

(Es)Omeprazole and regurgitated gastric content discoloured – an update

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 related dyspepsia, reflux-oesophagitis or reflux symptoms and in Zollinger-Ellison's syndrome*. Esomeprazole is the S-isomer of omeprazole. It has the same indication range as omeprazole [2].

The use of (es)omeprazole in children under the age of one year is off-label [1,2]. Nevertheless, (es)omeprazole is regularly used by paediatricians to treat reflux symptoms in this group of patients. For esomeprazole a registered granulate for oral suspension is available, but this is not the case for omeprazole. 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.

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

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, resulting in a purple/reddish regurgitated gastric content (sometimes in combination with the presence of granules) [5].

Reports

Between 2008 and February 6th 2019, the Netherlands Pharmacovigilance Centre Lareb received 11 reports of discoloured gastric content associated with the use of omeprazole (n=6) and esomeprazole (n=5).

In addition, Lareb also received ten reports of discoloured gastric content associated with the use of an omeprazole suspension. Since these latter reports are about a compounded product which is not registered through the Medicines Evaluation Board, they are not taken into account in this signal. The Dutch Healthcare Inspectorate (IGJ) was notified of these reports in 2017 [6].

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

Patient, Number, Sex, Age, Source	Drug, daily dose Indication for use	Concomitant Medication	Suspected adverse drug reaction	Time to onset, Action with drug, outcome
A NL-LRB-142718 M, 0-1 years General	omeprazole od 10mg gastroesophageal reflux		gastric content discoloured	1.5 month discontinued recovered

Practitioner				
B NL-LRB-104943 M, 0-1 years Pharmacist	omeprazole od 10mg gastroesophageal reflux		gastric content discoloured eczema	7 hours 1 day discontinued recovered
C NL-LRB-103536 M, 0-1 years pharmacist	omeprazole od 10mg gastroesophageal reflux		gastric content discoloured eczema	7 hours 1 day discontinued recovered
D NL-LRB-76097 M, 0-1 years Pharmacist	omeprazole od 10mg gastroesophageal reflux		gastric content discoloured	5.5 weeks no change not recovered
E NL-LRB-00280794, M, 51-60 years, Co-assistent	omeprazol tablet msr 40mg od for reflux oesophagitis		gastric content discoloured, vomiting	2 Days Not applicable Recovered
F NL-LRB-228924, F, 0-1 years, Hospital pharmacist	omeprazol dosage form for Gastroesophageal reflux	vigabatrine	gastric content discoloured	2 Months Action unknown Outcome unknown
G NL-LRB-206514, F, 0-1 years , Specialist doctor	esomeprazol gran voor voor susp. 10mg 1 dosage form for Drug use for unknown indication		gastric content discoloured	TTO unknown Action unknown Outcome unknown
H NL-LRB-188628, M, 0-1 years , Consumer	esomeprazol gran voor susp. 10mg 5mg for Gastroesophageal reflux		gastric content discoloured	16 Days Not applicable Outcome unknown
I NL-LRB-188421, F, 0-1 years , Pharmacist	esomeprazol gran voor susp. 10mg 5mg per 1 day for Drug use for unknown indication		gastric content discoloured	365 Days Not applicable Not recovered/
J NL-LRB-163160, F, 0-1 years , Specialist doctor	esomeprazol gran voor susp. 10mg 10mg per 1 day for Gastroesophageal reflux		gastric content discoloured	2 Days Dose not changed Not recovered
H NL-LRB-149587, F, 0-1 years, Physician	esomeprazol gran voor susp. 10mg 10mg per 1 day for Gastroesophageal reflux		gastric content discoloured	13 days Drug withdrawn Recovered

od = once a day

Although sputum discolouration was coded in MedDRA®, it is likely and plausible that sputum discolouration was confused with the reflux of discoloured gastric content.

In case A omeprazole capsules were opened and the coated particles were inserted in the buccal space. After 45 days of treatment a purple discolouration of the sputum was reported. This case was strengthened by a photo of the purple discolouration of the sputum. After discontinuation of omeprazole the purple discolouration of the sputum disappeared. Case B and C describe twins who were treated with omeprazole tablets. Before administration the tablets were dissolved in water. Seven hours after the first intake both of the twins spit out red granules. The twins also suffered from eczema located on the chest. After discontinuation of omeprazole the presence of red granules in the sputum disappeared. Eczema was recovering at the moment of reporting. These cases were also strengthened by a photo.

In case D the mother of the patient mentioned purple granules in the sputum of the patient 5.5 weeks after treatment with omeprazole capsules. The method of administration was not mentioned in this report. Considering the age of the patient, it is presumable that the capsule was opened before intake.

In case E a male aged 51-60 years experienced 'purple vomit' and vomiting following administration of omeprazol tablets 40 mg with enteric coating for reflux oesophagitis with a latency of 2 days after start. Omeprazol was withdrawn and patient recovered the day after withdrawal.

In case F a female aged 0-1 years experienced purple discolouration of vomit following administration of omeprazole for gastrooesophageal reflux with a latency of 2 months after start. Details on drug cessation and recovery are unknown. The time between omeprazole intake and feeding was increased, there is no information if this had the desired effect.

