1.1. Trimethoprim/sulfamethoxazole and tooth- and tongue discoloration

Introduction

Cotrimoxazole® and Bactrimel® tablets or oral suspensions are antibacterial combination products of trimethoprim and sulfamethoxazole, in the ratio 1:5. It is indicated *for the treatment of trimethoprim and sulfamethoxazole sensitive microorganisms* and also for *prophylaxis treatment of infections, in particular recurrent urinary tract infections and pneumocystis carinii pneumonitis in immunosuppressed patients* [1,2]. The combination of trimethoprim and sulfamethoxazole has been granted marketing authorization in the Netherlands since 1971 [2].
Trimethoprim and sulfamethoxazole inhibit two consecutive steps in the biosynthesis of nucleic acids and proteins essential to many bacteria. Trimethoprim blocks the production of tetrahydrofolic acid from dihydrofolic acid reversibly inhibiting the required enzyme, dihydrofolate reductase. Sulfamethoxazole inhibits bacterial synthesis of dihydrofolic acid by competing with para-aminobenzoic acid [3].

Several antibacterial agents are associated with tooth or tongue discoloration [4,5]. Oral flora changes can results in plaque formation on teeth as well as the tongue. However, for trimethoprim and sulfamethoxazole these reactions are not described in the SmPC or literature. The normal color of primary teeth is bluish white whereas the color of permanent teeth is grayish white or yellowish white. Tooth discoloration can be extrinsic or intrinsic. Extrinsic discoloration is present on the outer surface of teeth and is caused by e.g. tea, coffee and tobacco smoking. Such types of staining can be removed by scaling and polishing of teeth. In intrinsic discoloration, stains are deposited within the enamel of dentin during the development of tooth (e.g., tetracycline stains).
The current observation describes the association between trimethoprim and sulfamethoxazole and the occurrence of tooth- or tongue discoloration in 37 patients.

Reports

In the period from December 8th, 1992 until June 16, 2015, the Netherlands Pharmacovigilance Centre Lareb received 13 reports of tooth discoloration and 24 reports of tongue discoloration associated with the use of trimethoprim/sulfamethoxazole. Of these reports there was one with both tooth and tongue discoloration.
In respect to the reports with tooth discoloration; 5 concerned men and 8 women. Nine were children between one and ten years old (median age is two years) and four adults between 22 and 77 years old (median age is 50 years). The color of the discoloration was specified in nine reports: in three reports there was a yellow discoloration and in six reports a brown/black discoloration. In four reports the type of discoloration was not further specified. Time to onset varied from one day until three years after start with a median of 14 days. In five patients the tooth discoloration recovered after withdrawal of trimethoprim/sulfamethoxazole. One patient had not recovered after withdrawal at time of reporting. In two reports it is mentioned that the tooth discoloration was (partly) removed by a dentist. For the other patients no information about recovery is available.
For the reports concerning tongue discoloration; there were 11 men and 13 women between 20 and 85 years old (median is 62 years). In 21 reports it was specifically reported that there was a brown/black discoloration. For the three other reports, one report mentioned a white deposit, one a yellow deposit and the other a painful red tongue. Time to onset was reported in 20 reports and varied from 1 to 17 days after start with a median of 6 days. In four patients the tongue discoloration recovered after withdrawal of trimethoprim/sulfamethoxazole. Three patients were not recovered at time of reporting. For the other patients there is no information reported about recovery.

See appendix 1 for an overview of the reports.

Other sources of information

SmPC

Tooth and tongue discoloration are not mentioned in the Dutch SmPC of trimethoprim/sulfamethoxazole tablets and oral suspension [1,6]. Also in the SmPC of trimethoprim tablets and the FDA package leaflet of trimethoprim/sulfamethoxazole these reactions are not described [3,7].

Literature

There is no literature available about tooth or tongue discoloration associated with the use of trimethoprim/sulfamethoxazole. However for other antibiotics, such as amoxicillin/clavulanic acid (Augmentin®) these adverse drug reactions are labelled in the SmPC [8].

