1.1. Fluoroquinolones and stomatitis, a possible group effect

Introduction

Fluoroquinolone antibiotics are indicated for *treatment of infections caused by fluoroquinolone-sensitive bacteria.* Indications include *acute and chronic, uncomplicated and complicated urinary tract infections, and urinary tract infections associated with urologic surgery or nephrolithiasis* [1-4], *upper and lower respiratory infections, genital infections, gastro-intestinal and intra-abdominal infections, infection of bones, skin and joints and cystic fibrosis* [2, 4].
Stomatitis refers to inflammation of the mucous lining of any of the structures in the mouth, which may involve the cheeks, gums, tongue, lips, and roof or floor of the mouth. The word "stomatitis" literally means inflammation of the mouth. The inflammation can be caused by conditions in the mouth itself, such as poor oral hygiene, poorly fitted dentures, or from mouth burns from hot food or drinks, or by conditions that affect the entire body, such as medications, allergic reactions, or infections [5].
The Netherlands Pharmacovigilance Centre Lareb received 17 reports of stomatitis associated with the use of a fluoroquinolone.

Reports

On November 2nd, 2010, the database of the Netherlands Pharmacovigilance Centre Lareb contained five reports of stomatitis associated with the use of norfloxacin, three for ciprofloxacin, six for levofloxacin, two for ofloxacin and one for grepafloxacin. The reports are listed in Table 1.

Table 1. Reports of stomatitis associated with the use of fluoroquinolones

Patient, Number, Sex, Age	Drug (daily dose) Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 6136 M, 61 – 70 years	norfloxacin 2dd 400mg	ranitidine, fluoxetine, temazepam	stomatitis	3 days discontinued not reported
B 25637 F, 21 – 30 years	norfloxacin 2dd 400mg cystitis		stomatitis	1 days discontinued not reported
C 71314 F, 61 – 70 years	norfloxacin 2dd 400mg	acenocoumarol, venlafaxine, oxazepam	headache, stomatitis, ageusia, nausea	8 days discontinued unknown
D 74818 F, 51 – 60 years	norfloxacin 2dd 400mg cystitis	candesartan	stomatitis	7 days no change recovered with sequelae
E 104664 M, 51 – 60 years	norfloxacin 2dd 400mg epididymitis	sildenafil, pravastatin, levothyroxine, carbasalate calcium	stomatitis, glossitis	5 days discontinued recovered
F 58194 F, 70 years and older	levofloxacin 2dd 500 mg	pantoprazole, claritromycine, bisoprolol	stomatitis, vaginal inflammation, dysgeusia, tendinitis, mouth dry	3 days discontinued recovered from the stomatitis, vaginal inflammation and dysgeusia
G 22135 M, 31 – 40 years	levofloxacin 1 dd 500mg		stomatitis	4 days discontinued not reported

Patient, Number, Sex, Age	Drug (daily dose) Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
H 22274 F, 70 years and older	levofloxacin1dd 500mg	sotalol, xylometazoline	stomatitis	10 days discontinued not reported
I 33978 F, 70 years and older	levofloxacin 2dd 500 mg cough	ibuprofen, fluticasone (nasal), desloratadine, omeprazole	stomatitis	not reported discontinued, not yet recovered one month after report
J 80103 F, 61 – 70 years	levofloxacin 1dd 500mg sinusitis, depo medrol back pain	esomeprazole, rosuvastatin, atenolol, candesartan	burning sensation in eye, stomatitis, anaesthesia tongue	5 days levofloxacin discontinued recovered
K 109731 M, 51 – 60 years	levofloxacin 250mg		stomatitis	6 days discontinued recovered
L 46447 M, 41 – 50 years	ciprofloxacinum 4 dd 250mg acute prostatitis	ibuprofen	mouth irritation, tooth ache	1 day no change not recovered
M 59234 M, 41 – 50 years	ciprofloxacin 2 dd 500mg		stomatitis	hours discontinued recovered
N 87777 M, 5 – 7 years	ciprofloxacin 2dd 250mg, prophylaxis vincristinesulphate injection 1mg, acute lymphoid leukaemia,	mercaptopurine, itraconazole, doxorubin, asparaginase, amitriptyline, dexamethasone	stomatitis, arthralgia, obstipation,flatulence, rash	10 days discontinued, not yet recovered, treatment with paracetamol, ibuprofen, morphine and macrogol
O 31356 M, 61 – 70 years	ofloxacin 2 dd 400mg cystitis	budesonide, amoxicillin, formoterol, oxazepam, verapamil	stomatitis	2 days discontinued recovered
P 18754 M, 70 years and older	ofloxacin 2dd 200mg	fluticasone, ipratropium, prednisone, digoxin furosemide salbutamol, salmeterol	stomatitis, nausea, alopecia	6 days discontinued not reported
Q 24772 F, 61 – 70 years	grepafloxacin 1dd 600mg bronchitis	furosemidum, doxycycline, enalapril, captopril, oxazepam	stomatitis, herpes labialis, photosensitivity reaction	5 days discontinued not reported

