

Metronidazole associated seizures: a case report and review of the pharmacovigilance literature

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ABSTRACT

Seizures are a rare side-effect associated with the use of metronidazole. This report describes the case of an 83-year old patient with previous cerebral injury in whom new onset seizures were triggered soon after the commencement of treatment with metronidazole at conventional adult doses for *Clostridium difficile*-associated diarrhoea.

A brief review of the medical pharmacovigilance literature in relation to metronidazole and seizures is presented. Two causality assessment systems are applied to the index case report, to illustrate their potential use in supporting increased objectivity when reporting suspected ADRs in clinical practice.

Keywords: Metronidazole, Adverse drug reaction, Seizures, Causality, Adverse drug reaction reporting systems, Pharmacovigilance

INTRODUCTION

Metronidazole is used routinely as a treatment option for a range of clinical indications, most notably those involving many anaerobes and protozoal infections. Uncommon but recognised neurotoxic side-effects of metronidazole include polyneuropathies, cerebellar effects, encephalopathies, psychoses and seizures. This report describes an older patient in whom seizures were associated with the use of metronidazole.

CASE REPORT

An 83-year old lady was admitted following a fall and fracture to the right femoral neck. She had a medical history of hypertension that was controlled on bendroflumethiazide 2.5mg daily. The hip fracture was repaired surgically under spinal anaesthesia (Bupivacaine

hydrochloride 0.5%) with target controlled propofol by infusion. She received maintenance intraoperative oxygen supplementation, with oxygen saturations ranging between 92% and 100%. The surgery and anaesthesia were otherwise uneventful but she was noted to be persistently unresponsive post-operatively. She required a period of care in the intensive care unit with temporary tracheal intubation for airway support. Assessments suggested the possibility of hypoxic brain injury, supported by Computerised Tomography (CT) scans showing features consistent with evolving acute ischaemic changes to both occipital lobes and some associated cerebral oedema. She gradually regained consciousness over a seventy two hour period with spontaneous eye opening, but remained markedly dysphasic, and had persistent motor weakness with muscle strength of 1 over 5 in all limbs. She required a period of nasogastric tube feeding, and was fit for transfer

of care to an acute medical ward fifteen days post-operatively. Thereafter, she had the uneventful insertion of a Percutaneous Endoscopic Gastrostomy (PEG) tube because of persistent dysphagia.

During the third month of rehabilitation in hospital, she developed clinical and radiological signs of aspiration pneumonia. The pneumonia resolved following treatment with co-amoxiclav 625mg thrice daily via PEG tube for five days. However, this treatment was subsequently complicated by the development of *Clostridium difficile*-Associated Diarrhoea (CDAD) and she was started on liquid metronidazole 400mg thrice daily via the PEG tube. The introduction of metronidazole was seventeen weeks after the hip surgery.

Following the fifth dose of metronidazole, she developed new onset of motor seizures involving the right facial muscles (peri-orbital and peri-oral), the right upper and lower extremities, and accompanying altered sensorium. The seizures were protracted, lasting over an hour before the eventual achievement of initial seizure control using intravenous (IV) lorazepam 4mg and a total IV phenytoin infusion of 900mg (15mg/Kg dosing regimen). Subsequent seizure control was maintained with sodium valproate 300mg twice daily, initially administered IV and subsequently via the PEG tube. The metronidazole was discontinued, and its re-introduction / re-challenge deemed clinically inappropriate. The CDAD resolved uneventfully with vancomycin 125mg four times daily for ten days administered through the PEG.

Other medications that had been ongoing for many weeks, and which had remained unchanged during the time of the occurrence and subsequent management of the seizures included: subcutaneous enoxaparin 20mg daily for prophylaxis against deep vein thrombosis, paracetamol 1 gram four times daily via PEG for analgesia, and bendroflumethiazide 2.5mg daily via PEG for systemic hypertension.

Prior to the occurrence of these seizures, there had been no preceding history of any seizure activity or epilepsy, and there was no family history of relevance. Her renal, liver and thyroid function tests were normal. Blood, urine and PEG site skin cultures were negative. Other potential risk factors for seizures that were considered and either sufficiently excluded, or judged to be unlikely in this case included: a new cerebrovascular event or other intracranial pathology (a repeat non-contrast cerebral CT scan was performed which showed no new abnormalities and also confirmed resolution of the earlier noted cerebral oedema), cerebral or meningeal infection, hyperpyrexia, electrolyte imbalance, other metabolic disorders (e.g. uraemia, continuing hypoxia, hypoglycaemia), acid-base disorders, ethanol use/withdrawal, nicotine use/withdrawal, cardiac arrhythmia, porphyria, drug interactions, and sleep deprivation.

DISCUSSION

Metronidazole

Metronidazole is a 5-nitroimidazole compound that is used extensively as a treatment option for a range of indications including many anaerobic and protozoal infections. For example, metronidazole is commonly employed in clinical practice as a first line treatment for mild to moderate severity CDAD.¹ The occurrence of CDAD is itself a recognised and unwelcome issue in frail hospitalised,² institutionalised or even community dwelling older patients; in some cases occurring even when they might have received judicious antibiotic therapy for clinically justifiable indications.

Metronidazole is described as a drug with very good oral bioavailability and it also has good central nervous tissue (CNS) penetration. Metronidazole is metabolized in the liver, and its excretion is mainly renal, although some excretion also takes place via the biliary system.

