Proton pump inhibitors and fundic gland polyps

Introduction

The first proton pump inhibitor (PPI), omeprazole (Losec®, Buscozol®), was introduced in 1988 and followed by lansoprazole in 1992 (Prezal®), pantoprazole in 1995 (Pantozol®, Pantorc®, Ipraalox®), rabeprazole in 1997 (Pariet®) and esomeprazole in 2000 (Nexium®). PPIs are indicated for the treatment of gastroesophageal reflux disease, gastric and duodenal ulcer, Zollinger-Ellison syndrome, in combination with antibiotics for the eradication of Helicobacter pylori and as prophylaxis (NSAIDs) [1-5]. PPIs inhibit the H⁺/K⁺-ATPase enzyme in the gastric mucosal parietal cells, which is responsible for H⁺ secretion in exchange for K⁺ in the gastric lumen [6]. Generally, PPIs have a mild adverse drug reaction (ADR) profile. The most common ADRs are headache and gastrointestinal symptoms like abdominal pain, constipation, diarrhoea, flatulence and nausea/vomiting [1-5]. Depending on the indication, PPIs are used short-term and long-term. Especially during long-term use new and potential ADRs are detected [7-9]. The current observation describes the possible association between PPIs and fundic gland polyps (FGPs).

Polyps are abnormal growths in mucous membranes and commonly found in the colon, stomach, uterus and nose. There are several types of gastric polyps, including fundic gland polyps (FGPs), hyperplastic polyps, and adenomas, which are associated with different clinical contexts. FGPs are mainly located in the body and the fundus of the stomach, and are tiny sessile polyps of the acid-secreting gastric mucosa. FGPs occur in several distinct clinical contexts, for example sporadic, in familial adenomatous polyposis (FAP), in Zollinger-Ellison syndrome and in gastrinoma induced hypergastrinemia. Sporadic FGPs account for approximately 50% of all gastric polyps and may be observed in up to 1.9% of patients undergoing upper gastrointestinal endoscopy [10]. Usually, FGPs are asymptomatic and incidentally discovered at endoscopy. But in some cases they can reach a size which could cause symptoms like abdominal pain and vomiting. Normally sporadic FGPs have low malignant potential, but FGPs in patients with FAP often show dysplasia which seldom progress to cancer [11-13].

Reports

Netherlands Pharmacovigilance Centre Lareb

In the period from December 23rd 1996 until June 30th 2015, the Netherlands Pharmacovigilance Centre Lareb received 8 reports of gastric polyps associated with the use of a PPI [14]. In two reports the gastric polyps are specifically reported as FGPs. The details of the received reports are presented in table 1.

Table 1. Reports of gastric polyps associated with the use of a PPI

<table>
<thead>
<tr>
<th>Patient, Number, Sex, Age, Source</th>
<th>Drug, daily dose Indication for use</th>
<th>Concomitant medication</th>
<th>Suspected adverse drug reaction</th>
<th>Time to onset, Action with drug, outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>A, 79409, F, 71 years and older, consumer/MAH</td>
<td>pantoprazole 20 mg gastroesophageal reflux</td>
<td>levothyroxine sodium, losartan</td>
<td>gastric polyps</td>
<td>7 months, unknown, not recovered</td>
</tr>
<tr>
<td>B, 195789, F, 71 years and older, pharmacist</td>
<td>pantoprazole 40 mg 1 time a day, prophylaxis</td>
<td>folic acid, methotrexate, nebivolol, salmeterol/fluticasone, hydroxychloroquine, losartan/hydrochlorothiazide</td>
<td>gastric polyps</td>
<td>7 years, drug withdrawn, recovered (polypectomy performed)</td>
</tr>
<tr>
<td>C, 157282, M, 71 years and older, pharmacist</td>
<td>omeprazole 40 mg 1 time a day, prophylaxis against drug-induced ulcer (NSAIDs)</td>
<td>carbasalate calcium, calcium/calcium/calcium, alendronic acid, metoprolol, valproic acid, salbutamol, midazolam, nifedipine, acenocumarol, simvastatin</td>
<td>gastric polyps</td>
<td>6 years, no change, not recovered</td>
</tr>
<tr>
<td>D, 24950, M, 51-60 years, physician</td>
<td>omeprazole 20 mg 1 time a day, reflux esophagitis</td>
<td>calcium carbonate/magnesium carbonate</td>
<td>gastric polyps</td>
<td>4 years, dose not changed, unknown</td>
</tr>
</tbody>
</table>
Patient A
The concomitant medication has not been associated in literature with polyps as ADR.

Patient B
The patient underwent a polypectomy and recovered. The prophylactic use was described as gastric protection. None of the concomitant medication has been associated in literature with the development of polyps.

Patient C
The report mentions specifically fundic gland cysts. The medical history indicates that the patient had polyps in the ascending colon. During the first five years the patient used 20 mg omeprazole a day and during the last two years the dose was increased to 40 mg a day. None of the concomitant drugs are associated in literature with polyp formation. Statins use may even have a protective effect against the development of colorectal adenomatous polyps [15].

