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CASE REPORT

Disulfiram-like effect and serotoninergic syndrome in a patient treated with Cotrimoxazole: a case report

Efecto disulfiram y síndrome serotoninérgico en paciente con tratamiento con Cotrimoxazol, presentación de un caso

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ABSTRACT

Introduction: the disulfiram-like effect from cotrimoxazole is an adverse reaction characterized by ethanol intolerance manifested through autonomic symptoms. Although scientific evidence supporting this specific interaction is limited, its widespread clinical use increases the risk of concomitant alcohol exposure.
Case presentation: a 42-year-old male on his third day of cotrimoxazole treatment presented with a throbbing headache, intense flushing, tachycardia (118 bpm), and hypotension (95/60 mmHg) one hour after consuming alcohol. He was managed in the emergency department with fluid therapy and symptomatic support, achieving full symptom resolution within six hours.
Conclusions: this case illustrates a relevant interaction requiring timely clinical diagnosis. Recent research suggests the underlying mechanism might be related to serotonin syndrome rather than acetaldehyde accumulation. It is essential to instruct patients on strict alcohol abstinence until 72 hours after completing treatment.

Keywords: Cotrimoxazole; Disulfiram-like Effect; Ethanol; Serotonin Syndrome; Drug Interactions.

RESUMEN

Introducción: el efecto tipo disulfiram por cotrimoxazol es una reacción adversa caracterizada por intolerancia al etanol que se manifiesta con síntomas neurovegetativos. Aunque la evidencia científica que respalda esta interacción específica es limitada, su amplio uso clínico aumenta el riesgo de exposición concomitante al alcohol.
Presentación del caso: paciente masculino de 42 años en su tercer día de tratamiento con cotrimoxazol que presentó cefalea pulsátil, rubefacción intensa, taquicardia (118 lpm) e hipotensión (95/60 mmHg) una hora después de ingerir alcohol. Fue manejado en urgencias con fluidoterapia y soporte sintomático, logrando la remisión completa de los síntomas en seis horas.
Conclusiones: el caso ilustra una interacción relevante que requiere un diagnóstico clínico oportuno. Investigaciones recientes sugieren que el mecanismo subyacente podría estar relacionado con un síndrome serotoninérgico más que con la acumulación de acetaldehído. Es fundamental instruir a los pacientes sobre la abstinencia estricta de alcohol hasta 72 horas después de finalizar el tratamiento.

Palabras clave: Cotrimoxazol; Efecto Disulfiram; Etanol; Síndrome Serotoninérgico; Interacciones Farmacológicas.

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INTRODUCTION

Disulfiram-like effects are pharmacological adverse reactions characterized by ethanol intolerance, which manifests as symptoms such as facial flushing, sweating, palpitations, shortness of breath, nausea, vomiting, tachycardia, and hypotension, all of which typically appear within minutes of alcohol consumption. Traditionally, this phenomenon has been attributed to the accumulation of acetaldehyde in the blood due to the inhibition of hepatic aldehyde dehydrogenases. Although disulfiram is the prototypical agent that produces this reaction, various commonly used drugs, including cotrimoxazole (sulfamethoxazole-trimethoprim), known as sulfaprim in several Latin American countries, have been shown to cause similar effects.[1,2,3]

Cotrimoxazole is among the most widely prescribed antimicrobials worldwide for the treatment of urinary tract infections, acute otitis media, chronic bronchitis, shigellosis, Pneumocystis jirovecii pneumonia, and traveler diarrhea. Its widespread use in clinical practice, both in hospital and outpatient settings, increases the likelihood of concomitant exposure to alcohol among patients receiving this treatment. However, evidence of disulfiram-like reactions associated with cotrimoxazole has been limited, and a recent systematic review by the U.S. National Institute on Alcohol Abuse and Alcoholism revealed that although these reactions have been associated with trimethoprim-sulfamethoxazole, the evidence supporting them is limited.[4]

The exact incidence of the disulfiram-like effect associated with cotrimoxazole has not been precisely established in large-scale epidemiological studies. Sulfonamides in general are associated with adverse reactions in approximately 3 % of treatment courses, with skin reactions being the most frequent.(However, the specific frequency of disulfiram-like reactions with cotrimoxazole remains underreported, likely because of a lack of clinical recognition of this drug–alcohol interaction and the absence of pharmacovigilance systems specific to this type of event. Sulfonamides represent the second most commonly reported drug allergy in electronic health records, underscoring the clinical importance of understanding all adverse reactions associated with this drug class.[5]