In case G a female aged 0-1 years experienced sputum discoloured (brown) following administration of esomeprazole with unknown latency. Details on drug cessation and recovery are unknown.

In case H a male aged 0-1 years experienced sputum purple discoloured following administration of esomeprazole for gastrooesophageal reflux with a latency of 17 days after start. Details on drug cessation and recovery are unknown. The reporter mentioned that it was known that the product can turn purple when the granulate is kept in water for a longer period, however not that the sputum can turn purple and that this is not mentioned in the Farmacotherapeutisch Kompas.

In case I a female aged 0-1 years experienced purple discolouration of the sputum which made beetroot colour stains in her clothes following administration of esomeprazole for unknown indication. The action taken for esomeprazole is unknown. The patient has not recovered.

In case J a female aged 0-1 years experienced sputum discoloured (purple) following administration of esomeprazole for gastrooesophageal reflux with a latency of 1 day after start. The dose for esomeprazole is not changed. The patient has not recovered. The medical history indicates that the patient was a premature baby 31 weeks.

In case H a female aged 0-1 years spit up purple granules following administration of esomeprazole for gastrooesophageal reflux with a latency of 13 days after start. At first it was thought there was spitting up blood in reflux. The drug esomeprazole was withdrawn. The patient recovered after 8 days.

Other Sources of information

SmPC

Discoloured regurgitated gastric content or alternative descriptions are not mentioned in the SmPC of (es)omeprazole [1,2].

Considering the instructions for use; In the SmPC of omeprazole capsules it is mentioned that 'if you or your child has difficulty swallowing the capsules':

- Open the capsules and swallow the contents immediately with half a glass of water or add the content in a glass of ordinary (non-sparkling) water, an acidic fruit drink (e.g. apple, orange or pineapple juice) or apple juice.
- Always stir the mixture just before drinking (the mixture is not clear). The mix should be drank immediately or within 30 minutes.
- To be sure that you have already drunk all the medicine, rinse the glass afterwards with half a glass of water, and drink it [1].

in the SmPC of esomeprazole granulate it is mentioned that the granules can be dispersed in non-sparkling water (15 ml per sachet) and has to be drank within 30 minutes of dissolution of the granules. The solution can also be administered via a probe [2]. Both SmPCs state that the granules should not be chewed or crushed [1,2].

Literature

Lareb has described a case series of six of the above-mentioned cases in *J Pediatr Pharmacol Ther* in 2016 [7] and more recently in the *Pharmaceutisch Weekblad* [8].

Cases in the literature describe this phenomenon in both children and adults; Tuleu et al. [9] report the appearance of dark purple coloured 'poppy seed'-like structures found in the aspirated stomach contents and faeces of a 3-month-old infant receiving an omeprazole liquid via nasogastric tube, prepared by dispersing an omeprazole tablet (10 mg MUPS) in water.

Beers et al. [10] report a case of a three-week-old boy who developed purple gastric juice discolouration after receiving omeprazole. Omeprazole capsules were opened and the coated particles were inserted in the buccal space, immediately followed by breastfeeding. After five weeks of treatment the boy's refluxed gastric juice contained purple particles. The case was supported with a photo. The omeprazole administration regime was changed. After administration in the buccal space the boy sucked a dummy teat for a few minutes in order to swallow the administered particles. Consequently he was breastfed. The purple particles were then observed only twice in a couple of months.

Chang et al. [11] report a case of an 87-year-old woman who suffered from purple fluid regurgitated from a nasogastric tube after esomeprazole 40 mg/d with enteric coating was started. No occult blood in the purple fluid was found and this phenomenon was resolved rapidly after adding prokinetics.

Mechanism

The postulated mechanism by which (es)omeprazole can cause discoloured gastric content is by degradation of (es)omeprazole in the acidic stomach. Omeprazole and esomeprazole are 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].

Discussion and Conclusion

Lareb received 11 reports of discoloured gastric content associated with the use of (es)omeprazole in young infants (age below 1 years is off-label use [1,2]) and one adult. In addition, Lareb also received ten reports of discoloured gastric content associated with the use of an omeprazole suspension. The Dutch Healthcare Inspectorate (IGJ) was notified of these reports in 2017 and in addition the signal was sent to the pharmaceutical compounding company [6]. These cases could be seen as additional case-evidence that discoloration of regurgitated stomach contents can occur with (es)omeprazole. In the literature similar cases for infants [9,10] and an adult [11] are described. This phenomenon is not a 'typical' adverse drug reaction but more related to quality aspects of the product. Instructions for use/dissolution of the products are given in the SmPC [1,2], from the reports it is not known in all cases how the (es)omeprazole was dissolved and administered, From the Lareb reports it is not clear if this is a sign of a *clinically relevant* reduced effect due to the fact that (es)omeprazole is in contact with the acidic stomach content and could degrade.

Nevertheless, (care-takers of) patients might find the discoloration worrisome, as is described in case J, and it is not mentioned in the product information of (es)omeprazole. Furthermore, healthcare professionals should be made aware of this phenomenon as the purple-brownish speckles in gastric content might easily be misinterpreted as signs of gastric hemorrhage.

References

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This signal has been raised on March 27, 2019. It is possible that in the meantime other information became available. For the latest information, including the official SmPC's, please refer to website of the MEB www.cbq-meb.nl