

Disulfiram-like Reaction With Metronidazole: An Unsuspected Culprit

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The association of disulfiram-like reaction with concomitant use of metronidazole and alcohol has been reported in the literature; however, alcohol containing oral liquids may not always be identified as a culprit. A case of a 14-year-old patient who experienced a possible disulfiram-like interaction while receiving metronidazole and Prednisone Intensol solution is reported. Metronidazole oral suspension was initiated for treatment of *Clostridium difficile*-associated diarrhea. Later, a 5-day course of oral Prednisone Intensol solution was initiated. On day 2 of concomitant metronidazole and steroid therapy, the patient experienced severe discomfort and abdominal distention accompanied by new onset tachycardia. A disulfiram-like reaction between the steroid solution and metronidazole was suspected; therefore, the Prednisone Intensol was discontinued. The patient's mother reported that, following discontinuation, the patient slept well for the first time in 2 days. Use of the Naranjo Adverse Drug Reaction Probability Scale indicated a possible relationship (score of 4) between the concomitant medication use and the gastrointestinal discomfort and tachycardia. If this interaction between metronidazole and alcohol containing medications occurs, it may be initially unrecognized, potentially resulting in patient discomfort or harm. It is important for healthcare professionals to identify these potential drug-drug interactions so that alternative medications may be utilized and offending agents can be avoided or replaced.

ABBREVIATIONS IV, intravenously; OTC, over the counter

KEYWORDS adverse effect; alcohol; disulfiram-like reaction; metronidazole; pediatrics

J Pediatr Pharmacol Ther 2019;24(5):445–449

DOI: 10.5863/1551-6776-24.5.445

Introduction

There are different adverse effects that can result from the intake of alcohol or ethanol while using certain prescription medications. These effects range in severity, but ultimately, can result in dangerous or unfavorable outcomes. More specifically, concomitant use of alcohol and disulfiram which acts as an aldehyde dehydrogenase inhibitor, results in an extremely unpleasant response with consumption of even a small amount of ethanol.¹ Under normal metabolism, ethanol is converted to acetaldehyde, a toxic by-product, which is then quickly broken down by acetaldehyde dehydrogenase to be eliminated from the body.² In the absence or reduced activity of the dehydrogenase enzyme, acetaldehyde accumulates causing unpleasant effects, including nausea, vomiting, abdominal pain, flushing, tachycardia, throbbing headaches, and syncope.¹ In severe cases, patients may experience respiratory depression, cardiovascular collapse, arrhythmias, convulsions, and death.¹

Metronidazole is an antibiotic that has been commonly associated with disulfiram-like reactions.^{1,3} In the pediatric population, metronidazole is used in the inpatient and outpatient setting to treat *Clostridium difficile*-associated diarrhea, intra-abdominal infec-

tions, and other infections for which treatment against anaerobic bacteria is needed.⁴ Pharmacists routinely counsel patients regarding exposure to alcohol or alcohol containing products, including mouthwash, while on metronidazole therapy. The alcohol content of prescribed medications is often overlooked. We report a case of an adolescent who experienced severe abdominal pain while being treated with metronidazole and an alcohol-containing medication, Prednisone Intensol (Hikma Pharmaceuticals USA Inc., Eatontown, NJ) solution (30% alcohol).⁴ The possibility of a disulfiram-like reaction with metronidazole has been reported in the literature; however, this is the first report to describe this reaction with another commonly used, alcohol-containing medication. This report will highlight the need for healthcare professionals to be aware of this interaction and use caution when the concomitant use of metronidazole and medications formulated with alcohol is necessary.

Case

A 14-year-old Caucasian female presented to the emergency department with a 2-day history of symptoms consistent with an upper respiratory tract infection and a 1-day history of bloody diarrhea. She had an extensive medical history that included Pallister-

Killian mosaic syndrome, craniosynostosis, cerebral palsy, asthma, and a small bowel resection. She was also ventilator and gastrostomy tube dependent. She was globally delayed, non-communicative, and only weighed 15 kg. Her only home medication included famotidine oral suspension 8 mg (0.5 mg/kg) twice daily. The patient had no known drug allergies.

