Metronidazole and tinnitus: A potential side effect?

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VERIFIABLE CPD PAPER

IN BRIEF

- Discusses clinical indications for metronidazole prescription.
- Documents a case with an unusual side effect after metronidazole prescription.
- Explores the literature for similar cases.
- Explains how to report adverse drug reactions if they occur.

PRACTICE

As a healthcare profession, dentists have a role in ensuring the safety of prescribed medicines by reporting adverse drug reactions using the Yellow Card Scheme. This article briefly describes a case where metronidazole, an antibiotic commonly prescribed by dentists, may have caused ototoxicity and explores the evidence around this. It also highlights the method for reporting such effects.

INTRODUCTION

Metronidazole is a synthetic nitroimidazole based on a natural antiparasitic substance derived from a Streptomyces species in 1955. It was first approved for management of bacterial infections in 1981. It is active only against bacteria that are obligate anaerobes and acts by entering the cell causing DNA damage that leads to cell death.[1] Currently in the UK, metronidazole is used for treatment of anaerobic bacterial infections, protozoal infections, Helicobacter pylori eradication, fistulating Crohn's disease and topically for skin conditions.[2] Metronidazole accounted for 2.0% of antibiotics dispensed in Scotland in 2012.[3] In England in 2011, 1,919,600 prescriptions for metronidazole were dispensed by community pharmacies.[4]

Metronidazole is widely prescribed in dentistry as many intra-oral infections are assumed to have a predominantly anaerobic flora. In England in 2011, 1,089,447 dental prescriptions for metronidazole were dispensed by community pharmacies.[5] Dental prescriptions therefore represented 56.8% of total metronidazole prescriptions dispensed in England in 2011.[4,5] Metronidazole is most commonly recommended in the following situations:[6]

1. In patients with a dental abscess with spreading infection or systemic involvement who are allergic to penicillin. Or as an additional drug to penicillin in this situation in a non-allergic patient
2. In patients with pericoronitis or acute necrotising ulcerative gingivitis that has failed to respond to local measures.

Some evidence indicates that metronidazole can be a useful addition to non-surgical management in carefully selected patients with chronic and aggressive periodontitis. This antibiotic has been shown in systematic reviews to significantly decrease probing depths, decrease bleeding on probing and increase clinical attachment loss gain when compared to non-surgical management alone.[7-9] However, it must be used as an adjunct to conventional therapy.

Metronidazole is viewed as a relatively safe antibiotic when used in the short-term. The British National Formulary (BNF) lists the following side effects of the drug: gastrointestinal disturbances, taste disturbances, furred tongue, oral mucositis, and anorexia. Very rarely occurring side effects are listed as: hepatitis, jaundice, pancreatitis, drowsiness, dizziness, headache, ataxia, psychotic disorders, darkening of urine, thrombocytopenia, pancytopenia, myalgia, arthralgia, visual disturbances, rash, pruritus, and erythema multiforme.[2] Rarely, use of metronidazole can lead to neurological adverse effects.[10]

CASE REPORT

The patient, a 53-year-old female, was referred to the restorative dentistry department in Aberdeen Dental School and Hospital by her general dental practitioner (GDP) with regard to her periodontal disease. She was medically fit and healthy with no prescribed or other medications. On presentation she had BPE scores of 4*/4/4 4/1/4.

She had five teeth of unfavourable prognosis extracted before commencing treatment. She had two courses of non-surgical periodontal treatment carried out by a member of staff in the department. At the last visit of her second course of treatment she was prescribed 400 mg metronidazole tds for seven days.

Upon review three months later, her periodontal health had improved to the extent that she was able to be discharged to her GDP for maintenance care. However, at this review she advised that she had completed the course of metronidazole and felt that this had given her tinnitus. On day three of taking the antibiotic she became aware of a low-grade, mild tinnitus. Her aural symptoms had remained unchanged in the three month interim period, with both ears affected, although the left side was considerably worse than the right. The patient was only aware of the tinnitus when in bed or if it was quiet.

A review of the BNF revealed no documented side effect of ototoxicity and the complaint was initially deemed as a coincidental onset. However, a literature search was conducted and it revealed that metronidazole use and ototoxicity has been previously reported.

The patient was referred to the ENT department for assessment. At this appointment it was noted that she was aware of bilateral fizzing and whining sounds in quiet environments only. No factors were identified which could lead to impaired cochlear function. Routine examination indicated that

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both tympanic membranes were normal and an audiogram showed slight high frequency sensorineural hearing loss within normal limits for her age. A diagnosis was made of slight tinnitus which is likely to become less problematic with time. It was not possible to determine if her tinnitus was triggered by administration of metronidazole. No treatment was indicated and the patient was discharged from the ENT department. No further appointments for review were arranged in the Restorative Dentistry department as her periodontal health was stable.

A Yellow Card report was submitted for our patient documenting the findings as above.

