

## Alcohol-Medication Interactions: The Acetaldehyde Syndrome

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### Abstract

Medications that inhibit aldehyde dehydrogenase when coadministered with alcohol produce accumulation of acetaldehyde. Acetaldehyde toxic effects are characterized by facial flushing, nausea, vomiting, tachycardia and hypotension, symptoms known as acetaldehyde syndrome, disulfiram-like reactions or antabuse effects. Severe and even fatal outcomes are reported. Besides the aversive drugs used in alcohol dependence disulfiram and cyanamide (carbimide), several other pharmaceutical agents are known to produce alcohol intolerance, such as certain anti-infectives, as cephalosporins, nitroimidazoles and furazolidone, dermatological preparations, as tacrolimus and pimecrolimus, as well as chlorpropamide and nilutamide. The reactions are also observed in some individuals after the simultaneous use of products containing alcohol and disulfiram-like reactions inducers. Depending on the pharmacological inducer, reactions may occur several days after treatment completion. Disulfiram-alcohol reaction includes moderate decrease in blood pressure, but severe life-threatening arterial hypotension and shock sometimes develop. Myocardial infarction secondary to disulfiram-alcohol reaction has been also reported. For severe hypotension resulting from a disulfiram-ethanol reaction, adrenaline or noradrenaline have been employed as the pressor agent of choice. Fomepizole, an alcohol dehydrogenase inhibitor, may be a safe and effective treatment of severe reactions. When medications that produce antabuse effects are prescribed or dispensed, patients should be instructed to avoid medicines and other products containing alcohol, such as syrups, fermented vinegar, sauces and lotions. It is essential that doctors, nurses and pharmacists instruct patients to avoid alcohol during treatment with aversive drugs and disulfiram-like reactions inducers. Likewise, even when scientific evidence is inconclusive, such instructions should be provided in leaflets, which are often the only source of information for patients and a guide for health professionals.

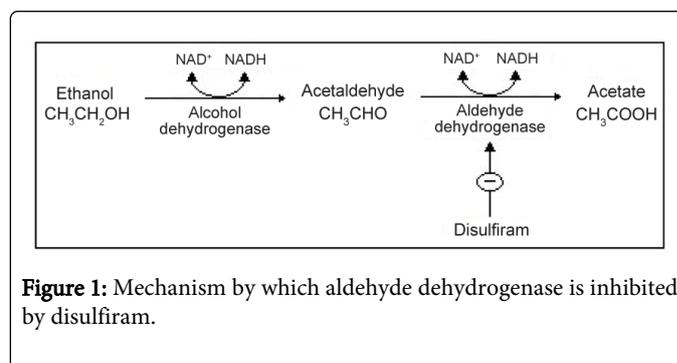
**Keywords:** Adverse drug events; Antabuse; Disulfiram-like reaction; Drug interaction

### Introduction

After absorption, ingested ethanol is enzymatically converted to acetaldehyde, which is implicated in the adverse effects of alcoholic beverages, such as headache, flushing, nausea and vomiting [1]. Acetaldehyde is rapidly converted to acetate by aldehyde dehydrogenase, which generally prevents or reduces its effects on those occasions when low and moderate doses of ethanol are consumed. This process is the pharmacokinetic basis of alcohol aversion therapy used in the treatment of alcoholism.

Disulfiram, also called antabuse, is a drug used for alcohol aversion therapy. This drug inhibits aldehyde dehydrogenase, thereby promoting the accumulation of acetaldehyde [2] and therefore the manifestation of its toxic effects, characterized by facial flushing, nausea, vomiting, tachycardia and hypotension, symptoms known as antabuse effect. This mechanism produces intolerance to alcohol and promotes abstinence from alcoholic beverages.

Some medications, usually inhibitors of aldehyde dehydrogenase, can induce disulfiram-like effect when combined with alcohol (Figure 1). Certain anti-infectives, as cephalosporins [3], nitroimidazoles [4] and furazolidone [5], dermatological preparations, as tacrolimus and pimecrolimus [6], as well as chlorpropamide [7] and nilutamide [8] are known to produce disulfiram-like reactions.



