

1.1. Metronidazole and tongue discolouration

Introduction

Metronidazole (Flagyl®) is a nitro-imidazole derivate which forms nitrosoradicals under anaerobic circumstances. These radicals break the DNA of an infected cell, finally leading to apoptosis of these microbial cells. Metronidazole is indicated for the treatment of urethritis and vaginitis due to *Trichomonas vaginalis* and *Gardnerella vaginalis*. It is also indicated for the treatment of amoebiasis, anaerobic infections, prophylaxis of postoperative infections (e.g. *Bacteriodes spp.* and anaerobic streptococcus) and angina of Plaut-Vincent, an one-sided necrotising, infectious tonsillitis.

Metronidazole is available in tablets, suspension, ovules, gel and as a drug for infusion and is available on the Dutch market since July 07 1971 [1-6].

Stomatitis, glossitis and a coated tongue are described as adverse drug reactions with unknown frequency [1-3]. This observation describes the association between tongue discolouration and the use of metronidazole.

Reports

On January 23th, 2012 the database of the Netherlands Pharmacovigilance Centre Lareb contained ten reports concerning tongue discolouration with the use of metronidazole. These reports are listed in Table 1.

Tongue discolouration varied from white (case A), white/yellow (case B), black (cases D, E, F and I), brown to brown/yellow (G, H) and green (case J). In case C the colour is unknown. Some of the patients also had taste disorders, pharyngitis or glossitis. Latency time varies between 1 day and 2 weeks but was mostly 2 to 5 days. In most of the cases the outcome was not reported. In two cases (D and E) the patient recovered or was recovering during the use of metronidazole. Patient F recovered after drug withdrawal. Patient G was treated with miconazole without improvement.

In cases A up to including D, no concomitant medication was reported. Patient F up to including J used other antibiotics which were also reported as suspected drugs. Patient E used chlorohexidine mouth wash for concomitant medication.

Table 1. Reports of tongue discolouration associated with the use of metronidazole

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 4457 F, 31 – 40 years general practitioner	metronidazole 500mg	not reported	tongue discolouration (white), pharyngitis	1 day unknown not reported
B 66768 F, 21 – 30 years consumer	metronidazole 500mg amoebiasis	not reported	tongue white/yellow, malaise, palpitations, muscle weakness	2 day dose reduction not yet recovered
C 126013 F, 21 – 30 years pharmacist	metronidazole 500mg infection	not reported	tongue discolouration (colour unknown), taste metallic	3 day no change recovering
D 102705 M, 21 – 30 years consumer	metronidazole 500mg infection	not reported	tongue black, urine discoloration, headache, stools abnormal, dizziness	3 day no change recovered

Patient, Sex, Age	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
E 90316 F, 51 – 60 years dentist	metronidazole 500mg abscess	chlorohexidine	tongue black	7 day no change not recovered
F 22019 F, 51 – 60 years pharmacist	metronidazole 250mg	amoxicillin*	tongue black, later glossitis	5 day discontinued recovered (black tongue) not reported (glossitis)
G 48645 F, 51 – 60 years pharmacist	metronidazole 500mg	amoxicillin* simvastatin losartan	tongue discolouration (brown/yellow)	2 week discontinued not recovered
H 105104 F, 51 – 60 years general practitioner	metronidazole 500mg	amoxicillin*	tongue brown, taste metallic, nausea	2 day unknown unknown
I 13490 F, 21 – 30 years general practitioner	metronidazole 500mg	amoxicillin/ clavulanic acid* beclomethasone salbutamol terbutaline	tongue black	5 day discontinued not reported
J 15079 F, 41 – 50 years general practitioner	metronidazole 500mg	clarithromycin* lormetazepam omeprazole doxazosin	tongue discolouration (green), taste alteration	3 day no change not reported

* also reported as a suspected drug

Other sources of information

SmPC

Tongue discoloration is not mentioned in the SmPC's of metronidazole containing products [1-6]. Stomatitis and coated tongue is described in some SmPC's of metronidazole [1,2]. Glossitis is described in one of the SmPC's of metronidazole [3]. The US SmPC describes furry tongue and glossitis [7].

