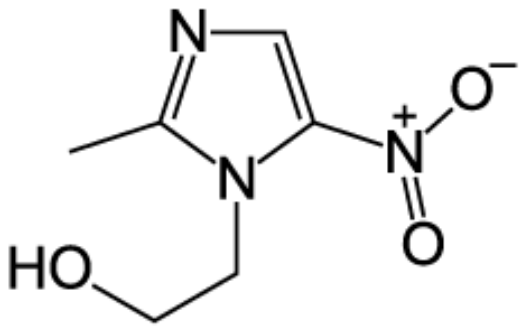


How much metronidazole is too much?

Rebecca R. Marcinak, PharmD

PGY2 Infectious Diseases Pharmacy Resident

Pharmacy Grand Rounds

February 18, 2019

Disclosures

Nothing to disclose

Objectives

- Discuss the incidence of metronidazole-induced central nervous system toxicity
- Consider which patients are at increased risk of metronidazole-induced encephalopathy
- Relate published literature regarding this phenomena to a patient case

Patient Case

CA is a 73 YOF presented with headache and facial pain

HPI: Pt had a one-week history of frontal headache, sinus pressure, cough, fever, and chills

- Went to urgent care, given doxycycline for sinusitis
- 2 days later, presented to OSH with continued symptoms and blurry vision

Left AMA and presented to BMC the following day

- Continued headache, facial pain, new-onset altered mental status
- Became lethargic and obtunded in ED

Background- Metronidazole

- Nitroimidazole antimicrobial agent
- Highly active against Gram-positive and Gram-negative **anaerobic** bacteria
  - Low resistance rates

Clostridium spp.	*Bacteroides* spp.
Eubacterium spp.	*Fusobacterium* spp.
Peptococcus spp.	*Prevotella* spp.
Peptostreptococcus spp.	

Background- Clinical Uses

Anaerobic Infections

- Central nervous system
- Oral and dental tissue
- Respiratory tract
- Intra-abdominal
- Gynecologic
- Intestinal **C. difficile*
- Bone and joint
- Skin and soft tissue

Protozoal Infections

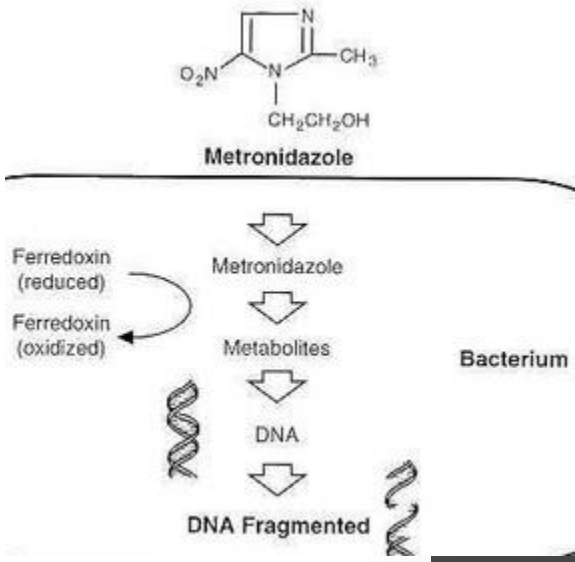
- Trichomoniasis
- Amoebiasis
- Giardiasis

Other diseases

- Stomach and/or intestinal ulcer **H. pylori*
- Rosacea
- Bacterial vaginosis
- Crohn's Disease

Lofmark S et al. Clin Infect Dis. 2010;50:S16-23.

Background- MOA



Prodrug enters cell

Reduction → nitroso free radical

- Cytotoxic, interacts with DNA molecules

Inhibition of DNA synthesis

DNA damage by oxidation

- Single- and double-strand breaks

DNA degradation and cell death

Lofmark S et al. Clin Infect Dis. 2010;50:S16-23.

Metronidazole- PK

A:

- Well absorbed, high oral bioavailability
- Low plasma protein binding

D:

- Extensive penetration into various tissues and body fluids
  - Crosses BBB; CSF concentrations similar to plasma

M:

- Hepatic metabolism (oxidation, glucuronide conjugation)
  - Active hydroxyl metabolite, maintains parent compound activity

E:

- Urine (unchanged drug and metabolites: 60-80%)
- Feces (6-15%)

Metronidazole- PK

Renal Impairment	ESRD → 2-fold higher Cmax of hydroxy-metronidazole, 5-fold higher Cmax of metronidazole-acetate
	Potential accumulation of metronidazole metabolites
Hepatic Impairment	114% higher mean AUC24 with severe (Child-Pugh C) hepatic impairment
	~50% higher in mild and moderate (Child-Pugh A and B) hepatic impairment
	No significant changes in the AUC24 of hydroxyl-metronidazole

Background- ADE

CNS: Headache, metallic taste, dizziness

GI: Nausea, abdominal pain, diarrhea

GU: Vaginitis

Although generally well-tolerated, patients may experience serious neurologic side effects.

