Ingestion of minoxidil associated with elevated transaminases in the absence of ischemic hepatitis

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Abstract

Minoxidil is a direct-acting vasodilator that induces relaxation of the vascular endothelium, and historically, it has been used as an antihypertensive agent. It caused hypertrichosis, resulting in its typical use today as an alopecia treatment. Toxicity is characterized by hypotension and tachycardia, often requiring treatment with α-adrenergic agonists. A previously healthy 18-year-old woman presented to the emergency department three hours after ingesting 60 mL of 5% W/V topical minoxidil solution. Initial vitals included sinus tachycardia at 117 beats per minute and a blood pressure of 92/44 mmHg. Laboratory analyses performed three hours post-ingestion revealed elevated aspartate and alanine aminotransferases (224 and 384 IU/L, respectively). Acetaminophen and ethanol concentrations were undetectable. Isotonic crystalloid, N-acetylcysteine, phenylephrine, and midodrine were administered. She developed pulmonary edema, requiring diuresis and supplemental oxygen *via* a nasal cannula. She was discharged 108 hours post-ingestion after a full recovery. Minoxidil toxicity may be an uncommon etiology of abnormal transaminase concentrations.

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Introduction

Minoxidil is a direct-acting vasodilator that causes smooth muscle relaxation of the vascular endothelium.[1] Historically, it was used to treat refractory hypertension, though it is more commonly used today in a topical formulation to treat androgenic alopecia. Toxicity is characterized by hypotension and reflex tachycardia, often requiring treatment with α-adrenergic agonists including phenylephrine, norepinephrine, and midodrine.[2-4] Cardiac ischemia and renal injury are rarely reported,[5,6] but to our knowledge, abnormal transaminase concentrations or other evidence of hepatotoxicity after acute overdose have not been reported. We present a case of oral ingestion of topical minoxidil solution associated with elevated transaminase concentrations.

Case Report

An 18-year-old woman with no known chronic medical problems presented to the emergency department with a chief complaint of lightheadedness and palpitations approximately three hours after reportedly ingesting 60 mL of 5% W/V topical minoxidil solution (approximately 40 mg/kg of minoxidil) diluted in alcohol and propylene glycol. The patient denied suicidal intention and reported inadvertently consuming the minoxidil solution instead of an over-the-counter cold and influenza medicine for symptoms of rhinorrhea and nasal congestion. Initial vital signs in the emergency department were notable for sinus tachycardia at a rate of 117 beats per minute (bpm) and hypotension with a blood pressure of 92/44 mmHg. Oxygen saturation and temperature were normal. The electrocardiogram (ECG) revealed sinus tachycardia with normal axis, normal intervals, and septal and lateral ST segment depression (Figure 1). There was no prior ECG for comparison. Laboratory analyses obtained at three hours post-ingestion revealed elevated aspartate aminotransferase (AST) and

alanine aminotransferase (ALT) of 224 IU/L and 384 IU/L, respectively (Figure 2).

Bilirubin fractionation, the international normalized ratio, electrolytes, and creatinine were normal. Lactate was 3.6 mmol/L. Troponin was undetectable. Acetaminophen, ethanol, and salicylate concentrations were undetectable. Hemoglobin was 13.4 g/dL, and white blood cell count was 8.6× 10^3/mcL. Hepatitis serologies, COVID-19, influenza, and respiratory syncytial virus tests were negative. Procalcitonin was 0.11 ng/mL. The urine pregnancy test was negative. Point-of-care ultrasound showed no pericardial effusion or intraabdominal free fluid. The patient was treated with intravenous isotonic crystalloid as well as a 21-hour intravenous N-acetylcysteine protocol. After 3 L of isotonic crystalloid, the patient continued to experience sinus tachycardia to the 140s bpm and mild hypotension with a mean arterial pressure of 60 mmHg; therefore, phenylephrine continuous infusion was initiated at 25 mcg/min seven hours post-ingestion (HPI) and uptitrated over the next several hours to 100 mcg/min. Because minoxidil is expected to cause isolated vasodilation, and she was already tachycardic without evidence of decreased inotropy on point-of-care transthoracic echocardiogram, α-adrenergic agonism without concomitant β-adrenergic or dopaminergic agonism was preferred.

