Toxic Metronidazole-Induced MRI Changes

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OBJECTIVE: To report a case of changes documented by magnetic resonance imaging (MRI) of the head probably due to accumulation of metronidazole in a patient with liver dysfunction.

CASE SUMMARY: A 34-year-old Hispanic man with cirrhosis and hepatitis C being treated with metronidazole for *Bacteroides fragilis* meningitis and bacteremia developed ataxia, disorientation, and peripheral neuropathy. An MRI at the time meningitis was diagnosed was negative. After the patient received >60 g of metronidazole, an MRI revealed increased signal intensity below, behind, and lateral to the fourth ventricle. Concomitant metronidazole serum concentration was toxic at 35.1 µg/mL.

DISCUSSION: This is the second reported case of metronidazole-induced MRI changes. Metronidazole is known to accumulate in patients with liver dysfunction and can cause peripheral neuropathy and central nervous system (CNS) dysfunction; these effects may take up to two years to completely resolve.

CONCLUSIONS: Metronidazole dosages should be reduced in patients with liver dysfunction to prevent the accumulation of metronidazole, which can lead to CNS dysfunction and peripheral neuropathy.

KEY WORDS: metronidazole, magnetic resonance imaging.

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Metronidazole is a 5-nitroimidazole antibiotic used for a variety of indications, including treating anaerobic infections. Metronidazole is fairly safe when used at appropriate dosages, but it can produce peripheral neuropathies and cerebellar dysfunction, especially with dosages >2 g/d for prolonged periods of time.[1] We report the second case of magnetic resonance imaging (MRI) changes probably due to metronidazole toxicity.

CASE REPORT

A 34-year-old Hispanic man with a past medical history significant for cirrhosis, alcohol abuse since age 9, intravenous drug abuse, documented hepatitis C for seven years, and an initial Child–Pugh classification of C was admitted on June 21, 1999, with chief complaints of nausea, vomiting, malaise, fever, and diarrhea for the previous three days. Laboratory results determined on June 22 were white blood cell count $11.7 \times 10^3/mm^3$ (neutrophils 74%, bands 13%, lymphocytes 6%, monocytes 5%, eosinophils 0%, basophils 0%), hemoglobin 13.3 g/dL, hematocrit 36.8 g/dL, platelets $38 \times 10^3 \times mm^3$, sodium 124 mEq/L, potassium 3.3 mEq/L, chloride 93 mEq/L, carbon dioxide 19 mEq/L, glucose 148 mg/dL, blood urea nitrogen 17 mg/dL, creatinine 1.0 mg/dL, calcium 7.3 mg/dL, total protein 6.1 g/dL, albumin 2.2 g/dL, total bilirubin 4.0 mg/dL, alkaline phosphatase 159 IU/L, aspartate transaminase (AST) 105 IU/L, and alanine transaminase 45 IU/L; γ-glutamic transaminase 235 IU/L was determined on June 25. A lumbar puncture and blood cultures revealed *Bacteroides fragilis* meningitis and *B. fragilis* bacteremia. On hospital day 4, intravenous metronidazole 250 mg every six hours was begun. An MRI of the head without contrast (Figure 1) done on June 25 was essentially normal, with some heterogeneous signal intensity in the basal ganglia. The patient was discharged on July 15, with prescriptions for spironolactone 200 mg/d, furosemide 40 mg/d, lactulose 30 mL four times daily, amitriptyline 10 mg at bedtime, propranolol 10 mg twice daily, and metronidazole 500 mg four times daily for at least four more weeks.