With respect to the dose of alcohol that could trigger this reaction, the medical literature does not specify exact amounts. In the case of true disulfiram, symptoms typically begin between 5 and 15 minutes after ethanol ingestion in patients who have taken the medication between 3 and 123 hours prior. However, specifically for cotrimoxazole, there are no published data establishing the alcohol dose thresholds required to provoke symptoms. This lack of quantitative information reflects the general scarcity of clinical evidence regarding this interaction.[6]

With respect to risk factors, no specific populations with increased susceptibility to this reaction to cotrimoxazole have been identified. The literature does not mention factors such as advanced age, impaired liver function, polypharmacy, or genetic variants that might predispose patients to this interaction. This lack of characterization of risk factors contrasts with other well-documented adverse reactions to cotrimoxazole, such as severe skin reactions or myelosuppression, which are particularly common in HIV-positive patients, where adverse reaction rates range from 20 % to 85 %.[7]

Cotrimoxazole, like other antimicrobials associated with disulfiram-like reactions, acts by inhibiting hepatic aldehyde dehydrogenase, resulting in the accumulation of acetaldehyde in the blood following alcohol consumption. This accumulation of acetaldehyde produces the characteristic symptoms of facial flushing, sweating, palpitations, dyspnea, hyperventilation, tachycardia, hypotension, nausea, vomiting, and drowsiness.[7]

The aim of this article is to describe a case of a disulfiram-like reaction in a patient treated with cotrimoxazole and analyze the clinical and therapeutic aspects.

CASE REPORT

A 42-year-old white male from a rural area, with no significant medical history except for sporadic episodes of dyspepsia, presented to the emergency department complaining of the sudden onset of severe throbbing headache, intense facial flushing, palpitations, nausea, and two episodes of vomiting of food. The patient was on his third day of outpatien y treatment with cotrimoxazole (160 mg of trimethoprim/800 mg of sulfamethoxazole every 12 hours), which was prescribed for acute bacterial prostatitis.

During the interview, the patient admitted to attending a social gathering approximately half an hour after taking the second daily dose of cotrimoxazole (in the late afternoon or early evening) and one hour before the onset of symptoms, where he reported drinking two glasses of rum (approximately 500 ml in total). He denied recreational drug use, the intake of other medications, or a history of known drug allergies.

On physical examination upon admission, the patient appeared anxious and diaphoretic. His vital signs revealed marked tachycardia, with a heart rate of 118 beats per minute; mild hypotension, with a blood pressure of 95/60 mmHg; a respiratory rate of 22 breaths per minute; and an oxygen saturation of 98 % on room air. Notably, intense flushing affected the face, neck, and upper chest. Cardiopulmonary auscultation was rhythmic and without murmurs, and the abdomen was soft, depressible, and without signs of peritoneal irritation, although with increased hydroaerial sounds. Neurological examination revealed the presence of clonus, hyperreflexia, and generalized muscle rigidity, suggesting a significant autonomic response and neuromuscular irritability.

The results of emergency laboratory tests, which included a complete blood count, a basic metabolic panel, and markers of myocardial damage, were within normal limits, ruling out an acute cardiovascular event or severe electrolyte disturbances. An electrocardiogram showed sinus tachycardia with no abnormalities in the ST segment or T wave.

Unlike standard emergency protocols, specific measurements were also performed to confirm the interaction and rule out secondary damage:

1. Acetaldehyde and Serotonin Profile:
    - Serum Acetaldehyde: Elevated (148 µmol/L; normal: < 2 µmol/L), confirming inhibition of the aldehyde dehydrogenase enzyme.
    - Plasma serotonin concentration was 160 ng/mL (normal range: 50–200 ng/mL), which allowed us to rule out

primary serotonergic e syndrome despite the neuromuscular symptoms.

2. Ruling out Type 2 Myocardial Infarction:
    - Serial troponin I measurements (0, 3, and 6 hours) were performed, with results of <0,01 ng/mL, 0,01 ng/mL, and 0,01 ng/mL, respectively, ruling out myocardial damage due to hypotension and tachycardia.

3. Liver Function:
    - AST: 22 U/L, ALT: 25 U/L, GGT: 30 U/L, total bilirubin: 0,9 mg/dL. Normal values confirm that there was no preexisting liver disease altering drug metabolism.

To determine the relationship between the drug and the clinical event, the Naranjo algorithm was applied, yielding a score of 5 points (probable) as follows:

- Existence of previous reports of the interaction (+1).
- Onset of the event after administration of the suspected drug (+2).
- Improvement following discontinuation of the drug/alcohol (+1).
- Absence of confirmed alternative causes (+1).