Background- Warnings

WARNINGS

Central and Peripheral Nervous System Effects

Encephalopathy and peripheral neuropathy: Cases of encephalopathy and peripheral neuropathy (including optic neuropathy) have been reported with metronidazole.

Encephalopathy has been reported in association with cerebellar toxicity characterized by ataxia, dizziness, and dysarthria. CNS lesions seen on MRI have been described in reports of encephalopathy. CNS symptoms are generally reversible within days to weeks upon discontinuation of metronidazole. CNS lesions seen on MRI have also been described as reversible.
Peripheral neuropathy, mainly of sensory type has been reported and is characterized by numbness or paresthesia of an extremity.

Convulsive seizures have been reported in patients treated with metronidazole.

Aseptic meningitis: Cases of aseptic meningitis have been reported with metronidazole. Symptoms can occur within hours of dose administration and generally resolve after metronidazole therapy is discontinued.

The appearance of abnormal neurologic signs and symptoms demands the prompt evaluation of the benefit/risk ratio of the continuation of therapy (see **ADVERSE REACTIONS**).

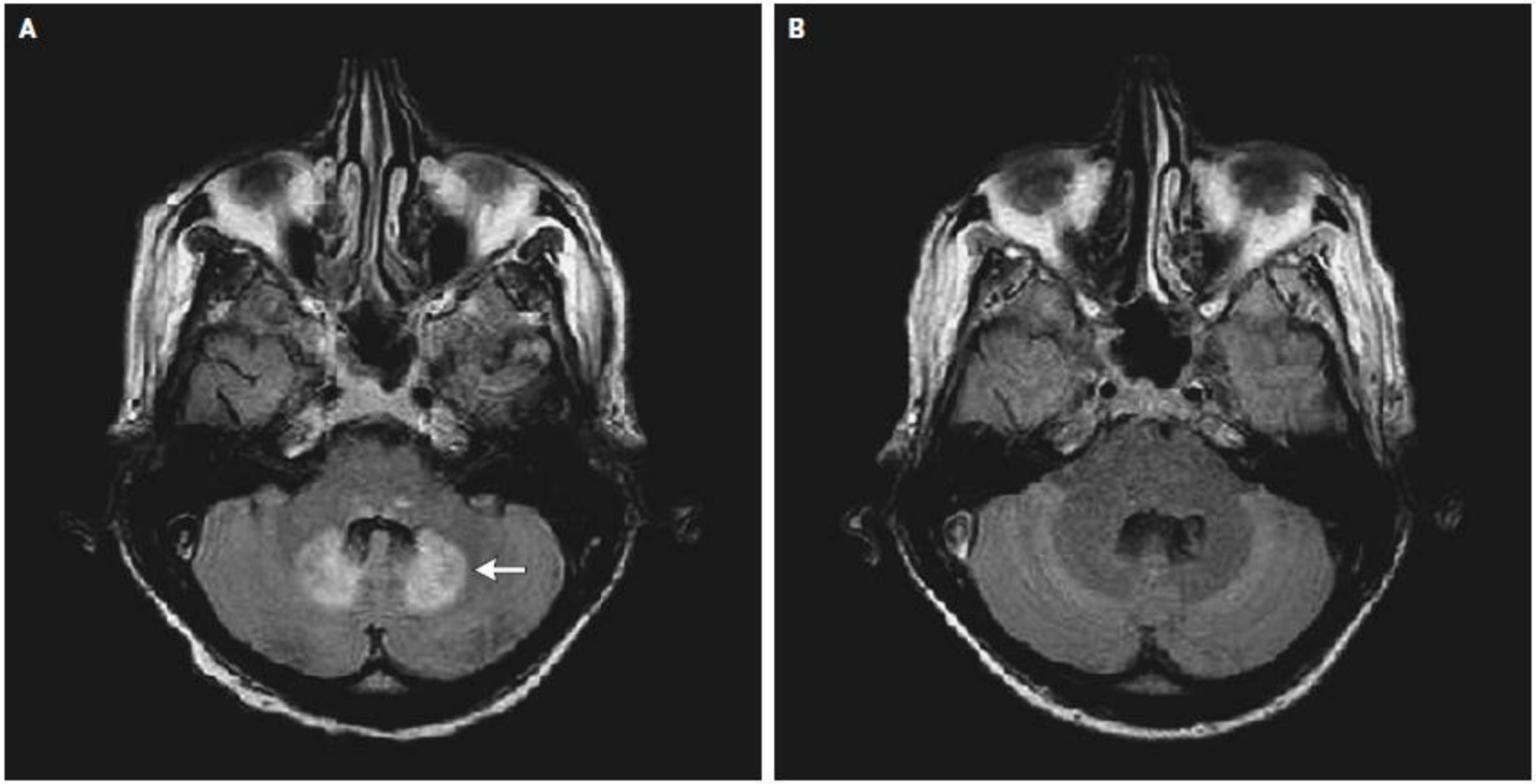
CENTRAL NERVOUS SYSTEM TOXICITY?