Two weeks after discharge, the patient returned to the clinic for a follow-up appointment. He had no complaints and stated he was compliant with therapy. He was also evaluated in the clinic on August 11; his only symptom at that time was some tingling in his hands and feet. Five days later, the patient presented to the emergency department with tingling in his feet, dizziness, inability to walk, occasional disorientation to person, slowed speech and incoherence, and vomiting for the past two days. Physical examination revealed that the patient was afebrile, but was jaundiced and had shifting dullness. Neurologic examination was significant for horizontal nystagmus in the extremes of vision. He exhibited past-pointing on the finger-to-nose test. He was severely ataxic and was unable to walk unassisted without falling. He had no pronator drift, no tremor, no Kernig's sign, no Brudzinski's sign, and no asterixis. Initial laboratory results included normal complete blood cell count and differential, sodium 136 mEq/L, calcium 8.7 mg/dL, albumin 2.5 g/dL, international normalized ratio 1.74, total bilirubin 3.1 mg/dL, alkaline phosphatase 142 IU/L, AST 148 IU/L, and arterial ammonia 14 µg/dL (normal 36–121). A serum metronidazole concentration drawn on August 15 was 35.1 µg/mL (therapeutic range 18–25; personal communication, Barbara J Struthers PhD DABT, Searle Healthcare Information Services, Skokie, IL, August 17, 1999). A cerebrospinal fluid (CSF) metronidazole concentration was not obtained, but it has been reported[1] that CSF and serum concentrations of metronidazole are approximately equivalent.

Eight weeks after the initial diagnosis of *B. fragilis* meningitis (August 17), metronidazole was discontinued to see whether this

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was the cause of his symptoms. An MRI of the head with contrast was performed that day and revealed a venous angioma in the medial right frontal lobe just anterior to the frontal horn; peculiar areas of increased signal intensity in the inferior basal ganglia lateral to the hypothalamus and also below, behind, and lateral to the fourth ventricle; and acute mastoiditis (Figure 2). It was believed that the areas of increased signal intensity were most likely due to drug toxicity. A lumbar puncture was done the following day and the CSF results were unremarkable.

The patient was diagnosed with metronidazole-induced central nervous system (CNS) dysfunction and peripheral neuropathy thought to be secondary to his cirrhosis and accumulation to toxic metronidazole serum concentrations with normal therapeutic dosing. The MRI findings shown in Figure 2 are consistent with this neuropathy. By the day of discharge (August 18), the patient's speech was coherent, cerebellar signs were much improved, and he could walk, although he remained unsteady.

At a follow-up appointment on September 1, the patient no longer displayed any cerebellar signs of toxicity. He only reported continued numbness, tingling, and pain in his hands and feet, which worsened with cold temperatures and at bedtime; an MRI was not performed at this visit.

Discussion

There is only one other report of metronidazole-induced toxicity documented by MRI changes. Ahmed et al.[2] reported the case of a 45-year-old woman treated with approximately 35 g of metronidazole for nearly 30 days. She developed nausea, vomiting, vertigo, confusion, ataxia, and peripheral neuropathy with this dosage. An MRI showed "symmetric abnormal signal within supratentorial white matter, including the corpus callosum, and within the cerebellum, including the cerebellar deep gray matter nuclei." No metronidazole concentration was obtained. Nearly complete resolution of the MRI changes was documented with a follow-up MRI six weeks later.

Our patient exhibited the classic symptoms of metronidazole-induced CNS dysfunction and peripheral neuropathy. He received approximately 66 g of metronidazole over 55 days. An MRI performed shortly after metronidazole was started was essentially negative, whereas the MRI done on the second admission showed bilateral areas of increased signal intensity. Although a follow-up MRI was not performed, the temporal relationship of the patient's signs and symptoms highly suggests that the MRI changes may be the result of a toxic accumulation of metronidazole. The symptoms began to improve once metronidazole was discontinued. According to the Naranjo probability scale,[3] this reaction would be considered probable.