Upon arrival in the emergency department, stool samples were obtained and sent for culture for pathogenic causes of diarrhea, and *C difficile* toxin testing was performed. On hospital day 1, the patient was noted to be *C difficile* positive via toxin testing. The patient had no prior history of *C difficile* infection and no history of recent antibiotic use. She was started on metronidazole oral suspension 110 mg (7.3 mg/kg/dose) every 6 hours administered via feeding tube. On day 2, she was diagnosed with influenza A and right upper and middle lobe pneumonia. The patient was started on ceftriaxone 1500 mg (100 mg/kg) intravenously (IV) every 24 hours, vancomycin 300 mg (20 mg/kg/dose) IV every 8 hours, and oseltamivir 30 mg (2 mg/kg/dose) via feeding tube every 12 hours. Once the methicillin-resistant *Staphylococcus aureus* surveillance screen resulted with no methicillin-resistant *S aureus* detected, vancomycin was discontinued and ampicillin-sulbactam 750 mg (50 mg/kg/dose) IV every 6 hours was added. On day 7, ceftriaxone and ampicillin-sulbactam were discontinued and the patient was transitioned to oral amoxicillin-clavulanate 330 mg (22 mg/kg/dose of amoxicillin) every 12 hours for a 7-day course. She also continued to receive metronidazole 110 mg (7.3 mg/kg/dose) every 6 hours until hospital day 15.

On days 9 and 10, she experienced several episodes of tachypnea and oxygen desaturations. After consultation with the pulmonologist on day 10, she was started on a 5-day course of oral Prednisone Intensol solution 15 mg (1 mg/kg/dose) via feeding tube twice daily. On the second day of steroid use (day 11), she began to cry out frequently while grimacing. Her mother reported that her agitation had persisted throughout the night and she had noticed the recent onset of abdominal distention. These symptoms continued throughout day 12 and were accompanied with new onset tachycardia ranging from 100 to 133 beats per minute.

On day 12, it was considered that the patient's abdominal discomfort might be due to a disulfiram-like reaction caused by the 30% alcohol content in the Prednisone Intensol solution used concomitantly with metronidazole. At this time, Prednisone Intensol solution was discontinued and prednisolone oral solution 15 mg (1 mg/kg/dose) every 12 hours was initiated. The patient's mother reported that, approximately 24 hours following this medication change, the patient slept well for the first time in 2 days. For the remainder of the patient's stay, she no longer experienced abdominal pain or symptoms consistent with a disulfiram-like reaction. She was discharged on day 16.

Discussion

Metronidazole is a first-line agent for *C difficile* diarrhea or anaerobic infections in children. Although there is a possibility of a disulfiram-like reaction with metronidazole and alcohol, many healthcare professionals may not always consider this a concern in children because alcohol consumption is not intentional, and they are unaware of the incidental exposure from concomitant use of alcohol containing medications. Alcohol is commonly used in oral liquid medications as a solvent and preservative, although it may not always be clear which medications contain this excipient or what percentage of alcohol they contain. This report emphasizes the need for all healthcare professionals to be aware of this interaction with metronidazole and alcohol containing medications and the need for close monitoring of symptoms and identification of non-alcohol containing alternate agents in patients receiving metronidazole.