Patient D
Fundic gland polyps were discovered during a gastroscopy and located in both the fundus as the body of the stomach. Past drug therapy indicates ranitidine for one year.

Patient E
Five years after the start of pantoprazole the gastroenterologist discovered a few small polyps in the patient’s stomach. Again five years later, the patient underwent laparoscopic fundoplication. During this surgery the gastroenterologist discovered that the whole stomach was filled with polyps.

Patient F
The reporter mentioned hyperplasia in stomach/gastric polyps.

Patient G
Besides gastric polyps the reporter mentioned duodenal polyps as well.

Patient H
The patient showed growth of existing polyps of ½ cm to 1 cm in two years and a vigorous increase in the number of polyps. None of the concomitant medication is associated with polyp formation.
Eudravigilance

The Eudravigilance database contains 182 reports, including the 8 reports from Lareb, of gastric polyps with the use of a PPI (43 omeprazole, 73 esomeprazole, 31 lansoprazole, 17 pantoprazole and 10 rabeprazole). A case by case review of these reports strengthen the association. From the 182 reports, 26 report specifically report FGPs of which in 14 histology is described in the report. Some of the well documented FGPs reports are described in detail in the addendum. Furthermore there are many reports of fundal gastric polyps as well, but it cannot be excluded that these polyps potentially concern hyperplastic polyps or adenomatous polyps [16].

Other sources of information

SmPC

Besides in the Dutch SmPC for omeprazole, gastric polyps or related ADRs are not mentioned in the Dutch SmPC of the PPIs pantoprazole, lansoprazole, rabeprazole and esomeprazole. The Dutch SmPC of omeprazole mentions that during long-term use an increased frequency of gastric glandular cysts have been reported. These changes are a physiological consequence of inhibition of acid secretion. The changes are benign and appear to be reversible [1-5].

Polyps are described in several ways as an ADR in all US SmPCs of PPIs. The US SmPC of pantoprazole mentions that benign polyps were seen during preclinical studies. During treatment with omeprazole gastric FGPs have been noted rarely. The incidence of hyperplasia of the enterochromaffin-like (ECL) cells increased with time. The US SmPC of esomeprazole and lansoprazole describe respectively, benign polyps and gastric nodules/fundic gland polyps [17].

Literature

The possible relationship between polyps and PPI use is extensively described in the literature [18-22]. However, the data are not conclusive. Some studies suggest that long-term therapy leads to the development of FGPs. Others consider that FGPs are an incidental finding or the result of an underlying disease. Zelter et al. concludes that PPI use was the strongest risk factor associated with the presence of FGPs. PPI intake was detected in 49 patients with FGPs (63.6%) and 264 without FGPs (15.5%) (p<0.0001). This prospective study examined in an outpatient facility 1,780 patients who underwent a gastroduodenal endoscopy. PPI intake for at least 12 months, female gender and age were evaluated as risk factors. The three variables remained significant in the multiple model: PPI intake p<0.0001, OR 9.00 (95% CI 5.44-14.89); female gender p=0.0001, OR 2.95 (95% CI 1.69-5.15); age: p=0.001, OR 1.03 (95% CI 1.01-1.05) [19]. Another larger Chinese study investigated patients (n=10,904) who underwent gastroduodenal endoscopies. The use of PPIs, female sex and H. pylori infection were statistically evaluated. Age (p<0.01 OR 1.69 (95% CI 1.31–2.18)) and the long-term use of PPIs (P<0.01 OR 14.11 (95% CI 4.15–47.93)) were risk factors for the presence of FGPs. Using PPIs for longer than 12 months were defined as long-term use of PPIs [18].

In contrast to these studies, a prospective study involving 105 patients (PPI users and non-users) undergoing upper-gastrointestinal endoscopy, concludes that chronic use of PPIs for the duration for at least 6 months was not associated with significant gastric changes. The subjects underwent biopsies of different regions of the stomach, a visual evaluation of the presence of polyoid or epithelial hyperplasia and gastrin levels were measured [20]. In addition a retrospective 12-month study from Vieth et al. compared 2,251 patients without H. pylori infection receiving PPI therapy (duration of treatment at least 4 weeks) with a control group of 28,096 patients who did not have H. pylori infection and were not receiving PPI therapy. No significant differences were present between the groups with respect to the presence of gastritis or age or sex. The study concludes that a causal relationship between PPI therapy and FGPs is unlikely [22]. A drawback of these last two studies might be a short follow-up time. Based on the described reports and a retrospective analysis from Choudhry et al. FGPs seem to occur mainly after long-term use. Choudhry et al. observed FGPs after a mean PPI treatment of 32.5 months [23].

Databases

Table 2. Reporting odds ratios of PPIs and gastric polyps in the database of the Netherlands Pharmacovigilance Centre Lareb, the WHO and the Eudravigilance (EMA) database [14,16,24].

