Metronidazole-Induced Central Nervous System Toxicity: A Systematic Review

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Objective: To assess patient and medication factors that contribute to metronidazole toxicity.

Data Sources: We searched PUBMED from 1965 through April 7, 2011, and performed a hand search of bibliographies.

Study Selection: Case reports or case series reporting metronidazole-induced central nervous toxicity.

Data Extraction: Two authors independently abstracted demographics, metronidazole indication, dose and duration, neurological manifestations, and outcomes as well as brain imaging findings.

Data Synthesis: Among 64 patients, 48 (77%) had cerebellar dysfunction, 21 (33%) had altered mental status, and 8 (15%) had seizures. Patients' ages averaged 53.3 years (range, 12–87 years), and 64% were male. The median duration of metronidazole was 54 days, although 26% had taken it less than a week and 11% had taken it less than 72 hours. Among cases with outcome data, most patients either improved (n = 18 [29%]) or had complete resolution of their symptoms with discontinuation of metronidazole (n = 41 [65%]). There was no difference in resolution of symptom by age ($P = 0.71$) or sex ($P = 0.34$). The patients with cerebellar dysfunction were less likely to experience complete resolution than those with mental status changes or seizures (relative risk, 0.67; 95% confidence interval (CI), 0.49–0.92). Nearly all patients (n = 55 [86%]) underwent imaging of the brain: 44 (69%) underwent magnetic resonance imaging (MRI) and 12 (19%) underwent computed tomographic studies. All patients with cerebellar dysfunction had abnormalities on imaging: 93% (n = 39) had a cerebellar lesion, although numerous areas in the brain were affected. On follow-up MRIs, 25 patients (83%) had complete resolution of abnormalities.

Conclusions: Metronidazole can rarely cause central nervous system toxicity; it does not seem to be a dose- or duration-related phenomenon. Most patients will have MRI abnormalities. Prognosis is excellent with metronidazole cessation.

Key Words: metronidazole, adverse effects, cerebellar toxicity, systematic review

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Metronidazole is a 5-nitroimidazole antibiotic with potent activity against anaerobic bacteria and protozoa. The range of its use is broad and includes trichomonal infection, amebiasis, management of Crohn disease, hepatic encephalopathy, treatment of *Helicobacter pylori* infection and *Clostridium difficile*–associated diarrhea. While metronidazole is fairly safe and well tolerated, it can rarely cause serious neurological adverse events, including peripheral neuropathy,[1–6] cerebellar dysfunction, encephalopathy, ototoxicity,[7] seizures, visual impairment,[8–10] and altered mental status. It has been suggested that neurological toxicity may be related to prolonged administration, high doses, or high cumulative doses of metronidazole.[11–14]

We recently had an illustrative case: an 83-year-old woman with a surgical history of choledochojejunostomy for common bile duct stone 35 years ago who was transferred to our emergency department in shock and found to have a multilobular liver abscess. She was discharged on cefoprazone but presented a month later with recurrent liver abscess. She was subsequently discharged on ciprofloxacin (250 mg 2 times a day) and metronidazole (500 mg 3 times a day). After 2 days, she began to experience difficulty in speaking and dysarthria. Over the next couple of weeks, she developed an unsteady gait and bilateral lower extremity paresthesia and by day 14, she was unable to stand or walk. A magnetic resonance image (MRI) demonstrated lesions in the splenium of corpus callosum (Fig. 1), felt to be metronidazole-induced cerebellar toxicity, and metronidazole was discontinued. She experienced gradual but complete resolution of symptoms by day 20 and a follow-up MRI of the brain 28 days after discharge revealed complete resolution of the previous abnormalities (Fig. 2).

Our review of the literature revealed several case reports but no distillation of the literature and uncertainty about the role of dose or duration and the course and outcome of metronidazole toxicity. The purpose of this study was to perform a systematic review to synthesize the literature on this unusual adverse event.