The NEW ENGLAND JOURNAL of MEDICINE

IMAGES IN CLINICAL MEDICINE

Lindsey R. Baden, M.D., *Editor*

Metronidazole-Associated Encephalopathy



Farmakiotis D et al. N Engl J Med. 2016; 374(15): 1465.

“Metronidazole- Induced Encephalopathy” (MIE)

First case published in 1977

3 common patterns of toxicity

- Cerebellar dysfunction
- Mental status changes
- Convulsive seizures

Can also cause: peripheral neuropathy, ototoxicity, visual impairment

May result from both short term and chronic use

Kuriyama A et al. Clin Neuropharmacol. 2011; 34(6): 241-7.

“Metronidazole- Induced Encephalopathy” (MIE)

Neuroimaging forms the backbone in diagnosis

- Characteristic pattern
- >80% of patients displaying T2/FLAIR abnormalities in the cerebellar dentate nuclei

Typical sites of involvement:

- Cerebellum, brain stem and corpus callosum
- *usually symmetric

Kuriyama A et al. Clin Neuropharmacol. 2011; 34(6): 241-7.

Metronidazole-Induced Central Nervous System Toxicity: A Systematic Review

Akira Kuriyama, MD, Jeffrey L. Jackson, MD, MPH,† Asako Doi, MD,‡ and Toru Kamiya, MD§*

- **Objective:** To assess patient and medication factors that contribute to metronidazole toxicity
- **Systemic Review:**
  - **Included:** articles that reported cases of metronidazole-induced CNS toxicity
  - **Excluded:** articles that focused on peripheral neuropathy
- Review of 266 articles → 46 articles for inclusion
  - **64 unique cases** of metronidazole-induced CNS toxicity

Kuriyama A et al. Clin Neuropharmacol. 2011; 34(6): 241-7.

Patient Demographics

- **Mean age:** 53.4 years (95% CI: 48.8-57.9)
  - Ranged from 12-87 years, peak in 50s-60s
- **Gender:** 64% male
- **Indication:**
  - Abscess: 48%
  - IBD: 12%
  - *C. difficile*: 8%
  - Cellulitis: 7%

Kuriyama A et al. Clin Neuropharmacol. 2011; 34(6): 241-7.

Exposure History

- **Median duration of treatment:** 54 days (95% CI: 21.2-87.9)
  - **<7 days:** 26% of patients
  - **<3 days:** 11% of patients
- **Average daily dose:** 719 mg (range: 250-2000mg)
- **Average cumulative dose:** 93.4 g (range: 0.25-1095 g)

Kuriyama A et al. Clin Neuropharmacol. 2011; 34(6): 241-7.

Types of CNS Toxicity

Cerebellar dysfunction (75%)

- Dysarthria (66%)
- Ataxia (56%)
- Dysmetria (33%)
- Nystagmus (8%)

Altered mental status (33%)

Seizures (13%)

Kuriyama A et al. Clin Neuropharmacol. 2011; 34(6): 241-7.

Types of CNS Toxicity

Cerebellar dysfunction	Altered mental status	Seizures
71% male	65% male	75% **female**
Average age: 53	Average age: 43	Average age: 65
Median duration: 30 days (2-730 days)	Median duration: 15 days (1-90 days)	Median duration: 12 days (5-70 days)

Kuriyama A et al. Clin Neuropharmacol. 2011; 34(6): 241-7.

