Can Metronidazole Cause a Disulfiram-Like Reaction? A Case-Control Study Propensity Matched by Age, Sex, and Ethanol Concentration

Ryan Feldman, PharmD; Rachael Jaszczenski, PharmD

ABSTRACT

Introduction: There is controversy over the existence of a metronidazole-induced disulfiram-like reaction. Uncontrolled case reports suggest metronidazole can cause a severe disulfiram-like reaction in combination with ethanol. Criticism of these cases suggest the observed effects appear to be as likely caused by ethanol as by a drug interaction. Controlled experimental data refute these reports, demonstrating metronidazole does not increase acetaldehyde and cannot reliably produce disulfiram-like reactions. The purpose of this study is to retrospectively assess the incidence of clinical effects consistent with a disulfiram-like reaction in a population of patients with confirmed ethanol use who received metronidazole. As alcohol may also be responsible for the effects seen, the incidence of effects is assessed against a control group matched for age, sex, and ethanol concentration.

Methods: A retrospective chart review was performed from December 1, 2010, through December 31, 2020 on emergency department patients with ethanol use confirmed via detectable ethanol concentration who received metronidazole while ethanol was predicted to still be present in the serum. A matched comparator group with the same ethanol concentrations, as well as sex and age, was generated for comparison. The incidence of disulfiram-like reaction symptoms documented in the medical record was compared between groups.

Results: Thirty-six patients were included in the study: 18 in the metronidazole group and 18 in the ethanol concentration matched control group. The mean age in both groups was 46 years. The metronidazole group was 50% male, and the mean ethanol concentration was 0.21 g/dL. The control group was 44.4% male. There was significantly less hypertension in the metronidazole group compared to the control group (16.7% vs 61.1%, $P < 0.0001$). There were no other significant difference in disulfiram-like effects between the two groups. No patients who received metronidazole and had a detectable ethanol concentration had a suspected disulfiram-like reaction documented in the medical record.

Conclusions: This data set further supports the lack of a disulfiram-like reaction when metronidazole is used in patients with recent ethanol use in the acute care setting. Additionally, it highlights that the clinical effects of a disulfiram-like reactions may be present at baseline from ethanol ingestion or underlying disease regardless of metronidazole use. These findings are consistent with well-controlled human and animal data demonstrating no increase in acetaldehyde concentrations or disulfiram-like symptoms when metronidazole is co-administered with ethanol. In patients where metronidazole is indicated as the superior agent, its use should not be avoided due to concern about an interaction with ethanol.

INTRODUCTION

Use of alcoholic beverages (drinks containing ethanol) is extremely common among adults in the United States. Survey estimates suggest 86% of US adults have used alcohol at least once in their life.[1] In 2020, 1.8% of all emergency department (ED) visits in the US were related to alcohol.[2] This is only a minimum estimate of how often alcohol and acute health care intersect, as alcohol use is also commonly discovered in patients presenting for other reasons, such as traumatic injury.[3] Due to the frequency of alcohol use in patients intersecting with health care, it is important to understand when drugs have a significant interaction with alcohol.

The "disulfiram reaction" is an unpleasant syndrome of nausea, vomiting, flushing, tachycardia, hypertension, and dysphoria that occurs when ethanol is co-consumed with disulfiram.[4] Ethanol

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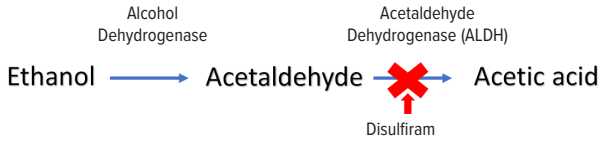
Author Affiliations: Froedtert & the Medical College of Wisconsin (MCW), Department of Pharmacy, Milwaukee, Wisconsin (Feldman); MCW, School of Pharmacy, Milwaukee, Wis (Feldman, Jaszczenski); MCW, Emergency Medicine/Medical Toxicology, Milwaukee, Wis (Feldman).

