Metronidazole (Flagyl®; 1-(β-hydroxy-ethyl)-2-methyl-5-nitroimidazole) is an antiprotozoal and antimicrobial agent commonly used in clinical practice. It was first introduced in 1959 for the treatment of *Trichomonas vaginalis*. Although metronidazole is usually well tolerated, common side effects include metallic taste, nausea, vomiting, diarrhea, abdominal cramps, dark urine, headache, dizziness and disulfram-like reaction with exposure to alcohol.

Metronidazole is primarily metabolized by the liver with peak serum levels of the drug (between 20 to 80 μg/mL) achieved within one hour of oral administration of recommended doses of 1 to 2 g/day. It is a lipophilic compound that readily crosses the blood-brain barrier, is renally excreted, and has a half life of approximately eight hours.

Chronic metronidazole administration is not limited to the treatment of refractory infections – its use has become widespread in the context of a variety of clinical scenarios. The first is in the management of hepatic encephalopathy when treatment with lactulose alone is insufficient. Second, metronidazole is used in the treatment of inflammatory bowel disease (IBD) as enteric flora are thought to contribute to its pathogenesis (e.g.,). Finally, and purely from a historical perspective, high doses of metronidazole were evaluated as a potentiating agent in radiotherapy but it was subsequently found to be ineffective.

Metronidazole can be neurotoxic and produce a variety of neurologic syndromes including a cerebellar syndrome, encephalopathy, seizures, and optic, autonomic and peripheral neuropathies (Table 1). As many of the neurologic syndromes are fully reversible upon discontinuation of the drug, it is likely that metronidazole’s neurotoxicity may not be recognized or reported. We previously described two cases with a cerebellar syndrome following prolonged exposure to metronidazole.

**Table 1: Known neurological side effects of metronidazole (Adapted from)**

<table>
<thead>
<tr>
<th>Neurological side effects of metronidazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebellar syndrome</td>
</tr>
<tr>
<td>Encephalopathy</td>
</tr>
<tr>
<td>Seizures</td>
</tr>
<tr>
<td>Optic neuropathy</td>
</tr>
<tr>
<td>Autonomic neuropathy</td>
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<tr>
<td>Peripheral neuropathy</td>
</tr>
</tbody>
</table>

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review is aimed at summarizing current literature pertaining to neurologic toxicity produced by this widely used antibiotic, including clinical syndromes, neuroradiological findings, prognosis and proposed pathophysiology. Case reports of metronidazole toxicity were identified through a PubMed search.

Clinical Syndromes: 1. Cerebellar Syndrome
The cerebellar syndrome induced by metronidazole was first described by Kusumi et al more than 30 years ago. Their patient was a 45-year-old female who received a cumulative dose of 84g of metronidazole over 28 days for the treatment of...
an anterior mediastinal abscess. She developed a global cerebellar syndrome as well as a painful peripheral neuropathy. Although the cerebellar syndrome resolved six days post discontinuation of antibiotic treatment, neuropathic symptoms persisted for four months\(^{10}\).

Since the initial description, there have been many similar case reports (summarized in Table 2;\(^{9,19-26}\)). The cerebellar syndrome typically consists of dysarthria, gait and appendicular ataxia, nystagmus and saccadic pursuit. The ataxia is typically symmetrical save one case report\(^{27}\) which described a patient with more severe involvement on one side correlating with greater T2 hyperintensity within the dentate nucleus and lower blood perfusion ipsilaterally in the cerebellum. The cumulative dose in these various case reports ranges widely from 7.5 g\(^{16}\) to 1095 g\(^{15}\) suggesting individual patient vulnerability. Duration of treatment resulting in the cerebellar syndrome generally consists of at least one to two months (e.g.,\(^{9,11,20,23}\)) although the syndrome can result from a shorter course of treatment\(^{16}\). No obvious risk factors have been identified other than pre-existing hepatic encephalopathy with end-stage liver cirrhosis\(^{16}\). Systemic clearance of metronidazole was shown to be reduced in patients with hepatic dysfunction\(^{20}\) and Horlen et al\(^{21}\) also implicated this as a contributing cause in their description of a cerebellar syndrome in a patient with liver cirrhosis.