Databases

Table 1. Reports of tooth and tongue discolouration with the combination of trimethoprim and sulfamethoxazole in the database of the Netherlands Pharmacovigilance Centre Lareb [9] and the WHO [10]*.

Drug	Number of reports	ROR (95% CI)
Trimethoprim and sulfamethoxazole and tooth discolouration	Lareb: 13 WHO: 68	9.4 (5.4-16.5) 2.0 (1.5-2.5)
Trimethoprim and sulfamethoxazole and tongue discolouration	Lareb: 24 WHO: 83	12.3 (8.1-18.7) 2.4 (1.9-3.0)

** Eudravigilance data is lacking because Lareb was not able to trace the combination product trimethoprim and sulfamethoxazole in the Eudravigilance database.*

Prescription data [11]

Drug	2010	2011	2012	2013	2014
Trimethoprim and sulphonamides*	275,070	261,660	243,500	210,670	176,350
Trimethoprim and sulfamethoxazole	126,540	119,070	111,050	97,898	83,257

** Also includes monotherapy of trimethoprim or sulphonamides*

Mechanism

It is plausible that the tooth and tongue discoloration as described in these reports have an extrinsic nature. Extrinsic discoloration can be due to direct staining, e.g. due to the color of food (coffee, tea) or indirect caused by a chemical interaction at the tooth surface [12].
Concerning the tongue discoloration, this reaction has similarities with a black hairy tongue (BHT). Hairy tongue may also appear brown, yellow, green, blue [13]. This corresponds to the yellow and white deposit of the tongue described in our reports. The etiology of BHT remains unclear and is likely multifactorial. Studies showed that BHT is positively correlated with increasing age. Other factors that increase the risk for BHT are among others oncological disorders, smokers, consumption of coffee and black tea and poor oral hygiene [13]. In BHT there is a defective desquamation of the dorsal surface of the tongue. Excessive growth of the filiform papillae may than collect debris, bacteria, fungi or other foreign materials which contribute to the discoloration [14].
Another possible explanation of the tooth- and tongue discoloration is overgrowth of bacteria and yeast. These microorganisms synthesize porphyrins [15]. Porphyrins are a group of heterocyclic macrocycle organic compounds. They are highly conjugated systems and consequently they typically have very intense absorption bands in the visible region and may be deeply colored.
The Lareb database contains one report of a red painful tongue. This is probably due to Candida overgrowth, which is described in the Dutch SmPC of trimethoprim and sulfamethoxazole [1].

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received 13 reports of tooth discoloration and 24 of tongue discoloration associated with the use of trimethoprim/sulfamethoxazole. Because of the relatedness in reaction between tooth- and tongue discoloration, both reactions were described in one report. It is interesting that most reports of tooth discoloration concerned children between one and ten years old. It is likely that this is related to the formulation of the drug (oral suspension) that is used for children. All children below the age of 10 used the oral suspension. Lareb reported a same association with amoxicillin oral suspension [5]. In one case (J) the child experienced tooth discoloration after

breast feeding. The mother used trimethoprim/sulfamethoxazole, time to onset is unknown. Trimethoprim/sulfamethoxazole is in small amounts excreted in breast milk. The SmPC of trimethoprim/sulfamethoxazole describes that breastfeeding may be given during treatment, with exception of children with children with glucose-6-phosphate dehydrogenase deficiency [1]. However, the mother also used cefradine in this case and the contribution of the breast infection in the mother is unknown.

Reports of tongue discoloration all concern adults. The type of discoloration that was mostly reported is a black/brown discoloration. Information about the action taken on the drug and recovery were moderately documented. In total, nine patients recovered of the tooth or tongue discoloration after withdrawal of trimethoprim/sulfamethoxazole. No information was reported concerning risk factors for tooth and tongue discoloration [4,13].

In the database of the WHO there were respectively 68 and 83 case reports. In both databases the associations were disproportional present.

Although no information was found in literature, our data suggests that treatment with trimethoprim/sulfamethoxazole can cause tooth and tongue discoloration. This reactions are labelled in the SmPC for other antibiotics, for instance amoxicillin/clavulanic acid (Augmentin®) [8]. Although it is highly likely that the discoloration is reversible, it would be preferable if information on this reaction is available in the SmPC of this product.