MATERIALS AND METHODS

Data Sources and Searches

We searched PUBMED using several search strategies: (1) (metronidazole or flagyl) AND (seizures [meSH heading {MH}] or encephalitis or neurotoxicity syndromes [mh] or ataxia [mh] or confusion [mh] or cerebellar diseases [mh] or cerebellar dysfunction or dysmetria or delirium [mh]); (2) metronidazole AND (case reports [publication type {ptyp}] AND brain diseases/*chemically induced [mh]); and (3) case reports [ptyp] AND metronidazole/*adverse effects, from 1966 to March 2011.

Study Selection

We included all articles that reported cases of metronidazole-induced central nervous system toxicity. We excluded non-English or Japanese articles and those focusing on peripheral neuropathy.

Data Extraction and Quality Assessment

From each article, we abstracted demographics (age, sex, and ethnicity), exposure history (dose and duration), and specific toxicity. The accumulative doses were estimated by multiplying the daily dose by the medication duration. We also abstracted data regarding symptom outcome, including how much improvement

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Drs Jackson and Kuriyama had full access to the data and take full responsibility for the integrity of the data and analysis of the same.

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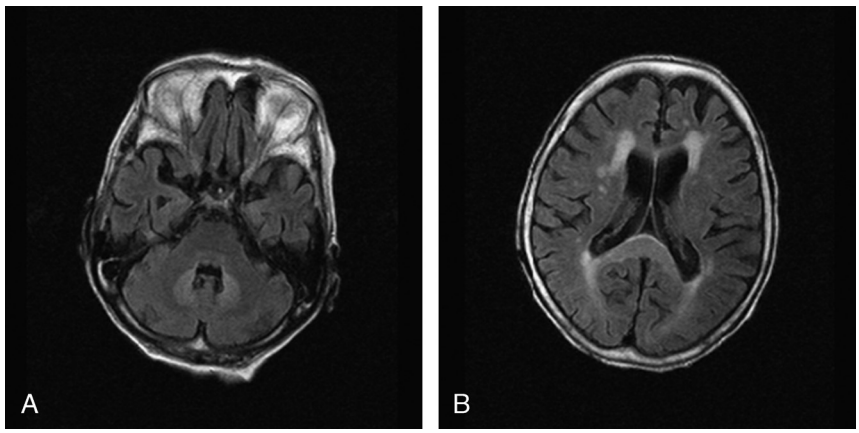

FIGURE 1. Admission MRI.

occurred and length of time after cessation of metronidazole for symptoms to resolve. Finally, we abstracted information reported regarding MRI findings.

Data Synthesis and Analysis

Our process yielded patient-level data. We provided descriptive statistics (means, medians, and proportions) for all data abstracted. We compared continuous variables between different groups using either analysis of variance or the Kruskal-Wallis test, depending on the underlying distribution. Categorical variables were compared using the χ^2 test.

RESULTS

The literature search yielded 261 unique articles. Hand review of the bibliographies of these yielded 5 additional articles. Review of these 266 articles yielded 46 English and Japanese articles that reported 64 cases of metronidazole-induced central nervous system toxicity (Table 1).[2,8,9,11–21,23–54] Reasons for exclusion are given in Figure 3. Of the 64 cases, 23 (35%) were from the United States,[11,13–15,19–21,23,24,26,31,32,36,39,40,42,45,50,52,53] 19 (30%) were from Korea,[9,17,35,38,48] 3 were from India[29,34,43] and Japan,[33,49] 2 each were from Australia,[37,47] Canada,[44] and the United Kingdom,[27,51] and single cases were from Belgium,[8] Chile,[25] Germany,[46] Israel,[18] the Netherlands,[28] Nigeria,[41] Taiwan,[2,41] Tunisia,[30,41] and Turkey.[16] The first case report appeared in 1977[26]; 37 (59%) of the reports have occurred since 2004. The mean age of affected patients was 53.4 years (95% confidence interval [CI]: 48.8–57.9). The patients ranged in age from 12 to 87 years, with the peak occurring in the fifth and sixth decades. Forty-one (64%) of the patients were male. The most common indication for metronidazole treatment was abscess (n = 29 [48%]), followed by inflammatory bowel disease (n = 7 [12%]), *C. difficile* (n = 5 [8%]), and cellulitis (n = 4 [7%]). The mean duration of metronidazole treatment was 54 days (95% CI, 21.2–87.9), although 26% of the patients had taken the drug for less than a week and 11% had taken it for less than 3 days. The average daily dose was 719 mg (range, 250–2000 mg), and the average cumulative dose of metronidazole was 93.4 g (range, 0.25–1095 g).

