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Case report
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Naphazoline poisoning associated with bradycardia and persistent hypertension: Case report

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ABSTRACT

Naphazoline (NA) is an α-adrenergic agonist derived from imidazoline. Due to its vasoconstrictor action, it is widely used as a nasal decongestant with a rapid onset of action. It presents few studies on its side effects, with most case studies of accidental ingestion in children under two years of age. We report a case on the relationship between NA intoxication and symptomatic bradycardia, reversed after administration of intravenous Naloxone, in a young adult patient.

KEYWORDS: Naphazoline; Bradycardia; Naloxone.

INTRODUCTION

Naphazoline (NA) is an α-adrenergic agonist derived from imidazoline. Due to its vasoconstrictive action, it is widely used as a nasal decongestant with rapid onset of action[1]. Introduced in 1940, it presents sporadic studies, most of them as reports of isolated cases, which have warned about the risk of indiscriminate use of these medications, especially in children under two years of age[2]. NA acts on both central α-2 and peripheral α-1 receptors. Stimulation of central α-2 receptors causes decreased catecholamine secretion through a negative feedback mechanism. Stimulation of peripheral α-1 receptors primarily increases blood pressure through induced vasoconstriction.

Central α-2 agonist toxicity can occur due to acute or nonacute overdose of central α-2 agonists or misuse of topical α-1 agonists, which, when administered, stimulate α-2 receptors, often associated with intentional overdose and accidental pediatric ingestion[3]. There are few literary reports on the side effects of NA overdose, the most common

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being hypertension, hypotension, bradycardia, pallor, sweating, drowsiness, agitation, diaphoresis, hypothermia, miosis, mydriasis, which can lead to serious complications, such as respiratory depression and intense peripheral vasoconstriction[4]. Hypertension was reported in 37% of children[5]. The α agonists may lose selectivity for the target receptor when ingested or misused[3]. In overdose, there is a global depletion of catecholamines, leading to central nervous system depression, along with bradycardia and hypotension. Paradoxically, in overdose, there is also transient stimulation of peripheral α-1 receptors and postsynaptic α-2 receptors, causing a brief release of catecholamines, which leads to early and transient hypertension. The symptomatology is not necessarily dose-dependent[3].

The diagnosis of α-agonist toxicity is clinical. Central α-agonists are not detectable on standard urine drug screens, and specific drug concentrations are not routinely available[3]. There is no specific antidote for imidazoline derivatives. Therapy should be symptomatic, consisting of expansion of intravascular volume in cases of hypotension and favorable chronotropic treatment with drugs such as atropine in cases of bradycardia. In some reports, hypertension has been corrected with phentolamine. Careful observation of the neurological picture and hemodynamic status for at least 24 hours is indicated in all cases of drug exposure[5].

This report aims to demonstrate the relationship between NA intoxication and symptomatic bradycardia, reversed after intravenous (IV) naloxone administration, in a young adult patient. This study was approved by the Ethics Committee of CEP/HUGO under protocol number 85497418.2.0000.0033.

CASE REPORT

A 33-year-old female patient sought emergency care complaining of recurrent dizziness, pressure-type headache, blurred vision, and pre-syncope, also associated with sporadic palpitations. In the last week, she reported daily symptoms associated with burning retrosternal chest pain in the presence of intense headaches. On the day of treatment, she reported having measured blood pressure (BP) with a systolic BP of 160 mmHg and heart rate (HR) of 40 beats per minute (bpm). On examination, BP was 160/90 mmHg, and HR was 39 bpm. Fundus oculi without papilledema and other findings on physical examination were within normal limits.

She denies smoking or illicit drug use and has no family or personal history of coronary syndrome. She has a history of sleeve gastrectomy associated with cholecystectomy, hiatal hernia repair in 2021, and anxiety disorder. She uses contraceptives, trazodone 50 mg, and nasal naphazoline. She has lost 35 kg since the surgical procedure (body mass index from 35 to 23). She was hospitalized two months earlier for sinus bradycardia and prolonged QT (corrected QT: 516 ms), which returned to normal within 24 hours after hydration. A cranial tomography scan was performed without alterations, and an echocardiogram was within the normal range. She was referred for outpatient follow-up with an arrhythmologist. A tilt test did not reproduce symptoms, with no findings compatible with neurocardiogenic syndrome.

