

Omeprazole suspension and regurgitated gastric content discoloured

Introduction

Omeprazole (Losec®), a substituted benzimidazole, belongs to the class of proton pump inhibitors (PPIs) which strongly reduce gastric acid secretion by the parietal cell [1]. 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].

Omeprazole has been registered since November 1988 and *is indicated for use in gastroduodenal ulcer disease, acid relate dyspepsia, reflux-oesophagitis or reflux symptoms and in Zollinger-Ellison's syndrome*. Other PPIs available on the Dutch market are esomeprazole, lansoprazole, pantoprazole and rabeprazole [2].

The stability of omeprazole is pH dependent. Below a pH value of 4 omeprazole rapidly degrades to a dark purple compound [4], possibly leading to a reduced effectiveness. Therefore the registered dosage forms of omeprazole contain an enteric coating that prevents the release of the drug before it reaches the intestine.

The use of omeprazole in children under the age of one year is off-label. Nevertheless, omeprazole is regularly used by paediatricians to treat reflux symptoms in this group of patients. There is no registered liquid omeprazole product available and patients who have difficulties swallowing, require extemporaneous liquid dispersion of solid dosage forms or a non-registered omeprazole suspension. According to the Dutch National Formulary for Children [3] the granules in omeprazole capsules can be dispersed in a slightly acid liquid (e.g. fruit juice, yoghurt or buttermilk). Tablets contain enteric-coated granules and can be disintegrated in water, and subsequently administered by probe.

There are several pharmaceutical compounding companies (CENTRALE VAL BV, BUFA and FAGRON) producing a kit (OMEPRAZOL AND SYRSPEND ALKA KIT 2 MG/ML) for the preparation of omeprazole suspension. This concerns a non-registered product. The kits are supplied to other pharmacies as well and contain the active pharmaceutical ingredient omeprazole and calciumcarbonate in order to prepare an alkaline suspension. This type of suspension is not recommended in the Dutch National Formulary for Children because of safety concerns [3].

In October 2013 the Netherlands Pharmacovigilance Centre Lareb published a signal about the association between omeprazole and gastric content discolouration. This signal involved four reports of discoloured gastric contents when using tablets and capsules. The tablets were dissolved in water and the capsules were opened to administer the coated granules content orally. The conclusion of this signal was that dissolving the grains in water or administering the granules into the cheek mucosa may lead to too rapid dissolution of the coating. In combination with delayed gastric emptying in children, this may lead to a reduced effect due to the fact that omeprazole comes into contact with acidic gastric contents [5].

At the time of the signal in October 2013 the database of Lareb hadn't receive any reports of discoloured gastric contents when using the omeprazole suspension. On July 6th 2017 the Lareb database contained six reports of discoloured gastric contents associated with use of an omeprazole suspension. The current observation describes the association between omeprazole suspension and gastric content discolouration.

Reports

Between April 11th 2014 and July 6th 2017, the Netherlands Pharmacovigilance Centre Lareb received six reports of discoloured gastric content associated with the use of an omeprazole suspension. The reports are listed in Table 1.

Table 1. Reports of discoloured regurgitated gastric content associated with the use of omeprazole

Report date, Patient, Sex, Age, Reporter	Drug, dose Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug Outcome
April 11 th , 2014 A 171886 M, 0 – 1 years Consumer	Omeprazole susp oral 2mg/ml (kit) BRAND UNKNOWN 0,5 2dd Reflux oesophagitis		Sputum discoloured (+photo)	minutes unknown unknown
March 19 th , 2015 B 193977 M, 0 – 1 years Pharmacist	Omeprazole susp and SYRSPEND SF ALKA KIT 2mg/ml BRAND FAGRON 1 1dd unknown indication		Pharmaceutical product complaint Sputum discoloured	unknown not changed recovered
Aug 12 th , 2015 C 202716 M, 0 – 1 years Physician	Omeprazole susp BRAND UNKNOWN 4 1dd Reflux oesophagitis	Lactulose sir	Sputum discoloured (+photo)	55 days dose not changed unknown
June 8 th , 2016 D 220389 M, 0 – 1 years Physician	Omeprazole susp and SYRSPEND SF ALKA KIT 2mg/ml BRAND FAGRON 6 ml Reflux oesophagitis		Sputum discoloured (+photo)	5 weeks unknown not recovered
November 2 nd , 2016 E 228538 F, 0 – 1 years Pharmacist	Omeprazole susp and SYRSPEND SF ALKA KIT 2mg/ml BRAND FAGRON 2,5 ml (5mg) 1dd Gastrooesophageal reflux	Lactulose sir	Sputum discoloured	1 day moment of intake changed, recovered
February 13 th , 2016 F 234400 M, 0 – 1 years Pharmacist	Omeprazole susp BRAND UNKNOWN 2,5 1dd Reflux oesophagitis		Sputum discoloured	6 weeks dose not changed not recovered

Note: In these reports "Sputum discoloured" was chosen as MedDRA-term for coding. However the reports concerns regurgitated discoloured gastric content.

In case A the child already had regurgitated discoloured gastric content while using Nexium® (esomeprazole) granulate. The reporter indicated that a change of food (because of cow's milk allergy) could be another cause. This case was strengthened by a photo of the purple discoloration of the regurgitated gastric content.