With metronidazole discontinuation, recovery is gradual and fully reversible within days (e.g.,\(^{10}\)) to weeks (e.g.,\(^{13,18,27}\)). Computed tomogram (CT) head in patients with this cerebellar syndrome is typically normal except for one case report describing cerebellar hypodensities\(^{19}\). Typical magnetic resonance (MR) changes in this same group of patients show characteristic bilateral symmetric T2/FLAIR hyperintensities within the dentate nuclei with no mass effect or enhancement (e.g.,\(^{9}\)). These radiological features resolve with drug discontinuation and parallel clinical recovery.

Approximately one third of the described patients with a metronidazole-induced cerebellar syndrome also present with concurrent peripheral neuropathy (e.g.,\(^{19,21}\)) and, occasionally, with encephalopathy (e.g.,\(^{10}\)). Therefore, metronidazole-induced neurotoxicity likely represents a spectrum of neurological involvement rather than distinct clinical syndromes.

**Clinical Syndromes: 2. Encephalopathy**

Metronidazole-induced encephalopathy can range from confusion (e.g.,\(^{21}\)) to decreased level of consciousness and even coma (e.g.,\(^{22,23}\)). (Some reports in the literature, however, use the term encephalopathy to describe any central nervous system toxicity induced by metronidazole even when there are no specific changes in mental status. For consistency, cases labeled as ‘encephalopathy’ in the literature were included in this group even if by clinical description they appear to have an isolated cerebellar syndrome). Correspondingly, patients with metronidazole-induced encephalopathy appear to have more widespread involvement of the brain on MR imaging, in comparison to the aforementioned cerebellar syndrome. Thus, in addition to symmetrical signal abnormalities within the dentate nuclei, patients with metronidazole-induced encephalopathy can show T2 weighted changes in the subcortical white matter, basal ganglia, corpus callosum (splenium portion in particular) and brainstem\(^{31,34,35}\). Generally, clinical and radiological features of encephalopathy are fully reversible upon discontinuation of metronidazole within days (see Table 3;\(^{31,45}\)).

However, three patients presented with severe encephalopathy and did not recover\(^{22,33}\). One of these patients had atypical features on the MRI that included signal changes within the centrum semiovale and middle cerebellar peduncles\(^{32}\) and presented to medical care after two weeks of ongoing symptoms including dysarthria, somnolence and eventually coma. She had received off-label dosing of intravenous metronidazole as an outpatient (1.5 g IV once daily) and presumably high peak serum doses may have contributed to the severity of her presentation and poor prognosis. Another two patients described by Kim et al\(^{33}\) included a patient that remained in a persistent vegetative state at six months despite only receiving a six-day course of metronidazole and another patient who improved clinically but did not fully recover even at a ten month follow-up. The daily and/or cumulative dose of metronidazole is not known for these cases.

Individual variability of patients to both cumulative dose and duration of treatment is also evident in this subgroup of patients (see Table 3). Although most descriptions of metronidazole-induced encephalopathy include prolonged (two to six months) exposure of 1.5 to 2 g daily, some patients develop symptoms in less than one week (e.g.,\(^{33,36,43}\)). As with the cerebellar syndrome, the reason for this variability is uncertain.

**Clinical Syndromes: 3. Seizures**

Metronidazole may produce a variety of seizure semiology including (summarized in Table 4;\(^{45-50}\)) myoclonus evolving into generalized seizures\(^{46}\), generalized tonic clonic seizures\(^{47,50}\) and seizures associated with obtundation and encephalopathy\(^{45,48}\).

The electroencephalography (EEG) in this group of patients is typically normal (e.g.,\(^{47}\)) or may reveal an encephalopathic picture with diffuse slowing but no focal abnormalities (e.g.,\(^{45,46}\)). Cumulative doses of metronidazole ranged from 20.7 g\(^{48}\) to 165 g\(^{50}\) on relatively short course of the antimicrobial. Wienbren et al\(^{45}\) describe a patient with seizures starting five days after metronidazole was discontinued and persisting in the first 24 hours despite a phenytoin load.

Some of the reported cases used high daily doses of metronidazole (up to 10.4 g daily) when it was still being utilized as a radiation sensitizer\(^{47}\). Therefore, high peak doses of metronidazole may potentially decrease seizure threshold. However, metronidazole levels within the cerebrospinal fluid do not directly correlate with likelihood of seizures\(^{47}\). As most of the studies reporting metronidazole-induced seizures are older, there is a lack of radiological correlation in this subgroup of patients other than a normal CT head in some of the cases\(^{45,47}\).