She became febrile with an oral maximum temperature of 38.3°C from 9 to 21 HPI. She developed pulmonary edema with bilateral crackles on auscultation of the lungs and associated hypoxemia, requiring 1-2 L of supplemental oxygen by nasal cannula from 11 to 79 HPI. Vital signs concerning interventions are displayed in Figure 3. A formal transthoracic echocardiogram performed at approximately 18 HPI revealed no pericardial effusion, normal valve structure, trace tricuspid regurgitation, normal left ventricular wall morphology and function with an ejection fraction of 70%, mild dilation of the right ventricle but with normal tricuspid annular plane systolic excursion, and plethoric inferior vena cava. The maximum phenylephrine infusion rate was 250 mcg/min at 24 HPI, then weaned off at 29 HPI. Serum lactate cleared, but troponin concentration increased, reaching a peak concentration of 0.8 ng/mL at 29 HPI. Oral midodrine was administered (5 mg every six hours) from 32 to 78 HPI. Furosemide (20 mg IV every eight hours) was administered from 59 to 83 HPI for peripheral and pulmonary edema. The patient's tachycardia and ST depression on the ECG resolved at 78 HPI. Her blood pressure and oxygen saturation normalized, and she was discharged 108 HPI.

Discussion

Ingestion of minoxidil was not confirmed by serum or urine testing for the parent compound itself or its metabolites, as these tests were not available to the investigators. However, the signs and symptoms observed within hours after reporting the minoxidil ingestion, in the absence of evidence of severe bacterial infection or cardiogenic shock and followed by relatively rapid complete recovery, are consistent with the clinical diagnosis of toxicity from acute ingestion of a direct-acting vasodilator. While hypotension and tachycardia are anticipated effects of supratherapeutic minoxidil ingestion, abnormal transaminases are somewhat uncharacteristic and have not been reported in other cases of acute overdose. Though these laboratory abnormalities were temporally associated with acute minoxidil overdose, causation cannot be confirmed, especially since both AST and ALT only decreased during admission. Though total bilirubin increased, it never exceeded the upper limit of normal, and there were no other signs or symptoms of hepatic dysfunction. There is no known direct hepatotoxic effect of minoxidil, though for patients with significant hypotension after overdose, it is possible that ischemic hepatitis can contribute to abnormal transaminase concentrations. However, ischemic hepatitis is typically characterized by significant abnormalities in transaminase concentrations and other markers of hepatic function after a period of impaired systemic blood flow.[7] In this case, the transaminases normalized despite increasing pressor requirements, and peak levels were less than 1000 IU/L, which also suggests a nonischemic etiology. This patient does not meet the generally accepted diagnostic criteria for ischemic hepatitis; thus, this was not considered a likely etiology of the observed transaminase abnormalities. The undetectable serum ethanol level, absence of clinical intoxication, and minimally elevated serum lactate are not

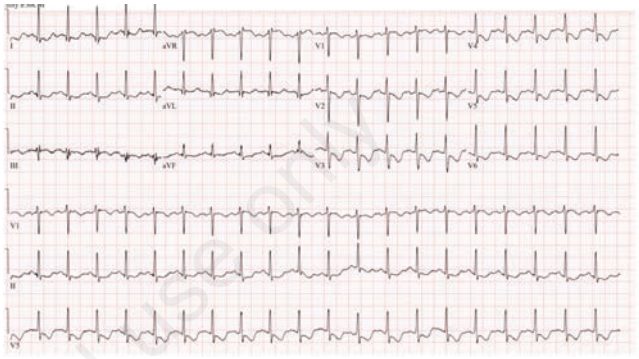

Figure 1. Electrocardiogram from three hours post-ingestion.