On admission, an electrocardiogram (ECG) showed sinus bradycardia and QT interval within normal limits (Fig. 1). Laboratory tests showed electrolytes and thyroid function within normal limits. During hospitalization, a 24-hour Holter monitoring was requested, showing sinus bradycardia with a mean of 45 bpm and a minimum of 34 bpm, without the presence of atrioventricular blocks or significant pauses (Fig. 2). An exercise test was also performed to assess the chronotropic response, with a drop in BP during exercise and symptoms of pre-syncope. The test was interrupted after BP improved, with an inappropriate increase in HR (Table 1).

Coronary angiotomography was requested to investigate any anomalous coronary artery origin, with normal results. An atropine test was performed to assess response to the parasympathetic blockade, with a positive response (Fig. 3). Immediately after the procedure, the patient developed high-intensity headache, tachycardia, and hypertension with systolic blood pressure up to 210 mmHg. A cranial magnetic resonance imaging was performed, and the case was discussed with Neurology, with suggestive findings secondary to the abrupt increase in blood pressure (Fig. 4).

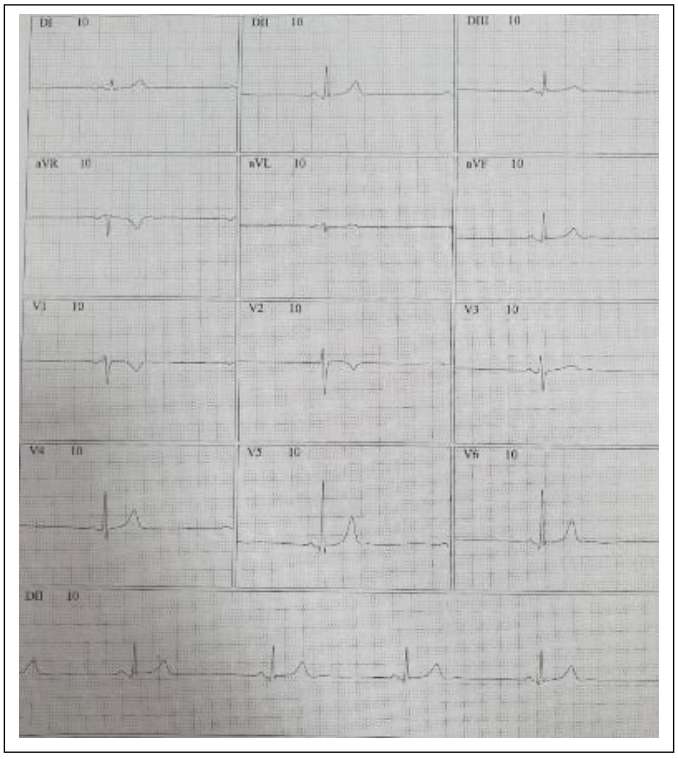

Figure 1. Admission ECG with sinus bradycardia

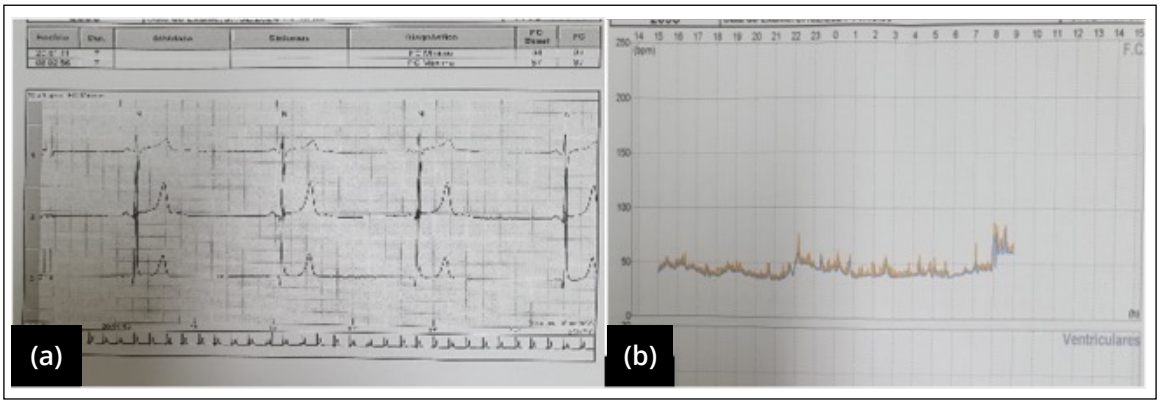

Figure 2. Holter tracings; a) Holter with sinus bradycardia; b) Average HR 45 and lowest HR 50 bpm for 16h and 25min

Table 1. Behavior of heart rate and blood pressure before, during and after the ergometric test performed by the patient

Variables analyzed	HR (bpm)	PAS (mmHg)	PAD (mmHg)
Rest	44	160	80
4th minute of effort	56	130	80
Peak effort	81	100	70
Recovery 1st minute	113	80	40
Recovery 2nd minute	86	90	60

Caption: HR: heart rate; SBP: systolic blood pressure; DBP: diastolic blood pressure; bpm: beats per minute; mmHg: millimeters of mercury.

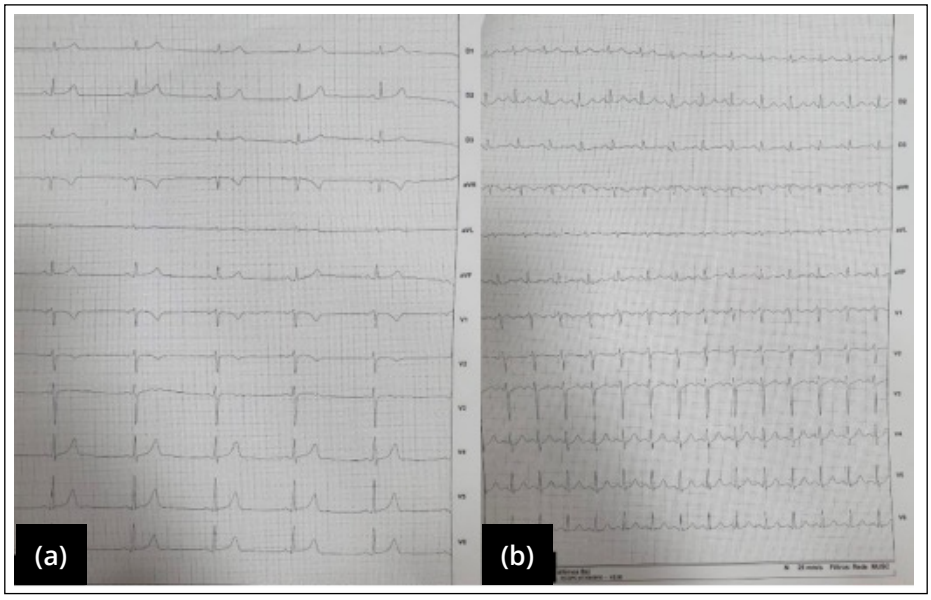

Figure 3. Positive atropine test with HR increase greater than 90 bpm in the first 15 minutes; a) Before atropine; b) After atropine

