1.1. Proton pump inhibitors and tongue discolouration

Introduction

Proton pump inhibitors (PPIs) are widely *used for the treatment of oesophageal reflux disease, treatment and prophylaxis of (NSAID-associated) duodenal and benign gastric ulcers and relief of dyspeptic symptoms* [1-5]. The PPIs available in the Netherlands are: esomeprazole (Nexium®), lansoprazole (Prezal®), omeprazole (Losec®), pantoprazole (Pantozol®) and rabeprazole (Pariet®). Their mechanism of action 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 [1-5].
Tongue discolouration is an, often harmless, abnormal colour change of the tongue. It can be caused by an altered oral microbial growth. Tongue discolouration is not mentioned as possible adverse drug reaction in the SmPCs of PPIs [1-5]. Here, the reports received by the Netherlands Pharmacovigilance Centre Lareb concerning tongue discolouration associated with the use of PPIs will be discussed.

Reports

On July 14, 2009, the database of the Netherlands Pharmacovigilance Centre Lareb contained eight reports (Table 1) concerning tongue discolouration in association with the use of a proton pump inhibitor. In two of these patients a black (hairy) tongue was reported with concomitant use of omeprazole and an antibiotic. As a black (hairy) tongue is a well known ADR of antibiotics these reports are not mentioned in Table 1.

Table 1. Reports of tongue discolouration associated with the use of proton pump inhibitors.

Patient, sex, age	Drug, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
A 77525 F, 6	omeprazole (Losec® mups)		tongue discoloration (yellow)	days discontinued recovered + rechallenge
B 84060 F, 44	omeprazole (omeprazole actavis) prophylaxis	ibuprofen	tongue discoloration (black)	2 days discontinued recovered a week after discontinuation
C 25222 M, 28	pantoprazole (Pantozol®)		tooth disorder saliva increased bitter taste white tongue	not reported discontinued recovering
D 32230 F, 78	omeprazole (Losec® mups)	acetylsalicylic acid oxazepam	tongue discolouration (orange) dry mouth taste perversion	22 months discontinued recovering
E 19497 F, 75	omeprazole (Losec® capsule)	colestyramine mogadon simvastatin loratadine beclometasone (nasal)	taste alteration malaise vomiting tongue discolouration (red/black)	2 days discontinued not reported

Patient, sex, age	Drug, indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
F 48484 M, 16	omeprazole pantoprazole (Pantozol®)	nifedipine	tongue discolouration (orange)	4 months discontinued not recovered (tongue discolouration started during omeprazole used and continued when substituted to pantoprazole)

Two patients (A, B) recovered after withdrawal of the drug. The other four patients (C, D, E, F) were not recovered or were recovering at time of reporting. A positive rechallenge was reported in one patient (A). The reported colour of the tongue varied: red/black (E), white (C), yellow (A) and black (B) were reported once and an orange discolouration of the tongue was reported twice (D, E). Patient D takes the drug in the evening; the discolouration of the tongue diminishes during the day. The time between start of the drug and discolouration of the tongue varied from two days to almost two years.

Other sources of information

SmPC

None of the PPI SmPCs mentions tongue discoloration as possible adverse drug reaction [1-5].

Literature

Tongue discolouration has been associated with the use of PPIs as eradication therapy combined with antibiotics [6]. None of the proton pump inhibitors has been associated with tongue discolouration when used as single therapy before.

Databases

On July 14, 2009, reports of PPIs and tongue discoloration were disproportionally present in both the Lareb and the WHO database (Table 2). Although it must be taken into account that of the WHO-cases 24 patients used antibiotics concomitantly (11x lansoprazole, 9x omeprazole, 2x pantoprazole, 1x esomeprazole, 1x rabeprazole).

Table 2. The reporting odds ratios of PPIs and tongue discolouration in the database of the Netherlands Pharmacoviglance Centre Lareb and the WHO.

Drug and ADR	Number of reports	ROR (95% CI)
PPI and tongue discolouration	Lareb: 6	2.4 (1.1-5.5)
	WHO (omeprazole): 40	3.1 (2.3-4.3)
	WHO (pantoprazole): 8	3.4 (1.7-6.7)
	WHO (esomeprazole): 12	2.2 (3.8-6.7)
	WHO (lansoprazole): 22	3.8 (5.7-8.7)
	WHO (rabeprazole): 5	1.3 (3.2-7.8)

Prescription data

The increasing number of patients using PPIs in the Netherlands is shown in Table 3.

Table 3. Number of PPI users in the Netherlands between 2005 and 2008 [7]

Drug	2005	2006	2007	2008
omeprazole	762,460	895,440	1,026,000	1,260,000
pantoprazole	413,640	458,260	504,250	575,570
lansoprazole	28,096	26,712	23,700	23,489
rabeprazole	67,276	70,748	68,749	77,624
esomeprazole	225,350	256,730	280,900	325,090
Total	**1,496,822**	**1,707,890**	**1,903,599**	**1,936,683**

Mechanism

The decreased gastric acid production caused by PPIs leads to an increased pH in the stomach and in the oral saliva [8]. An increased oral pH could affect oral microbial growth [9]. PPIs can also influence oral microbial growth by causing a decreased saliva production [1-5]. Alterations in oral microbial flora can lead to tongue discolouration. Overgrow of chromogene micro-organisms on the tongue papillaes and colorings can be responsible for discolouration of the tongue [11]. Another possible explanation is the use of red, black and yellow ferric oxide (E172) in Losec® capsules and MUPS, Pantozol® tablets, Prezal® capsules, Pariet® tablets and Nexium® tablets [1-5,10], although no supportive literature for this possible mechanism was found. Patient A, C, D, E and F in Table 1 used one of these formulations.

Discussion

PPIs can probably induce tongue discolouration due to their ability to decrease saliva production and increase the pH of the oral mucosa and therefore cause an altered microbial flora. Six cases of tongue discoloration were reported in association with PPIs, including one patient with a positive rechallenge. No supportive case reports for this association were found. This association was disproportionally present in both the Lareb and the WHO database.

Not all patients were recovered 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 [10]. Possible other causes for this adverse event could be the use of red, back and yellow ferric oxide (colour) in the formulations and, for example, cigarette smoke and alcohol use [10,12].

The time to onset was a couple of days in four patients (A, B, C, E) and respectively four and 22 months in patients D and F. This could indicate that two different mechanisms for PPI induced tongue discolouration exist: altered microbial flora and discolouration by the colourant used in the capsule or tablet.

Conclusion

Tongue discolouration should be added as possible adverse drug reaction in the SmPCs of all proton pump inhibitors.

References

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3. Dutch SPC Pariet® (version date: 23-9-2008, access date: 8-7-2009) http://db.cbg-meb.nl/IB-teksten/h23210.pdf.
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This signal has been raised on October 2009. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbg-meb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).