Types of Metronidazole-Induced Central Nervous System Toxicity

Of the 64 patients, 48 (75%) had cerebellar dysfunction, 21 (33%) had altered mental status, and 8 (13%) had seizures; 11 (17%) patients had both cerebellar dysfunction and altered mental status. One case each had cerebellar dysfunction and seizures; one had all 3 manifestations. Among the 48 patients with cerebellar dysfunction, dysarthria (n = 32 [66%]) and ataxia (n = 27 [56%]) were common; 16 (33%) had dysmetria and 4 (8%) nystagmus.

Among the patients with cerebellar dysfunction, 34 (71%) were male. The average age was 53 years, and the patients had been on metronidazole for a median of 30 days (range, 2–730 days). The patients with acute mental status changes were younger, 43 years of age, and 13 (65%) were male. The median duration of treatment was 15 days (range, 1–90 days).

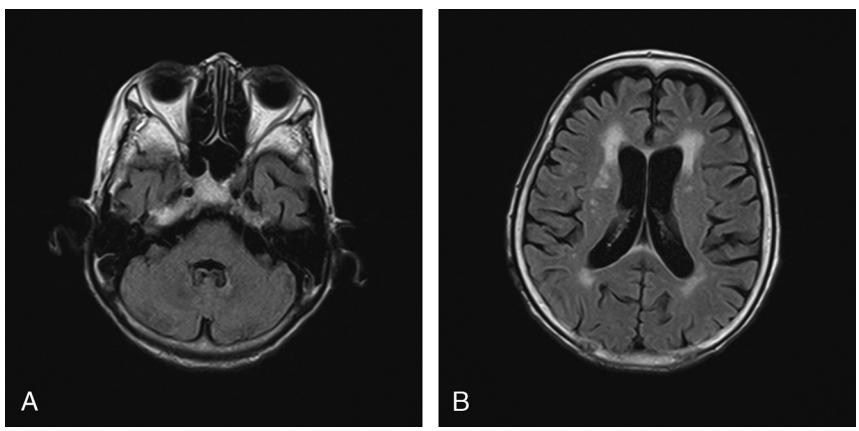

FIGURE 2. Follow-up MRI.