There are several case reports describing peripheral neuropathy with metronidazole.[2,4-8] Seizures[9] and encephalopathy[2,7,10,11] have also been reported. Most cases of peripheral neuropathy develop with large daily doses (>2 g/d) and prolonged courses of therapy.[6] Complete or partial resolution may occur after discontinuation of therapy; however, symptoms may take up to two years to completely resolve.[6] The exact mechanism for these adverse effects is not known. Large doses of metronidazole have been shown to bind the RNA of rat nerve cells.[8]

Metronidazole has antibacterial activity against anaerobic organisms, including *B. fragilis*. Since it also effective-

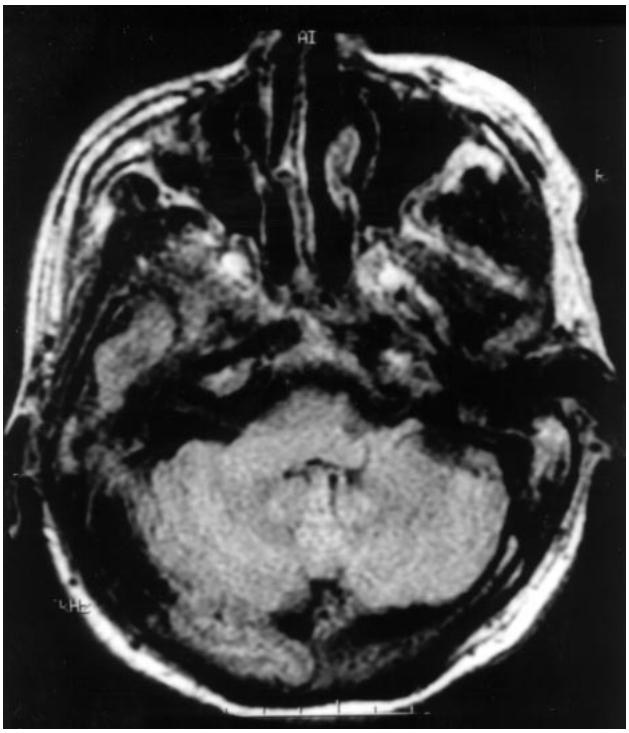

Figure 1. Magnetic resonance imaging in patient with *Bacteroides fragilis* meningitis prior to initiation of metronidazole therapy.

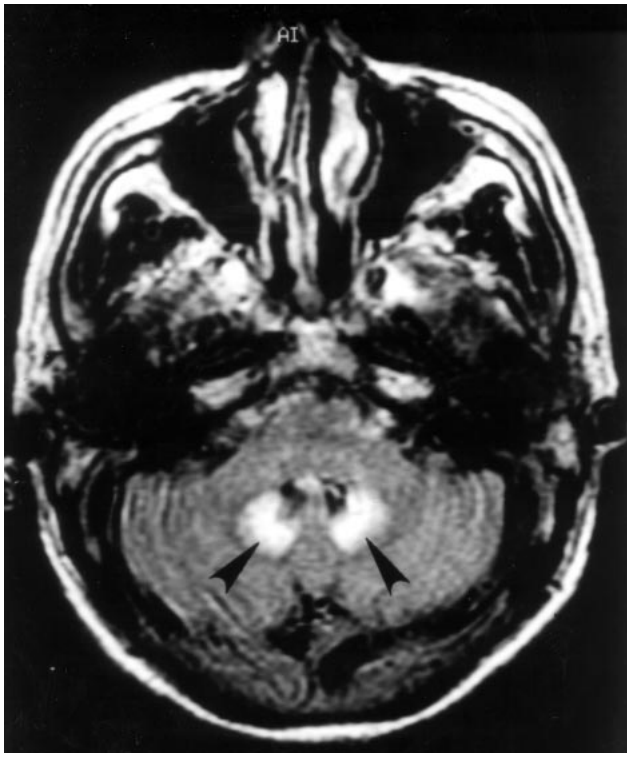

Figure 2. Magnetic resonance imaging after eight weeks of metronidazole therapy, with toxic metronidazole serum concentrations and metronidazole-induced central nervous system dysfunction and peripheral neuropathy. The arrows mark the increased signal intensity below, behind, and lateral to the fourth ventricle.