Outcomes

- With discontinuation of metronidazole, most of the patients
  - Improved (29%)

    or
  - Had complete resolution of their symptoms (65%)

- No difference in the resolution of symptom by age or sex
- Patients with **cerebellar dysfunction** less likely to experience complete resolution than those with mental status changes or seizures (RR, 0.67; 95% CI, 0.49-0.92)

Kuriyama A et al. Clin Neuropharmacol. 2011; 34(6): 241-7.

Brain Imaging Findings

86% of patients underwent imaging

Cerebellar dysfunction

- Nearly all had cerebellar lesions (93%)
  - Cerebellar dentate nuclei involved in most patients (81%)
  - Corpus callosum, midbrain, pons, or medulla involved in 26% to 40%

Altered mental status

- Most had cerebellar dentate lesions (89%)
- Only 2 had altered mental status as their only neurological manifestation
  - Both had lesions in the cerebellar dentate nuclei and subcortical white matter

Kuriyama A et al. Clin Neuropharmacol. 2011; 34(6): 241-7.

Brain Imaging Findings

30 patients had a second brain MRI, performed 3 days to 3 months after cessation of metronidazole

- 83% had resolution of MRI abnormalities

Poor correlation between symptom outcome and MRIs

Kuriyama A et al. Clin Neuropharmacol. 2011; 34(6): 241-7.

What disease state might this mimic?

Wernicke's Encephalopathy

Multiple Sclerosis

Mechanisms of Toxicity

Metronidazole concentration is fairly high in the extracellular space of brain

Induces oxidation of norepinephrine, dopamine and other catecholamine derivatives

→ semiquinone and nitro anion radicals

- Reduce tissue oxygen and generate the superoxide radical
- Increases water content and causes axonal swelling

Mechanisms of Toxicity

Intermediate metabolites of metronidazole may bind to RNA or DNA of the neuronal cells

- Inhibition of neuronal protein synthesis via binding to RNA

GABA receptor modulation within the cerebellum and vestibular systems

- Flumazenil and metronidazole share a imidazole component.
- May bind specifically to GABA receptors in the cerebellar and central vestibular system
  - → Loss of inhibition, similar to the effect of flumazenil

Increased Risk

- Severe hepatic dysfunction
- Alcoholism
- Uremia
- Large cumulative doses (total cumulative dose >20 g)
- Prolonged courses (majority >2 weeks)
- High peak plasma concentration
  - *hepatic dysfunction
- Use caution in patients with a history of seizures
- Parkinsonism medications
- Ethnic factors?

Farmakiotis D et al. N Engl J Med. 2016; 374(15): 1465.
Horlen CK et al. Ann Pharnacother. 2000; 34(11): 1273-5.

Management

- Withholding metronidazole as early as possible
- Supportive therapy
- Alternative antimicrobial therapy
- Thiamine?
- Benzodiazepines?

- Monitoring:
  - Resolution of findings on MRI
    - Repeat MRI imaging is not required for patients who experience improvement in their symptoms
  - Clinical improvement

Thiamine deficiency in metronidazole-induced encephalopathy: A metabolic correlation?

Dosuke Iwadate, Kenichiro Sato, Mami Kanzaki, Chinatsu Komiyama, Chizuru Watanabe, Tomoaki Eguchi and Yoshikazu Uesaka

Journal of the Neurological Sciences, 2017-08-15, Volume 379, Pages 324-326, Copyright © 2017 Elsevier B.V.

- Potential role of metronidazole as an antagonist of thiamine in catabolism
  - → Possible association between underling pathological mechanisms in MIE and thiamine deficiency

Case report: 76 YOM with MIE who simultaneously presented with significant thiamine deficiency

Iwadate D et al. J Neuro Sci. 2017; 379: 324-6.

Thiamine deficiency in metronidazole-induced encephalopathy: A metabolic correlation?

Dosuke Iwadate, Kenichiro Sato, Mami Kanzaki, Chinatsu Komiyama, Chizuru Watanabe, Tomoaki Eguchi and Yoshikazu Uesaka

Journal of the Neurological Sciences, 2017-08-15, Volume 379, Pages 324-326, Copyright © 2017 Elsevier B.V.