Corresponding Author: Ryan Feldman, PharmD, Froedtert & the Medical College of Wisconsin Froedtert Hospital Pharmacy, 9200 W Wisconsin Ave, Milwaukee, WI 53226; phone 262.844.9646; email ryan.feldman@froedtert.com; ORCID ID 0000-0002-6630-3288

Figure 1. Mechanism of Disulfiram Reaction With Ethanol



The syndrome is caused by disulfiram inhibiting ALDH, halting metabolism at the acetaldehyde phase, and leading to build up of acetaldehyde.

normally undergoes metabolism via alcohol dehydrogenase to acetaldehyde, which is then metabolized via acetaldehyde dehydrogenase (ALDH). Disulfiram inhibits ALDH and causes a buildup of acetaldehyde, leading to the adverse effects seen in the disulfiram reaction (Figure 1). This is both a drug interaction and the basis of disulfiram's entire pharmacologic effect. Its utility as a deterrent from alcohol use lies in its ability to reliably inhibit ALDH and reproduce the unpleasant disulfiram reaction whenever alcohol is present.[4]

In 1964, an observational study evaluating side effects of metronidazole use reported a single patient who experienced a reduced urge to drink alcohol and potentially had a disulfiram-like reaction during 1 of the 3 times he was exposed to metronidazole.[5] This observation led to the suggestion that metronidazole may have a disulfiram-like effect on ALDH and can cause disulfiram-like reactions when combined with alcohol.[6]

Subsequent to this uncontrolled case report, a number of controlled studies assessed metronidazole's ability to induce disulfiram-like effects in patients administered alcohol.[6-10] While common metronidazole side effects such as nausea or a metallic taste were reported by participants, many studies reported no disulfiram-like effects in patients, and no study was able to reproduce a clear disulfiram-like reaction as had been reported in the index case (ie, flushing, dysphoria, vomiting, hypertension, tachycardia). An increase in acetaldehyde is fundamental to generating a disulfiram reaction. Controlled human and rodent studies verify that metronidazole does not inhibit ALDH and that systemic acetaldehyde concentrations do not rise when alcohol and metronidazole are coadministered.[6,10,11] These findings appear to objectively refute the existence of metronidazole's ability to cause a disulfiram-like reaction.

In spite of the controlled evidence refuting the interaction, the initial suggestion from the uncontrolled 1964 case report that metronidazole can cause this interaction persists. Case reports continue to be published asserting that metronidazole use with alcohol has led to severe and sometimes fatal disulfiram reactions.[12] Reviews of these cases are critical of their conclusions. A case report cannot demonstrate causation or differentiate if the effects reported are from metronidazole, ethanol itself, a concurrent illness, or a potential ethanol-metronidazole disulfiram-like reaction.[12] The symptoms of the disulfiram reaction are somewhat nonspecific and may be caused by a number of disease states or from ethanol itself (eg, flushing, nausea, vomiting, tachycardia). A clinician who has heard of this possible interaction with metronidazole and ethanol may recognize these symptoms in a patient who has them from another cause and misattribute them to a disulfiram-like reaction.

The persistent belief of this interaction in the face of contrary evidence appears controversial. Nevertheless, the numerous case reports have prompted warnings from the drug manufacturer to avoid coadministration of metronidazole and alcohol within 72 hours.[13] It is listed as a drug interaction of significant concern in most drug references.[14] Moreover, many pharmacies are required to label metronidazole prescriptions as "avoid with alcohol," and it is a common counseling point for most pharmacists.

Metronidazole is a frequently used drug, both inpatient and outpatient. It is used for intrabdominal infections, bacterial vaginosis, preoperatively for emergent abdominal surgery, and many other scenarios in which anaerobic organisms need to be targeted. In some cases, it is the only available treatment option (eg, trichomoniasis). Prescribers should know whether alcohol is, in fact, contraindicated when metronidazole is prescribed, and there is limited controlled data assessing this interaction in the acute care setting. The purpose of this study is to retrospectively assess the incidence of clinical effects consistent with a disulfiram reaction syndrome in a population of patients with analytically confirmed ethanol use who received metronidazole compared to a matched cohort of those with ethanol use who did not receive metronidazole.