- Tooth and tongue discoloration should be labelled in the SmPC of trimethoprim/sulfamethoxazole.

References

1. Dutch Medicines Eveluation Board. Dutch SmPC of Co-trimoxazol® (trimethoprim and sulfamethoxazol). (version date: 2012, access date: 26-10-2015) http://db.cbg-meb.nl/IB-teksten/h09714.pdf.
2. Dutch Medicines Evaluation Board. Dutch SmPC of Bactrim (sulfamethoxazole and trimethoprim). (version date: 2014, access date: 22-1-2016) http://db.cbg-meb.nl/IB-teksten/h06214.pdf.
3. USA SmPC of Bactrim (sulfamethoxazole and trimethoprim). (version date: 2014, access date: 26-10-2015) http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/017377s074lbl.pdf.
4. Kumar A, Kumar V, Singh J, Hooda A, Dutta S. Drug-induced discoloration of teeth: an updated review. Clin Pediatr (Phila) 2012;51(2):181-5.
5. Meyboom RH, Verduijn MM, Steenvoorden MG, Dekens-Konter JA, van Puijenbroek EP. [Reversible tooth discoloration during oral use of antibiotics]. Ned Tijdschr Geneeskd 1996;140(4):207-9.
6. Dutch Medicines Eveluation Board. Dutch SmPC of Co-trimoxazol® oral suspension (trimethoprim and sulfamethoxazol). (version date: 2012, access date: 26-10-2015) http://db.cbg-meb.nl/IB-teksten/h10550.pdf.
7. Dutch Medicines Evaluation Board. Dutch SmPC of trimethoprim. (version date: 2013, access date: 22-1-2016) http://db.cbg-meb.nl/IB-teksten/h09596.pdf.
8. Dutch Medicines Eveluation Board. Dutch SmPC of Augmentin® (amoxicillin/clavulanic acid). (version date: 2014, access date: 26-10-2015) PrFont34Bin0BinSub0Frac0Def1Margin0Margin0Jc1Indent1440Lim0Lim1http://db.cbg-meb.nl/IB-teksten/h14740.pdf.
9. Lareb database. (version date: 2016, access date: 5-1-2016) http://www.lareb.nl/Bijwerkingen/Zoek-op-geneesmiddel.
10. WHO Global Individual Case Safety Reports database (Vigibase). (version date: 2016, access date: 5-1-2016) https://tools.who-umc.org/webroot/ (access restricted).
11. Dutch Health Care Insurance Boards. Drug Information System. (version date: 2015, access date: 26-10-2015) .
12. Watts A, Addy M. Tooth discolouration and staining: a review of the literature. Br.Dent.J 2001;190(6):309-16.
13. Gurvits GE, Tan A. Black hairy tongue syndrome. World J Gastroenterol 2014;20(31):10845-50.
14. Khasawneh FA, Moti DF, Zorek JA. Linezolid-induced black hairy tongue: a case report. J Med Case.Rep. 2013;7:46
15. McGrath EE, Bardsley P, Basran G. Black hairy tongue: what is your call? CMAJ. 2008;178(9):1137-8.

This signal has been raised on March 2015. 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 http://www.cbg-meb.nl/

Appendix 1

Table 1 Reports of tooth discoloration associated with the use of trimethoprim/sulfamethoxazole