The reporter (pharmacist) of case B contacted Fagron (the manufacturer of the suspension kit) who told him that purple discoloration can occur when the prepared suspension is not stored in the fridge. In case D the reporter indicated that due to the earlier signal Lareb wrote in 2013, he found out about the cause of discoloration of the gastric content. This case as well as case C was strengthened by a photo of the purple discoloration of the regurgitated gastric content.

In case E the suspension was first administered on empty stomach after which purple discoloration of the gastric content occurred. Later on the child was first fed (milk) to create a less acidic gastric environment and reduce the risk of degradation of omeprazole in the stomach.



Picture 1: Photo's gastric contents discoloration of cases A, C and D (left to right)

Other Sources of information

Product information of the pharmaceutical compounding companies

Because the omeprazole suspension kits aren't registered by the Medicines Evaluation Board (MEB) there are no SmPC's available. Fagron, one of the producers of the omeprazole suspension kit, provides a preparation instruction for the pharmacy but doesn't provide any product information for the patient. On the website of Fagron a brochure can be found about the Syrspend® SF suspension Alka Kit. This brochure provides the following information: "Syrspend® SF Alka is buffered to pH > 7 for APIs (active pharmaceutical ingredients) that are not stable in an acidic environment (such as omeprazole). Shelf life of omeprazole suspension: 60 days stable when stored in a refrigerator between 2 °C and 8 °C". The brochure also contains a disclaimer indicating that there is no statement regarding use, safety, efficacy or bioavailability [6]. According to the representative of BUFA, that is also a pharmaceutical compounding company, the product of BUFA is the same product as that of Fagron [7].

Literature

No literature could be found about the effectiveness and safety of omeprazole suspension kit as available in the Netherlands (OMEPRAZOL AND SYRSPEND ALKA KIT 2 MG/ML). Some literature was found about other alkaline omeprazole suspensions, but it was unclear whether these suspensions contained the same components [8,9].

The Dutch National Formulary for Children "Kinderformularium" has some safety concerns about the omeprazole suspension. In this formulary, it is stated that the suspension contains calcium carbonate (buffer) in such an amount, that side effects due to the high dose of calcium could occur, and that this issue is still insufficiently investigated. Furthermore, it is doubted whether the pH in the stomach can sufficiently be increased by the weak buffering capacity of calcium carbonate. This formulary also describes that the effect of the suspension on the gastric pH has not been investigated [3].

Mechanism

The postulated mechanism by which omeprazole can cause discoloured gastric content is by degradation of omeprazole in the acidic stomach. Omeprazole is pH dependent and decomposes in an acidic environment at a pH of less than 4 to a dark purple substance, possibly resulting in a reduced bioavailability and reduced effectiveness of the treatment [4,10].

To avoid acid-induced degradation of omeprazole in the acidic stomach, the omeprazole suspension is made with the alkaline base SyrSpend® SF Alka, which is buffered to pH > 7 by use of calcium carbonate. Assumed is, that alkaline suspension will increase the stomach pH sufficiently to avoid the acid-induced degradation of omeprazole. Nevertheless, the effect of the SyrSpend® SF Alka base on the gastric pH has never been demonstrated [3].

Discussion and Conclusion

Lareb received six reports of discoloured gastric content associated with the use of omeprazole suspension in young infants. These reports suggest that degradation of omeprazole can occur with the use of this suspension.

The Lareb signal published in 2013, about omeprazole and discolouration of the gastric content, focused on the use of tablets and capsules [5]. In the four reports described in this previous signal, the tablets were dissolved in water and the capsules were opened to administer the content with coated granules. It was concluded that dissolving the granules in water or administering the granules into the mucosa of the cheek, may lead to a too rapid dissolution of the coating. In combination with delayed gastric emptying in children, this may lead to a reduced effect due to the fact that omeprazole is in contact with the acidic stomach content and could degrade.

In case of the omeprazole suspension the situation is different. The suspension contains the active pharmaceutical ingredient omeprazole which is dissolved in an alkaline suspension base. There is no coating of omeprazole and it's unsure whether the suspension base has sufficient buffer capacity to protect the omeprazole against degradation in the acid stomach.

The Dutch National Formulary for Children "Kinderformularium" gives no recommendations on the use of the omeprazole suspension, because of concerns about effectiveness and safety of the suspension in young children. This formulary does provides instructions for the use of opened omeprazole capsules and recommends to solve the granules in a slight acid liquid [3]. Theoretically, this might not be a good advice for the administration of the omeprazole suspension, which contains the active pharmaceutical ingredient omeprazole in an alkaline suspension. It could be questioned whether healthcare professionals are aware of this.

There is no literature that supports the effectiveness of the omeprazole suspension as available in the Netherlands. At personal communication between the manufacturer Fagron and Pharmacovigilance center Lareb, the Fagron representative confirmed that the stability of the omeprazole suspension in the stomach has not been examined. It was indicated that the same suspension kit has been available in other countries for several years, but that the manufacturer hadn't received any reports of discoloured gastric content before [11].

It is recommended to investigate the efficacy and safety of the omeprazole suspension, including the use in young children, and to formulate a clear accessory intake advice.

References

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(e-mail contact with Fagron on: 08-2017)

This overview was published on November 1, 2017. It is possible that in the meantime other information became available.