ly crosses the blood–brain barrier and is almost 100% bioavailable, metronidazole is a good choice to treat *B. fragilis* meningitis. However, metronidazole undergoes biotransformation in the liver to both active and inactive metabolites. It has been shown[12-14] that in patients with hepatic disease, there is a tendency toward a longer elimination half-life and reduced total body clearance for metronidazole compared with normal controls. There are no specific dosage recommendations for patients with hepatic failure, but it is reasonable to use a reduced dosage or increased dosing interval in these patients, especially when prolonged courses of therapy are expected.

Summary

This is the second case reported in the literature in which MRI changes were noted in a patient receiving metronidazole who developed peripheral neuropathy and CNS dysfunction. Due to the temporal relationship with metronidazole exposure, the clinical signs and symptoms, and a toxic metronidazole concentration, the MRI findings are probably related to toxic metronidazole exposure. Patients with a history of cirrhosis should have metronidazole doses reduced and if peripheral neuropathy and CNS dysfunction occur, metronidazole toxicity should be suspected. Serum and CSF metronidazole concentrations should be drawn and an MRI may be useful in delineating the cause.

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EXTRACTO

OBJETIVO: Informar un caso de cambios en la imagen de resonancia magnética (IRM) debido, probablemente, a la acumulación del metronidazol en un paciente con disfunción hepática.

RESUMEN DE CASO: Una hombre hispano de 34 años de edad con cirrosis y hepatitis C que recibía tratamiento con metronidazol para meningitis y bacteremia causadas por *Bacteroides fragilis* desarrolló ataxia, desorientación, y neuropatía periférica. Un IRM realizado para diagnosticar la meningitis resultó negativo. Después de recibir >60 g del metronidazol, un IRM reveló una intensidad aumentada en la señal debajo, detrás y lateral al cuarto ventrículo. Concomitantemente, la concentración sérica del metronidazol era tóxica, con un nivel de 35.1 µg/mL.

DISCUSIÓN: Este es el segundo caso reportado de cambios en la IRM inducido por metronidazol. El metronidazol se puede acumular en pacientes con disfunción hepática y puede causar neuropatía periférica y disfunción del sistema nervioso central (SNC). Esto puede tardar hasta dos años en resolverse.

CONCLUSIONES: La dosis del metronidazol se debe reducir en pacientes con disfunción hepática, para de esta manera, prevenir la acumulación del metronidazol que puede ser causante de disfunción del SNC, y de neuropatía periférica.

Rafaela Mena de Giraldi

RÉSUMÉ

OBJECTIF: Décrire un cas des changements à l'imagerie par résonance magnétique électronique (IRM) probablement associés à une accumulation de métronidazole chez un patient avec problème hépatique.

RÉSUMÉ DU CAS: Un homme de 34 ans avec cirrhose et hépatite C traité avec métronidazole pour une méningite et une bactériémie au *Bacteroides fragilis* a présenté de l'ataxie, de la désorientation et une neuropathie périphérique. Le IRM au moment du diagnostic de la méningite était négatif. Après avoir reçu plus de 60 g de métronidazole, le IRM a révélé une augmentation de la densité sous, à l'arrière et du côté latéral de quatrième ventricule. Les concentrations plasmatiques du métronidazole étaient toxiques soit à 35.1 µg/mL.

DISCUSSION: Les auteurs rapportent le deuxième cas dans la littérature des changements au IRM associés au métronidazole. Il est bien connu que le métronidazole s'accumule chez les patients en insuffisance hépatique et peut causer une neuropathie périphérique et des problèmes au niveau du système nerveux central qui peut prendre deux ans avant de disparaître.

CONCLUSIONS: La posologie du métronidazole doit être réduite chez les patients avec insuffisance hépatique pour prévenir une accumulation et les effets toxiques.

Louise Mallet