Metronidazole neurotoxicity

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Metronidazole is a commonly used antibiotic for various anaerobic and protozoal infections. Inappropriate use in an excess dose can result in neurological complications, both in central and peripheral nervous systems. Neurological complications are common when the drug is used in a dose exceeding 2 g/day for prolonged periods.[1]

Magnetic resonance imaging (MRI) abnormalities have been described with metronidazole overdosage; however, it is not clear why only few patients develop these abnormalities and also with serum levels in the therapeutic range.[2] MRI brain lesions are hyperintense on T2-weighted and FLAIR sequences with no mass effect. The lesions may show restricted diffusion and are non-enhancing on contrast administration. Characteristically, these lesions are mostly symmetric and bilateral involving cerebellar dentate nuclei, midbrain, dorsal pons (the vestibular nucleus, abducens nucleus, and superior olivary nucleus), splenium of the corpus callosum, and the dorsal medulla. Unusual sites are the inferior olivary nucleus and cerebellar white matter.[3-6] MR spectroscopy abnormalities have been postulated to a reversible mitochondrial dysfunction in susceptible patients.[7] Reversal of clinical as well as MRI abnormalities after cessation of drug intake is characteristic feature of metronidazole intoxication.

Animal studies with metronidazole reveal the following. High doses of metronidazole in rats were found to induce lesions in the cerebellum.[8] These alterations were qualitatively and topographically comparable to central nervous system lesions induced by thiamine deficiency in rats and in Wernicke’s encephalopathy in humans. Studies in dogs have found Purkinje cell lesions after prolonged metronidazole administration[9] and other studies in mice have revealed carbon-labeled metronidazole detected in the cerebellum.[10] Why cerebellum is characteristically involved is not clear? Similarly, the mechanisms that underlie metronidazole neuronal toxicity remain unclear. The suggested mechanisms include the following: 1) intermediate metabolites of metronidazole modulate inhibitory neurotransmitter GABA receptor, especially within the cerebellar and vestibular systems and 2) the reactions with catecholamine neurotransmitter generate semiquinone and nitro anion neurotoxic radicals.[11-13] Similar lesions involving the cerebellum have also been reported with ornidazole usage.[14]

Most of the reported patients with metronidazole induced encephalopathy presented neurological disturbance within 1–12 weeks following metronidazole exposure and the imaging abnormalities resolve between 3 and 16 weeks after stopping metronidazole. Some, not all, of the studies with metronidazole induced encephalopathy reported concomitant neuropathy. It is not clear whether metronidazole induced encephalopathy is also dose related like peripheral neuropathy. The sequential involvement of peripheral sensory, sensory–motor, and then autonomic involvement may or may not be seen in commonly encountered acquired neuropathies.
However, its observation in one case needs to be substantiated in animal studies. We need to learn lots of lessons from the patient reported by Park and colleagues\cite{15} in this issue of the journal. The initial presenting feature in this patient was neuropathy; at that stage itself, one should have considered the possibility of metronidazole neurotoxicity. Instead, he was treated for possible Guillain–Barre’s syndrome and he continued to receive metronidazole, resulting in florid metronidazole neurotoxicity. This case also suggests that most of the metronidazole neurotoxicity is dose related.

References