In patients with metronidazole induced seizures, there may be overlap with other metronidazole-induced clinical syndromes as was the case in our patient\(^{8}\) with concurrent cerebellar syndrome, worsening peripheral neuropathy and seizures who showed characteristic isolated dentate nucleus hyperintensities on MRI. Importantly, there are no reported cases of ongoing seizures after metronidazole discontinuation.
Table 3: Summary of case reports of metronidazole-induced encephalopathy. Cases described in the literature as cerebellar syndrome but labeled as encephalopathy are indicted by asterisks (*).

<table>
<thead>
<tr>
<th>Reference</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Onset (d)</th>
<th>Duration (d)</th>
<th>Diagnosis</th>
<th>Imaging</th>
<th>Resolution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kim et al., 2004 (33)</td>
<td>70, M</td>
<td>n/a</td>
<td>n/a</td>
<td>44d</td>
<td>Cerebellar syndrome</td>
<td>MRI</td>
<td>Marked improvement at 4 days</td>
</tr>
<tr>
<td>Kim et al., 2011 (41)</td>
<td>70, M</td>
<td>24d</td>
<td>144 IV</td>
<td>17d g</td>
<td>Cerebellar syndrome</td>
<td>MRI</td>
<td>Marked improvement at 7 days</td>
</tr>
<tr>
<td>Lee et al., 2009 (42)</td>
<td>68, M</td>
<td>8g</td>
<td>144 IV</td>
<td>17d g</td>
<td>Cerebellar syndrome</td>
<td>MRI</td>
<td>Marked improvement at 7 days</td>
</tr>
<tr>
<td></td>
<td>60, F</td>
<td>129g</td>
<td>60d</td>
<td>Cerebellar syndrome</td>
<td>MRI</td>
<td>Marked improvement at 15 day follow-up</td>
<td></td>
</tr>
<tr>
<td></td>
<td>54, F</td>
<td>109g</td>
<td>50d</td>
<td>Gait disturbance</td>
<td>MRI</td>
<td>Marked improvement at 15 day follow-up</td>
<td></td>
</tr>
<tr>
<td></td>
<td>43, M</td>
<td>45g</td>
<td>30d</td>
<td>Cerebellar syndrome</td>
<td>MRI</td>
<td>Marked improvement at 15 day follow-up</td>
<td></td>
</tr>
<tr>
<td></td>
<td>78, F</td>
<td>8g</td>
<td>40d</td>
<td>Gait disturbance</td>
<td>MRI</td>
<td>Marked improvement at 8 day follow-up</td>
<td></td>
</tr>
<tr>
<td></td>
<td>76, F</td>
<td>109g</td>
<td>50d</td>
<td>Dysarthria</td>
<td>MRI</td>
<td>10 days post stroke</td>
<td></td>
</tr>
<tr>
<td></td>
<td>61, M</td>
<td>129g</td>
<td>60d</td>
<td>Cerebellar syndrome</td>
<td>MRI</td>
<td>Marked improvement at 15 day follow-up</td>
<td></td>
</tr>
<tr>
<td></td>
<td>47, M</td>
<td>109g</td>
<td>50d</td>
<td>Dysarthria</td>
<td>MRI</td>
<td>Marked improvement at 15 day follow-up</td>
<td></td>
</tr>
<tr>
<td>Hummel et al., 2007 (90)</td>
<td>61, M</td>
<td>31g</td>
<td>51</td>
<td>Cerebellar, vestibular, gasserian column and pyramidal involvement</td>
<td>MRI</td>
<td>Marked improvement at 15 day follow-up</td>
<td></td>
</tr>
<tr>
<td></td>
<td>48, M</td>
<td>n/a</td>
<td>3d</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>Park et al., 2011 (44)</td>
<td>67, M</td>
<td>56g</td>
<td>(25.5g total)</td>
<td>56d</td>
<td>Peripheral neuropathy, cerebellar syndrome, atonic involvement</td>
<td>MRI</td>
<td>Marked improvement at 8 day follow-up</td>
</tr>
<tr>
<td></td>
<td>74, F</td>
<td>90g</td>
<td>90d</td>
<td>Cerebellar syndrome, peripheral neuropathy and ataxia</td>
<td>MRI</td>
<td>Marked improvement at 15 day follow-up</td>
<td></td>
</tr>
<tr>
<td></td>
<td>43, F</td>
<td>18.2 g IV, 30g (25.5g total)</td>
<td>12d, 10d</td>
<td>Cerebellar and auditory</td>
<td>MRI</td>
<td>Marked improvement at 15 day follow-up</td>
<td></td>
</tr>
</tbody>
</table>

