Metronidazole and tinnitus

Introduction

Metronidazole is an antibiotic that is used to treat a *wide variety of infections*. Metronidazole is a 5-nitro-imidazol-derivate, with activity against anaerobic protozoa and bacteria (1).
Tinnitus is a perception of sound in proximity to the head in the absence of an external source. It can be perceived as being within one or both ears, within or around the head, or as an outside distant noise. The sound is often a buzzing, ringing, or hissing, although it can also sound like other noises (2) Approximately 10% of the population has ever experienced long-term (longer than 5 minutes) complaints of ringing in the ears (3).

Reports

On October 3rd 2018, the Netherlands Pharmacovigilance Centre Lareb database contained eight reports of tinnitus associated with the use of metronidazole. Of these reports, seven were reported for metronidazole tablets specifically and for one report the dose from was unknown, but it was administered orally. The latency varied from one to a few days. Six patients did not recover, of which three withdrew the drug (4). The reports are listed in table 1.

Table 1: Reports of tinnitus with the use of metronidazole (4).

Patient, Sex, Age, (years), Source	**Drug, Indication for use**	**Concomitant medication**	**Suspected adverse drug reaction**	**Time to onset, Action with drug, Outcome**
46845 F, 21-30 years, Pharmacist	metronidazole tablet 500mg, 2dd 500 mg Acute vaginitis	clotrimazol	dizziness diplopia paraesthesia **tinnitus** oropharyngeal pain somnolence stomatitis affect lability muscle spasms	1 day, drug withdrawn, not recovered
129603 F, 11-20 years, GP	metronidazole tablet 500mg, 3dd 500mg, Amoebiasis		**tinnitus**	3 days, dose not changed, Recovering
161460 M, 71 years and older, Consumer	metronidazole tablet 500mg, 2dd 1000 mg, Helicobacter pylori infection	acenocoumarol digoxine levofloxacine amoxicilline	oedema peripheral dysgeusia headache **tinnitus**	day, dose not changed, not recovered
200263 M, 41-50 years, Specialist	metronidazole, Gastrointestinal infection		**tinnitus**	day, drug withdrawn, not recovered
39550 /39420 F, 31-40 years, GP/ Pharmacist	metronidazol tablet 500mg, 2dd 500 mg, Bacterial infection NOS		conjunctival discolouration alopecia **hypoacusis (**acute deafness and unilateral cracking)	3,5 year / days, drug withdrawn, not recovered

Patient, Sex, Age, (years), Source	Drug, Indication for use	Concomitant medication	Suspected adverse drug reaction	Time to onset, Action with drug, Outcome
NL-LRB-00286659 F, 31-40 years, Consumer	metronidazole tablet 500mg, 2dd 500mg, Abdominal discomfort* ofloxacine tablet 400mg, 2dd 400mg, Abdominal discomfort & Body temperature increased		anxiety dysgeusia ear discomfort feeling abnormal hallucination headache hot flush hyperhidrosis mucosal dryness neuropathy peripheral nightmare pain palpitations paraesthesia parosmia **tinnitus** tongue discolouration	same day as start of both drugs, drug withdrawn, recovered
NL-LRB-00288165 M, 41-50 years, Consumer	metronidazole tablet 500mg, 3dd 500mg, Irritable bowel syndrome*		confusional state pyrexia **tinnitus**	2 days, not applicable, not recovered
NL-LRB-243148 F, 61-70 years, Consumer	metronidazole tablet 500mg, 1dd 1000mg, Intestinal parasitism		abdominal discomfort abnormal faeces dizziness dysgeusia feeling abnormal nausea poor quality sleep **tinnitus**	Unknown Days, drug withdrawn, recovering

* Indications as reported by the patient themselves and not further specified

Other sources of information

SmPC

In 2016, the marketing authorization holder of Flagyl® requested a type II variation, to add tinnitus to the list of adverse drug reactions in the SmPCs of metronidazole ovules and suspension. Tinnitus was added to these SmPCs (5-6). However, tinnitus is not described in the Dutch SmPCs of metronidazole tablets (1;7). Table 2 provides an overview of the Dutch SmPCs and the labelling of tinnitus.

Table 2: Overview SmPCs of metronidazole oral formulations and the description of tinnitus (1;7).

Product	Registration number	Tinnitus in SmPC
Flagyl, ovula 500 mg	RVG 00238	Yes
Flagyl, suspensie 200 mg/5 ml	RVG 10322	Yes
Metronidazol Aurobindo 250 mg, filmomhulde tabletten	RVG 07074	No
Metronidazol Aurobindo 500 mg, filmomhulde tabletten	RVG 08652	No
Metronidazol Sandoz 250, omhumde tabletten 250 mg	RVG 17848=07074	No
Metronidazol Sandoz 500, omhulde tabletten 500 mg	RVG 17849=08652	No
Metronidazol Teva 250 mg, omhulde tabletten	RVG 21419=07074	No
Metronidazol Teva 500 mg, omhulde tabletten	RVG 21420=08652	No