Time to onset varied from one to ten days. In six cases a positive dechallenge was reported. In patient H, P and Q the suspected drug was already withdrawn at the time the reaction occurred.

Below characteristics of some of the reports are discussed:
In patient E both stomatitis and glossitis is reported. In addition Lareb received one other report of glossitis after two days of norfloxacin use by a male aged 31 – 40 years (report number 10348).

Patient F also used the antibiotic claritromycin in the same period as levofloxacin. Claritromycin was not reported as a suspect drug; however in the SmPc of this drug oral candidiasis and stomatitis are mentioned as possible adverse drug reactions [6]. In addition to the stomatitis, dry mouth and dysgeusia this patient also suffered from vaginal inflammation, an ADR that could possibly be caused by a similar mechanism to the mechanism for stomatitis (imbalance of microbial flora).

Patient N suffered from acute lymphoid leukaemia and is treated with vincristine and mercaptopurine. Stomatitis is mentioned in the SmPC of vincristine [7]. The SmPC of mercaptopurine mentions mouth ulcerations [8].
The reporter mentioned that the stomatitis in this patient was not typical for the mucositis seen with chemotherapy. The reaction consisted of vesicles on the mouth and lips, without red discoloration of the mouth mucosa. The patient did not experience any adverse effects after the use of vincristine in the past (he had six doses during the induction phase of the ALL protocol). Ciprofloxacin was replaced by sulfamethoxazole/trimethoprim in this patient.

Patient O also suffered from a swollen upper-lip in addition to the stomatitis (originally reported as painful mouth mucosa of tongue and cheeks).

Inhalation of corticosteroids, as in patient O and P, could also be a risk factor for developing stomatitis [9].

Other sources of information

SmPC

Stomatitis is not mentioned as a possible adverse drug reaction in either of the SmPCs of the Dutch norfloxacin containing products [1,10-13] nor in the SmPCs of some other fluoroquinolones available on the Dutch market, like levofloxacin (Tavanic®) [4], ciprofloxacin (Ciproxin®) [2] and ofloxacin (Tarivid®) [3], although the SmPC of this last drug mentions fungal infection as a possible adverse drug reaction. In the SmPC of ciprofloxacin (Ciproxin®) mycotic superinfections are mentioned [2].
The Dutch SmPC of moxifloxacin (Avelox®) [14] does mention stomatitis as a seldom occurring adverse drug reaction. Furthermore, in the American SmPC of norfloxacin (Noroxin®) [15], stomatitis is described as well.

Literature

To the best of our knowledge, there are no publications on a possible association between norfloxacin and stomatitis. It is not mentioned in Micromedex® [16] or Meylers' Side Effects of Drugs [17]. Micromedex® mentiones that in clinical trials of oral ciprofloxacin gastrointestinal side effects, which occurred in less than or equal to 1% of patients, include painful oral mucosa and oral candidiasis. This information was taken from the US SmPC of ciprofloxacin [18]. For levofloxacin it is mentioned that in 29 pooled phase 3 clinical trials (n=7,537; mean age, 50 yr) stomatitis was reported in 0.1% to 1% of patients receiving levofloxacin at doses of 750 mg/day, 250 mg/day, or 500 mg once or twice daily for an average of 10 days (range, 3 to 14 days) [19].

Databases

On February 4th, 2011 the database of the Netherlands Pharmacovigilance Centre Lareb contained 17 reports of stomatitis associated with the use of fluoroquinolones (ATC codes beginning with J01MA): three for ciprofloxacin, six for levofloxacin, two for ofloxacin and one for grepafloxacin. The combined ROR for all fluoroquinolones was 2.3 (95% CI 1.4-3.8), which is disproportional.

