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A case of cardiotoxicity following intramuscular injection of tropicamide and phenylephrine ophthalmic solution in a drug-addicted young woman

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Abstract

We report the case of a 40-year-old woman with a history of an opioid use disorder who presented to our emergency department complaining of palpitations, chest pain, and headache after the intramuscular injection of an ophthalmic solution containing tropicamide and phenylephrine (Visumidriatic Phenylephrine® 100 mg/mL + 5 mg/mL, Visufarma S.p.A., Italy) a few hours earlier for a voluntary purpose. She developed cardiac toxicity with hypertension, tachycardia, and high levels of high-sensitivity cardiac troponin I, which required continuous cardiac monitoring for 48 hours with complete resolution of the cardiac damage without complications. Based on the current literature, this is the first reported case of cardiotoxicity induced by an ophthalmic solution of tropicamide and phenylephrine used intramuscularly for voluntary purposes.

Introduction

Topical tropicamide and phenylephrine is a safe and effective combination widely used for pupillary mydriasis before cataract surgery in adult patients[1] and even in children.[2] Tropicamide is a short-acting anticholinergic agent used as a mydriatic and cycloplegic, that inhibits the parasympathetic constrictor muscle of the iris, with an effect starting within 15-20 minutes after instillation and lasting for 4-6 hours. Although topical ophthalmic preparations are safe to use, they may cause side effects due to systemic absorption through the cornea, conjunctiva, and nasal mucosa through the lacrimal sac. The most common adverse reactions associated with tropicamide are local complications such as conjunctivitis, blepharitis, and itching; however, systemic complications such as nausea, headache, shock, and anaphylaxis have also been reported.[3,4] The risk of systemic adverse reactions may be reduced by using a small drop size.[5] Tropicamide fails to give good pupillary dilatation when used alone, especially in patients with diabetes mellitus,

dark-pigmented irides, and in the elderly, but if combined with phenylephrine, it can promptly induce maximal mydriasis resistant to the intense light of the operating microscope.

Phenylephrine is a direct-acting sympathomimetic agent used topically in the eye as a mydriatic, available in concentrations up to 10%. In the literature, many reports suggest a systemic absorption of this agent as a source of severe adverse drug reactions, including severe hypertension and the onset of arrhythmias, all explainable by the alfa1-adrenergic action of phenylephrine.[6-11] These complications and pulmonary edema have also been reported in children with an incidence of 2.1%.[4] For these reasons, patients should always be monitored during surgery and for a few hours after surgery to prevent and promptly treat adverse reactions to phenylephrine. In addition, multiple and frequent instillations of drops should be avoided to prevent any cumulative dosage effect in the blood due to systemic absorption.[1]

We herein report the case of a woman who developed cardiac toxicity after an intramuscular injection of 2.5 mL of an ophthalmic solution containing tropicamide and phenylephrine (Visumidriatic Phenylephrine® 100 mg/mL + 5 mg/mL, Visufarma S.p.A., Italy). To the best of our knowledge, this is the first reported case of cardiotoxicity induced by an ophthalmic formulation of tropicamide and phenylephrine used intramuscularly for voluntary purposes.

Case report

A 40-year-old woman presented to our emergency department complaining of chest pain, palpitations, and headache after the voluntary intramuscular (left deltoid) administration of 2.5 mL of ophthalmic solution containing tropicamide and phenylephrine (Visumidriatic Phenylephrine® 100 mg/mL + 5 mg/mL, Visufarma S.p.A., Italy) a few hours earlier for a voluntary purpose. She also reported pain at the injection site. The patient had a diagnosis of opioid use disorder treated with methadone (85 mg daily) and alprazolam (1 mg 3 times a day), and she was regularly followed in the drug and alcohol treatment outpatient clinic of our hospital. She used to inject tropicamide ophthalmic solution (Visumidriatic®) intramuscularly to achieve loss of contact with reality and altered thinking, as known side effects due to the muscarinic blocking activity of tropicamide.[12] She had never used the combined solution of tropicamide and phenylephrine before. On admission, physical examination resulted normal. No signs of infection were observed around the injection site. The body temperature was 36.5 ºC, blood pressure 160/90 mmHg, pulse 110/min regular, respiratory rate 16/min, and pulse oximetry 97%. The electrocardiogram (ECG) showed sinus tachycardia with normal P-R interval, QRS complex, and QTc. Bedside ultrasound documented an

A-line pattern without pleural effusion and excluded the bladder globe. Echocardiography showed a normal cardiac ejection fraction (55%) with mild mitral insufficiency and no pericardial effusion.

