1.1. Metronidazole and peripheral oedema

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 tot 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*.
Metronidazole which has been on the Dutch market since July 1971, is available in tablets, suspension, ovules, gel and as a drug for infusion [1-8].

Peripheral oedema is not described as an adverse drug reaction in the Dutch SmPC of metronidazole. This observation describes the association between peripheral oedema and the use of metronidazole.

Reports

On March 27th, 2012 the database of the Netherlands Pharmacovigilance Centre Lareb contained nine reports, including one duplicate, concerning peripheral oedema with the use of metronidazole. These reports are listed in Table 1.

The locations of peripheral oedema were hands/fingers (case A, B and G), fingers/toes (case C), and legs/ankles (case E, F, H and I). No cardiovascular disease or concomitant medication which might indicate cardiovascular disease was reported for any of the patients. Latencies were between 24 hours and 5 days, which seems plausible for peripheral oedema. After withdrawal of metronidazole, three patients recovered and one was recovering at the time of reporting. For patient I the peripheral oedema was unilateral, making a causal relationship with metronidazole less likely.

Table 1. Reports of peripheral oedema associated with the use of metronidazole

Patient, Sex, Age, Reporter	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
A 3107 F, 31 to 40 years general practitioner	metronidazole 250mg	ethinylestradiol / levonorgestrel	oedema peripheral, nausea	3 days unknown not reported
B 7887 F, 21 to 30 years general practitioner	metronidazole 500mg	Levothyroxine	skin discolouration, oedema peripheral	1 day no change not reported
C 44013* F, 51 to 60 years pharmacist	metronidazole 500mg bacterial infection NOS	estradiol / norethisterone	taste alteration, oedema of extremities	5 days discontinued recovered
D 44529* F, 51 to 60 years consumer	metronidazole 250mg vulvitis	estradiol / norethisterone	oedema of extremities, taste loss	3 days no change not recovered
E 49146 F, 31 to 40 years pharmacist	metronidazole 250mg		oedema legs	24 hours discontinued recovering

Patient, Sex, Age, Reporter	Drug Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug outcome
F 50093 F, 51 to 60 years specialist doctor	metronidazole 500mg giardiasis	diazepam codeine	sleep disorder, headache, hallucination, confusion, abdominal distension, dystonia, oedema peripheral, attention impaired, nervous system disorder, angina pectoris, muscle cramp, chills, pain legs	not reported withdrawn recovered
G 76647 F, 31 to 40 years consumer	metronidazole 500mg	diclofenac estradiol / norethisterone	peripheral oedema, migraine	1 day not applicable unknown
H 120228 F, 71 years and older pharmacist	metronidazole 500mg periodontitis tranylcypromine 10mg bipolar affective disorder	quetiapine levothyroxine	pruritus, ankle oedema	3 days no change recovered
I 127798 F, 41 to 50 years pharmacist	metronidazole 500mg diarrhoea NOS	fluticasone, ciclesonide	oedema legs	4 days discontinued recovered

* Reports C and D are duplicate reports

Other sources of information

SPC

Peripheral oedema is not mentioned in the SmPC's of metronidazole containing products [1-8].

Literature

A Pubmed search revealed no articles describing peripheral oedema in relation to the use of metronidazole.

Databases

On January 27th, 2012 the database of the Netherlands Pharmacovigilance Centre Lareb contained eight reports of peripheral oedema associated with the use of metronidazole, which was reported disproportionally (ROR = 2.7, 95% CI 1.3 – 5.4).
On January 27th, 2012, the WHO database of the Uppsala Monitoring Centre contained 144 reports of peripheral oedema associated with the use of metronidazole and this was reported disproportionally (ROR = 0.64, 95% CI 0.6 – 0.8), indicating a statistically protective effect.

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

Drug	Number of reports	ROR (95% CI)
Metronidazole	Lareb: 8 WHO: 144	2.7 (1.3 – 5.4) 0.6 (0.6 – 0.8)

On April 4 2012, the Eudravigilance database contained 25 reports of peripheral oedema in association with metronidazole, which was reported disproportionally (ROR = 0.6, 95% CI: 0.4 – 0.9). It concerned eighteen females and seven males and the median age was 49 years (range 15 – 89 years). In one case, the age was not reported. A total of 21 reports were classified as serious. The criteria for seriousness were mainly “hospitalisation” and “other”.

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 [9].

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

Mechanism

The mechanism for metronidazole-induced peripheral oedema is unknown. In general, drug-induced oedema is caused by enhanced renal sodium absorption [10], or orthostasis in case of e.g. antihypertensive drugs. However, no evidence for either mechanism could be found in the literature for metronidazole.

Discussion and conclusion

The Netherlands Pharmacovigilance Centre Lareb received nine reports of peripheral oedema associated with the use of metronidazole. Latencies were between 24 hours and 5 days, which seem plausible for peripheral oedema, and in five cases there was a positive dechallenge. Cardiovascular disease or the use of concomitant medication which might indicate cardiovascular disease were not reported for any of the patients. It is noteworthy that most of the patients in the reported cases are rather young. This seems to strengthen the hypothesis that the cause of the observed peripheral oedema is most likely not cardiovascular.

The association between metronidazole and peripheral oedema is statistically supported by the database of the Netherlands Pharmacovigilance Centre Lareb. The data from the WHO and Eudravigilance database however, do not seem to suggest a signal. The latter may partially be explained by the fact that peripheral oedema accounts for a large proportion (approximately 1%) of the ADRs in both databases, possibly due to selective reporting.

The number of cases, latencies and positive dechallenges suggest a relationship between metronidazole and peripheral oedema , which is further supported by a statistically significant disproportionality in the Lareb database. Further investigation of the information of the marketing authorisation holders for this signal is advisable.

- Further investigation of the information of the marketing authorization holders is advisable.

References

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2. Dutch SmPC metronidazol Actavis. (version date: 6-1-2012, access date: 27-3-2012) http://db.cbg-meb.nl/IB-teksten/h08652.pdf.
3. Dutch SmPC metronidazol Lagap. (version date: 18-4-1996, access date: 27-3-2012) http://db.cbg-meb.nl/IB-teksten/h11478.pdf.
4. Dutch SmPC metronidazol i.v. Braun. (version date: 29-5-1996, access date: 27-3-2012) http://db.cbg-meb.nl/IB-teksten/h12087.pdf.
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6. Dutch SmPC Rozex. (version date: 10-11-2010, access date: 27-3-2012) http://db.cbg-meb.nl/IB-teksten/h14416.pdf.
7. Dutch SmPC Rosiced. (version date: 3-8-2011, access date: 27-3-2012) http://db.cbg-meb.nl/IB-teksten/h30115.pdf.
8. Dutch SmPC Nidazea. (version date: 11-5-2010, access date: 27-3-2012) http://db.cbg-meb.nl/IB-teksten/h33518.pdf.
9. College voor Zorgverzekeringen. GIP Databank. College voor Zorgverzekeringen. GIP Databank. (version date: 22-3-2011, access date: http://www.gipdatabank.nl/.
10. UpToDate. UpToDate. (version date: 2012, access date: 17-1-2012) http://www.uptodate.com/.

This signal has been raised on October 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).