Legend: CT = computed tomography; MRI = magnetic resonance imaging; DWI = diffusion-weighted imaging; ADC = apparent diffusion coefficient; MRE = magnetic resonance elastography; CI = confidence interval; n/a = not available; VEMP = visual-evoked potential; 1st ME = first month; 3rd ME = third month; 6th ME = sixth month; 10th ME = tenth month; 15th ME = fifteenth month; 17 ME = seventeenth month; 28 ME = twenty-eighth month; 30 ME = thirtieth month; 33 ME = thirty-third month; 36 ME = thirty-sixth month; 38 ME = thirty-eighth month; 40 ME = fortieth month; 42 ME = forty-second month; 45 ME = forty-fifth month; 47 ME = forty-seventh month; 50 ME = fifty months; 54 ME = fifty-four months; 60 ME = sixty months; 72 ME = seventy-two months; 84 ME = eighty-four months; 108 ME = one hundred and eight months; 120 ME = one hundred and twenty months; 144 ME = one hundred and forty-four months; 170 ME = one hundred and seventy months; 180 ME = one hundred and eighty months; 210 ME = two hundred and ten months; 240 ME = two hundred and forty months.
Clinical Syndromes: 4. Optic Neuropathy

Optic neuropathy may be a rare complication of metronidazole treatment (summarized in Table 5). The link in the literature is not as clearly established. Patients have been described to develop subacute to chronic changes in visual acuity after prolonged treatment regimens of one to two years. Marked improvement within days to weeks occurs immediately after discontinuation of metronidazole but full recovery was reported to take as long as a year (e.g.,). Putnam et al. reported a series of seven patients collectively by reviewing the National Registry of Drug-Induced Ocular Side Effects (Casey Eye Institute, Oregon Health Sciences University, Portland, Oregon). The reported symptoms consisted of abnormal color vision, scotomas and reduced visual acuity. One of the patients developed symptoms after only seven days of metronidazole therapy and in two of the reported patients the deficits were irreversible.

While at least one patient had a normal MRI another had isolated splenium of the corpus callosum hyperintensities. Cecil et al. describe a patient with a thickened splenium of the corpus callosum and marked signal changes within the basal ganglia and midbrain. Magnetic resonance spectroscopy (MRS) revealed elevated lactate peaks within the involved structures. Interestingly, there are no case reports of metronidazole-induced signal changes within the optic nerve.

Clinical Syndromes: 5. Autonomic Neuropathy

There is only one convincing case description of autonomic neuropathy secondary to metronidazole. This patient, a 15-year-old girl, developed severe painful peripheral sensorimotor neuropathy with absent sympathetic skin responses following a short course (reported as days of treatment) of metronidazole. Extensive investigations were completed to rule out an alternative diagnosis or contributing cause. These included lumbar puncture, serum protein electrophoresis, rheumatoid factor, vitamin B12, porphyrins, erythrocyte sedimentation rate (ESR), Lyme titer, antinuclear antibodies and lead, mercury and arsenic plasma levels. Symptoms were not immediately reversible upon discontinuation of metronidazole and multiple interim medications were required for the management of disabling neuropathic pain. Electrophysiological parameters and patient symptoms normalized at six months post cessation of metronidazole. Wienbren et al. suspected autonomic involvement in their patient who had urinary retention for 48 hours as well as concurrent seizures.

Clinical Syndromes: 4c. Peripheral Sensory or Sensorimotor Neuropathy

There are numerous reports of metronidazole-induced peripheral neuropathy in the literature and it remains the best-recognized neurologic side effect of metronidazole (selected cases are summarized in Table 5). In fact, many of the patients reported as having a cerebellar syndrome or encephalopathy, had co-existing neuropathic symptoms and/or findings (see Table 2 and 3). The neuropathy can be painful, severe and cause significant permanent disability.