Laboratory data showed leucocytosis (28.470/mm^3, normal range 4.000-10.000) with neutrophilia (23.430/mm^3) and slightly increased C-reactive protein (1.33 mg/dL, normal range <0.5), significantly increased values of high-sensitivity cardiac troponin I (hsTnI) (279.8 ng/L, normal value <12; Beckman coulter). Coagulation times, renal function, and serum electrolytes were all in the normal range.

We consulted the Pavia Poison Control Center, which confirmed the diagnosis of drug-induced cardiac damage and indicated the following recommendations: continuous ECG monitoring for 48 hours; repeat hsTnI; administration of benzodiazepines in case of agitation and/or hallucinations; monitoring of diuresis and alvus for the appearance of signs of urinary retention and constipation; and antibiotics in case of signs of infection at the injection site and/or fever.

The patient was hydrated with 0.9% 1000 mL of sodium chloride intravenously (iv) and treated with Delorazepam 2 mg iv for agitation. We repeated the hsTnI assay at 3 and 6 hours, which was 1162 ng/L and 1124 ng/L, respectively, in the absence of chest pain, shortness of breath, and bedside ultrasound, ECG, and echocardiographic changes. Blood pressure returned to normal. On the day following her admission, the patient was completely asymptomatic. Blood tests were repeated and showed normal full blood count and C-reactive protein. Second-level toxicological tests were performed by the Clinical Chemistry Laboratory Unit, Specialized Section of Toxicology, IRCCS Policlinico San Matteo Foundation in Pavia, and revealed the presence of tropicamide in the patient's urine (GC-MS method).

After a 48-hour observation time in our emergency department observation unit, in the absence of clinical symptoms and with normal ECG monitoring and echocardiography, the patient was discharged with a planned cardiological follow-up and the strong recommendation to remain at rest, to avoid physical exertion, and not to use Visumidriatic® or Visumidriatic Phenylepfrine®, and call the emergency number in the case of palpitations and/or chest pain and/or shortness of breath.

We reassessed the patient 5 days after her discharge. The patient remained asymptomatic throughout. The blood pressure and heart rate were normal. An ECG documented sinus rhythm. Echocardiography was unchanged. The hsTnI value was significantly reduced (18 ng/L). The final diagnosis was acute reversible myocardial damage due to intramuscular administration of tropicamide and phenylephrine.

Discussion and Conclusions

Tropicamide is also known as a cheap alternative to heroin in Eastern Europe and the Soviet Union,[13] and its misuse has increased over the last decade. Over the past 10 years, several cases of tropicamide abuse via intravenous injection have been reported in several countries, including Turkey, Italy, France, Tajikistan, and Kazakhstan, but also Italy.[14]