For the separate fluoroquinolones, stomatitis was reported disproportionally for norfloxacin and levofloxacin. Disproportionality was not assessed separately for ofloxacin and grepafloxacin due to the low number of reports.

Table2. Reports of stomatitis associated with the use of fluoroquinolones in the Lareb database

Drug	Number of reports	ROR (95% CI)
Norfloxacin	5	3.0 (1.2- 7.4)
Levofloxacin	6	5.9 (2.6- 13.3)
Ciprofloxacin	3	1.0 (0.3- 2.3)
Ofloxacin	2	Not Applicable*
Grepafloxacin	1	Not Applicable*
Fluoroquinolones total	17	2.3 (1.4- 3.8)

* Due to the low number of reports

On February 4th, 2011, the WHO database of the Uppsala Monitoring Centre contained 270 reports of stomatitis associated with use of fluoroquinolones. The combined ROR for all fluoroquinolones in the WHO database was 1.2 (95% CI 1.1- 1.3), which is disproportional.

Table 3. Reports of stomatitis associated with the use of fluoroquinolones in the WHO database

Drug	Number of reports	ROR (95% CI)
Norfloxacin	55	2.6 (2.0- 3.4)
Ciprofloxacin	94	1.1 (0.9 -1.4)
Ofloxacin	43	1.1 (0.8 -1.5)
Moxifloxacin	38	1.0 (0.7- 1.4)
Levofloxacin	38	0.8 (0.6- 1.1)
Grepafloxacin	2	Not Applicable*
Fluoroquinolones total	270	1.2 (1.1- 1.3)

* Due to the low number of reports

On December 2nd 2010, the Eudravigilance database contained four serious (CIOMS category of seriousness was “hospitalization”) reports of stomatitis in association with the use of norfloxacin. One of the reports was a duplicate report.
In case A (a duplicate report) stomatitis is reported (described as “oral redness”) and in addition the following reactions; Allergic reaction, conjunctival redness, dyspnoea, erythematous rash, facial flushing, fever, ocular hyperemia, rubella. The patient was hospitalized.
In casus B stomatitis is reported (described in the report as “oral erosion” en “oral mucosa redness”) and also the following adverse reactions; blister, decreased appetite, drug eruption, erythema (multiforme), fever, general malaise, papule. The patient was hospitalized.
Case C is poorly documented. Stomatitis and vasulitic rash are the only adverse drug reactions mentioned. The patient was hospitalized.

Prescription data

The number of patients using norfloxacin and other fluoroquinolones in the Netherlands is shown in Table 2.

Table 2. Number of users of fluoroquinolones in the Netherlands between 2006 and 2009 [20]

Drug	2006	2007	2008	2009
Norfloxacin	130,220	124,780	115,690	108,300
Ciprofloxacin	201,030	218,280	235,940	247,770
Levofloxacin	32,679	31,946	29,945	28,572
Moxifloxacin	27,293	35,193	20,352	19,319
Ofloxacin	29,637	26,767	24,065	21,692

Mechanism

There is a plausible biological mechanism. Antibiotics cause an imbalance of the oral microflora. Fluoroquinolones reduce the number of fluoroquinolone-sensitive bacteria, allowing (over-)growth of other pathogenic bacteria. Stomatitis may occur as a result of an altered balance of the oral microflora. The role of oral flora changes in the genesis of oral mucosal changes is scarcely described in literature, e.g. [21].
Alternatively, a local allergic reaction to the drug may be considered.

Discussion and conclusion

The occurrence of stomatitis during the use of fluoroquinolones can be explained by the mechanism of action of these (and other) antibiotics. The SmPC of moxifloxacin does mention stomatitis as a seldom occurring adverse drug reaction, but stomatitis is not mentioned in the Dutch product information of other fluoroquinolones.

The association between fluoroquinolones and stomatitis is supported by the disproportional number of reports both in the Lareb and WHO database and the mechanism of action of these antibiotics. Stomatitis is expected to be a group effect, which is supported by the reports in the Lareb and WHO database and by the fact that it is mentioned in the SmPC of moxifloxacin [14]. The association with stomatitis is supported most strongly for norfloxacin and - in the Lareb database also for - levofloxacin, but can be expected to be valid for all fluoroquinolones. Therefore, we recommend that stomatitis is mentioned in the SmPC of norfloxacin and levofloxacin and preferably in the SmPCs of all fluoroquinolones.