METHODS

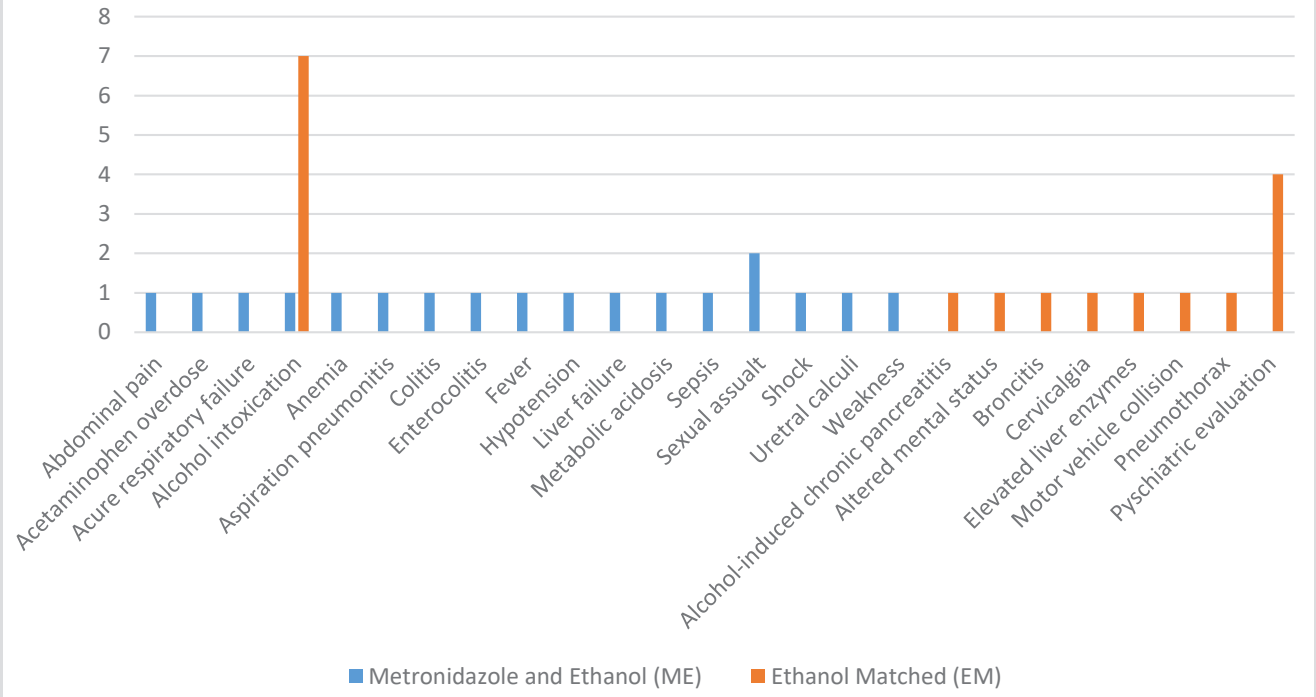
Study Setting and Design

This study was a cross-sectional case-control retrospective chart review of patients presenting to a single academic medical center ED from December 1, 2010, through December 31, 2020. Institutional review board approval with waiver of consent was obtained prior to conducting any research activities. The ED is located in an urban center in Milwaukee, Wisconsin and has approximately 72,000 visits annually.

Outcomes

The primary outcome was the incidence of disulfiram-like effects documented in the medical record in patients with detectable ethanol concentrations who had received metronidazole when ethanol was expected to still be present compared to patients with detectable ethanol concentrations who did not receive metronidazole. Disulfiram-like effects were defined as any documented occurrence of nausea, vomiting, flushing, tachycardia (heart rate > 100 beats per minute), hypertension (systolic blood pressure > 160 mmHg or diastolic blood pressure > 105 mmHg), hypotension (systolic blood pressure < 90 mmHg or mean arterial pressure < 65 mmHg) or use of an antiemetic medication. Antiemetics were

Figure 2. Admission Diagnosis



defined as serotonin receptor antagonists (eg, ondansetron) or dopamine antagonists (eg, metoclopramide, prochlorperazine, haloperidol, olanzapine). Steroids or benzodiazepines were included if the medical record specifically noted their indication was for nausea. Medical records were searched for the term "disulfiram." Rates of hospital admission, continued antibiotic use, and mortality data also were gathered.

Population

Patients were included if they were 18 years or older, had analytically confirmed ethanol concentrations, and had nursing documentation of metronidazole administration within the medication administration record. Only patients with nursing documentation of metronidazole administration in the medication administration record were included to avoid potential confounding by nonadherence with outpatient regimens. Patients were excluded if their medical record was incomplete, if they were pregnant, or if they were calculated to not have ethanol present at the time of metronidazole administration. Prediction of ethanol level was done utilizing zero order kinetics and a conservative estimated elimination rate of 0.015 g/dL/hour. This elimination rate was chosen due to its frequent use in forensic toxicology to extrapolate blood alcohol levels.[15]

The equation for predicted ethanol concentration at time of metronidazole administration was measured blood alcohol concentration – ([time of blood alcohol drawn – time of metronidazole given] *0.015).