- Treated with oral metronidazole (1500 mg/day) and ciprofloxacin for osteomyelitis due to diabetic foot infection

Day 33
- Depression and reduced appetite

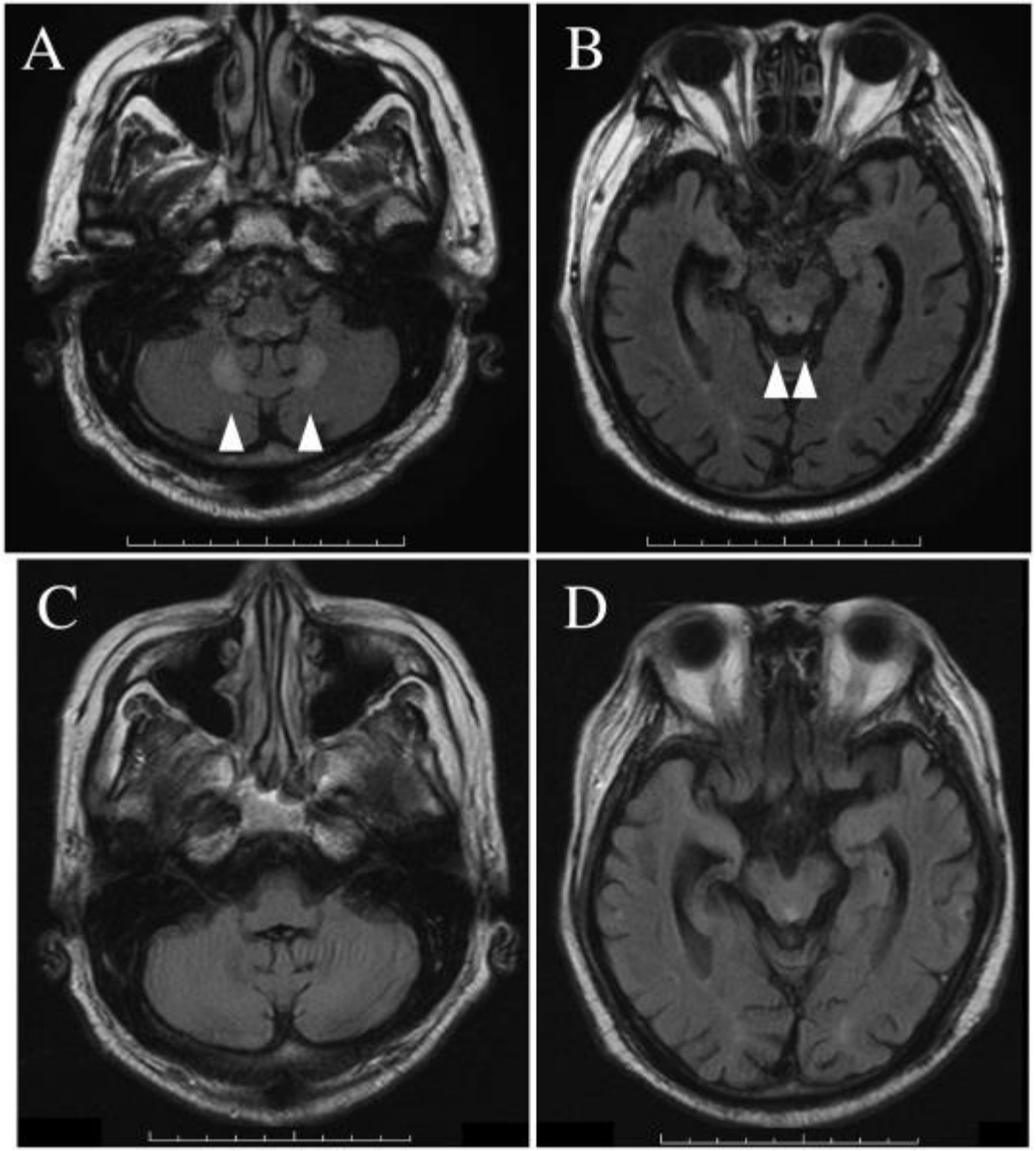
Day 41
- Dysarthria and ataxia
- Rapidly worsened

Neuro consult
- Gaze-evoked nystagmus
- External opthalmoplegia
- Dysarthria
- Limb and truncal ataxia

Thiamine: 17 ng/mL

Iwadate D et al. J Neuro Sci. 2017; 379: 324-6.

Thiamine deficiency in metronidazole-induced encephalopathy: A metabolic correlation?



Iwadate D et al. J Neuro Sci. 2017; 379: 324-6.

