1.1. Pantoprazole and taste disorders

Introduction

Pantoprazole is a proton pump inhibitor (PPI) that is widely *used for the treatment of esophageal reflux disease, treatment and prophylaxis of (NSAID-associated) duodenal and benign gastric ulcers and relief of dyspeptic symptoms* [1]. The mechanism of action of PPI's is based on inhibition of the hydrogen-potassium adenosine triphosphatase enzyme system (the 'proton pump') in the gastric parietal cells, which is the final stage in the production of gastric acid in the stomach. The inhibition is dose dependent and affects both basal and stimulated acid secretion [1].
A decreased gastric acid production leads to an increased pH in the stomach and in the oral saliva [2]. An increased oral pH could affect oral microbial growth [3]. PPI's can also influence oral microbial growth by causing a decreased saliva production [1]. Alterations in oral microbial flora can lead to a range of oral ADRs. The SmPCs of the proton pump inhibitors (PPIs) are not consistent in mentioning dysgeusia and ageusia. These are not mentioned in the SmPC of pantoprazole [1], but are mentioned in the SmPCs of all other proton pump inhibitors [4-7]. Here, the reports received by the Netherlands Pharmacovigilance Centre Lareb concerning dysgeusia and ageusia associated with the use of pantoprazole will be discussed.

Reports

Pantoprazole and dysgeusia

On January 7, 2010 the database of the Netherlands Pharmacovigilance Centre Lareb contained ten reports (Table 1) concerning dysgeusia in association with the use of pantoprazole.

Table 1. Reports of dysgeusia associated with the use of pantoprazole.

Patient, Sex, Age category	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug Outcome
A 56471 F, 51 to 60	pantoprazole reflux esophagitis		dysgeusia (salt)	7 weeks discontinued recovered
B 37095 M, 61 to 70	amoxicillin inflammation pantoprazole inflammation		taste perversion	7 days discontinued recovered
C 35119 F, 41 to 50	pantoprazole fluticasone bronchitis salmeterole/fluticasone	naproxen rofecoxib simvastatin valproic acid omeprazole	metallic taste	unknown discontinued (omeprazole and pantoprazole) recovered
D 25222 M, 21 to 30	pantoprazole		tooth disorder saliva increased bitter taste white tongue	not reported discontinued recovered with sequelae
E 30766 F, 61 to 70	pantoprazole oesophagitis	rofecoxib paracetamol acetylsalicylic acid	metallic taste	3 days discontinued recovered wit sequelae

Patient, Sex, Age category	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug Outcome
F 25982 F, 51 to 60	pantoprazole duodenal ulcer		lips swelling rash taste perversion	2 days discontinued not reported
G 37059 F, 70 and older	pantoprazole	simvastatin propranolol glycerol oxazepam	taste alteration (salt) xerostomia	not reported no change not reported
H 38394 F, 61 to 70	amoxicillin claritromycin pantoprazole prophylactic chemotherapy		taste perversion	hour unknown not recovered
I 83957 M, 70 and older	pantoprazole losartan acetylsalicylic acid verapamil simvastatin	vaseline/lanette cream mometasone ointment	dysgeusia	3 months unknown unknown
J 90932 M, 61 to 70	pantoprazole Prophylaxis	glyceryl trinitrate simvastatin cetirizine clopidogrel amlodipine	taste alteration (milky)	hours discontinued unknown

Of the nine reports, four (B, F, H, I) reported a taste perversion, two (C, E) a metallic taste, two (A, G) a salt taste, one (D) a bitter taste and one a milky taste (J). Three patients (A, B, C) recovered after withdrawal of the drug and two patients (D, E) recovered with sequel. The other patients (F, G, H, I, J) were not recovered at time of reporting. Before the start of pantoprazole patient E had a cerebrovascular accident which caused a slight alteration in taste, which was aggravated after the pantoprazole was started and improved again when the drug was withdrawn. The reported latencies varied from hours to three months after start of the drug. Four patients (C, G, I, J) used simvastatin concomitantly with the PPI which has previously been associated with taste disorders [8].

Pantoprazole and ageusia

On January 7, 2010, the database of the Netherlands Pharmacovigilance Centre Lareb contained five reports (Table 2) concerning ageusia in association with the use of pantoprazole.

Table 2. Reports of ageusia associated with the use of pantoprazole.