A 10-year sample was selected as a convenience sample as well as the longest duration of time when complete patient records were expected to be available per the data acquisition team.

Generation of Matched Control

A demographic and ethanol concentration matched cohort was generated to compare the incidence of effects using demographic variables that may influence the incidence of disulfiram affects occurring at baseline (age, sex, ethanol concentration). After the list of patients with detectable ethanol levels who had received metronidazole was generated (case), a comparator (control) was selected from a list of all patients who had a detectable ethanol concentration. A patient of the same age, sex, and ethanol concentration was then selected from that list if available. If multiple candidates existed, the first candidate from the list was selected. If no exact match was available, the candidate closest in age with an exact ethanol match was chosen.

Data Collection

Data were collected within a predesigned data collection tool; all patients were collected in duplicate, and discrepancies were resolved by a third-party review. In the metronidazole group, the outcomes of interest (disulfiram effects) were recorded at any point after metronidazole administration. In the matched group, the effects were recorded if they occurred at any time during the ED visit.

Statistical Analysis

Assuming a 10% baseline incidence of disulfiram reaction symptoms in each group, a sample size of 16 patients in each group

Table. Demographics and Incidence of Disulfiram-like Reaction Effects in Patients Predicted to Have Detectable Ethanol Concentration at Time of Metronidazole Administration

	Metronidazole + Ethanol n = 18	Ethanol Alone n = 18	*P* value
Age (years) mean (SD, range)	46.2 (14.4, 22-76)	45.6 (12.6, 26-62)	0.912
Male, n (%)	9 (50%)	8 (44.4%)	1
Admission, n (%)	15 (83.3%)	1 (5.5%)	<0.00001
Ethanol level (g/dl) (mean SD)	0.21 (0.09, 0.047-0.375)	0.21 (0.09, 0.047-0.375)	1
Gastrointestinal-related diagnosis, n (%)	5 (27.7%)	2 (11.1%)	0.20
Tachycardia, n (%)	6 (33.3%)	9 (50%)	0.31
Nausea, n (%)	4 (22.0%)	2 (11.1%)	0.37
Vomiting, n (%)	2 (11.1%)	1 (5.5%)	0.55
Flushing, n (%)	0 (0.0%)	0 (0.0%)	1
Hypertension, n (%)	3 (16.7%)	11 (61.1%)	0.0153
Hypotension, n (%)	0 (0.0%)	1 (5.5%)	1
Antiemetic required, n (%)	6 (33.3%)	2 (11.1%)	0.22
Disulfiram-like reaction suspected, n (%)	0 (0.0%)	0 (0.0%)	1
Death, n %)	3 (16.6%)	0 (0.0%)	0.23

was calculated to detect a 60% difference in incidence of clinical effects using 80% power and an alpha of 0.05. With 18 in each group, the study was powered to detect a 46% difference in clinical outcome within either group. Data on incidence of clinical effects in alcohol-intoxicated patients compared to those experiencing a disulfiram effect while intoxicated is lacking; however, 1 study evaluated presenting ED patients on disulfiram and assessed their likelihood of experiencing a disulfiram reaction. Patients possibly experiencing disulfiram reactions had rates of many symptoms, including flushing, nausea, and vomiting, occurring at differences greater than 35% versus those not deemed to be having a reaction (flushing 89.5% vs 0%, nausea 71.3% vs 5.6%, vomiting 47.7% vs 8.3%, respectively). Ordinal variables were compared using Fisher exact test and continuous variables via a Mann-Whitney U test. Significance was defined as $P < 0.05$ (2-tailed).

RESULTS

A total of 24 patients met inclusion for detectable ethanol concentrations and receipt of metronidazole. After prediction formulas were applied for ethanol being present at time of metronidazole, 6 were excluded; no patients were excluded for any other reason. This left 18 patients who received metronidazole while ethanol was present in their blood (ME group). After generation of an ethanol-, age-, and sex-matched comparator group (EM group), 36 patients were included in the study: 18 in each group. Distribution of demographics and incidence of disulfiram-like effects are listed in Table. The mean age in the ME group was 46 years (SD ±14.4 years, range 22-76 years) and the mean ethanol concentration was 0.21 g/dL (SD ± 0.09 g/dL, range 0.047-0.375 g/dL). In the EM group, the mean age was 46 years (SD ±12.6, range 26-62 years). The ME group was 50% male, and the EM group was 44.4% male.

