Metronidazole-Induced Neurotoxicity

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Abstract
A 50 year old male with history of prolonged intake of metronidazole for treatment of liver abscess developed acute ataxia, disorientation, distal symmetrical sensory and proximal motor neuropathy. Patients being treated with metronidazole particularly those on high doses for prolonged period should be monitored for neurotoxicity.

INTRODUCTION
Metronidazole is a 5-nitroimidazole and has potent activity against anaerobic bacteria, several protozoa including Entamoeba, Giardia, Trichomonas and B. coli, H. pylori and Guinea worm. It is generally well tolerated and common side effects include nausea, dizziness, ataxia, seizures, encephalopathy and neuropathy.1 We are presenting a case report of a patient who developed a combination of neurotoxic manifestations following prolonged intake of metronidazole.

CASE REPORT
A previously healthy, 50 year old man with unremarkable medical history presented with fever, chills and right upper abdominal pain of 3-4 days duration. On examination, he was febrile with temperature of 38.5°C. His pulse rate was 110/min with no icterus or lymphadenopathy. Systemic examination was unremarkable except for tender hepatomegaly (liver was palpable 4-5 cms below right costal margin). Ultrasonographic examination revealed two large liver abscesses of size 9x9 cm and 8x7 cm in the right lobe of the liver. Amoebic serology was also positive. Patient was put on metronidazole 800 mg TDS orally. Patient started showing improvement in all symptoms within 2 to 3 days and was discharged after about a week. He was advised to continue metronidazole at same doses for another week, and to follow up in OPD. Patient went back to his village and continued to take oral metronidazole as before on the advice of local chemist for mild persistent pain in right upper abdomen. After about 12 weeks of discharge, patient presented with history of dizziness, diplopia, disorientation, inability to walk, slowed speech, incoherence and vomiting of three days duration. Neurological examination was significant for horizontal nystagmus in extremes of vision. He exhibited past-pointing on finger-nose test. He was severely ataxic and was unable to walk unassisted without falling. Routine laboratory results including CSF examination were unremarkable. CT scan (head) revealed hypodense areas in the cerebellum (Fig. 1). Within 3 to 4 days of stopping metronidazole patient’s condition improved remarkably with normal mentation, his speech became coherent, cerebellar signs were much improved, and he could walk unassisted although he remained unsteady. He then disclosed that after about three weeks of initial discharge, he had developed progressive numbness, tingling and pain in both lower limbs. Symptoms started distally and slowly progressed proximally and involved both hands as well. After 3 to 4 weeks he also experienced difficulty in standing from a squatting position followed by difficulty in

Fig. 1 : CT scan (head) showing bilateral symmetrical hypodense areas in the cerebellum (arrows).
raising his hands above his head. Detailed sensory examination revealed graded sensory loss to pain, temperature and touch over distal lower and upper limbs in a stocking and glove distribution. Joint position and vibration sense were also impaired. Romberg’s sign was positive. Motor examination revealed loss of bulk of thigh muscles with decreased tone. Power of muscle groups acting at hip and shoulder joints was reduced (grade III/V at hip and IV/V at shoulder). Bilateral ankle jerks were absent and both plantars were flexor. Electrophysiological studies (NCV and EMG) indicated severe sensory polyneuropathy affecting lower and upper limbs with moderate axonal asymmetrical motor neuropathy affecting lower limbs. Observation of the patient for next two weeks revealed only marginal improvement in symptoms.

**DISCUSSION**

The patient discussed here took about 200 gm of metronidazole over a period of 12 weeks and presented with a combination of neurotoxic manifestations which included features of acute cerebellar toxicity, distal sensory peripheral neuropathy, and proximal motor neuropathy. Symptoms of vomiting, vertigo, confusion and ataxia dramatically improved after stopping the drug. However neuropathic symptoms failed to improve. Though a follow up CT or MRI was not performed, the temporal relationship of the patient’s signs and symptoms strongly suggest that the hypodense lesions in the cerebellum were in all probability the result of toxic accumulation of metronidazole. There are only a few reports of metronidazole induced acute neurotoxicity and cerebellar dysfunction. Ahmed et al reported a case that developed nausea, vomiting, vertigo, confusion and ataxia with approximately 35 gm of metronidazole intake. MRI done revealed symmetrical abnormal signal within the cerebellum. There are several case reports describing distal symmetrical predominantly sensory peripheral neuropathy with metronidazole and even with another nitroimidazole, ornidazole. Our patient also had similar type of neuropathy. However, in addition, there was significant proximal motor involvement confirmed by electrophysiological studies. To our knowledge this type of motor neuropathy associated with metronidazole toxicity is yet to be reported in the literature. Most cases of peripheral neuropathy develop with large daily dose (> 2 g/day) and prolonged courses of therapy. Complete or partial resolution may occur after discontinuation of therapy. However symptoms may take up to two years to completely resolve. The underlying pathogenesis of metronidazole-induced neuropathy is believed to be secondary to axonal degeneration. In rodent experiments, metronidazole has been found to bind selectively to neuronal RNA, thus inhibiting protein synthesis resulting in axonal degeneration. Electron microscopic studies of human sural nerve biopsy specimen have also confirmed axonal degeneration of both the myelinated and unmyelinated fibers. Thus this drug which is widely and empirically prescribed is clearly associated with neurotoxicity. Metronidazole should be used with some caution and with clear indications particularly during prolonged courses and when prescribed in relatively large doses. We suggest that a careful neurological examination and studies of sensory and motor nerve conduction should be performed in patients who complain of paraesthesias, pain, muscle cramps, weakness or other abnormal sensation during treatment with metronidazole.

**REFERENCES**