Patient, Number Sex, Age Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 27414 F, 0-1 Pharmacist	trimethoprim / sulfamethoxazole oral suspension 240 mg/5ml		yellow tooth discolouration	unknown, unknown, unknown
B 19281 M, 2-4 Pharmacist	trimethoprim/ sulfamethoxazole oral suspension 240 mg/5ml		yellow tooth discolouration	1 day, dose not changed, unknown
C 92493 M, 8-10 Pharmacist	trimethoprim / sulfamethoxazole tablet 480 mg tonsillar hypertrophy		yellow tooth discolouration	2 weeks unknown, unknown
D 181921 M, 0-1 Specialist doctor	trimethoprim / sulfamethoxazole oral suspension 240 mg/5ml upper respiratory tract infection		brown tooth discolouration	1 month, dose not changed, recovered spontaneously after 3-4 months
E 199762 M, 2-4 Pharmacist	trimethoprim / sulfamethoxazole oral suspension 240 mg/5ml ear infection	fluticasone salbutamol	black tooth discolouration	14 days, unknown, not recovered
F 82453 M, 5-7 Pharmacist	trimethoprim / sulfamethoxazole oral suspension 240 mg/5ml desloratadine azithromycin amoxicillin	flucitcasone mometasone promethazine montelukast dexchlorpheniramine	brown tooth discolouration	unknown, desloratadine unknown and other drugs withdrawn, unknown
G 106381 F, 5-7 Consumer	trimethoprim / sulfamethoxazole oral suspension 240 mg/5ml nitrofurantoin amoxicillin clavulanic acid amoxicillin trimethoprim recurrence cystitis	child used these antibiotics the last 2 years. now, her new adult teeth have a brown discolouration.	brown tooth discolouration	unknown, unknown, unknown
H 166402 F, 31-40 General practitioner	trimethoprim / sulfamethoxazole tablet 960 mg wegener's granulomatosis		brown tooth discolouration	9 weeks, drug withdrawn, recovered after treatment by dentist
I 57997 F, 61-70 Pharmacist	trimethoprim / sulfamethoxazole tablet 960 mg	furosemide nitrazepam	black tooth discolouration black tongue discolouration	4 days, drug withdrawn, recovered
J 31857 M, 0-1 General practitioned	trimethoprim / sulfamethoxazole tablet 960 mg cefradine 500mg breast inflammation		tooth discolouration due to use of mother who is breast feeding	unknown, both drugs withdrawn, not recovered

Patient, Number Sex, Age Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
K* 84197 F, 2-4 Pharmacist	trimethoprim / sulfamethoxazole oral suspension 240 mg/5ml prophylaxis with congenital airway narrowing	macrogol	tooth discolouration	3 years dose not changed unknown
L 133703 F, 21-30 Consumer	trimethoprim / sulfamethoxazole tablet 480 mg prophylactic antibiotic therapy	fluticasone montelukast pantoprazole fexofenadine	tooth discolouration tooth erosion	3 weeks, drug withdrawn, recovered after treatment by dentist
M 65403 F, 71 years and older Pharmacist	trimethoprim / sulfamethoxazole tablet 480 mg urinary tract infection	irbesartan acetylsalicylic acid	tooth discolouration glossitis	6 days, drug withdrawn recovered

* Due to the indication it is possible that trimethoprim / sulfamethoxazole was used for prolonged period. The latency period is extensive, it is not known if there was another contributing factor for the tooth discoloration to develop after 3 years.

Table 2. Reports of tongue discolouration associated with the use of trimethoprim/sulfamethoxazole

Patient, Number Sex, Age Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 40668 F, 51-60 Pharmacist	trimethoprim / sulfamethoxazole tablet		black tongue discolouration	2 days, unknown, recovered
B 13616 M, 31-40 General practitioner	trimethoprim / sulfamethoxazole tablet 960 mg		brown tongue discolouration	days, unknown, unkown
C 15357 M, 51-60 General practitioner	trimethoprim / sulfamethoxazole tablet 960 mg bronchitis acute		black tongue discolouration	5 days, dose not changed, unknown
D 18578 M, 31-40 Pharmacist	trimethoprim / sulfamethoxazole tablet 960 mg prostatitis	ofloxacine, fenprocoumon zidovudine zalcitabine carbasalate calcium simvastatin captopril	black tongue discolouration	2 days, drug withdrawn, unknown
E 24247 M, 31-40 Pharmacist	trimethoprim / sulfamethoxazole tablet 960 mg erysipelas	beclomethasone salbutamol	black tongue discolouration	unknown, dose reduced, unknown
F 37985 F, 61-70 Pharmacist	trimethoprim / sulfamethoxazole tablet 960 mg urinary tract infection	enalapril lorazepam acenocoumarol estradiol temazepam	black tongue discolouration	6 days, drug withdrawn, unknown