More patients in the ME group were admitted to the hospital and more continued receiving antibiotics (any antibiotic after first dose of metronidazole, including metronidazole itself) compared to the EM group (admission: ME n = 15, EM n = 1, $P < 0.00001$; antibiotics: ME n = 15, EM n = 0, $P < 0.0001$). There were more patients in the ME group who had a potentially confounding gastrointestinal-related diagnosis; however, this was not statistically significant (ME n = 5, EM n = 2, $P = 0.4$). See Figure 2 for the full list of admission diagnoses for each. Two patients in the ME group died; however, both had elevated lactate levels and hypotension prior to metronidazole administration. Their admitting diagnoses were unspecified hypotension and liver failure without hepatic coma.

No patients in the ME group had a suspected disulfiram-like reaction documented in the medical record. There was no significant difference in incidence of tachycardia, nausea, vomiting, flushing, hypotension, or antiemetic use between groups. There was significantly more hypertension in the EM group compared to the ME group (ME n = 3, EM n = 11, $P < 0.006$).

DISCUSSION

This small data set is consistent with past literature in supporting the safety of metronidazole use in patients with confirmed ethanol use. This study was not able to identify any patients where a disulfiram-like reaction was suspected after metronidazole administration, though it is limited by its retrospective design. Most patients in both groups had at least 1 symptom of a disulfiram-like reaction; however, the symptoms occurred at an equal frequency to the EM cohort who did not receive metronidazole. Our hypothesis was that if metronidazole were to cause this drug interaction, the ME group would demonstrate higher rates of any of these disulfiram-like symptoms. We were unable to reject our null hypothesis. The only symptom that occurred more often was hypertension, which occurred in the EM cohort. These data highlight that disulfiram-like effects are prevalent amongst ethanol-intoxicated patients regardless of metronidazole exposure. The symptoms also may be present due to baseline illness comorbidities (eg, liver disease-causing hypotension) or acute infection necessitating metronidazole.

While this study did control for confounding variables, such as ethanol use, some variables were not able to be matched. More patients who received metronidazole were admitted to the hospital and received ongoing antibiotics. While this highlights that the populations may have had baseline differences in demographics that could influence the prevalence of disulfiram-

like symptoms, it also biases the results toward observing disulfiram-like reactions more often in the ME group. This group was observed longer than the EM matched control and, thus, had more opportunity to document symptoms. Regardless, no disulfiram-like reactions were identified, and clinical effects were similar amongst both groups. Our data are consistent with past studies showing no observed disulfiram-like effects with metronidazole and, once again, call into question the existence of this reported interaction.

The first suggestion of a metronidazole-induced disulfiram-like interaction with alcohol was reported in 1964 by Jo Ann Taylor.[5] Reviewing this index report is valuable in understanding how the belief of metronidazole's interaction with ethanol came to exist and persist in the medical community. Taylor was completing a 3-year observational study on the side effects of metronidazole use and, from a cohort of 463 patients, highlighted a single case where a patient stopped drinking after using metronidazole. The patient drank alcohol daily and had been hospitalized multiple times for detoxification. His wife reported that while he was being treated with metronidazole for trichomoniasis, he did not finish his alcoholic beverage 3 different times. The wife remembered this effect and, at a later date when the patient had been binge drinking for 3 days and was described to be in a stupor, gave him a dose of metronidazole in hopes of ending the drinking binge. Twenty minutes later, he became more alert and accused his wife of giving him disulfiram, a drug he had previously taken and refused to take again due to the unpleasant reaction with alcohol. He had flushing, nausea, epigastric pain, and a feeling of impending doom. The symptoms worsened after another sip of alcohol but then resolved 4 hours later.

Several explanations could be considered for the observed syndrome of effects in this patient, including a psychosomatic reaction to believing his wife had given him disulfiram, abdominal pain from excess drinking, or acute withdrawal due to cessation of alcohol after a 3-day binge. Additionally, in the very same report, the author provided evidence that the reaction was not reproducible. The patient presented a year later to a hospital after a 10-day drinking binge, acutely intoxicated but beginning to experience delirium tremens. He was given metronidazole on arrival and instead of having a disulfiram reaction, the author asserted it significantly reduced his symptoms and led to the improvement of his liver function tests. The author reported a number of extraordinary conclusions from this case example: that metronidazole could reverse signs of liver disease, create aversions to alcohol, treat symptoms of withdrawal, and reduce cravings. The publication endorsed that 53 other patients within the 463 studied patients also reported alcohol aversions on metronidazole but provided no actual data or case details.

