homeostasis is important for a proper function of inner ear structures. Gastric-type H^+/K^+ -ATP-ase are present in the inner ear and might be involved in the pathogenesis of Meniere's disease [21]. It is plausible to assume that alterations of this proton pump, including inhibition by PPIs, could result in changes in ionic concentrations which could in turn lead to hydrops, causing Meniere-like symptoms including tinnitus.

The gastric type of H^+/K^+ -ATP-ase is expressed in the cochlear lateral wall in stria vascularis and in the fibrocytes of spiral ligament, spiral limbus, and suprastrial zone. The H^+/K^+ -ATP-ase plays an important role in the formation of the endocochlear potential (approximately +80mV), which is crucial for the high sensitivity of the hair cells to mechanical stimulation. Theoretically, PPIs could inhibit H^+/K^+ -ATP-ase in the inner ear, leading to suppression of the endocochlear potential. Disturbance of the endocochlear potential may lead to hearing loss and/or tinnitus.

Inhibition of H^+/K^+ -ATP-ase, with the specific gastric H^+/K^+ -ATP-ase inhibitor Sch-28080, in both stria vascularis and spiral ligament results in suppression of the endocochlear potential [22]. However, vascular or perilymphatic perfusion of omeprazole did not significantly affect endocochlear potential [22]. These findings can be explained by the acidity of the extracellular solution in the cochlea which might not be acidic enough. Omeprazole is only activated in a strong acidic environment of pH <5 [22]. Even though, it cannot be ruled out that PPIs reach the inner ear after absorption. Since H^+/K^+ -ATP-ase extrudes H^+ in exchange to K^+ from intracellular milieu to extracellular fluid, this pump might also be involved in the pH control of cochlear fluids [22]. Theoretically the inhibition of H^+/K^+ -ATP-ase may increase the intracellular pH.

Class effects

Beside the described cases of (aggravated) tinnitus associated with (es)omeprazole, the Lareb database contains 2 cases of tinnitus associated with other PPIs: 1 case associated

with lansoprazole and 1 case associated with pantoprazole. Reported information about these cases is limited. Given the postulated mechanism, the disproportionality in the WHO database and since all PPIs act on the same target (H^+/K^+ -ATP-ase), one may assume a class effect.

Discussion and conclusion

Lareb received ten reports of (aggravated) tinnitus associated with the use of (es)omeprazole. Six cases describe a positive dechallenge and one case describes a positive rechallenge. The WHO- and Eudravigilance database showed marginal disproportionality of (aggravated) tinnitus associated with the use of both omeprazole and the total group of PPIs. Additionally, tinnitus is already described in US product monographs and the US SmPC of (es)omeprazole [15-18]. These findings supports a causal relationship.

The reports in the Lareb database contain several possible confounders which are discussed in the section Reports. A postulated mechanism is described in the section Mechanism. However, it is unlikely that oral administration of (es)omeprazole can lead to the inhibition of H^+/K^+ -ATP-ase in the inner ear. This is supported by the findings of Shibata et al. that showed that omeprazole was unable to affect endocochlear potential in mice [22]. Some literature suggests a favourable effect of (es)omeprazole on the inner ear function in Meniere's disease [21]. The association is not disproportionately present in the Lareb database. The ROR for esomeprazole alone seems to suggest a protective effect in the WHO database, for which we have no explanation.

A possible association between (es)omeprazole and tinnitus cannot be ruled out.

- Further investigation of the information of the marketing authorization holders is advisable

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This signal has been raised on July 2013. 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).