Given the clinical suspicion of a disulfiram-like reaction induced by the interaction between sulfamethoxazole and ethanol, management was primarily supportive. A peripheral intravenous line was established for fluid therapy with 0,9 % saline solution (1000 ml as an initial bolus) to correct hypotension and facilitate the elimination of toxic metabolites. Intravenous ondansetron (4 mg over one minute) was administered to control emetic symptoms.

The patient was kept under close observation in the emergency department. Over the next three hours, the autonomic symptoms and flushing gradually subsided. His heart rate stabilized at 78 beats per minute, and his blood pressure rose to 115/75 mmHg. After six hours of monitoring and once he was asymptomatic, the patient was discharged with strict instructions to abstain from alcohol consumption for the remainder of the cotrimoxazole treatment and for 72 hours after its completion.

This case report was prepared in accordance with the ethical principles established in the Declaration of Helsinki for medical research in human subjects. The patient provided written informed consent, authorizing the publication of his clinical information and laboratory results for academic and scientific purposes, with the goal of protecting his identity and ensuring the confidentiality of his personal data. Furthermore, the protocol for this study was reviewed and approved by the Ethics Committee of the Faculty of Medicine at the University of Medical Sciences of Villa Clara.

DISCUSSION

The case presented illustrates a drug-induced adverse reaction characterized by the sudden onset of severe autonomic symptoms following alcohol consumption in a patient being treated with cotrimoxazole. The observed clinical picture, which includes severe throbbing headache, intense facial flushing, palpitations, tachycardia, mild hypotension, nausea, and vomiting, together with the clear temporal relationship between alcohol consumption and the onset of symptoms, strongly suggests an adverse reaction induced by the interaction between sulfamethoxazole-trimethoprim and ethanol.(

Recent guidelines from the U.S. National Institute on Alcohol Abuse and Alcoholism, published in 2025, explicitly state that although disulfiram-like reactions have been associated with metronidazole and trimethoprim-sulfamethoxazole, the evidence supporting them is limited, in contrast to the stronger evidence that exists for certain cephalosporins containing specific side chains such as methylthio-tetrazole or methylthio-dioxotriazine rings.[6]

The mechanism traditionally proposed to explain disulfiram-like reactions with cotrimoxazole is the inhibition of hepatic aldehyde dehydrogenases, resulting in the accumulation of acetaldehyde in the blood following alcohol intake. Acetaldehyde is a toxic metabolite of ethanol that, when it accumulates, produces the characteristic symptoms of flushing, tachycardia, hypotension, nausea, and vomiting. However, recent experimental research has fundamentally challenged this hypothesis. An experimental study in rats demonstrated that, unlike disulfiram, cefamandole, and procarbazine, cotrimoxazole does not increase blood acetaldehyde levels following ethanol administration. Instead, cotrimoxazole significantly increased the levels of cerebral serotonin, suggesting that the underlying mechanism might be a toxic serotonin syndrome rather than a true acetaldehyde-mediated disulfiram-like reaction.[7]

A particularly striking feature of this case is the presence of clonus, hyperreflexia, and generalized muscle rigidity. These neuromuscular findings are not characteristic of a classic disulfiram reaction, whose symptoms are predominantly autonomic and gastrointestinal (flushing, tachycardia, hypotension, nausea, vomiting). In contrast, the triad of neuromuscular excitability (clonus, hyperreflexia, rigidity), autonomic dysfunction (tachycardia, hypotension, diaphoresis), and gastrointestinal symptoms (nausea, vomiting, increased bowel sounds) is precisely the clinical constellation of serotonin syndrome.[8]

The patient presented with all the characteristics of classic serotonin syndrome, such as hyperreflexia and clonus, and the presence of tachycardia, hypotension, diaphoresis, agitation, and gastrointestinal symptoms was consistent with a mild form of serotonin toxicity. Ethanol also has well-established effects on brain serotonin, and the combination of cotrimoxazole and alcohol could have resulted in serotonergic hyperstimulation that produced the observed symptoms. Cases reported in the literature have documented the development of serotonin syndrome following alcohol intake in patients treated with serotonergic agents, supporting the plausibility of this mechanism.[9,10]

To determine the likelihood of serotonin syndrome (SS) in this patient, Hunter's toxicity criteria were applied, which are the clinical gold standard because of their high sensitivity (84 %) and specificity (97 %). Unlike other systems, Hunter's algorithm is a series of "if/then" decision rules based purely on physical examination.[11]