In addition to Prednisone Intensol solution, here are a variety of prescription and over-the-counter (OTC) medications that contain up to 30% alcohol. Tables 1 and 2 include common prescription and OTC medications listed on the Top 200 Drugs list that contain alcohol.⁵ Some of the highest alcohol concentrations are present in syrups and elixirs.³ As a reference point, a 12-ounce bottle of light beer or a 5-ounce glass of wine contains approximately 4.5% or 11.6% alcohol by volume, respectively. The package insert for metronidazole states that the consumption of alcohol or products containing propylene glycol should be discontinued during drug therapy and for at least 3 days after therapy.⁹ Although this warning is included in the package insert, some investigators have noted that this disulfiram-like reaction with metronidazole does not occur for all patients.¹⁰ A double-blind study by Visapää et al¹⁰ involving 12 healthy, adult male volunteers concluded that metronidazole had no effect on blood acetaldehyde concentrations when used with ethanol.¹⁰ In addition, subjects who ingested the 2 substances simultaneously did not experience any objective or subjective symptoms of disulfiram-like reaction. Additionally, Williams et al¹¹ examined 6 case reports sharing the same conclusion that a disulfiram-like reaction with metronidazole and ethanol took place; however, they concluded that there was insufficient evidence to justify this universal conclusion since they believed that alternative explanations were clear in all cases.¹¹ It is possible that disulfiram-like reactions can occur in some subgroups and by other mechanisms than the inhibition of hepatic acetaldehyde dehydrogenase. A rat study by Tillonen et al¹² suggested that the disulfiram-like reaction could be explained by the replacement of intestinal anaerobes by acetaldehyde-containing aerobes in the gut flora, therefore, not involving the liver at all. Furthermore, there may be some patient-specific factors that influence the potential for this reaction to occur. Overall,

Table 1. Prescription Medications That Contain Alcohol (Not All Inclusive)^{6–8}

Generic Prescription Drug*	Alcohol Concentration (%)†
Dexamethasone elixir	5.1
Dexamethasone Intensol ⁷	30
Diazepam solution	0.5
Diazepam Intensol	19
Diclofenac sodium solution	12
Digoxin elixir ⁸	10
Ferrous sulfate elixir	5
Furosemide solution	11.6
Guaifenesin and codeine syrup	3.5
Hydrocodone bitartrate and acetaminophen solution	6.7
Hydrocodone bitartrate and acetaminophen elixir	7
Hydrocodone bitartrate and guaifenesin expectorant	10
Hydroxyzine syrup	0.5
Lithium citrate solution and syrup	0.3
Nystatin suspension	0.5
Phenytoin sodium IV solution	10
Potassium chloride 10% and 20% solutions	5
Prednisolone solution and syrup	5
Prednisone Intensol concentrated solution	30
Prednisone solution	5
Promethazine and dextromethorphan solution	7
Promethazine expectorant syrup	7
Promethazine expectorant with codeine syrup	7
Promethazine solution	7.1
Promethazine syrup	7
Promethazine with codeine solution	7
Ranitidine syrup	7.5
Sertraline hydrochloride solution	12
Sulfamethoxazole/trimethoprim injectable	12.2

* Each package insert should be checked for differing manufacturers to ensure accurate alcohol concentrations.

† Alcohol concentrations obtained from Micromedex Solutions⁶ unless cited otherwise.

this reaction may not occur in all patients concomitantly exposed to metronidazole and alcohol, and no report has identified the specific quantity of alcohol or dose of metronidazole needed to illicit this response. For this patient case, a Naranjo score was applied to determine the causality of this interaction with the patient's clinical presentation.¹³ A score of 4, indicating possible association, was calculated. Most importantly, the abdominal pain resolved after discontinuation of the Prednisone Intensol solution.

Although disulfiram-like reactions are widely patient specific, it is important that healthcare professionals are aware of the various offenders that could cause

this problem and make suggestions for alternative therapies. This reaction can occur when a new alcohol-containing medication is added for a patient already receiving metronidazole, as in this case, or in a patient receiving an alcohol-containing medication and metronidazole is newly added. If a patient who is receiving metronidazole experiences new onset nausea, abdominal discomfort, vomiting, headache, flushing, or tachycardia, it is necessary to perform a thorough review of both prescription and OTC medications they are receiving to identify the presence of alcohol in these medications. Healthcare professionals should keep in mind that this drug interaction may not be identi-

Table 2. OTC Medications That Contain Alcohol (Not All Inclusive)

Generic OTC Generic Drug	Trade Name	Alcohol Concentration (%)*
Acetaminophen Dextromethorphan Doxylamine Pseudoephedrine	Vicks Nyquil Liquid	25
Dextromethorphan Pseudoephedrine	Robitussin Syrup	1.4
Diphenhydramine	Benadryl Solution or Elixir	14
	Benadryl Syrup	5
Guaifenesin	Mucinex Solution and Syrup	3.5
Loperamide	Imodium A-D	5.25

OTC, over the counter

* Alcohol concentrations obtained from Micromedex Solutions.⁶

fied using drug-interaction tracking software, such as Lexi-comp (Lexi-Interact, Wolters Kluwer Clinical Drug Information; Hudson, OH), and it is not always readily apparent which liquid medications contain alcohol. Manufacturers may change excipients, or different manufacturers of the same drug may have varying amounts of alcohol, so it is imperative to check the alcohol content in all drugs that are being administered to the patient, regardless of indication. Definitive product information can be found in the package insert of each individual agent.