Although patients with coexisting central nervous system involvement have the typical radiological findings, patients with isolated peripheral sensory neuropathy do not appear to as demonstrated by one case report that included a normal MRI brain and cervical spine.

Metronidazole-induced neuropathy is characterized by a slowly progressive symmetric distal sensory neuropathy with primary small fiber involvement. Large fibers are affected subclinically in most cases. Routine electrodiagnostic studies may therefore be normal and quantitative sensory testing (QST), quantitative sudomotor autonomic reflex testing (QSART) and skin biopsy are more sensitive in this clinical setting. Gupta et al. described the only patient with a severe distal sensory neuropathy and an associated proximal motor neuropathy without resolution post discontinuation of metronidazole.

The proposed pathophysiology in metronidazole induced peripheral sensory neuropathy is axonal degeneration and this may account for prolonged symptoms even after drug cessation. Human sural nerve biopsy studies have confirmed axonal degeneration in both myelinated and unmyelinated fibres. Wallerian degeneration was confirmed in about 56% of fibers while demyelination was relatively rare involving only 4%. The latter was thought to be a consequence of axonal pathology.

MR Imaging findings of Metronidazole Toxicity

The most common radiological abnormality induced by metronidazole consists of bilateral and symmetrical T2 and FLAIR hyperintensities within the dentate nuclei of the cerebellum on MR imaging (see Figure 1). There is no associated mass effect or enhancement but, occasionally, there is a subtle T1...
hypointensity noted (e.g., 20). This finding of involvement of the cerebellar dentate nuclei, is almost pathognomonic, although a small, less likely differential can be invoked (e.g., Wernicke’s encephalopathy, Friedreich’s ataxia, CADASIL, cerebrotendinous xanthomatosis). Typically, patients with these changes on MR imaging show a cerebellar syndrome, with or without a peripheral neuropathy.

In patients with metronidazole-induced encephalopathy, involvement of the splenium of the corpus callosum is also frequently found either in isolation or in association with dentate nuclei signal abnormalities (e.g., 31, 34, 35). Other sites of involvement, include midbrain, pons, medulla, subcortical white matter, basal ganglia, anterior commissure and middle cerebellar peduncle31,34,35.

Generally, MR signal abnormalities are fully reversible with drug discontinuation and are therefore attributed to axonal swelling (i.e., increased water content) instead of a demyelinating process35. Alternatively, Ahmed et al11 proposed that these changes may represent vascular spasm and transient reversible ischemia.

Many case reports of MRI findings describe high diffusion weighted imaging (DWI) signal associated with low apparent diffusion coefficient (ADC) values suggesting cytotoxic edema within the corpus callosum, basal ganglia, brainstem and subcortical white matter, basal ganglia, anterior commissure and middle cerebellar peduncle31,34,35.

Table 5: Summary of case reports of optic, autonomic and selected cases of peripheral neuropathy secondary to metronidazole treatment