Patient, Number Sex, Age Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
G 38881 M, 61-70 Pharmacist	trimethoprim / sulfamethoxazole tablet 960 mg urinary tract infection		black tongue discolouration	11 days, drug withdrawn, recovered
H 39430 M, 61-70 Pharmacist	trimethoprim / sulfamethoxazole tablet 960 mg urinary tract infection	omeprazole ofloxacine metoprolol carbasalate calcium diclofenac	black tongue discolouration stomatitis	unknown, drug withdrawn, not recovered
I 39632 F, 61-70 Pharmacist	trimethoprim / sulfamethoxazole tablet 960 mg upper respiratory infection		black tongue discolouration	unknown, drug withdrawn, recovered
J 42609 F, 61-70 Pharmacist	trimethoprim / sulfamethoxazole tablet 960 mg urinary tract infection	carbasalate calcium simvastatin	black tongue discolouration dysgeusia	10 days, drug withdrawn, not recovered
K 53642 F, 61-70 Pharmacist	trimethoprim / sulfamethoxazole tablet 960 mg	esomeprazole folic acid etoricoxib tiotropium diazepam	black tongue discolouration	unknown, drug withdrawn, recovered
L 57997 F, 61-70 Pharmacist	trimethoprim / sulfamethoxazole tablet 960 mg	furosemide, nitrazepam	black tooth discolouration black tongue discolouration	4 days, drug withdrawn, recovered
M 62381 M, 11-20 Pharmacist	trimethoprim / sulfamethoxazole oral suspension 240 mg/5ml	folic acid	brown tongue discolouration	weeks, dose not changed, not recovered
N 65092 M, 71 years and older General practitioner	trimethoprim / sulfamethoxazole tablet 960 mg prostatitis		black tongue discolouration	2 days, dose not changed, not recovered
O 76043 F, 61-70 Pharmacist	trimethoprim / sulfamethoxazole tablet 960 mg	codein	black tongue discolouration	3 days, dose not changed, recovering
P 76710 M, 61-70 Pharmacist	trimethoprim / sulfamethoxazole tablet 960 mg urinary infection	tamsulosin	black tongue discolouration	4 days, unknown, not recovered
Q 77386 M, 61-70 Pharmacist	trimethoprim / sulfamethoxazole tablet 960 mg bacterial infection		black tongue discolouration	1 week, drug withdrawn, unknown
R 84591 F, 71 years and older Pharmacist	trimethoprim / sulfamethoxazole tablet 960 mg ear infection	hydrochlorothiazide alendronic acid	black tongue discolouration	17 days, dose reduced, unknown

Patient, Number Sex, Age Source	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
S 150092 F, 61 -70 Pharmacist	trimethoprim / sulfamethoxazole oral suspension 240 mg/5ml	acetylsalicylic acid baclofen esomeprazole hydromorphone hydroxycobalmin methadone metoprolol ondansetron glucosamine	black tongue discolouration dysgeusia	2 weeks, drug withdrawn, unknown
T 151984 F, 41-50 Pharmacist	trimethoprim / sulfamethoxazole tablet 960 mg		black tongue discolouration dry mouth hypoesthesia oral	2 days, dose not changed, recovered
U 192326 F, 61-70 Consumer	trimethoprim / sulfamethoxazole tablet 960 mg lung infection		black tongue discolouration	2 days, unknown, recovered
V 180142 F, 41-50 Consumer	trimethoprim / sulfamethoxazole tablet 960 mg respiratory tract infection	ciclesonide mometasone rupatadine	white tongue discolouration myalgia diarrhea headache rash dry eye drug mouth	1 day, drug withdrawn, recovered
W* 74938 F, 71 years and older Pharmacist	trimethoprim / sulfamethoxazole tablet 960 mg	nitrazepam cimetidine	red tongue discolouration lip swelling	6 days, dose not changed, unknown
X 6495 M, - General practitioner	trimethoprim / sulfamethoxazole tablet 960 mg		yellow tongue discolouration tongue oedema	1 day, dose not changed, unknown

* This patient experience a red painful tongue. We believe that she experienced Candida overgrowth although this was not specifically reported.