The patient in this case did not experience some of the traditional symptoms (e.g., flushing, vomiting) of a disulfiram-like reaction; however, this may have been secondary to her developmental delay and inability to verbalize nausea. She did not experience any life-threatening reactions from the simultaneous use of Prednisone Intensol and metronidazole; however, significant discomfort could have been avoided if an alternate agent was used. The abdominal pain resolved after switching to the non-alcohol containing prednisolone solution.

Conclusion

The concomitant use of alcohol-containing medications with metronidazole may cause serious adverse reactions and discomfort for the patient. Healthcare professionals need to watch for symptoms of a disulfiram-like reaction when initiating metronidazole or adding concomitant liquid medications to metronidazole therapy. Significant patient discomfort can be avoided if this interaction is proactively identified; however, drug-interaction software may not recognize this interaction. In this case, if healthcare professionals are aware of this interaction, then they can discontinue or replace the offending agent at the initial onset of symptoms.

ARTICLE INFORMATION

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Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all patient information in this report and take responsibility for the integrity and accuracy of the report.

Accepted September 23, 2018

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REFERENCES

1. Karamanakos PN, Pappas P, Boumba VA, et al. Pharmaceutical agents known to produce disulfiram-like reaction: effects on hepatic ethanol metabolism and brain monoamines. *Int J Toxicol*. 2007;26(5):423–432.
2. National Institute on Alcohol Abuse and Alcoholism. Alcohol metabolism: an update. Alcohol Alert. NIAAA Publications Distribution Center, 2007; Vol. 72. <http://pubs.niaaa.nih.gov/publications/AA72/AA72.pdf>. Accessed April 19, 2019.
3. Weathermon R, Crabb DW. Alcohol and medication interactions. *Alcohol Res Health*. 1999;23(1):40–54.
4. Prednisone Intensol. Lexi-Drugs Online. Hudson, OH: Lexi-Comp, Inc. <http://online.lexi.com/crlonline>. Updated July 23, 2019. Accessed August 30, 2018.
5. Kane SP. ClinCalc DrugStats Database, Version 18.0. <http://clincalc.com/DrugStats>. Updated February 3, 2018. Accessed April 19, 2019.

6. IBM Micromedex DRUGDEX. Greenwood Village, CO: IBM Watson Health. <http://www.micromedexsolutions.com/>. Updated Month day, year. Accessed August 31, 2018.
7. Dexamethasone Oral Solution USP, Intensol [package insert]. Columbus, OH: Roxane Laboratories, Inc.; 2015.
8. Digoxin Elixir [package insert]. Columbus, OH: Roxane Laboratories, Inc.; 2004.
9. Metronidazole. Pediatric and Neonatal Lexi-Drugs Online. Hudson, OH: Lexi-Comp Inc. <http://online.lexi.com/crlonline>. Updated July 11, 2019. Accessed August 30, 2018.
10. Visapää JP, Tillonen JS, Kaihovaara PS, Salaspuro MP. Lack of disulfiram-like reaction with metronidazole and ethanol. *Ann Pharmacother*. 2002;36(6):971–974.
11. Williams CS, Woodcock KR. Do ethanol and metronidazole interact to produce a disulfiram-like reaction? *Ann Pharmacother*. 2000;34(2):255–257.
12. Tillonen J, Väkeväinen S, Salaspuro V, et al. Metronidazole increases intracolonic but not peripheral blood acetaldehyde in chronic ethanol-treated rats. *Alcohol Clin Exp Res*. 2000;24(4):570–575.
13. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30(2):239–245.