When taken in large doses, tropicamide can produce stimulant, euphoric, and hallucinogenic effects,[15] with a mechanism not completely understood but probably due to the block of the muscarinic receptor M4.1,[16] that causes a central anticholinergic syndrome with the occurrence of agitation, often with pressured speech, delirium, and visual and/or auditory hallucinations. Some patients have been seen picking at non-existent objects on their bedsheets and/or clothes, which is likely because of visual perceptual disturbances during delirium.[17] More serious effects of anticholinergic toxicity include coma, seizures, tachycardia, and cardiac arrhythmias due to QRS prolongation.[17] As reported in a recent review by Bellman *et al.*,[13] the misuse of anticholinergic eye drops has become widespread among people with intellectual disabilities and mental disorders, and it should be suspected in all patients who develop an unusual array of symptoms, that include excitability, tachycardia, hyperthermia, hallucinations, delirium, dysphoria, unconsciousness, and ‘‘open eye’’ dreams when used intravenously. An increasing number of cases of tropicamide intravenous injection have been reported in Europe, including Italy.[14] Bersani *et al.* analyzed this phenomenon, which represents a serious health risk. According to the authors, it is mainly secondary to primary opioid (especially heroin) addiction and seems to be associated with the enhancement of the 'positive' effects of heroin, the decrease and delay of heroin withdrawal symptoms, the easy availability, low costs and fast effects, and the visibility of self-reported experiences on the Internet.[18]

Phenylephrine is an alpha-1 adrenergic agonist used to treat hypotension, generally in the surgical setting associated with the use of anesthetics, dilate the pupil, and induce local vasoconstriction, depending on the route and location of administration. An intranasal formulation is used to treat congestion, and a topical formulation to treat hemorrhoids. Off-label uses include situations requiring local blood flow restriction, such as the treatment of priapism.[19] The action of phenylephrine was first described in the literature in the 1930s.[20] Phenylephrine was granted FDA approval in 1939. Ophthalmic formulations of phenylephrine act for 3-8 hours, while intravenous solutions have an effective half-life of 5 minutes and an elimination half-life of 2.5 hours.[21] Drug-induced cardiotoxicity can be observed during the administration of sympathomimetic agents, such as phenylephrine. Systemic phenylephrine acts through agonism on alpha-1 adrenergic receptors,

raising systolic and diastolic pressure as well as peripheral vascular resistance. Increased blood pressure stimulates the vagus nerve, causing reflex bradycardia and severe or fatal complications, such as myocardial infarction, coronary artery spasm, arrhythmias including AV block and ventricular extrasystoles, a hypertensive crisis with subarachnoid hemorrhage and pulmonary edema. As reported by Li *et al*., phenylephrine eye drops combined with intravenous atropine have cardiovascular effects, such as a significant heart rate and blood pressure increase, that can be reversed by neostigmine. According to the authors, this drug combination should be used carefully for ophthalmic surgery, especially in patients with cardio-cerebrovascular diseases.[22] Severe hypertension and heart rate alterations have also been reported in pediatric patients undergoing ophthalmic surgery when treated with phenylephrine eye drops.[4] Patients can also complain of gastrointestinal disorders (nausea, vomiting), chest pain and dyspnea, nervous system manifestations (headache, nervousness, paraesthesia, tremor, excitability), diaphoresis, pallor, and piloerection.[23] Overdose may be treated by supportive care and discontinuing phenylephrine, chronotropic medications, and vasodilators.[19]

Based on the current literature, no cases of intramuscular use of tropicamide and phenylephrine for voluntary purposes have been reported. Our patient used the combined ophthalmic solution instead of tropicamide alone, which caused acute cardiac damage with complete resolution in the absence of complications. It is well known that in patients with severe heart failure or cardiogenic shock, phenylephrine may cause worsening of heart failure as a consequence of induced vasoconstriction (increased afterload), but no cases of acute cardiac damage with spontaneous resolution have been reported in the literature. Our patient presented with a rise in blood pressure that did not induce pre-edema or pulmonary edema and did not require antihypertensive therapy, resolving with intravenous administration of benzodiazepines for agitation. Echocardiography excluded a diagnosis of Tako-Tsubo. In conclusion, in our patient, the mechanism of cardiac damage is therefore unclear.

This case was reported to the Pavia Poison Control Centre, which declared an alert 2 (risk of serious damage to health) according to the SNAP (Sistema Nazionale di Allerta Precoce)[24] with a strong recommendation to immediately report any further case of tropicamide and phenylephrine intoxication. We believe that other reports could contribute to a better understanding of the mechanism of cardiotoxicity with acute myocardial damage even in the absence of echocardiographic and ECG changes.

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