This uncontrolled index case report was popularized by lay media discussion (radio and television) and prompted a spree of research into metronidazole's role on alcohol use disorder.[15] An additional 20 studies were performed in the next 8 years.[6] The majority, however, evaluated the drug's ability to maintain abstinence and were not well-designed to assess for disulfiram reactions. None reported significant disulfiram reactions in patients who continued to drink, and only 4 of the subsequent trials assessed the ability of metronidazole to produce a disulfiram effect in a controlled setting.[15]

Only one of these controlled studies appears to provide any support to the proposed metronidazole disulfiram-like effect with ethanol. This study randomly assigned 41 volunteers to take metronidazole or a placebo. The participants then took part in a party where they could drink as many alcoholic beverages as desired. Participants given metronidazole reported a higher incidence of headache, nausea, and bitter taste compared to the placebo group. It should be noted that nausea and a bitter taste are potential side effect of metronidazole alone. There was no comparator group who took only metronidazole, so it is not clear if these symptoms would have occurred regardless of ethanol use. All of the reported effects were mild, and no participants reported severe symptoms consistent with disulfiram-like reaction.

Two additional studies placed abstinent patients on metronidazole for 2 weeks and challenged them with alcohol periodically.[8,9] During alcohol challenges, minor nonspecific symptoms were reported in some (change in taste of alcohol, coffee, and cigarettes; lack of desire to drink; headache; or feeling hot), while others reported increase in desire to drink and reduced tolerance. Once again, change in taste was noted, which is a known side effect of metronidazole. No patients reported disulfiram effects. A further study administered metronidazole for 10 days to abstinent patients with alcohol use disorder and then administered 2 ounces of whiskey. No disulfiram-like effects were seen.

While these controlled trials frequently reported metronidazole side effects (bitter metallic taste), it did not appear that disulfiram reaction symptoms could be reliably reproduced in a controlled setting. In fact, it was suggested after these studies that the metallic bitter taste induced by metronidazole was the mechanism for metronidazole producing an aversion to alcohol use as opposed to a disulfiram reaction. This prompted a study in 1972 to use a structurally related agent without a metallic taste (flundiazole) to assess if this also could induce an alcohol aversion.[6] In this small study of 11 healthy volunteers, flunidazole had no impact on producing aversion to ethanol. No one treated with flunidazole had disulfiram-like effects, and vital signs were not different than those treated with ethanol alone. Importantly, this study also measured acetaldehyde concentrations, the compound responsible for causing the clinical effects of the disulfiram reaction. There were no differences in acetaldehyde production between ethanol only or ethanol and flunidazole-treated groups (8.1 ng/ml vs 6.7 ng/ml). This study provided objective data that drugs within this class do not increase acetaldehyde production and do not cause a disulfiram-like reaction. However, it would

be nearly 30 years before these findings would be replicated with metronidazole in humans.

Several studies now exist assessing metronidazole's ability to increase acetaldehyde. In a 2000 study where rats were fed a 6-week diet of ethanol and metronidazole, metronidazole alone, or ethanol alone, it was demonstrated that metronidazole has no effect on blood acetaldehyde. Additionally, biochemical analysis in this study demonstrated metronidazole did not inhibit ALDH at all. This strongly supports the absence of a disulfiram-like reaction with metronidazole and ethanol. Notably, there was an increase in colonic acetaldehyde in metronidazole-treated rats. As metronidazole does not inhibit ALDH, the authors postulate this may be from metronidazole increasing the amount of alcohol dehydrogenase-producing aerobic bacteria in the gut, leading to more rapid acetaldehyde formation.[11] While chronic metronidazole use could theoretically increase systemic absorption of acetaldehyde, this was not observed after 6 weeks of use in the rodents.