Patient, Sex, Age category	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug Outcome
J 51017 M, 41 to 50	pantoprazole stomach upset	paracetamol/ codeine lormetazepam tramadol	feeling abnormal visual disturbances depression saliva viscid taste loss paraesthesia	1 day discontinued recovered

Patient, Sex, Age category	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug Outcome
K 39626 F, 70 and older	pantoprazole	furosemide nitrazepam potassium chloride amlodipine oxazepam lactulose	ageusia	unknown discontinued recovered
L 34216 M, 70 and older	enalapril pantoprazole	cisapride distigmine temazepam simvastatin	taste loss	unknown no change unknown
M 42475 F, 51 to 60	pantoprazole	atenolol	taste loss, tongue pain	17 days discontinued not recovered
N 76119 F, 61 to 70	pantoprazole oxazepam (anxiety) lactulose (constipation) isosorbide mononitrate acenocoumarol furosemide metoprolol potassium chloride atorvastatin		taste loss	unknown not reported not recovered

Two patients (J, K) recovered after withdrawal of pantoprazole. Patient J recovered one day after discontinuation of pantoprazole. In one report the patient (M) was not recovered after discontinuation of the drug at time of reporting. The other two patients (L, N) continued pantoprazole and did not recover. The latency was only reported twice and was one respectively 17 days. Patients L, K and N used concomitant drugs that have previously been associated with taste disorders; enalapril and simvastatin respectively amlodipine respectively atorvastatin [8-10].

On January 7, 2010 the database of the Netherlands Pharmacovigilance Centre Lareb also contained five reports concerning stomatitis in association with the use of pantoprazole. These reports are mentioned because stomatitis can be an underlying cause of taste disorders. None of the patients in these five reports mentioned dysgeusia or ageusia in addition to the stomatitis.

Other sources of information

SmPC

The SmPC of pantoprazole does not mention dysgeusia and ageusia [1], but these ADRs are mentioned in the SmPCs of all other proton pump inhibitors [4-7].

Literature

To our knowledge, pantoprazole has not been associated with either dysgeusia or ageusia before. However, ageusia and dysgeusia have been mentioned as a class effect of the PPIs [11].

Databases

On January 7, 2010, a case non-case comparison showed that reports of pantoprazole and dysgeusia and ageusia were not disproportionally present in the

databases of Lareb and the WHO, with the exception of the reports of pantoprazole and dysgeusia in the Lareb database (Table 3).

Table 3. Reporting odds ratios of pantoprazole and dysgeusia and ageusia in the database of the Netherlands Pharmacovigilance Centre Lareb and the WHO.

Drug and ADR	Number of reports	ROR (95% CI)
Pantoprazole and dysgeusia	Lareb: 10 WHO: 31	2.7 (1.4-5.0) 1.2 (0.9-1.8)
Pantoprazole and ageusia	Lareb: 5 WHO: 12	2.0 (0.8-4.9) 1.7 (0.9-2.9)

On December 23rd 2009, the Eudravigilance database contained 17 reports of pantoprazole associated dysgeusia. Mostly the taste alteration was part of a more extended clinical picture; the reaction was reported once as isolated reaction and three times in combination with discolouration of mucosal tissue or xerostomia. Four cases concerned reactions in which smell function was also disturbed. The reaction was rated serious in 15 cases, of which four cases due to the disabling character of the reaction and nine times due to other, not-specified reasons. Five male and eleven female patients were involved. In one case, no sex was specified.

On December 23rd 2009, the Eudravigilance database contained four reports of pantoprazole associated ageusia. Disability occurred once, in three cases non-specified reasons were ground for seriousness. Reactions occurred all in male patients, ages ranging from 45 to 64 years. In one case ageusia was part of a more complex reaction, with over forty reactions reported, possibly due to lupus erythematosus. In the remaining three cases ageusia was reported in combination with tongue discolouration.

Prescription data

The increasing number of patients using pantoprazole in the Netherlands is shown in Table 4.

Table 4. Number of PPI users in the Netherlands between 2005 and 2008 [12]

Drug	2005	2006	2007	2008
pantoprazole	413,640	458,260	504,250	575,570

Mechanism

Oral adverse drug reactions of pantoprazole can possibly all be addressed to the same mechanism, which is based, as mentioned in the introduction, on an altered microbial flora due to a decreased saliva production and an increased oral pH [3,13]. Taste disorders can be the result of an altered oral microbial flora as well and also of drying of the oral mucosa, which can lead to a limited access of chemical receptor sites [14]. Smell contributes to taste in a large extent. However in none of the Lareb cases of taste disorders and pantoprazole use, an altered smell was reported.

Discussion

Pantoprazole can induce oral adverse drug reactions due to their ability to decrease saliva production and an increased pH of the oral mucosa and therefore cause an altered microbial flora. Cases of pantoprazole and dysgeusia and ageusia were reported to the Netherlands Pharmacovigilance Centrum Lareb, although these associations were not statistically disproportional in the Lareb nor in the WHO database. However, these oral ADRs are mentioned in the SmPCs of all other PPIs, and a similar mechanism is plausible.
Not all patients were recovered from their oral ADR after withdrawal of the drug at time of reporting to Lareb, which could be explained by the fact that recovery of oral microbial flora can take weeks to months [11]. Possible other causes for these ADRs are concomitantly used drugs, such as statins, ACE-inhibitors and calcium antagonists, cigarette smoke, alcohol and gastric reflux (which could damage taste receptors for example) [11,14].

Conclusion

Dysgeusia and ageusia should be mentioned in the SmPC of pantoprazole.

References

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This signal has been raised on February 2010. 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).