Diazepam

J Vet Intern Med 2003;17:304–310

Diazepam as a Treatment for Metronidazole Toxicosis in Dogs: A Retrospective Study of 21 Cases

Jason Evans, Donald Levesque, Kim Knowles, Randy Longshore, and Scott Plummer

- Neurologic toxicity reported in dogs receiving >60mg/kg/day for an average of 3-14 days
- Reported recovery time: 1-2 weeks
- Retrospective chart review- 21 dogs
  - 8 dogs- supportive care
  - 13 dogs- diazepam Q8hr x 3 days

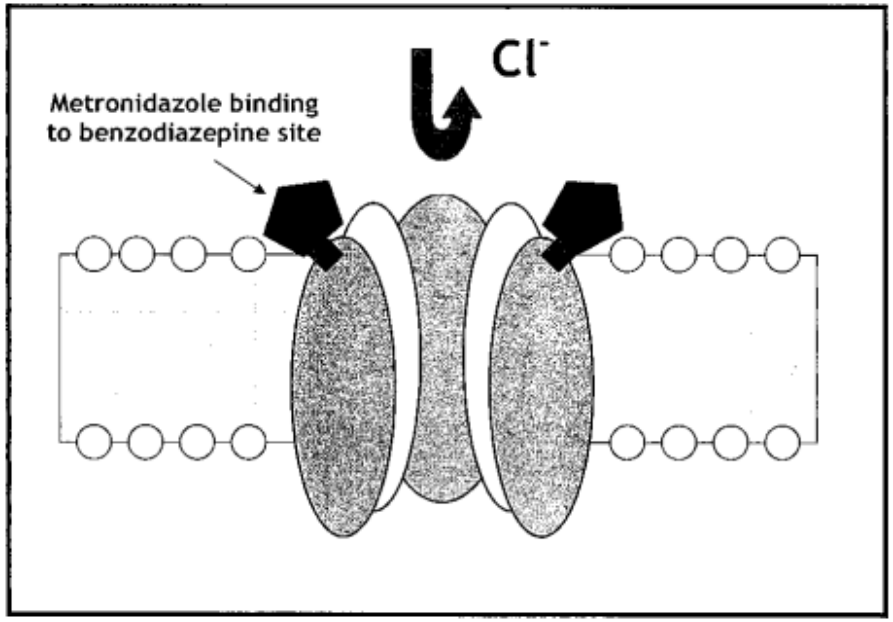
Evans J et al. J Vet Intern Med. 2003; 17: 304-310.

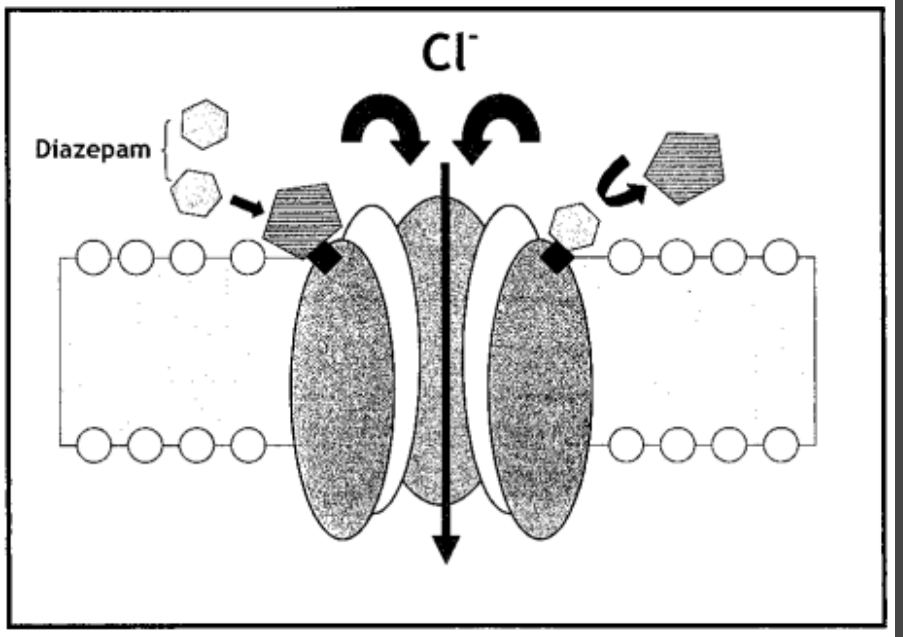
Diazepam

Parameter	Diazepam Group	Nontreated Group	P-value
Age (yr)	7.5	6.7	
Weight (kg)	13.4	20.4	
Metronidazole dosage (mg/kg/d)	65.1 ± 22.3	60.3 ± 17.5	P > 0.05
Metronidazole duration (days)	37.3 ± 34.9	127.5 ± 295.5	*if not considering 1 dog, duration in nontreated group= 44 days, P > 0.05
Diazepam dose (mg/kg)	-	0.43 ± 0.13	
Response time	4.25 ± 2.8 **days**	13.05 ± 9.8 **hours**	P < 0.05
Recovery time	11.6 ± 5.9 **days**	38.8 ± 15.6 **hours**	P < 0.05

Evans J et al. J Vet Intern Med. 2003; 17: 304-310.