A human study also corroborated these findings. In 2000, a randomized controlled trial assessed acetaldehyde production and incidence of disulfiram-like reaction effects (blood pressure, temperature, heart rate) in 6 participants who had been taking metronidazole 600 mg daily for 5 days and were then given a 0.4 mg/kg load of ethanol.[10] Both acetaldehyde production and disulfiram-like effects were compared to 6 participants who had been taking placebo for 5 days and received the same ethanol load. No disulfiram-like reactions were noted, and metronidazole had no impact on acetaldehyde production. In fact, there are data to support that metronidazole reduces acetaldehyde production. While it does not inhibit ALDH, at supratherapeutic concentrations, it can inhibit alcohol dehydrogenase, leading to a decrease in acetaldehyde.[16]

When examining the literature, no controlled experimental data appear to support the existence of this reaction. Yet, the persistence this single index case holds in the medical literature is exemplified by the case reports that continue to be published of this interaction each year.[12] As discussed previously, disulfiram-like effects are largely nonspecific (hypertension, flushing, nausea, tachycardia, headache) and may be caused by a number of confounding diseases for which metronidazole is warranted (infection) or ingestion of ethanol itself. In the studied population we report, some of the effects were even more common in those only exposed to ethanol (hypertension). Systematic reviews of these cases have drawn the same conclusions.[12,17] It is impossible to ascribe causality to a drug interaction within these reports as opposed to comorbid ethanol use, psychosomatic symptoms, or confounding medical conditions that may produce similar symptoms. Any clinician who has been informed of this interaction may be able to identify a consistent syndrome in patients who are suffering from infection or alcohol intoxication and believe they are observing it.

Despite the many limitations in supportive data, the drug manufacturer continues to warn of the interaction between metronidazole and ethanol. If there is an interaction, it objectively is not a disulfiram reaction. Our data confirm that metronidazole can be used safely in intoxicated patients for whom metronidazole is indicated. In some cases, metronidazole is the only agent available to manage certain infections (eg, trichomoniasis). Additionally, alcohol is a commonly encountered substance in the trauma population that may require emergent abdominal surgery and preoperative antibiotics with metronidazole. The presence of alcohol in a patient may cause a clinician to select an alternative agent that is potentially less optimal, which could cause undue harm—all in an effort to avoid an unsubstantiated interaction.

These data align with previous literature that demonstrates co-administration of metronidazole and ethanol does not cause a disulfiram-like reaction or any symptoms beyond regular metronidazole side effects. In patients who require metronidazole, it is likely safe to administer, regardless of concurrent ethanol use. This is consistent with the practice in our ED.

Limitations

This study is limited by its small sample size, which may have been inadequately powered to detect significant differences in specific disulfiram-like effects. Another significant limitation is the retrospective design, which makes it difficult to discern whether a patient is experiencing a disulfiram reaction. It is not possible to know if a disulfiram reaction was suspected if not documented in the chart or diagnosis code. Many patients did have multiple symptoms that are included in a disulfiram reaction syndrome, though these likely represent symptoms caused by alcohol or baseline illness. It is presumed if metronidazole does cause a disulfiram-like reaction, the ME group would consistently demonstrate higher rates of any symptoms, which it did not.

Confounding demographic factors may play a role in equalizing symptom incidence between groups. While age, sex, and ethanol concentration were matched, disease severity likely was not. This is exemplified by the fact that significantly more patients in the metronidazole group were admitted to the hospital. The need for antibiotics in the metronidazole group may have selected for a population with more complex medical needs. In the EM group, 55.5% of patients presented with a diagnosis of alcohol intoxication or isolated psychiatric problems. Future studies may consider propensity matching by admission status and receipt of antibiotics to better control for severity of illness. Additionally, a third control arm of patients receiving only metronidazole with no concurrent alcohol intoxication also may help differentiate between a disulfiram-like effect and metronidazole side effect profile.

CONCLUSIONS

There is significant controversy as to whether an interaction exists between metronidazole and ethanol. Its existence is purported by uncontrolled case reports yet refuted by controlled experimental data. This data set further supports the lack of a disulfiram-like reaction when metronidazole is used in patients with recent etha-

nol use in the acute care setting. Additionally, it highlights that the clinical effects of a disulfiram-like reaction may be present at baseline from ethanol ingestion or underlying disease, regardless of metronidazole use. This study was notably limited by a small sample size and inability to control for all confounding baseline variables. However, findings are consistent with well-controlled human and animal data demonstrating no increase in acetaldehyde concentrations or disulfiram-like symptoms when metronidazole is coadministered with ethanol. In patients where metronidazole is indicated as the superior agent, its use should not be avoided due to concerns about an interaction with ethanol.

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