<table>
<thead>
<tr>
<th>Reference</th>
<th>n</th>
<th>Age, Sex</th>
<th>Cumulative Dose (g)</th>
<th>Duration (d)</th>
<th>Resolution</th>
<th>Imaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optic Neuropathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cecil et al., 2002 (51)</td>
<td>1</td>
<td>17, M</td>
<td>n/a</td>
<td>n/a</td>
<td>Slight improvement in visual acuity at 1 month, marked improvement at 3 months and full resolution at 1 year (other symptoms: cerebellar syndrome and peripheral neuroprathy)</td>
<td>MRI: T2/FLAIR hyperintensities within the corpus callosum (associated with thickening), midbrain and basal ganglia. MRS: elevated lactate peaks (basal ganglia and putamen of the corpus callosum)</td>
</tr>
<tr>
<td>De Bleecker et al., 2005 (15)</td>
<td>1</td>
<td>20, M</td>
<td>1095g</td>
<td>~700d</td>
<td>Improvement within 2 weeks of d/c</td>
<td>MRS: T2/FLAIR signal hyperintensities within the splenium of the corpus callosum</td>
</tr>
<tr>
<td>McGraith et al., 2007 (53)</td>
<td>1</td>
<td>67, F</td>
<td>~36g</td>
<td>~300d</td>
<td>Resolution of optic neuropathy</td>
<td>MRI: normal</td>
</tr>
<tr>
<td>Punzani et al., 1991 (53)</td>
<td>7</td>
<td>28-53yo; 4W, 5M</td>
<td>n/a</td>
<td>7 to 365d</td>
<td>Two out of seven patients had residual deficits in vision; peripheral neuroprathy in two</td>
<td>n/a</td>
</tr>
<tr>
<td>Autonomic Neuropathy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Houston-Wells et al., 2006 (54)</td>
<td>1</td>
<td>15, T</td>
<td>n/a</td>
<td>Short course</td>
<td>Dramatic improvement 3 mo later Complete resolution by 6 mo</td>
<td>MRI/MRA: normal</td>
</tr>
<tr>
<td>Wimbren et al., 1985 (45)</td>
<td>1</td>
<td>43, F</td>
<td>18.5g IV, 1g (28.5g total)</td>
<td>12d, 10d</td>
<td>Urinary retention 1-48 hours—autonomic involvement suspected: ‘other causes GDC seizures after MTZ discontinuance’</td>
<td>CT: normal</td>
</tr>
</tbody>
</table>

Peripheral Neuropathy                           |   |          |                     |              |            |         |
| Bradley et al., 1977 (55)                       | 1 | 33, M    | ~336g               | 9mo          | Sensory symptoms started at 8 weeks EMG: distal, primarily sensory peripheral neuropathy | n/a |
| Coxon and Pulls, 1976 (56)                      | 2 | 60, F    | 30.6g               | 59d          | Improvement of symptoms at 1 month | n/a |
| George et al., 1982 (48)                        | 2 | 43, M    | 27.5g IV + 13.1g po | 56d          | No improvement at 1 month follow-up | n/a |
| George et al., 1984 (48)                        | 4 | 45, M    | 4.1g IV + 15.8g po  | 9d           | Severe sensory neuropathy | n/a |
| Gupta et al., 2001 (27)                         | 1 | 25, F    | 18g                 | 15d          | Improvement of symptoms upon discontinuation | n/a |
| Gupta et al., 2003 (27)                         | 1 | 50, F    | 200g                | 84d          | Other feature: cerebellar syndrome, encephalopathy | CT: hypodensities within the cerebellum |
| Kuwaki et al., 1980 (50)                        | 1 | 45, F    | 84g                 | 25d          | - | n/a |
| Ramoury, 1966 (58)                              | 1 | 43, M    | 135g                | 113d         | - | n/a |
| Sarma and Kanath, 2005 (59)                     | 1 | 45, F    | 3.6g                | 9d           | Improvement of symptoms upon discontinuation | n/a |
| Takayama et al., 1998 (60)                      | 1 | 67, M    | 101.25g             | -            | - | n/a |
| Tan et al., 2011 (61)                           | 1 | 53, M    | 146g                | 86d          | Length-dependent painful neuropathy | n/a |
| Zivkovska et al., 2001 (62)                     | 4 | 52, M    | 180g                | 90d          | Symptoms onset at 10 weeks | n/a |
|                                              | 34, F | n/a | 120d (intermittent) | -          | Symptoms resolved post discontinuation | MRI brain and C-spine: unremarkable |
|                                              | 55, M | 36.20g | 260d               | -           | - | n/a |
|                                              | 51, F | (topical) | 270d              | -           | - | n/a |

MRS findings in a patient with metronidazole toxicity demonstrating a high lactate peak.

Animal Studies of Metronidazole Toxicity

Reports of metronidazole-induced neurotoxicity in cats and dogs include a cerebellar syndrome, seizures, changes in level of consciousness and nystagmus64-67. It is not clear whether the doses are comparable to those used in humans. Scharer et al57 demonstrated clear loss of Purkinje cells in dogs exposed to metronidazole - clinical recovery would therefore be unexpected.

Experimental models aimed at studying metronidazole toxicity are not current. Animal studies have clearly shown that 14C-metronidazole crosses the blood-brain barrier and accumulates within the brain particularly within the hippocampus, olfactory bulb and cerebellum68. Moreover, autoradiographic studies of the hippocampus and cerebellum showed that these structures retain activity for longer periods of time68 perhaps accounting for the recognized clinical and radiological toxicity of metronidazole within the cerebellum noted within the human literature.