Metronidazole and seizures

Some uncommon but recognised neurotoxic side-effects of metronidazole include polyneuritis / polyneuropathies, cerebellar related effects (including dysarthria and ataxia), encephalopathies, psychoses and seizures.²⁻⁵

The mechanism(s) by which metronidazole predisposes to seizures remains a subject of hypotheses, with one possibility being the lowering of seizure thresholds, given both its good bioavailability and good CNS penetration profile.

Previous reports of seizures associated with metronidazole have suggested some predisposing factors²⁻⁹ including:

1. High cumulative doses of metronidazole,
2. Prolonged therapy with metronidazole,
3. Chronic renal failure (chronic kidney disease), and
4. Concurrent use alongside other medications that have been linked to seizures.

Both Halloran and Frytak et al. describe cases in which convulsive seizures were associated with high cumulative doses of metronidazole.^{6,7} Halloran postulated that it might have been the cumulative dose (which exceeded 40 grams in their case), rather than the serum level, which was more important in the pathogenesis of this complication.

Beloosesky et al. describe convulsive seizures with metronidazole use. These involved a case presenting initially as generalised seizures, and subsequent episodes presenting as myoclonus with muscle twitching which evolved into generalised seizures.² These seizures were reported as occurring in association with the use of metronidazole at the authors' local conventional adult treatment doses of 500mg thrice daily for CDAD. The

patient in the case described by Beloosesky was reported to have received three courses of metronidazole for CDAD recurrences (or re-infections) within an interval of just over two months. The cumulative doses received (and the time period from the introduction of metronidazole to the onset of seizures) were calculated as being 18 grams (twelve days), 10.5 grams (seven days), and 4.5 grams (three days) of metronidazole for the first, second, and third episodes of CDAD respectively. The authors indicate that this individual had chronic renal failure, and they postulated that the co-existent renal insufficiency predisposed to the accumulation of metabolites of metronidazole.² The report by Beloosesky et al.² would suggest that although high cumulative doses of metronidazole (as described in the cases by Halloran⁶ and Frytak et al.⁷) might be a distinct risk factor for seizures, the presence of renal impairment might be another important consideration in relation to the association between metronidazole and seizures occurring at lower cumulative doses.

Sopeña et al. reported a case involving a seizure that was noted during concurrent treatment with metronidazole and chloroquine.⁸ Semel et al. reported another patient who developed seizures in the context of possible drug interactions during concurrent treatment with theophylline, metronidazole and ciprofloxacin.⁹

The current report is notable because although the doses of metronidazole employed prior to the onset of the seizures would also be considered to be within the usual adult therapeutic dose (i.e. 400mg thrice daily), the seizures occurred in an individual with normal renal function, and who had only attained a fairly low cumulative dose of 2 grams (on day 2 of treatment). In this case, the metronidazole appears to have unmasked an underlying liability to seizures in an individual with previous brain injury, but who had been previously seizure free.

It is plausible that the seizure occurrences in this report were manifestations of delayed onset seizures arising in an individual with an underlying cerebral injury. The focal nature of the seizures with altered sensorium was clinically suggestive of complex partial status epilepticus (given the presentation and in view of the duration), and would suggest a focus of onset from abnormal left cerebral hemispheric activity. However, the prolonged interval (of seventeen weeks) between the initial brain injury and the sudden onset of the fairly protracted seizures in this case is contrasted with the alternative hypothesis that these were seizures triggered by the acute exposure to a medication that is known to be a rare cause of seizures. The latter is a particularly relevant consideration given that the seizures occurred soon (less than forty eight hours) after the institution of metronidazole therapy. The acute chronological sequence between exposure to the medication and the ensuing onset of the protracted seizures raised the distinct possibility of a medication associated temporal association.

Application of the Naranjo adverse drug reaction probability scale / score, and the WHO-Uppsala Monitoring Centre (WHO-UMC) causality assessment systems to the index case report

There is a recognition that many ADRs tend to fall within the category of 'suspected' rather than 'definite' ADRs. This is often because of the interplay of other confounding factors, as many of the cases earlier reported in the medical literature also indicate. Many systems and algorithms have been developed in an attempt to try and introduce more objectivity into the framework of the assessment of causality of ADRs.

This index case report applied two systems to test the hypothesis that the noted seizures were an ADR related to the treatment with metronidazole. Applying the Naranjo Scale to this case report generates a score of 2 which equates to a 'Possible' ADR classification. Applying the WHO-UMC method also translates to a 'Possible' ADR classification.¹⁰⁻¹⁴

CONCLUSION

As the population ages, the prevalence of cerebrovascular disease and other causes of cerebral pathology is rising. These conditions are in themselves relevant risk factors for seizures. This case report serves as a clinical reminder for caution when prescribing metronidazole to older patients, particularly in the presence of pre-existing cerebral co-morbid factors that can aggravate any predisposition to seizures. This case and the accompanying literature review illustrate the fact that although the clinical occurrence of seizures with metronidazole is rare, caution is required even where there has been no prior documented history of seizures.

Key points

- Seizures are a recognised but rare neurotoxic side-effect associated with metronidazole therapy.
- Seizures related to metronidazole use might be associated with higher cumulative doses, prolonged periods of therapy, the presence of chronic kidney disease, and the concurrent use of other medications that are themselves known to be associated with seizures: although these are not invariable features.
- Caution should also be exercised when prescribing metronidazole to individuals who are known to have pre-existing cerebral damage, as metronidazole could possibly trigger the onset of seizures, even in the absence of a prior history of seizures.
- The use of validated causality assessment systems can improve objectivity when ADRs are ascribed to medications, and thus potentially support an important facet of pharmacovigilance.

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