DISCUSSION

Ototoxicity is defined as the toxic capacity of certain drugs or toxins to the structures of the inner ear or the vestibulocochlear nerve (VIII). Ototoxic drugs can act on the cochlea or the vestibular system or both. Toxic damage can be shown by symptoms like tinnitus, vertigo, hyperacusis or deafness. Onset of symptoms can be unilateral or bilateral, reversible or irreversible, and rapid or gradual. In the most severe of cases, patients may experience severe functional hearing loss or complete deafness.[11]

Isolated case reports dating back to the 1980s exist to suggest that metronidazole has ototoxic effects in a small number of patients. In 1984, a case was reported where a patient experienced bilateral nerve deafness after administration of metronidazole.[12]

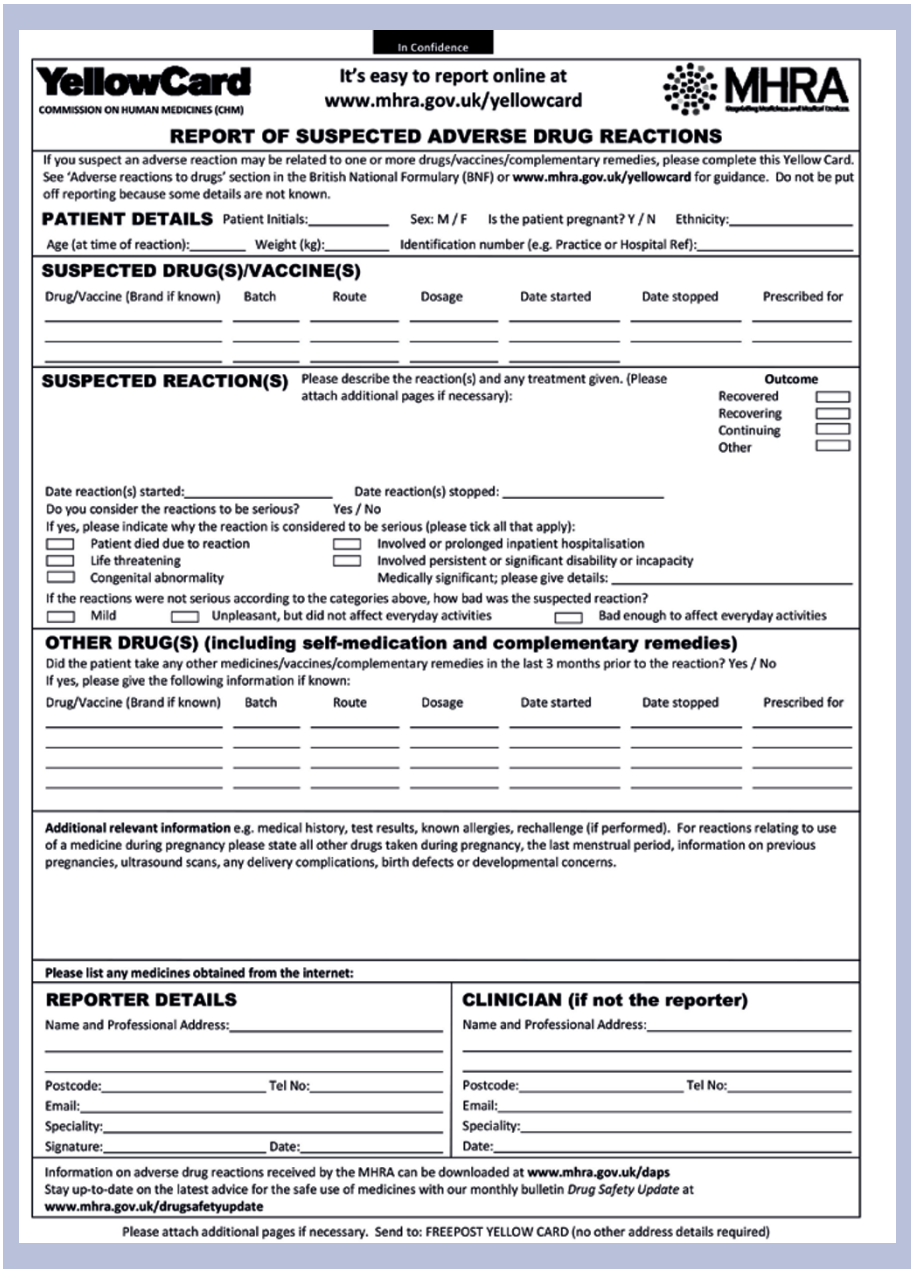
In 1999, a series of two cases was reported by Iqbal et al. where both patients had been prescribed metronidazole for dental pathology. Patient 1 reported unsteadiness, hearing loss and tinnitus in both ears after six 400 mg doses of metronidazole over two days. Patient 2 reported diminished hearing and tinnitus bilaterally after six 200 mg doses of metronidazole over two days. Patient 1 had complete recovery from symptoms after six weeks, whereas Patient 2 had an incomplete recovery with mild to moderate residual high frequency hearing loss at three months follow-up.[13]

In 2014, a case report was published where a patient presented with a three day history of tinnitus bilaterally accompanied by progressively decreasing hearing. She had experienced acute watery diarrhoea for which she had been prescribed metronidazole (750 mg tds) and on day four had discontinued the drug due to resolution of her symptoms. Her ear symptoms began on the same day. Ten days after treatment with intratympanic dexamethasone, oral prednisolone and oral acyclovir she reported that her hearing was gradually improving.[14]

In both cases mentioned previously, steroids (oral or intratympanic) were administered at presentation.[13,14] This is in accordance with the clinical practice guideline for sudden hearing loss issued by the American Academy of Otolaryngology.[15] The prognosis for recovery may be determined by time from the start of symptoms to treatment (among other factors).[15] Therefore a swift referral to ENT is indicated for a patient presenting with these symptoms.