<table>
<thead>
<tr>
<th>Drug and ADR</th>
<th>Number of reports</th>
<th>ROR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PPI and gastric polyp</td>
<td>Lareb:8</td>
<td>40.7 [13.32-124.52]</td>
</tr>
</tbody>
</table>

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**Prescription data**

Table 3. Number of PPI users in the Netherlands between 2010 and 2014 [25]. The decreasing number of users in 2012 is due to the fact that short-term PPI therapy is no longer compensated by the Dutch healthcare insurance.

<table>
<thead>
<tr>
<th>Drug</th>
<th>2011</th>
<th>2012</th>
<th>2013</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Omeprazole</td>
<td>1,690,000</td>
<td>980,240</td>
<td>1,029,000</td>
<td>1,078,000</td>
</tr>
<tr>
<td>Pantoprazole</td>
<td>696,690</td>
<td>528,110</td>
<td>581,930</td>
<td>648,820</td>
</tr>
<tr>
<td>Lansoprazole</td>
<td>17,416</td>
<td>14,786</td>
<td>13,945</td>
<td>13,260</td>
</tr>
<tr>
<td>Rabeprazole</td>
<td>56,376</td>
<td>39,264</td>
<td>34,666</td>
<td>32,140</td>
</tr>
<tr>
<td>Esomeprazole</td>
<td>336,130</td>
<td>243,370</td>
<td>233,470</td>
<td>228,320</td>
</tr>
</tbody>
</table>

**Mechanism**

There is a potential plausible mechanism for PPI induced FGPs. PPIs are powerful inhibitors of acid secretion and induce hypergastrinemia. The main goals of gastrin are to stimulate acid secretion and mucosal cell growth. In response to pH elevation by e.g. meal related nutrients or PPI therapy, G-cells found in the antrum of the stomach secrete gastrin, which in turn indirectly stimulates gastric acid secretion via release of histamine from the ECL cells and directly by stimulating the parietal cells. Both histamine and gastrin stimulate the parietal cells, which are localized in the fundus and body of the stomach, to secrete hydrochloric acid. Due to continuous stimulation of the parietal cells, hypertrophy and hyperplasia could occur [19,26]. On the other hand, it was observed that hypergastrinemia was not related to FGP formation [27]. Fossmark et al. demonstrated no difference in levels of gastric pH, serum gastrin and serum chromogranin A (an ECL marker) between PPI users with and without FGPs.

**Discussion and conclusion**

The Netherlands Pharmacovigilance Centre Lareb received 8 reports of gastric polyps associated with the use of PPIs (3 pantoprazole, 4 omeprazole, 1 esomeprazole). The gastric polyps were mostly identified after several years of drug use. In only two reports (C and D) the gastric polyps were further specified, as FGPs. In the other reports received by Lareb it cannot be ruled out for sure that the polyps concerned other types than FGPs. Several indications for PPI therapy, like *H. pylori* infection, gastroesophageal reflux disease and gastric ulcers are associated with hyperplastic polyps. These polyps are the result of hyper-regenerative epithelium in response to an underlying chronic inflammatory stimulus and may typically develop in the antrum of the stomach, although they can arise in the entire stomach. Imaging FGPs reveals a nonspecific pattern that can be seen in hyperplastic polyps as well. Therefore a causality assessment of polyps of the stomach requires identification of the specific polyp, information about the specific risk factors and results of preceding endoscopic and pathological investigations of the stomach [11,13]. Furthermore, in the reports received by Lareb information about risk factors like e.g. FAP were not specifically reported. Nor was there information about *H. pylori* status in the reports received by Lareb, what might have been informative. The incidence of *H. pylori* infection is very low in patients with FGPs [11]. This is in contrast with patients with hyperplastic polyps where an *H. pylori* infection is common [11]. However, the Eudravigilance database contains 26 reports where FGPs were specifically reported, and in some of the cases it was specifically described that other causes were excluded. In some cases there were also positive dechallenges present, although in the literature regression was also described to occur spontaneously [28]. The association is extensively described in the literature, however still inconclusive. The association is supported by a plausible pharmacological mechanism and a statistically significant disproportionality in the database of Lareb, Eudravigilance and the WHO. Although the literature has not yet resulted in a consensus, the reports from the Eudravigilance database with the reported exclusions of other causes and positive dechallenges suggest a possible relation between FGPs and the use of a PPI, although a
causal relationship remains hard to establish. Long-term use is possibly an important factor, so further investigation of the PSUR with focus on long-term therapy is recommended. Noteworthy is the discrepancy in information in the Dutch SmPCs for all the PPIs as well. Only the SmPC of omeprazole draws attention to this possible association and unifying is therefore needed.

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

References

This signal has been raised on October 2015. It is possible that in the meantime other information became available. For the latest information, including the official SmPC’s, please refer to the website of the MEB [http://www.cbg-meb.nl/]