Table 1. Serotonin syndrome criteria assessment

Decision Rule	Patient Finding	Does it meet the criteria?
Spontaneous clonus?	Not described (reported as exhaustible/ inducible).	No
Inducible clonus + Agitation OR Diaphoresis?	Yes. Bilateral clonus + diaphoresis/ anxiety.	YES
Ocular clonus + Agitation OR Diaphoresis?	Not examined/Not described.	-
Tremor + Hyperreflexia?	Yes. Generalized hyperreflexia (+++/++++).	YES
Hypertonia + Temp > 38°C + Clonus (ocular/inducible)?	Neck stiffness present, but no fever reported.	No

According to the algorithm, the presence of inducible clonus associated with diaphoresis or agitation is sufficient to establish a clinical diagnosis of serotonin syndrome. Results: Positive for serotonin syndrome. The diagnostic probability is high according to Hunter's criteria.[11]

The reported plasma serotonin concentration (160 ng/mL) was within the normal range (50–200 ng/mL), which may rule out serotonin syndrome. However, peripheral plasma serotonin levels do not adequately reflect brain serotonin levels, which is where the relevant abnormality is thought to occur. The diagnostic criteria for serotonin syndrome are clinical and not based on serum serotonin levels.[7]

The differential diagnosis in this case must consider several clinical entities. First, an acute cardiovascular event, particularly acute coronary syndrome, must be ruled out in any patient who presents with severe headache, palpitations, diaphoresis, and hemodynamic abnormalities. An electrocardiogram, which revealed only sinus tachycardia without ST-segment or T-wave changes, along with normal cardiac injury markers, makes this possibility unlikely.(Serial troponin I levels (at 0, 3, and 6 hours) <0,01 ng/ mL, 0,01 ng/mL, and 0,01 ng/mL, respectively, ruled out myocardial damage due to hypotension and tachycardia.[8]

Second, alcohol withdrawal syndrome should be considered, although the moderate amount of alcohol consumed and the absence of a history of chronic alcohol use make this possibility unlikely. Alcohol withdrawal syndrome is characterized by autonomic hyperactivity manifesting as tremor, tachycardia, sweating, nausea, and vomiting and may occur within the first 24 hours of abstinence. However, the patient consumed alcohol rather than abstaining, which rules out this diagnosis.[12,13]

Third, party heart syndrome, characterized by cardiac arrhythmias, particularly atrial fibrillation, occurring after excessive alcohol consumption, should be considered. Binge-drinking heart syndrome was first described in 24 patients hospitalized with atrial fibrillation following excessive alcohol consumption over the weekend. Although many of these patients develop atrial fibrillation at the time of intoxication, others may present 12 to 36 hours later. However, the electrocardiogram showed sinus rhythm, ruling out this possibility.[14]

Fourth, anaphylactic or anaphylactoid reactions to red wine should be considered, although the absence of urticaria, angioedema, bronchospasm, or significant respiratory compromise makes this diagnosis unlikely. Finally, acute alcohol intoxication should be considered, but the moderate amount of alcohol consumed makes this possibility unlikely.[15]

The clinical management implemented in this case was appropriate and consistent with current recommendations for the treatment of disulfiram-like reactions and mild serotonin syndrome. Management of serotonin syndrome involves the elimination of precipitating agents, the provision of supportive care, control of agitation, control of autonomic instability, and control of hyperthermia. Many cases of serotonin syndrome typically resolve within 24 hours after the initiation of therapy and the discontinuation of serotonergic drugs, although symptoms may persist in patients taking drugs with prolonged elimination half-lives, active metabolites, or a prolonged duration of action.[11]

The intensity of therapy depends on the severity of the condition. Mild cases, such as the one that presented with hyperreflexia and tremor but without fever, can generally be managed with supportive care, discontinuation of the precipitating drugs, and treatment with benzodiazepines. Control of agitation with benzodiazepines is essential in the management of serotonin syndrome, regardless of its severity. Benzodiazepines improve survival in animal models and attenuate the hyperadrenergic component of the syndrome. Intravenous fluid therapy with 0,9 % saline was appropriate to correct hypotension and facilitate the elimination of metabolites.[15]

Cotrimoxazole has elimination half-lives of approximately 10 hours for sulfamethoxazole and 8 to 10 hours for trimethoprim, with detectable levels present in the blood up to 24 hours after drug administration. This finding explains why the patient required several hours of observation before symptoms completely resolved. The peak plasma levels of the individual components occurred 1 to 4 hours after oral administration. During the administration of 800 mg of sulfamethoxazole and 160 mg of trimethoprim twice daily, the mean steady-state plasma concentration of trimethoprim was 1,72 µg/mL, and the mean steady-state plasma concentrations of free and total sulfamethoxazole were 57,4 µg/mL and 68,0 µg/mL, respectively. These steady-state levels were reached after three

days of drug administration.[16]

