1.1. (Es)omeprazole and vitamin B12 deficiency

Introduction

Omeprazole, a substituted benzimidazole, and esomeprazole, the S-isomere of omeprazole belong to the class of proton pump inhibitors (PPIs) which strongly reduce gastric acid secretion by the parietal cell. The pharmacological mechanism of action is based on inhibiting 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].
Proton pump inhibitors (PPIs) are widely approved for *the treatment of oesophageal reflux disease, treatment and prophylaxis of (NSAID-associated) duodenal and benign gastric ulcers and relief of dyspeptic symptoms* [2,3]. The net effect is a raise of the pH which can affect the absorption of other drugs and nutrients [1].
The pharmacodynamic activity of omeprazole and esomeprazole is comparable. Omeprazole has been registered since 1988 and is available as capsule, tablet and powder for infusion. Esomeprazole has been registered since 2000 and is available as tablet, capsules, granules for oral suspension, and powder for injection or infusion.

Vitamin B12 is found only in food of animal origin such as meat, liver, and to a lesser extend dairy products. Vitamin B12 functions as a co-enzyme in the production of DNA. It is indispensable for the functioning of all organ systems, but the deficiency is reflected first in blood disorders. Other disorders, such as neurologic complications occur later on [1].

The current observation describes the association between (es)omeprazole and decreased vitamin B12 serum levels and vitamin B12 deficiency.

Reports

On July 26, 2011 the database of the Netherlands Pharmacovigilance Centre Lareb contained 4 reports concerning decreased vitamin B12 levels or vitamin B12 deficiency (MedDRA preferred terms vitamin B12 deficiency and vitamin B12 decreased) with the use of (es)omeprazole. Specifications are shown in Table 1 below.

Table 1. Reports of decreased vitamin B12 associated with the use of (es)omeprazole

Patient, Sex, Age, reporter	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A, 110192 M 41-50 years Consumer	esomeprazole tablet enteric-coated 40 mg 1dd1 dyspepsia		vitamin B12 deficiency	2 years dose not changed not recovered
B 92278 M 51-60 years Pharmacist	esomeprazole enteric-coated 20 mg 1dd1 dyspepsia	pravastatin tablet 20 mg	vitamin B12 decreased; haemoglobin decreased	3 years drug withdrawn recovered
C 110469 F 31-40 years Physician	esomeprazole enteric-coated 20 mg 2dd1 prophylaxis	NSAID NOS	vitamin B12 deficiency	no information available

Patient, Sex, Age, reporter	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
D 102402 F 51-60 years Pharmacist	omeprazole capsule enteric-coated 40 mg 1dd1 dyspepsia	nitrazepam tablet 5 mg bromazepam tablet 3 mg mirtazepine tablet 30 mg	vitamine B12 deficiency	7 years dose not changed not recovered

Specific characteristics of the reports are described below:

Patient A, a male aged 41-50 years experienced symptoms of vitamin B12 deficiency after 2 years use of esomeprazole for dyspepsia. The patient received monthly vitamin B12 injections for supplementation. At the time of reporting the patient had not recovered.

Patient B, a male aged 51-60 years experienced a decreased blood level of vitamin B12 after 3 years use of esomeprazole for dyspepsia. The patient recovered.

Patient C, a female aged 31-40 years experienced vitamin B12 deficiency after using esomeprazole as prophylaxis for NSAID therapy. The latency time is not reported. The patient outcome is not reported.

Patient D, a female aged 51-60 years experienced vitamin B12 deficiency after 7 years use of omeprazole for dyspepsia. The patient was treated with hydroxocobalamin injections after a vitamin B12 level of 182 μmol/L (< 175 μmol/L is characteristic for a deficiency [4]). At the time of reporting the patient had not recovered.

Other sources of information

SmPC

Vitamin B12 deficiencies or decreased absorption are not mentioned in the SmPC for esomeprazole containing products [3].
Decrease in absorption of vitamin B12 due to hypochlorhydria is mentioned in omeprazole containing products in the ‘special warning and precautions for use’ section of the SmPC [2].
Decrease in absorption of vitamin B12 due to hypochlorhydria is mentioned in pantoprazole containing products in the ‘special warning and precautions for use’ section of the SmPC [5]
Vitamin B12 deficiencies or decreased absorption are not mentioned in the SmPC for lansoprazole containing products [6]
Vitamin B12 deficiencies or decreased absorption are not mentioned in the SmPC for rabeprazole containing products [7]

Literature

A Medline search revealed some publications on the possible association between (es)omeprazole and vitamin B12 deficiency. A few case reports [8,9], one clinical trial in patients with Zollinger-Ellison Syndrome (ZES) [10], and one rather small clinical trial in 10 healthy volunteers [11] were found. They all clearly show that omeprazole therapy, after 3 to 4 years, will decrease the absorption of

vitamin B12 by preventing its cleavage from dietary proteins. According to the publication, ZES patients and elderly are especially at risk.