**Figure 1:** Mechanism by which aldehyde dehydrogenase is inhibited by disulfiram.

Although disulfiram-alcohol and disulfiram-like reactions are usually mild or moderate (facial flushing, weakness, headache, tachycardia, nausea, vomiting, sweating, vertigo, hypotension) [9,10], they can trigger severe and potentially fatal events such as life-threatening arterial hypotension, shock and myocardial infarction [11-20]. The interaction may occur not only from the intake of oral medicines, but also due to the use by other routes, such as intravenous [3] and topical [6].

### Severe reactions with aversive drugs

Disulfiram-alcohol reaction includes moderate decrease in blood pressure, but severe life-threatening arterial hypotension and shock sometimes develop [11,13-16,18-19]. A 42-year-old woman developed intractable hypotension and non-ST-elevation myocardial infarction

as a result of a disulfiram-alcohol interaction. Coronary angiography performed three days after admission was normal [17]. In a patient with a severe disulfiram-alcohol reaction marked by flushing, confusion, generalized malaise, epigastric pain, and hypotension, cardiac biomarker and electrocardiographic changes were suggestive of myocardial infarction wherein heart catheterization showed no evidence of coronary artery disease [20]. Myocardial infarction secondary to disulfiram-alcohol reaction has been reported earlier [12].

Disulfiram is known to cause hepatitis and liver failure, which are often fatal, even in patients without a known history of liver disease [21-25]. A 49-year-old woman was started on disulfiram with liver function tests normal, without a known history of liver disease, developed jaundice 13 days after onset of treatment. Acute liver failure was diagnosed on the 18th day and the woman died 25 days after the onset of disulfiram treatment in hepatic coma due to a fulminant hepatitis [21]. In an alcoholic man aged 30 who died from liver damage, hepatitis was diagnosed after the use of disulfiram. There was a close temporal relationship between the occurrence of symptoms and disulfiram intake and biopsy showed massive hepatic necrosis without signs of alcoholic hepatitis [22]. In a man aged 34 year, immediate withdrawal of disulfiram administration on the earliest signs of hepatitis did not prevent severe hepatic necrosis [23]. Other similar cases of disulfiram-induced hepatitis that progressed to fatal fulminant hepatic failure were reported [24-25].

Patients undergo liver transplantation because of disulfiram toxicity [26]. A patient without a known history of liver disease was transplanted for fulminant hepatic failure secondary to disulfiram [27]. It is reported a case of liver transplantation for disulfiram-induced fulminant hepatic failure in a 16-year-old girl, secondary to short-term, low-dose disulfiram use [28].

Cyanamide (carbimide), which is also used in alcoholism treatment, may cause severe acetaldehyde syndrome when combined to alcohol. A rare case of cyanamide-ethanol reaction-induced shock in a 73-year-old man who was taking cyanamide for the treatment of alcohol dependence is reported [29]. Cyanamide is also the active ingredient of a plant growth regulator used in agriculture. After percutaneous absorption, the product named hydrogen cyanamide inhibits aldehyde dehydrogenase and can induce acetaldehyde syndrome in case of alcohol use. A report described two cases of occupational exposure to hydrogen cyanamide in which victims developed flushing of the face, tachycardia, dyspnea and arterial hypotension, before or after drinking alcoholic beverages [30]. Product labeling provides warnings regarding the risk of intolerance to alcohol, with recommendations to avoid alcoholic beverages 24-48 hours before or after use [31].

### Disulfiram-like reactions with anti-infective drugs

Cephalosporin antibiotics with structures that include the methylthiotetrazole side chain can cause a disulfiram-like reactions, manifested by flushing, tachycardia, bronchospasm, sweating and vomiting. The methylthiotetrazole group structurally resembles disulfiram and inhibits aldehyde dehydrogenase resulting in acetaldehyde accumulation. Disulfiram-like reactions have been reported in patients and normal healthy volunteers who have consumed alcohol after administration of cefoperazone [32-34], moxalactam [34-37], cefamandole [38,39] e cefotetan [40]. Recently, disulfiram-like reactions induced by cefuroxime, which do not contain the methylthiotetrazole side chain, was identified as the cause of sudden death [41].