- Stomatitis should be mentioned in the SmPC of norfloxacin, levofloxacin and preferably in the SmPCs of all fluoroquinolones.

References
1. Dutch SmPC Norfloxacine PCH. (version date: 20-10-2010, access date: 2-11-2010) http://db.cbg-meb.nl/IB-teksten/h22824.pdf.
2. Dutch SmPC Ciproxin® (ciprofloxacine). (version date: 27-4-2010, access date: 29-11-2010) http://db.cbg-meb.nl/IB-teksten/h12241.pdf.
3. Dutch SmPC Tarivid® (ofloxacine). (version date: 6-5-2010, access date: 29-11-2010) http://db.cbg-meb.nl/IB-teksten/h11939.pdf.
4. Dutch SmPC Tavanic® (levofloxacine). (version date: 9-1-2008, access date: 29-11-2010) http://db.cbg-meb.nl/IB-teksten/h21811.pdf.
5. Stomatitis. (version date: 2008, access date: 2-11-2010) http://medical-dictionary.thefreedictionary.com/stomatitis.

6. Dutch SmPC Klacid® (claritromycine). (version date: 31-1-2011, access date: 7-2-2011) http://db.cbg-meb.nl/IB-teksten/h21555.pdf.
7. Dutch SmPC Vincristinesulfaat TEVA. (version date: 9-6-1998, access date: 7-2-2011) http://db.cbg-meb.nl/IB-teksten/h10208.pdf.
8. Dutch SmPC Puri-Nethol® (mercaptopurine). (version date: 2011, access date: 7-2-2011) http://db.cbg-meb.nl/IB-teksten/h00859.pdf.
9. Orale bijwerkingen van geneesmiddelen. (version date: 1-12-2001, access date: 7-2-2011) http://gebu.artsennet.nl/Archief/Tijdschriftartikel/Orale-bijwerkingen-van-geneesmiddelen.htm.
10. Dutch SmPC Norfloxacine Ratiopharm. (version date: 29-12-2009, access date: 2-11-2010) http://db.cbg-meb.nl/IB-teksten/h23358.pdf.
11. Dutch SmPC Norfloxacine CF. (version date: 7-7-2010, access date: 2-11-2010) http://db.cbg-meb.nl/IB-teksten/h24265.pdf.
12. Dutch SmPC Norfloxacine Sandoz. (version date: 24-11-2009, access date: 2-11-2010) http://db.cbg-meb.nl/IB-teksten/h26800.pdf.
13. Dutch SmPC Norfloxacine Mylan. (version date: 16-4-2010, access date: 2-11-2010) http://db.cbg-meb.nl/IB-teksten/h29846.pdf.
14. Dutch SmPC Avelox® (moxifloxacine). (version date: 10-5-2010, access date: 29-11-2010) http://db.cbg-meb.nl/IB-teksten/h28118.pdf.
15. US SmPC Noroxin®. (version date: 29-11-2010, access date: 30-11-2010) http://www.accessdata.fda.gov/drugsatfda_docs/label/2006/019384s046lbl.pdf.
16. Thomson Micromedex, Greenwood Village Colorado USA. Micromedex® Healthcare Series, (electronic version). (version date: 2010, access date: 2-11-2010) http://www.thomsonhc.com.
17. Dukes MNG; Aronson JK. Meyler's side effects of drugs. 14 ed. 2000.
18. US Product Information: Cipro® (ciprofloxacin) tablets and oral suspension. Bayer Pharmaceuticals Corporation, West Haven, CT. 2004;
19. US Product Information: Levaquin® (levofloxacin) oral tablets, solution, IV injection. Ortho-McNeil Pharmaceutical,Inc. 2008;
20. College for health insurances. GIP database. (version date: 27-7-2010, access date: 2-11-2010) http://www.gipdatabank.nl/.
21. Napenas JJ, Brennan MT, Bahrani-Mougeot FK, Fox PC, Lockhart PB. Relationship between mucositis and changes in oral microflora during cancer chemotherapy. Oral.Surg.Oral.Med Oral.Pathol Oral.Radiol.Endod. 2007;103(1):48-59.

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