The 2 case reports show the decrease in vitamin B12 over time in a period of 4 years of PPI use. The cases are supported with vitamin B12 serum levels [8,9]. The clinical trial in patients with ZES shows that after omeprazole treatment of 4.5 years, vitamin B12 levels, but not serum folate levels or any hematological parameter, were significantly lower, especially in those with omeprazole-induced sustained hyposecretion or complete achlorhydria [10]. [12]

The small clinical trial shows that healthy volunteers taking widely used omeprazole doses of 1dd 20mg and 1dd 40mg led to significantly decreased vitamin B12 absorption within 2 weeks [11].

Databases

On July 20, 2011 the database of the Netherlands Pharmacovigilance Centre Lareb contained one case of vitamin B12 decreased and 3 cases of vitamin B12 deficiency in association with (es)omeprazole. This resulted in a reporting odds ratio (ROR) of 9.7 (95% CI: 2.8-33.9) for vitamin B12 deficiency.
The WHO database of the Uppsala Monitoring Centre contained 55 reports of vitamin B12 deficiency and 5 reports of vitamin B12 decreased following omeprazole administration, and contained 23 reports of vitamin B12 deficiency and 4 reports of vitamin B12 decreased following esomeprazole administration. The combined reporting odds ratio for esomeprazole and omeprazole with vitamin B12 deficiency and vitamin B12 decreased was 13.4 (95% CI: 10.8-16.7).
A summary of the above is shown in Table 2.

Table 2. Reports of vitamin B12 deficiency associated with (es)omeprazole in the WHO database

ADR (MedDRA PT)	Drug	Number of reports	ROR (95% CI)	
Vitamin B12 deficiency or Vitamine B12 decreased	esomeprazole or omeprazole	87	13.4	(10.8-16.7)

On August 15, 2011, the Eudravigilance database contained 21 reports of decreased levels or deficiency of vitamin B12, which was reported disproportionally (ROR = 4.2, 95% CI: 2.7 – 6.6). It concerns thirteen females and eight males. The median age of the patients was 68 years (range 38 – 81 years). In one case, the age was not reported. A total of seventeen reports were classified as serious, three were non-serious and in one case the seriousness was not reported.

Prescription data

The number of patients using omeprazole and esomeprazole in the Netherlands is shown in table 4.

Table 4. Number of patients using (es)omeprazole in the Netherlands between 2006 and 2010 [12].

Drug	2006	2007	2008	2009	2010
Omeprazole	895,460	1,039,000	1,220,000	1,376,000	1,604,000
Esomeprazole	256,770	284,320	310,670	344,680	342,530

Mechanism

Vitamin B12 is a water-soluble vitamin derived from microorganisms, and the vitamin is tightly bound to dietary protein. Hydrochloric acid and pepsin release vitamin B12 from dietary protein in the stomach where it binds to salivary R proteins. R proteins pick up vitamin B12 and transport it through the stomach into the small intestine. R proteins are found in many fluids in the human body including saliva and stomach secretion. After alteration of R proteins by pancreatic enzymes, vitamin B12 is rapidly transferred to intrinsic factor to form a complex that is resistant to proteolysis. Once the intrinsic factor-vitamin B12 complex is formed in the upper jejunum, it remains intact until it adheres to specific receptors in the distal ileum.
(Es)omeprazole acts by inhibiting the H^+/K^+ ATP-ase, a proton pump that seems to be specific to the gastric parietal cells. Prolonged omeprazole treatment can result in vitamin B12 deficiency by three possible mechanisms: 1) in hypo- or achlorhydria, protein-bound vitamin B12 may not be adequately released from food for transfer to R protein and intrinsic factor; 2) omeprazole may decrease intrinsic factor secretion after long-term therapy even though no effect on intrinsic factor secretion occurred after a single intravenous dose of omeprazole, and 3) achlorhydria causes gastric bacterial overgrowth that may accelerate the development of vitamin B12 deficiency by producing vitamin B12 analogs that compete with absorption and use of the vitamin [11].

Discussion and conclusion

Lareb received 4 reports concerning ‘vitamin B12 deficiency’ or ‘vitamin B12 decreased’ with the use of (es)omeprazole. In one case a positive dechallenge has been reported, in two cases the patient did not recover. One should expect more reports from omeprazole than for esomeprazole, since its longer on the market and more widely prescribed. Probably due to increased reporting shortly after introduction of a drug on the market, we received more reports from esomeprazole.
Latencies were rather consistent between cases, varying from two to three years with one outlier of seven years. The period of seven years could partially be explained by the nature of the symptoms which are often not immediately recognized and diagnosed. The latency of 2 years approaches the time period after which vitamin B12 deficiency may be expected. All together they can fit in the latency period found in literature [4].
According to the information Lareb received, the patients did not belong to the risk groups, ZES patients and elderly, associated with vitamin B12 deficiencies as a consequence of PPI use. This indicates that this association might be more common than previously assumed. However, since there is no information on the pre existence of vitamin B12 deficiency before starting with the proton pump inhibiter, protopathic bias cannot be excluded
Of the mentioned possible mechanisms, a decrease in absorption of vitamin B12 due to (es)omeprazole induced hypo- or achlorhydria is most plausible, most cited and already included in the SmPC of omeprazole containing products. According to this mechanism, all proton pump inhibiters share the property to decrease vitamin B12 absorption.

- These cases indicate the existence of vitamin B12 deficiency associated with the use of proton pump inhibiters.

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