Literature

A Pubmed search revealed one case report of a 53-year-old woman who developed a black hairy tongue during a 3-week course of amoxicillin clavulanic acid and metronidazole for suspected postoperative pelvic infection [8]. She had a high intake of caffeine, including six cups of tea and two cups of coffee each day. Tongue scrapings confirmed a Candida infection. The patient was treated with a short course of fluconazole and she recovered within 7 days.

Meyler's side effects of drugs [9] mentions that the occurrence of black hairy tongue seems to be quite common with the use of metronidazole.

No other publications of the possible association between metronidazole and tongue discoloration were found. However, transient tongue discoloration is a well-known adverse drug reaction with the use of antibiotics in general [10].

Databases

On January 23th, 2012 the database of the Netherlands Pharmacovigilance Centre Lareb contained ten reports of tongue discoloration in association with

the use of metronidazole, which was reported disproportionately (ROR = 12.1, 95% CI 6.4 - 22.9).

The WHO database of the Uppsala Monitoring Centre contained 90 reports of tongue discolouration in association with the use of metronidazole and this was also reported disproportionately (ROR = 11.6, 95% CI 9.4 - 14.4).

Table 2. Reports of tongue discolouration with metronidazole in the databases of the Netherlands Pharmacovigilance Centre Lareb and the WHO.

Drug	Number of reports	ROR (95% CI)
metronidazole	Lareb: 10 WHO: 90	12.1 (6.4 – 22.9) 11.6 (9.4 – 14.4)

On 30 January 2012, the Eudravigilance database contained 18 reports of tongue discoloration associated with the use of metronidazole. The reports concern twelve females and six males. The median age of the patients was 51 years (range 24 – 79 years). In one case, the age was not reported.

Tongue discoloration was reported disproportionately (ROR = 19.3, 95% CI: 12.1 – 30.9).

Prescription data

The number of patients using metronidazole in the Netherlands is shown in table 3.

Table 3. Number of patients using metronidazole in the Netherlands between 2006 and 2010 [11].

Drug	2006	2007	2008	2009	2010
metronidazole	136,090	142,650	144,900	146,640	149,580

Mechanism

The exact mechanism for tongue discolouration is unknown. Transient discolouration of the tongue may be of various colour [10]. Tongue discolouration is thought to be due to alterations in oral microbial flora [12]. Furry tongue, glossitis and stomatitis are associated with a sudden overgrowth of *Candida* during therapy [7]. Also secondary infections with porphyrin-producing chromogenic bacteria or yeast are mentioned [8]. Also hyperplasia of filiform papillae can lead to a yellowish or black hairy tongue. This is mostly seen during long-term use of antimicrobial agents like tetracyclines [13].

Penicillines and mouthwashes containing sodium perborate and chlorhexidine can cause a black or brown-yellow tongue [10,12-14].

Discussion

The Netherlands Pharmacovigilance Centre Lareb received 10 reports with tongue discolouration with the use of metronidazole. Latency time was mostly 2 to 5 days. In four of the patients no concomitant medication was reported. Some patients also used amoxicillin (with clavulanic acid), clarithromycin or chlorhexidine mouth wash, which can also cause tongue discolouration [10,13,15]. Smoking, certain beverages (coffee, tea) and bad oral hygiene are also risk factors for the occurrence of tongue discolouration [8,10,13]. It is not known if the patients of our cases had these risk factors.

Tongue discolouration is not widely described in literature, but a possible mechanism that antibiotics in general disturb the mouth flora is mentioned [12],

through which a secondary infection with porphyrin-producing chromogenic bacteria or yeast can occur [8].

The association between metronidazole and tongue discolouration is statistically supported by the databases of the Netherlands Pharmacovigilance Centre Lareb and the WHO.

Conclusion

The number of cases and latency time suggests a relationship between metronidazole and tongue discolouration, which is further supported by a mechanism due to disturbance of the mouth flora. Tongue discolouration should be mentioned in all SmPC's of metronidazole containing products.

- Tongue discolouration should be mentioned in all metronidazole containing SmPC's.

References

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This signal has been raised on April 2012. It is possible that in the meantime other information became available. For the latest information please refer to the website of the MEB www.cbgmeb.nl/cbg/en/default.htm or the responsible marketing authorization holder(s).