Literature
The Farmacotherapeutisch Kompas describes tinnitus for metronidazole ovule, suspension, solution for intravenous infusion and tablets (8). A patient, who received metronidazole 21 g over a 14-day period, developed ataxia, tinnitus, and reversible deafness. Symptoms resolved spontaneously 1 month after metronidazole was discontinued. The patient was subsequently treated with tinidazole with no adverse effects (9). Two cases of bilateral moderate to severe sensorineural hearing loss have been reported following oral metronidazole therapy (600 to 1200 mg/day). Symptoms, consisting of unsteadiness, tinnitus, and hearing loss, developed approximately 48 hours after therapy began. In both cases, tinnitus preceded hearing loss. Following discontinuation of metronidazole and treatment with steroids, hearing was gradually recovered over a period of 4 to 6 weeks (10).
Meyler's Side Effect of Drugs describes the following: CNS symptoms can occur with standard doses of metronidazole, but they are mainly seen with high doses and especially when such doses are given for a long time (11). There are also several case reports describing tinnitus/hearing loss associated with metronidazole in literature (9, 10, 12,13).

Mechanism
The mechanism of ototoxicity for metronidazole has not been identified as it is an uncommon finding. Several hypotheses of this mechanism exist: reactivity with iron compounds; inhibition of protein synthesis; vasogenic and cytotoxic oedema; mitochondrial dysfunction; toxicity to the vestibular organ and cochlea; and idiosyncratic drug reaction. Metronidazole has been reported to induce central nervous system toxicity and in this review the authors state that this is not related to duration and dose of metronidazole (11). The relative bioavailability of metronidazole suspension is less compared to oral formulations (around 80% vs. >90%). The systemic absorption of metronidazole ovules is low (1;6-7).

Prescription data

Table 3: Number of patients using metronidazole in the Netherlands between 2013 and 2017 (15).

Drug	2013	2014	2015	2016	2017
Metronidazole	140.760	141.050	131.860	127.500	120.280

Discussion and conclusion
The Netherlands Pharmacovigilance Centre Lareb received eight cases of tinnitus associated with the use of oral metronidazole. Tinnitus is described as an adverse drug reaction in the SmPCs of metronidazole ovules and suspension (Flagyl®) and in literature, but is not described in the Dutch SmPCs of generic metronidazole tablets. The bioavailability and systemic absorption of metronidazole tablets is higher than with metronidazole ovule and suspension, for which tinnitus is a labelled adverse drug reaction. In addition, there is no indication that metronidazole tablets have a different mechanism of action than the metronidazole suspension. The fact that tinnitus is described in literature for metronidazole and in the Flagyl® SmPC, can be confusing for patients and prescribers since tinnitus is not described in the other Dutch SmPCs of oral metronidazole formulations.

References
(1) Dutch SmPC metronidazol Aurobindo 250 mg, filmomhulde tabletten. // Sandoz 250 mg, omhulde tabletten. // Teva 250 mg, omhulde tabletten. (version date: 08-01-2017, access date: 03-10-2018) https://db.cbg-meb.nl/smpc/h07074_smpc.pdf.
(2) UpToDate. (version date: 12-04-2018, access date: 03-10-2018) https://www.uptodate.com/contents/etiology-and-diagnosis-of-tinnitus.
(3) Coles RRA, Davis A, Smith P. Tinnitus: its epidemiology and management. In: Hartvig Jensen J, editor. Presbyacusis and other age related aspects. Proceedings of the 14th Danavox symposium. Copenhagen: Danavox Jubilee Foundation, 1990
(4) Lareb database. (version date: 2018; access date: 03-10-2018) www.lareb.nl.
(5) Dutch SmPC Flagyl®, ovula 500 mg. (version date: 02-07-2018, access date: 03-10-2018) https://db.cbg-meb.nl/smpc/h00238_smpc.pdf.
(6) Dutch SmPC Flagyl®, suspensie 200 mg/5 ml. (version date: 02-07-2018, access date: 03-10-2018) https://db.cbg-meb.nl/smpc/h10322_smpc.pdf.
(7) Dutch SmPC metronidazol Aurobindo 500 mg, omhulde tabletten. // Sandoz 250 mg, omhulde tabletten. // Teva 500 mg, omhulde tabletten (version date: 08-01-2017, access date: 03-10-2018) https://db.cbg-meb.nl/smpc/h08652_smpc.pdf.
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(9) Lawford R & Sorrell TC: Amebic abscess of the spleen complicated by metronidazole-induced neurotoxicity: case report. Clin Infect Dis 1994; 19:346-348.
(10) Iqbal SM, Murthy JG, Banerjee PK, et al: Metronidazole ototoxicity - report of two cases. J Laryngol Otol 1999; 113(4):355-357.
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(12) O'Donnell KL and Barker D. Metronidazole and tinnitus: A potential side effect? Br Dent J. 2016 Mar 25;220(6):289-91
(13) Jafari G, Hosseini SM, Akhondzadeh S. Sudden hearing loss subsequent to diarrhea: what is the missing link? Daru J Pharmceut Sc. 2014 Jan 8;22(1):15.
(15) GIP database – Drug Information System of Dutch Health Care Insurance Board. (version date: 19-07-2018, access date: 03-10-2018) http://www.gipdatabank.nl.

This signal has been raised on December 5, 2018. 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