In a retrospective review [3], from 78 patients who had cephalosporin induced disulfiram-like reactions, five (6.41%) developed severe reactions too urgently to be rescued successfully. Clinicians should keep in mind that cephalosporin should not be prescribed for any alcoholics and educate patients that no alcohol should be used if one is taking cephalosporin [3].

Intolerance to alcohol can also be produced by consuming ethanol while receiving nitroimidazoles, such as metronidazole, ornidazole and tinidazole [4]. A death due to an ethanol/ metronidazole interaction [42] and features of disulfiram-like reactions with ornidazole [43] have been reported. And despite the considerable number of case reports describing the association with disulfiram-like reactions secondary to metronidazole and ethanol interaction, reactions do not occur in all patients, suggesting an individual susceptibility [44]. Besides, the mechanism by which metronidazole induces intolerance to alcohol remains unclear [45]. However, clear advice to abstain from alcohol is warranted when metronidazole or its congeners are prescribed [43].

Disulfiram-like reactions have been reported in patients who consume alcoholic beverages while being treated with furazolidone [46,47]. The inhibition of the activity of aldehyde dehydrogenase by furazolidone and chloramphenicol in rats has been shown [5,48].

### Disulfiram-like reactions with dermatological preparations

There are some reports of onset of disulfiram-like reactions related to topical administration. When combined with ethanol, tacrolimus and pimecrolimus, cream and ointment, respectively, may cause erythematous flushing even after consuming a small amount of beer or wine [6,49-51]. Patients with vitiligo of the face, treated with topical tacrolimus or pimecrolimus, experienced itching and burning, followed by flushing erythematous, 5-10 minutes after ingestion of alcoholic beverages. Reactions were not limited to the treated areas, spreading to healthy skin, but regressed in 20-30 minutes. After discontinuation of treatment, alcohol ingestion did not elicit these symptoms [6].

Sulfiram, a drug applied topically to treat scabies, also causes disulfiram-like reactions when coadministered with alcohol [6,52-54]. Although sulfiram is a weak inhibitor of aldehyde dehydrogenase *in vitro*, it is photoconverted to disulfiram, which may explain the adverse reaction to ethanol after sulfiram topical therapy [54].

### Other disulfiram-like reactions inducers

Disulfiram-like reactions have also been reported with concomitant use of chlorpropamide and alcohol [7,55,56]. Chlorpropamide decrease the activity of aldehyde dehydrogenase [48].

The antiandrogen nilutamide has been associated with alcohol intolerance that takes the form of a slight disulfiram-like reactions, with hot flashes and skin rash being the main symptoms [8,57,58]. The mechanism by which alcohol intolerance occurs is unknown and although it rarely leads to withdrawal of nilutamide, it may reduce compliance [57].

Abacavir may also act as an inhibitor of alcohol dehydrogenase, which raises the possibility of disulfiram-like reactions or reduced alcohol tolerance [59].

## Medicines and other products containing alcohol

Disulfiram-like reactions are also observed in some individuals after the simultaneous use of medicinal elixirs and antibacterial drugs which are common pediatric medicines (maxolactam, metronidazole, sulfonamides, chloramphenicol, cefamandole) [1,60-62].

The antiviral liquid formulation of lopinavir/ritonavir contains 42.4% ethanol and should not be combined with drugs capable of producing disulfiram-like reactions [63].

When medications that produce disulfiram-like reactions are prescribed or dispensed, patients should be instructed to avoid medicines and other products containing alcohol, such as syrups, fermented vinegar, sauces and lotions. Medicinal products containing ethanol, as elixirs, have been implicated in some cases of acetaldehyde syndrome [36,62].

