1.1. Ferrous fumarate and tooth discolouration

Introduction

Ferrous fumarate is a stable iron compound which contains 33 percent iron (Fe^{++}). The indication for this drug is *iron-deficiency anemia*.
In the human body, iron is mostly stored in the erythrocytes as hemoglobin-iron. The iron is absorbed by the mucous cells of the intestinal wall of the duodenum and first part of the jejunum. In plasma, the iron is bound to transferrin. This complex is transported to the bone marrow where it is incorporated into the hemoglobin.
Ferrous fumarate was granted marketing authorization in the Netherlands in 1992 [1].

Tooth discolouration can be classified according to the location of the stain, which can be extrinsic or intrinsic. Extrinsic discolouration is staining of the outer, superficial surface of the tooth structure. Poor oral hygiene, resulting in accumulation of dental plaque, calculus and food particles, is the most common cause of extrinsic tooth discolouration. A variety of food components like tannins in tea and coffee, tobacco and metallic compounds can also cause extrinsic discolouration. Intrinsic tooth discolouration can result from a change to the structural composition or thickness of the dental hard tissues. The extent of intrinsic discolouration can range from local to generalized. The causes are diverse: trauma, infections, caries, tooth wear, genetic defects, metabolic diseases and medication. Intrinsic discolouration is irreversible [2-4].

Reports

From 20 December 1986 until 8 June 2016 the Netherlands Pharmacovigilance Centre Lareb received ten reports concerning tooth discolouration associated with the use of oral iron preparations. Three reports concerned ferrous fumarate oral suspension (cases A, B and H), five reports concerned ferrous fumarate tablets (cases C, D, E, F, I) and in one report this was unknown (case G). There is one report of ferrous sulfate associated with tooth discolouration (case J). Three cases concerned male and seven female patients. The ages varied from two until 82 years and in one case age was unknown. The mean age was 38 years. Time to onset varied from five days until almost twelve weeks after start, with a median of fourteen days. The discolourations were described as black in four cases (E, F, G, I), grey in one case (B), brown in two (A, D), yellow also in two cases (C, H) and in one case (J) the colour was unknown. In two reports the reactions were treated through polishing by a dentist (cases B and F). Both cases recovered after treatment. Two patients used other drugs that were suspect for causing the reaction as well, these were amoxicillin/clarithromycin/pantoprazole (in case I) and doxycycline (in case E). Of both these drugs tooth discolouration is a labelled adverse drug reaction [5,6].

Table 1 Reports of tooth discolouration in the Lareb database

ID, Sex, Age, Source	Drug, daily dose, indication	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
A 5237 M, unknown, General Practitioner	ferrous fumarate oral susp 20mg/ml, 3dd2ml, unknown		tooth discolouration	1 week unknown unknown
B 18562 F, 2-4 years, Pharmacist	ferrous fumarate oral susp 20mg/ml, 3dd2ml, unknown		tooth discolouration	3 weeks drug withdrawn recovered
C 51117 F, 11-20 years, Pharmacist	ferrous fumarate tablet 200mg, 3dd1, anaemia		tooth discolouration	10 days dose not changed unknown
D 79938 M, 61-70 years, Pharmacist	ferrous fumarate tablet 200mg, unknown, unknown		tooth discolouration	11.5 weeks dose not changed unknown

ID, Sex, Age, Source	Drug, daily dose, indication	Concomitant medication	Suspected adverse drug reaction	Time to onset, action with drug, outcome
E 82403 F, 31-40 years, Pharmacist	ferrous fumarate tablet 200mg, 2dd1, iron deficiency anaemia		tooth discolouration	For the ferrous fumarate: 1 month dose not changed unknown
	doxycycline dispertablet 100mg, 1dd1, infection			For the doxycycline: hours dose not changed unknown
F 85299 F, 31-40 years, Physician	ferrous fumarate tablet 200mg, 2dd1, anaemia		tooth discolouration	unknown dose not changed recovered
G 209488 F, 71 years and older, Nursing home practitioner	ferrous fumarate, 3dd1, anaemia		tooth discolouration	14 days dose not changed unknown
H 214203 F, 2-4 years, Consumer	ferrous fumarate oral susp 20mg/ml, 2dd2.5ml, iron deficiency anaemia		tooth discolouration	10 days unknown unknown
I 215819 F, 51-60 years, Pharmacist	amoxicil/claritro/pantopra (pantopac/panclamox), 2dd3, helicobacter pylori infection	omeprazole, hydrochlorothiazide	tooth discolouration	For the amoxicil/claritro/pantopra: 3 days drug withdrawn unknown
	ferrous fumarate tablet 100mg, 3dd1, drug use for unknown indication			For the ferrous fumarate: 1.5 month drug withdrawn unknown
J 109393 M, 51-60 years, Pharmacist	ferrous sulfate tablet mga 105mg, 1dd1, deficiency anaemia iron	tamsulosine	tooth discolouration	5 days dose not changed not recovered