TABLE 1. Case Reports of Metronidazole Toxicity

Author, Year, Country	Age	Sex	Indication for Metronidazole	Duration of Metronidazole (Days)	Cumulative Dose (Grams)	Neurological Manifestation	MRI Done	Neurological Outcome
Ahmed,1995, USA[15]	45	F	*Blastocystis hominis* diarrhea	30	35	Cerebellar dysfunction Acute mental status change	Yes	Resolved
Alvarez,1983, USA[11]	20	F	*Bacteroides fragilis* pelvic abscess	18	25.5	Cerebellar dysfunction Acute mental status change	No	Resolved
Arik, 2001, Turkey[16]	58	F	Cellulitis	2	NS	Cerebellar dysfunction	Yes	Resolved
Bahn, 2010, Korea[17]	52	M	Brain abscess	20	40	Cerebellar dysfunction	Yes	Resolved
Bailes,1983, USA[14]	12	M	Peritonitis	4	4	Cerebellar dysfunction Acute mental status change	No	Resolved
Beloosesky, 2000, Israel[18]	87	F	*C. difficile* colitis	12	18	Seizure	No	Resolved
Bonkowsky, 2007, USA[19]	27	M	*C. difficile* colitis	14	NS	Cerebellar dysfunction Acute mental status change	Yes	Resolved
Bottenberg, 2011, USA[12]	55	M	Collagenous colitis	730	1095	Cerebellar dysfunction	Yes	Resolved
Cecil, 2002, USA[20]	17	M	Crohn disease	NS	NS	Cerebellar dysfunction	Yes	Resolved
Chatzkel, 2010, USA[21]	15	F	Crohn disease	7	NS	Cerebellar dysfunction	Yes	NS
Dainer, 1979, USA[22]	27	F	*Trichomonas*	1	0.25	Acute mental status change	No	Resolved
De Bleecker, 2005, Belgium[8]	20	M	Ulcerative colitis	730	1110	Cerebellar dysfunction	Yes	Impaired visual acuity
Deenadayalu, 2005, USA[23]	50	M	Peritonitis + hepatic encephalopathy	5	7.5	Cerebellar dysfunction	Yes	Improved
Frytak, 1978, USA[24]	77	F	Inoperable pancreatic carcinoma	5	NS	Seizure	No	Resolved
	75	F	Hepatic and pulmonary metastasis of rectal carcinoma	7	42	Seizure	No	Resolved
	52	F	Sensitizer for metastatic carcinoma of the stomach	5	52	Seizure	No	Resolved
Galvez, 2009, Chile[25]	60	M	Hepatic encephalopathy	NS	NS	Cerebellar dysfunction	Yes	Improved
Giannini, 1977, USA[26]	19	F	*Trichomonas*	7	5.25	Acute mental status change	No	Resolved
Graves, 2009, UK[27]	61	M	Kleb wound infection	77	92.4	Cerebellar dysfunction	Yes	Resolved
Groothoff, 2010, Netherlands[28]	38	F	*B. fragilis* wound of osteomyelitis	70	132.0	Cerebellar dysfunction Acute mental status change Seizure	Yes	Died
Gupta, 2003, India[29]	50	M	Amebic liver abscess	84	200.0	Cerebellar dysfunction Acute mental status change	No	Resolved
Halloran, 1982, USA[13]	56	M	Amebic liver abscess	16	33.6	Seizure	No	Resolved
Hammami, 2007, Tunisia[30]	51	M	Anal fistula	21	31.5	Cerebellar dysfunction Acute mental status change	Yes	Resolved
Heaney, 2003, USA[31]	74	M	Abdominal purulent abscess	56	84.0	Cerebellar dysfunction	Yes	Resolved

(Continued on next page)