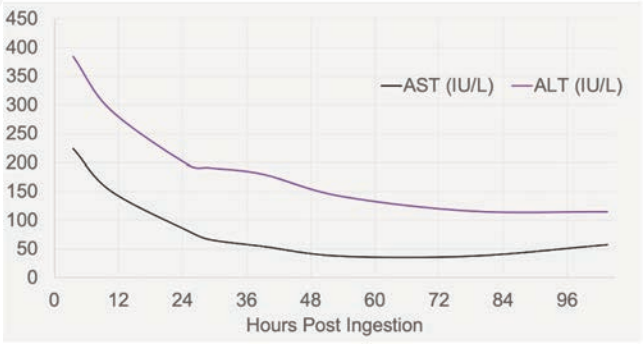

Figure 2. Aspartate (AST) and alanine aminotransferase (ALT) concentrations over time.

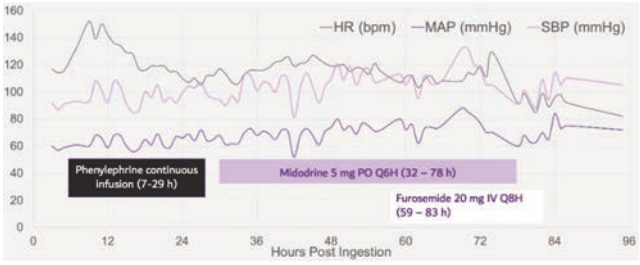

Figure 3. Vital sign trends and interventions over time. HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure.

consistent with hepatic effects from the ethanol and propylene glycol solvents in the ingested minoxidil solution.

Though uncommon, the isolated elevation in transaminase concentrations without other evidence of hepatic abnormality has previously been observed in patients using topical minoxidil chronically.[8,9] The underlying mechanism for these changes has yet to be elucidated, though minoxidil is metabolized by the liver into its active metabolite minoxidil sulfate.[5] As these patients were applying topical minoxidil percutaneously, which has limited systemic absorption, it is unclear how minoxidil may exert this effect. However, the presence of systemic symptoms that resolved after minoxidil was discontinued that were reproducible with minoxidil rechallenge, supports the hypothesis that minoxidil therapy was at least in part responsible for the observed signs and symptoms. It is unknown if the minoxidil formulations used in these cases, which were described in 1990 and 1994, contained other inactive ingredients that may have contributed to these patients' clinical courses.

Acetaminophen toxicity is a considerably more common etiology of abnormal transaminase concentrations than minoxidil toxicity. However, the serum acetaminophen concentration was undetectable at the time of presentation, and there was no history of acetaminophen exposure. This does not preclude remote acetaminophen ingestion from causing hepatic injury. Acetaminophen-protein adducts, which can be used as a marker of acetaminophen exposure detectable even when acetaminophen is no longer detectable, could not be obtained.[10] N-acetylcysteine was administered in case the cold and influenza medication taken by the patient before the minoxidil overdose, which was not identified, contained acetaminophen and had in fact caused the abnormal transaminase concentrations. Furthermore, as this patient had reported some symptoms of upper respiratory infection that preceded the overdose, it is possible that the abnormal AST and ALT were caused by a viral infection. COVID, influenza, and respiratory syncytial virus were not detected by nasopharyngeal swab testing, but a complete respiratory viral panel was not performed.

Conclusions

We present a case of moderately elevated transaminase concentrations after an acute overdose of topical minoxidil solution without any other obvious explanation for these laboratory abnormalities. While this has not been described in several previous acute overdoses, a few patients taking minoxidil chronically have developed abnormal transaminase concentrations without other etiologies. This suggests that there is a mechanism by which minoxidil can cause hepatic injury that has yet to be elucidated.

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