A: Brown staining of teeth.
B: Discolouration consisted of a grey line parallel to the gingival margin. The gingival margin is widening. It was not possible to brush off the discolouration. The staining was removed by a dentist and the patient switched to using tablets. It is uncertain whether the tooth discolouration started before or after withdrawal of ferrous fumarate.
C: Yellow teeth discolouration. It is possible that the patient chewed the tablets.
D: Brown spots on and between the teeth.
E: Black teeth discolouration. Azithromycin was also reported as suspect drug, but was started after the teeth staining appeared. Doxycycline was started on the same day of appearance of the tooth discolouration. The reporter mentioned that the patient had never dental issues. The patient swallowed the tablet whole with water.
F: Black spots in tooth grooves. The staining was polished by a dentist, thereafter the black spots were gone.
G: Black colour of the teeth. Not to remove through brushing. The reporter mentioned that the patient had swallowing difficulties because of a cerebrovascular accident.
H: Yellow teeth staining, not able to brush off.
I: Black discolouration of the teeth.
J: The patient swallowed the tablet whole. At the time of reporting, the patient has not recovered.

Other sources of information

SmPC

The Dutch SmPCs of ferrous fumarate, of both tablets and suspension, do not mention tooth discolouration as an adverse drug reaction [1,7]. Only the Dutch SmPC of ferrous gluconate does mention that suspensions can cause tooth discolouration [8].

Literature

Tooth discolouration, especially black staining, is associated with iron in the saliva and gingival exudate [2-4,9,10]. The clinical use of liquid iron products, such as antiseptic or caries-preventing mouth rinses can cause extrinsic staining of teeth [11,12]. This extrinsic black-staining is typically a dark line at the gingival margin of a tooth [3,13]. To prevent staining from oral iron preparations, it is recommended to dilute the liquid iron preparations, to administer the solution through a drinking straw to minimize the contact of the solution with the teeth, to take care of proper oral hygiene and if patients carry dentures, to remove these before intake of the drug. Concerning the tablets, it is also recommended to swallow the tablets with water [10,14-16].

Databases

Table 2. Reports of tooth discolouration associated with oral iron preparations, in the Lareb [17], WHO [18] and Eudravigilance database [19].

Database	MedDRA PT	Number of reports	ROR (95% CI)
Lareb			
Ferrous fumarate	Tooth discolouration	9	35.0 (17.7-69.1)
Ferrous sulfate	Tooth discolouration	1*	
WHO			
Iron∞	Tooth discolouration	129	15.5 (13.0-18.4)
Eudravigilance			
Ferrous fumarate	Tooth discolouration	6	95.7 (42.6-215.2)
Ferrous sulfate	Tooth discolouration	4	20.0 (7.5-53.4)

*For this association in the Lareb database no reliable ROR can be calculated because of the small number of reports.
∞ For this association only iron could be selected as suspect drug.

Prescription data

Table 3. Number of patients using ferrous fumarate and ferrous sulfate in the Netherlands between 2010 and 2014 [20].

Drug	2010	2011	2012	2013	2014
Ferrous fumarate	202,910	207,560	199,460	196,400	196,190
Ferrous sulfate	69,555	62,852	57,893	49,572	42,784

Mechanism

It is likely that the tooth discolouration described in these reports concerns extrinsic discolouration. This might be caused by the presence of chromogenic bacteria in combination with the metal salts. Tomasz Zyła et al, described that examination of the dental deposit revealed microorganisms embedded in the matrix, mostly Gram-positive rods. The stain is suggested to be a black insoluble ferric compound, probably ferric sulfide. This ferric sulfide is formed by the interaction between hydrogen sulfide, produced by bacteria, and iron in the saliva and gingival exudates [3,9].

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received ten reports concerning tooth discolouration associated with the use of oral iron preparations. The colour of the discolouration varied from black/grey to yellow and brown. In two reports the staining was successfully removed by a dentist. In one report the dose was not adjusted and the patient had not recovered at the time of reporting. For seven reports no information about recovery is available. In one case it is possible that

the patient chewed the tablets, in another case the patient had swallowing difficulties because of an cerebrovascular accident.
In the Lareb, WHO and Eudravigilance databases the association ferrous fumarate and tooth discolouration is disproportionally present.

Although it is reported in the literature that iron-containing products can cause tooth discolouration [2-4,9,10,13], it is not mentioned in the Dutch SmPCs of oral iron preparations, except for ferrous gluconate [1,7,8]. Based on the possible mechanism it is likely that the effect can result from all oral iron preparations. Because of the esthetical and social consequences and the likely effective precautions that can be applied to prevent this reaction, it is relevant to inform patients and healthcare professionals that this possible adverse effect in all oral iron products can occur. And to inform them about preventive measurements, like diluting the oral liquid, using a drinking straw for the solution to avoid contact with the teeth, avoiding chewing of the tablets, applying proper oral hygiene and removing artificial dental elements or prostheses, if possible, before intake of the drug.

References

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This signal has been raised on October 2016. 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.cbg-meb.nl