Metronidazole has been reported to potentiate the ototoxic effects of gentamicin in guinea pigs by significantly increasing hair cell loss and hearing loss when compared to gentamicin alone.[16] 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;[16] inhibition of protein synthesis; vasogenic and cytotoxic ooedema; mitochondrial dysfunction;[14] toxicity to the vestibular organ and cochlea; and idiosyncratic drug reaction.[13] 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.[16]

In this case, a report of this adverse reaction was submitted using the Yellow Card Scheme. The Medical and Healthcare products Regulatory Agency (MHRA) is a UK government body that is responsible for ensuring that medicines and medical devices work and are safe. For over forty years, healthcare professionals have had a role in ensuring the safety of medicines by reporting adverse drug reactions using the



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MHRA

REPORT OF SUSPECTED ADVERSE DRUG REACTIONS

If you suspect an adverse reaction may be related to one or more drugs/vaccines/complementary remedies, please complete this Yellow Card. See 'Adverse reactions to drugs' section in the British National Formulary (BNF) or **www.mhra.gov.uk/yellowcard** for guidance. Do not be put off reporting because some details are not known.

PATIENT DETAILS Patient Initials:_____ Sex: M / F Is the patient pregnant? Y / N Ethnicity:_____

Age (at time of reaction):_____ Weight (kg):_____ Identification number (e.g. Practice or Hospital Ref):_____

SUSPECTED DRUG(S)/VACCINE(S)

Drug/Vaccine (Brand if known)	Batch	Route	Dosage	Date started	Date stopped	Prescribed for

SUSPECTED REACTION(S) Please describe the reaction(s) and any treatment given. (Please attach additional pages if necessary):

Outcome
Recovered ☐
Recovering ☐
Continuing ☐
Other ☐

Date reaction(s) started:_____ Date reaction(s) stopped:_____
Do you consider the reactions to be serious? Yes / No
If yes, please indicate why the reaction is considered to be serious (please tick all that apply):
☐ Patient died due to reaction ☐ Involved or prolonged inpatient hospitalisation
☐ Life threatening ☐ Involved persistent or significant disability or incapacity
☐ Congenital abnormality Medically significant; please give details:_____
If the reactions were not serious according to the categories above, how bad was the suspected reaction?
☐ Mild ☐ Unpleasant, but did not affect everyday activities ☐ Bad enough to affect everyday activities

OTHER DRUG(S) (including self-medication and complementary remedies)
Did the patient take any other medicines/vaccines/complementary remedies in the last 3 months prior to the reaction? Yes / No
If yes, please give the following information if known:

Drug/Vaccine (Brand if known)	Batch	Route	Dosage	Date started	Date stopped	Prescribed for

Additional relevant information e.g. medical history, test results, known allergies, rechallenge (if performed). For reactions relating to use of a medicine during pregnancy please state all other drugs taken during pregnancy, the last menstrual period, information on previous pregnancies, ultrasound scans, any delivery complications, birth defects or developmental concerns.

Please list any medicines obtained from the internet:

REPORTER DETAILS
Name and Professional Address:_____
Postcode:_____ Tel No:_____
Email:_____
Speciality:_____
Signature:_____ Date:_____

CLINICIAN (if not the reporter)
Name and Professional Address:_____
Postcode:_____ Tel No:_____
Email:_____
Speciality:_____
Date:_____

Information on adverse drug reactions received by the MHRA can be downloaded at **www.mhra.gov.uk/daps**
Stay up-to-date on the latest advice for the safe use of medicines with our monthly bulletin *Drug Safety Update* at **www.mhra.gov.uk/drugsafetyupdate**

Please attach additional pages if necessary. Send to: FREEPOST YELLOW CARD (no other address details required)

Fig. 1 Yellow Card form

Yellow Card Scheme. Reports can be made for all medicines including vaccines, blood products and homeopathic remedies, and all medical devices.

By reporting issues with medicines or medical devices, new problems can be identified that were not previously known. Reports can now be submitted online at www.mhra.gov.uk/yellowcard or by filling in a paper copy which may be found in the BNF or downloaded from the MHRA website (Fig. 1). After a report is submitted, the MHRA will review it and take action as required to protect patients and minimise risk. It is crucial that, as prescribers, dentists follow the correct process for reporting any adverse drug reactions.

CONCLUSION

Metronidazole is a drug that is often prescribed by dentists and as such it is important that we are aware of potential adverse reactions. It is not the intention of the authors to suggest that there is a causal link between metronidazole administration and tinnitus, but merely to add to the limited literature on this potential adverse effect. Any adverse drug reactions should be reported to the MHRA using the Yellow Card Scheme.

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