TABLE 1. *(Continued)*

Author, Year, Country	Age	Sex	Indication for Metronidazole	Duration of Metronidazole (Days)	Cumulative Dose (Grams)	Neurological Manifestation	MRI Done	Neurological Outcome
Horlen, 2000, USA[32]	34	M	*B. fragilis* meningitis + bacteremia	50	75.0	Cerebellar dysfunction Acute mental status change	Yes	Resolved
Ito, 2004, Japan[33]	54	F	*H. pylori*	66	66.0	Cerebellar dysfunction	Yes	Resolved
Kalia, 2010, India[34]	43	M	Amebic liver abscess	60	72.0	Cerebellar dysfunction	Yes	Resolved
Kim, 2004, Korea[35]	31	M	Crohn disease	6 + chronic use	3 times usual dose + chronic use	Acute mental status change	Yes	Impaired cognition
	46	M	Acute cholangitis	6	NS	Acute mental status change	Yes	Vegetative state
Kim, 2007, Korea[9]	54	M	Spontaneous bacterial peritonitis	15	22.5	Cerebellar dysfunction Acute mental status change	Yes	Improved
	64	M	Intra-abdominal abscess	17	25.5	Cerebellar dysfunction	Yes	Improved
	55	M	Ischemic colitis	11	16.5	Cerebellar dysfunction	Yes	Improved
	71	M	DM foot	17	25.5	Cerebellar dysfunction	Yes	Improved
	61	F	Pseudomembranous colitis	24	36.0	Cerebellar dysfunction	Yes	Improved
	49	M	Crohn disease	52	78.0	Cerebellar dysfunction	Yes	Improved
	70	M	Brain abscess	22	33.0	Cerebellar dysfunction	Yes	Improved
This study (Kuriyama, 2011, Japan)	83	F	*K. pneumoniae* liver abscess	2	3.0	Cerebellar dysfunction	Yes	Resolved
Kusumi, 1980, USA[36]	45	F	*B. fragilis* anterior mediastinal abscess	28	84.0	Cerebellar dysfunction Acute mental status change	No	Resolved
Lawford, 1994, Australia[37]	30	M	Amebic liver abscess	14	21.0	Cerebellar dysfunction	No	Resolved
Lee, 2009, Korea[38]	47	M	Decubitus ulcer	50	100	Cerebellar dysfunction	Yes	Improved
	61	M	Liver abscess	60	120	Cerebellar dysfunction	Yes	Improved
	76	F	Liver abscess	50	100	Cerebellar dysfunction	Yes	Improved
	78	F	Lung abscess	40	80	Cerebellar dysfunction	Yes	Improved
	64	F	Peritoneal abscess	50	100	Cerebellar dysfunction	Yes	Improved
	68	M	Lung abscess	44	88	Cerebellar dysfunction	Yes	Improved
	60	M	Brain abscess	60	120.0	Cerebellar dysfunction	Yes	Improved
	43	M	Peritoneal abscess	30	45	Cerebellar dysfunction	Yes	Improved
Mahl, 2003, USA[39]	75	M	*C. difficile*	2	3.0	Acute mental status change	No	Resolved
Moosa, 2010, USA[40]	52	M	Osteomyelitis	35	37.5	Cerebellar dysfunction	Yes	Resolved
Omotoso, 1997, Nigeria[41]	48	M	Amebic liver abscess	3	3.6	Acute mental status change	No	Resolved
Patel, 2008, USA[42]	63	M	Submental abscess + mandibular osteomyelitis	42	80.0	Cerebellar dysfunction	Yes	Resolved
Rothagi, 2000, India[43]	55	M	Amebic liver abscess	1	0.75	Acute mental status change	No	Resolved

Sarna, 2009, Canada[44]	72	F	Intra-abdominal abscess	25	25.0	Cerebellar dysfunction	Yes	Resolved
	54	M	Bronchiectasis	60	60.0	Cerebellar dysfunction Seizure	Yes	Resolved
Schentag, 1982, USA[45]	65	M	Postoperative abscess	2	4.0	Acute mental status change	No	Resolved
Schreiber, 1997, Germany[46]	26	F	Adnexitis	5	5.0	Acute mental status change	No	Resolved
Scott, 1994, Australia[47]	81	M	*B. fragilis* hepatic abscess	29	37.2	Cerebellar dysfunction	No	Resolved
Seok, 2003, Korea[48]	74	F	Rectovaginal fistula associated with Crohn disease	90	90.0	Cerebellar dysfunction	Yes	Nearly resolved
Takase, 2005, Japan[49]	69	M	Amebic abscess	50	75.0	Cerebellar dysfunction	Yes	Resolved
Tan, 2010, Taiwan[2]	53	M	Peptostreptococcus brain abscess	88	146.0	Cerebellar dysfunction Acute mental status change	Yes	Resolved
Uhl, 1996, USA[50]	65	F	Portosystemic encephalopathy	90	NS	Acute mental status change	No	Resolved
Wienbren, 1985, UK[51]	43	F	*C. difficile*	12	18.5	Seizure	No	Resolved
Woodruff, 2002, USA[52]	74	M	Intra-abdominal abscesses	28	42.0	Cerebellar dysfunction	Yes	Resolved
	62	M	Epidural abscess	30	60.0	Cerebellar dysfunction	Yes	Resolved

NS indicates Not stated.