Diazepam


Cl-
Metronidazole binding
to benzodiazepine site


Cl-
Diazepam

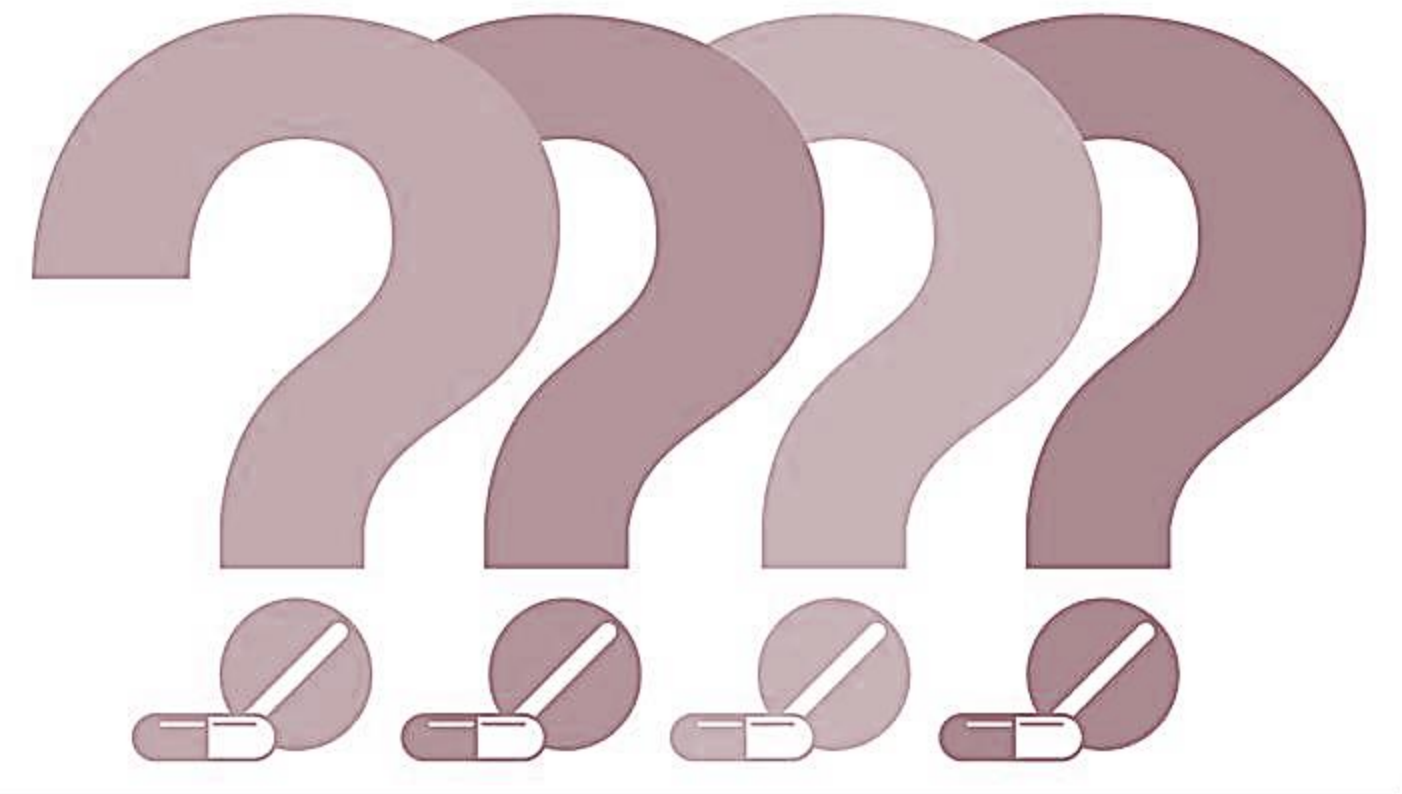
Patient Case

- Head imaging demonstrating a subdural empyema along the right falx
  - Likely secondary to sinusitis
- Underwent:
  - Bilateral frontal craniectomies for bilateral frontal sinus cranialization
  - Right frontoparietal mesial strip craniectomy for evacuation of subdural empyema and free flowing pus
- Concern for acute osteomyelitis of the frontal calvarium