## Period of abstinence from alcohol

Although in some cases, ethanol intolerance disappears after the end of treatment, certain drugs require a period of abstinence from alcohol even after the end of treatment, such as disulfiram, which irreversibly inhibits aldehyde dehydrogenase. Enzyme replacement depends on new synthesis, which may take several days [63].

According to Food and Drug Administration (FDA) draft guidance and leaflets, patients should avoid alcohol 12 hours before taking disulfiram, during treatment and until 14 days after completion. For sulfiram, alcohol should be avoided 48 hours before and after treatment.

As cyanamide (carbimide) may block a different isoform of liver acetaldehyde dehydrogenase than disulfiram, the alcohol reaction can occur up to 36 hours after treatment, which is much shorter than the duration of action of disulfiram [64].

When using metronidazole, the consumption of alcohol should be avoided by patients during treatment and until 24 hours after completion. For tinidazole, during treatment and until 72 hours, and for furazolidone and secnidazole, during treatment and until 96 hours after completion.

## Management of disulfiram and disulfiram-like reactions

For severe hypotension resulting from a disulfiram-ethanol reaction, adrenaline or noradrenaline have been employed as the pressor agent of choice [11,13]. In a patient with generalized flushing, tremor, and refractive hypotension after ingestion of alcohol 18 hours after disulfiram treatment, initial volume resuscitation and dopamine infusion failed to restore the blood pressure, and noradrenaline was required. Indeed, disulfiram inhibits dopamine  $\beta$ -hydroxylase, an enzyme that converts dopamine to norepinephrine, which results in reduced levels of norepinephrine. Use of adrenaline or noradrenaline as drugs of choice in conditions together with other therapeutic approaches leads to stabilization of hemodynamics and reversal of neurological symptoms [14,15,18,65-67].

Fomepizole is an alcohol dehydrogenase inhibitor used as a specific treatment for disulfiram-ethanol reaction [16,68]. In the cases of 20 and 47-year-old women with severe disulfiram-ethanol reaction, including tachycardia, and hypotension, antihistamines, steroids, and normal saline were given without improvement. In both cases, fomepizole 15 mg/kg was given with improvement, blood pressure and heart rate normalized, and they had no further sequelae. Fomepizole

may be a safe and effective treatment of severe disulfiram-ethanol reaction. It is suggested that 1 dose of fomepizole for severe disulfiram-ethanol reaction with hypotension unresponsive to fluid resuscitation or for angioedema unresponsive to antihistamines be administered [68].

A 48-year-old male with severe restlessness, palpitations, facial flushing and sweating, who had taken alcohol almost 2 h after taking ornidazole, was managed with oxygen inhalation, intravenous fluids and oral diazepam for relieving anxiety, with improvement of symptoms improved within 2 h [43].

## Conclusion

In many parts of the world, consumption of alcoholic beverages is common in social gatherings and about 16.0% of drinkers aged 15 years or older engage in heavy episodic drinking [69]. According to a survey on patterns of alcohol consumption in the Brazilian population, in 2007, 52% of subjects drink at least once a year. Of these, 60% of men and 33% of women reported having used large quantities, i.e. five drinks per occasion, in the last year preceding the survey. Of the male population, 28% reported consuming alcohol 1-4 times per week and 11%, all day [70]. And according to the Brazilian Ministry of Health, the proportion of individuals declaring heavy alcohol consumption in Brazil is growing, having jumped from 16.2% in 2006 to 18.9% of the population in 2009.

Taking into account several factors, such as high rate of alcohol consumption, the use of pharmaceutical products containing alcohol and alcohol-medication interactions, it is essential that doctors, nurses and pharmacists, at the time of prescribing, dispensing and administration of drugs that induce disulfiram-like reactions, should instruct patients to avoid alcoholic beverages and products containing alcohol. All products described as possible inducers of disulfiram-like reactions **should provide clear warnings** regarding the risk of acetaldehyde syndrome.

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