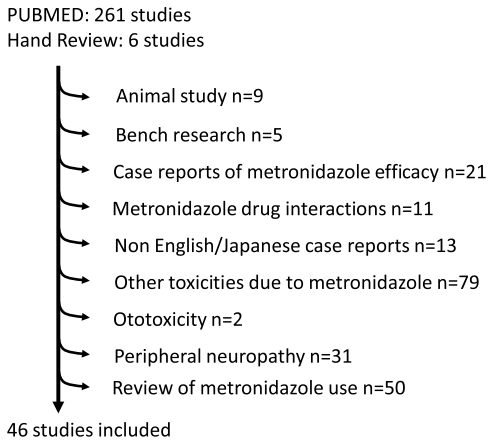

FIGURE 3. Flow of article selection.

Among the patients with seizures, the average age was 65, most (n = 6 [75%]) were women, and the median duration of treatment was 12 days (range, 5–70 days).

Among the 64 cases, 59 provided outcome data. Most of the patients either improved (n = 18 [29%]) or had complete resolution of their symptoms with discontinuation of metronidazole (n = 41 [65%]). One patient died from an unrelated cause and 2 (3%) experienced permanent cognition impairment. There was no difference in the resolution of symptom by age ($P = 0.71$) or sex ($P = 0.34$). The patients with cerebellar dysfunction were less likely to experience complete resolution than those with mental status changes or seizures (RR, 0.67; 95% CI, 0.49–0.92).

Brain Imaging Findings

Nearly all patients (n = 55 [86%]) underwent brain imaging: 44 (69%) underwent MRI examinations, and 12 (19%) underwent computed tomographic studies (one underwent both). Subjects with cerebellar dysfunction commonly had an MRI (n = 42 [88%]) while patients presenting with seizures underwent computed tomographic examinations (n = 6 [67%]).

All but one patient with cerebellar dysfunction who underwent imaging had an abnormality. Nearly all had cerebellar lesions (n = 39 [93%]), with the cerebellar dentate nuclei involved in most patients (n = 34 [81%]; Table 2). The corpus callosum, midbrain, pons, or medulla were involved in 26% to 40% of the patients with cerebellar dysfunction (Table 2). Among the 9 patients with altered mental status, most had cerebellar dentate lesions (89%). Of these 9 patients, only 2 had altered mental status as their only neurological manifestation, and both had lesions in the cerebellar dentate nuclei and subcortical white matter.

Among the 44 patients who underwent brain MRI, 30 patients had a second brain MRI, performed 3 days to 3 months after cessation of metronidazole. Twenty-five (83%) had resolution of MRI abnormalities. Five patients had incomplete resolution of lesions or new changes.[28,29,31,41,43] There was poor correlation between symptom outcome and MRIs. The MRI abnormalities resolved even when the symptoms persisted, and improvement of symptoms preceded or followed changes in MRI findings.

DISCUSSION

Metronidazole-induced central nervous system toxicity is a serious but uncommon event. In this case series, metronidazole toxicity occurred in both men and women and in adults of any age. Although previous literature has suggested that toxicity is