Patient Case

- Suspected to have organisms that colonize the sinuses
- OR culture of fluid from R. frontal subdural empyema: 1+ coagulase-negative *Staphylococci* spp.
- Concern for acute osteomyelitis of the frontal calvarium
  - → 6 weeks of antimicrobials

Alternative Antimicrobials



2018 IDSA *C. diff* Guidelines

- Use of oral metronidazole, however, should be restricted to an initial episode of nonsevere CDI in cases where other therapies are contraindicated or not available, and treatment should be limited to one course due to case reports of neurotoxicity with prolonged or repeated use

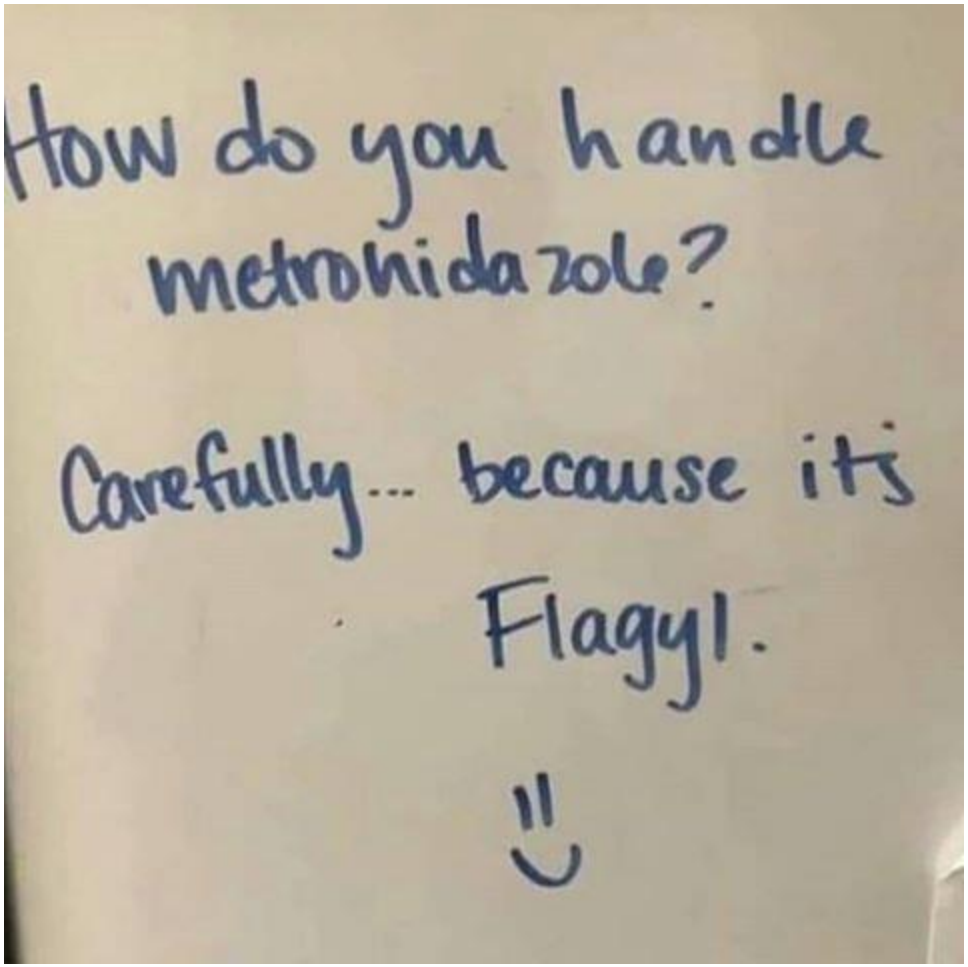
- Avoid repeated or prolonged courses due to risk of cumulative and potentially irreversible neurotoxicity

- Furthermore, metronidazole should not be used for long-term therapy because of the potential for cumulative neurotoxicity.

Conclusions

- CNS toxicity is a rare, but potentially devastating side effect of metronidazole exposure
- Metronidazole CNS adverse effects generally include:
  - Cerebellar dysfunction (ataxia, dysarthria, dysmetria, nystagmus)
  - Altered mental status
  - Seizures
- Treatment of CNS toxicity includes discontinuation of metronidazole, which results in high rates of symptom resolution
- Avoid repeated or prolonged courses due to risk of cumulative and potentially irreversible neurotoxicity

Questions?


How do you handle metronidazole?
Carefully... because it's Flagyl.

CE Credit

Text attendance code to 413-200-2444

Attendance code: BOHFUD