Administration of high doses of metronidazole to rats (800 mg/kg/day over six weeks) has been shown to produce symmetrical lesions within the vestibular and cochlear nuclei as well as cerebellar nuclei69. The involved sites were strikingly similar to those found in Wernicke’s encephalopathy. However, the doses were approximately 25-fold higher than the maximum...
recommended dose in humans. Furthermore, metabolism of metronidazole, at least in mice and rats, has been shown to be different than in humans and animal studies need to be extrapolated with caution. Administration of metronidazole to rats at doses comparable to humans, did not result in cerebellar or brainstem lesions. Radioactively-labeled metronidazole was found to bind to RNA and thus neurotoxicity may be related to inhibition of protein synthesis by metronidazole or one of its metabolites.

Pathophysiology

The pathophysiology underlying metronidazole neurotoxicity remains elusive although several possible mechanisms have been proposed. It is not known whether metronidazole itself is neurotoxic or whether the culprit is one of its metabolites. Metronidazole has been shown to bind to RNA and proposed to inhibit protein synthesis thereby presumably leading to axonal degeneration. Others have postulated that metronidazole leads to free radical formation.

Alston hypothesized that neurotoxicity may be related to metronidazole’s structural similarity to the thiazole precursor of thiamine. Gut flora possessing thiaminase activity may be involved in the conversion of metronidazole to a thiamine antagonist. Whether the neurotoxic side effects could be mitigated by supplemental thiamine administration has never been explored although the similarity in MR changes between Wernicke’s encephalopathy and metronidazole induced encephalopathy is intriguing.

Recently, similar neurotoxicity was described in a related 5-nitro-imidazole derivative, ornidazole. Symmetric and reversible T2/FLAIR hyperintensities within the dentate nuclei were also found. Interestingly, another related compound – tonidazole – did not cause neurotoxicity in a patient who previously developed a metronidazole-induced cerebellar syndrome. However, toxic doses of tonidazole in another patient who was self-medicating, resulted in side effects and radiological findings identical to metronidazole. Thus, neurotoxicity of 5-nitro-imidazole derivatives likely shares the same pathophysiology.

Metronidazole levels are not routinely measured in patients with neurologic complications. While some patients clearly have toxic metronidazole levels others do not. Although there are no consistent patient-related factors, some have suggested that advanced age as well as renal and hepatic dysfunction may confer a higher risk of developing metronidazole-related side effects.

Figure: Summary of metronidazole-induced MRI features from most common (left, A) to least common (right, D). Metronidazole-induced MRI FLAIR hyperintensities are found within the cerebellar dentate nuclei (A), corpus callosum (splenium) (B), inferior olives (C) and subcortical white matter (WD) (D). (Adapted from Kim et al. (40) with permission).
treatment regimens, 26% of patients developed symptoms in less than a week. The authors concluded that dose and duration of treatment are ultimately not correlated with central nervous system toxicity.

**DISCUSSION AND CONCLUSIONS**

Despite its widespread use in clinical practice, the neurotoxicity of metronidazole continues to be under-recognized. In fact, patients are not usually informed about the potential neurologic complications when being started on this antimicrobial. Fortunately, serious side effects continue to be relatively rare and often fully reversible before a diagnosis is made. These side effects may also be less obvious in complicated patients due to polypharmacy or coexisting conditions predisposing them to neuropathy, seizures or even ataxia.

More recently, there has been a surge of case reports on its neurotoxic effects likely attributable to more widespread and chronic use of metronidazole (i.e. more affected patients) as well as routine MRI imaging demonstrating the typical T2 and FLAIR signal changes (i.e. identification of metronidazole as an offending neurotoxic agent).

Recognition of the neurotoxic effects of metronidazole cannot be overemphasized, as prompt discontinuation is associated with a favorable long-term prognosis. Moreover, heightened index of suspicion about neurological syndromes produced by metronidazole may decrease the need for extensive investigations. When metronidazole is suspected to be the cause of neurological symptoms, however, it should remain a diagnosis of exclusion to ensure that no other reversible cause is missed particularly in the absence of characteristic MRI findings.

**REFERENCES**