Ondansetron is a selective serotonin 5-HT$_3$ receptor antagonist widely used as a first-line antiemetic in emergency departments because of its favorable safety profile: it does not cause significant sedation or extrapyramidal reactions (akathisia, dystonia), unlike alternatives such as metoclopramide, prochlorperazine, or promethazine. In the emergency department setting, it is the most commonly prescribed antiemetic in the United States, with more than 21,7 million annual uses. The dose administered in this case (4 mg IV) is standard and appropriate.[17]

From the perspective of a classic disulfiram-like reaction—mediated by acetaldehyde accumulation—ondansetron is a logical and safe choice for controlling nausea and vomiting, as it acts by blocking 5-HT$_3$ receptors both in the chemoreceptor trigger zone of the area postrema and in the gastrointestinal vagal afferents, without interacting with the acetaldehyde metabolic pathway. As a 5-HT$_3$ antagonist, ondansetron may have exerted a dual therapeutic effect: not only controlling vomiting but also partially attenuating the underlying serotonergic hyperactivity. In fact, ondansetron has been investigated as a modulator of the serotonergic system in the context of alcohol use disorder, where it acts by regulating the severity of consumption through this system.[13,18]

The recommendation to abstain from alcohol consumption for the remainder of treatment with cotrimoxazole and for up to 72 hours after discontinuation is prudent, although it is not specifically supported by high-quality evidence in the literature. This recommendation is based on the pharmacokinetics of cotrimoxazole, which shows that detectable amounts of the drug remain in the blood for up to 24 hours after administration, and on the precautionary principle to prevent a recurrence of the adverse reaction. However, it is important to recognize that the FDA label for cotrimoxazole does not include specific warnings about interactions with alcohol, reflecting uncertainty regarding the frequency and severity of these interactions.[16]

A comprehensive review of the literature reveals very few documented reports of this interaction (approximately 4 classic cases worldwide, including those by Heelon and White in 1998, who described a reaction characterized by flushing, palpitations, and dyspnea following beer consumption). Below is a comparative table between our patient and the typical findings of the limited published cases:[19]

Table 2. Comparison of the current case against previously reported cases

Characteristic	Previously published cases in the literature	Current case
Demographic Profile	Young to middle-aged adults	42 years old, Male
Drug involved	Trimethoprim/Sulfamethoxazole (standard dose)	Cotrimoxazole 800/160 mg every 12 hours
Alcohol intake	Variable (ranging from 1 beer to moderate amounts)	500 mL of rum (very high volume)
Latency of symptoms	15 to 30 minutes after alcohol consumption	60 minutes after alcohol consumption
Symptoms	Flushing, palpitations, shortness of breath, nausea, hypotension	Flushing, tachycardia, vomiting, hypotension
Treatment and prognosis	Supportive care, resolution within a few hours	Fluid therapy, resolution within 6 hours

Another critical point to discuss, one rarely addressed in the literature on these interactions, is the dose–response curve. The patient consumed 500 mL of rum within an hour. Assuming that the rum has a standard alcohol content of 40 %, the patient ingested approximately 200 mL of pure alcohol. This amount represents a massive dose that, on its own, can induce acute autonomic toxicity, vomiting, and hypotension in healthy subjects, making it difficult to discern where pure alcohol intoxication ends and where the drug interaction begins.[7]

CONCLUSIONS

The present case confirms that the disulfiram-like effect is a tangible and relevant clinical complication in patients treated with cotrimoxazole who consume alcohol, as evidenced by the sudden onset of flushing, tachycardia, and hypotension following ethanol ingestion. Although this syndrome is traditionally attributed to acetaldehyde accumulation, the presence of clonus and hyperreflexia in the patient suggests that the pathophysiology may involve mild serotonin syndrome, meeting Hunter's toxicity criteria.

A thorough differential diagnosis was performed, allowing us to rule out cardiovascular events via electrocardiography and serial troponin measurements, which validated the pharmacological nature of the reaction. Management based on fluid therapy and symptomatic support with ondansetron proved effective, achieving complete remission of symptoms within six hours and reinforcing the causal relationship of the event. Given the complexity of this interaction, it is imperative that prescribers instruct patients to strictly abstain from alcohol during treatment and for up to 72 hours after its completion to prevent avoidable harm.

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CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

AUTHORSHIP CONTRIBUTION

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