TABLE 2. Lesion Distribution on Imaging

Lesions	Cerebellar Dysfunction (n = 43), n (%)	Altered Mental Status (n = 9), n (%)
Cerebellum	40 (93)	9 (100)
Dentate nuclei	34 (81)	6 (67)
Cerebellar deep gray matter nuclei	1 (2)	1 (11)
Cerebellar peduncles	1 (2)	1 (11)
Cerebellar hemispheres surrounding the fourth ventricle	1 (2)	1 (11)
Posterior margin of the fourth ventricle in cerebellar parenchyma	1 (2)	
Below, behind, and lateral to the fourth ventricle	1 (2)	1 (11)
Periaqueductal region	1 (2)	1 (11)
Corpus Callosum	15 (36)	3 (33)
Midbrain	17 (40)	2 (22)
Inferior colliculus	7 (17)	
Tectum	5 (12)	
Tegmentum	5 (12)	1 (11)
Red nucleus	4 (10)	1 (11)
Substantia nigra	2 (5)	1 (11)
Pons	14 (33)	3 (33)
Vestibular nucleus	6 (14)	1 (11)
Superior olivary nucleus	6 (14)	1 (11)
Abducens nucleus	4 (10)	1 (11)
Dorsal pons	4 (10)	1 (11)
Medulla	11 (26)	3 (33)
Dorsal medulla	5 (12)	1 (11)
Lower medulla	1 (2)	
Inferior olivary nuclei	3 (7)	
Basal Ganglia	2 (5)	1 (11)
Putamen	1 (2)	
Caudate	1 (2)	
Globus pallidus	1 (2)	
Inferior basal ganglia lateral to the hypothalamus	1 (2)	1 (11)
Thalami	1 (2)	
Cerebral White Matter	6 (14)	5 (56)
Subcortical white matter	3 (7)	4 (44)
Trigone periventricular white matter	1 (2)	
Anterior commissure	1 (2)	
Centrum semiovale	1 (2)	1 (11)

Detail concerning "the bulbar region" mentioned by Hammani et al was missing and was not included in the table.

more common with higher doses or longer duration of therapy, we found that it occurs even with low doses or short exposure durations. There are 3 common patterns of toxicity: cerebellar dysfunction, mental status changes, and seizures. A smaller proportion of patients had more than one manifestation. Abnormalities in MRI are common, with cerebellar dentate lesions present in most images. The prognosis with cessation of metronidazole is good, with most of the patients improving or experiencing complete resolution of symptoms. Whereas most MRI findings will improve or resolve over time, there is only poor correlation between MRI resolution and symptom outcomes. A second MRI imaging is not required for patients who experience improvement in their symptoms.

The mechanism of metronidazole-induced central nervous system toxicity is uncertain. Proposed causes include binding of metronidazole to neural RNA to inhibit protein synthesis, modulation of inhibitory neurotransmitters γ-aminobutyric acid receptor within the cerebellar and vestibular, reversible mitochondrial dysfunction, and vasogenic and cytotoxic edema. Previous case reports have demonstrated evidence of vasogenic or cytotoxic edema on MRI, suggesting either as a potential mechanism of neurotoxicity. At least one case report suggests having found evidence of both vasogenic and cytotoxic edema occurring in different parts of the brain.

Primary treatment of metronidazole-induced central nervous system toxicity is drug cessation and supportive care. Diazepam was found to reduce the time to recover the debilitating signs of dogs with metronidazole toxicosis compared with supportive care alone. However, there are no reports on using diazepam in treating metronidazole-induced central nervous system toxicity in human beings.

CONCLUSIONS

Metronidazole-induced central nervous system toxicity is uncommon but can present as cerebellar dysfunction, altered mental status, or seizures. There does not seem to be an association between duration or dose of metronidazole and toxicity; small amounts of metronidazole can induce neurotoxicity. The underlying pathophysiology is uncertain, although some have argued for cytotoxic or vasogenic edema. Treatment is cessation of metronidazole and supportive care. Although prognosis is generally good, some subjects wind up with permanent disability. When T2-weighted fluid attenuated inversion recovery MRIs of the brain are obtained, abnormalities are common—present in 93% of subjects; cerebellar dentate nuclei lesions are the most frequent abnormality seen. Repeated MRIs generally show improvement or complete resolution of abnormalities.

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