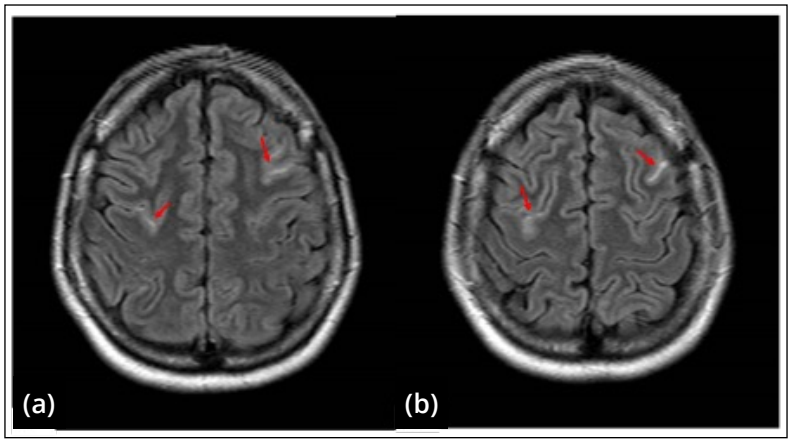

Figure 4. Skull MRI image: Presence of discrete hypersignal on FLAIR in some cortical sulci, predominating in the bilateral frontal region, as demonstrated by arrows in images (a) and (b).

During visits, excessive use of nasal NA was observed. A family member mentioned the use of two vials in three days. The case was discussed with an arrhythmologist, and the hypothesis of drug intoxication was raised. The patient was referred to the intensive care unit for observation of hypertensive conditions. According to a review of the literature and discussion with the Heart Team, it was decided to administer intravenous Naloxone (one vial) to assess the possible reversal of NA intoxication. After administration, the hypertension resolved with BP 140/80 mmHg and HR improved by approximately 100 bpm (Fig. 5).

During hospitalization in the ward, he presented symptoms of insomnia, anxiety and tachycardia. Benzodiazepines were started after the hypothesis of drug withdrawal and Ivabradine for CF control, with improvement in the condition and hospital discharge. After outpatient follow-up, he tolerated the suspension of Ivabradine and benzodiazepines with a change in anxiolytic treatment by psychiatry for escitalopram and mirtazapine.

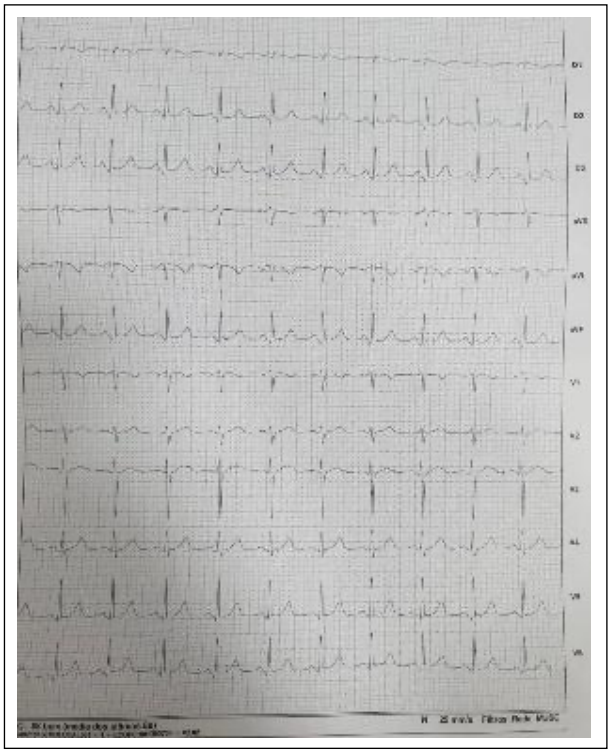

Figure 5. ECG after use of Naloxone

DISCUSSION

Naphazoline, sold since 1940, has few studies on its side effects, with most of them being case studies of accidental ingestion in children under two years of age[2]. In an analysis by the Belgian Poison Control Centre of exposure to imidazoline derivatives from 1986 to 1991, of the 261 cases, 89.6% were in children under 4. Of these, 75% were due to accidental ingestion and 25% after "therapeutic" use with nasal topicals or eye drops[2].

Imidazoline derivatives have a therapeutic effect close to side effects, which may be possible even with therapy at the appropriate dose. Due to rapid absorption, symptoms of intoxication usually develop within the first hour, peak after eight hours and disappear after approximately 12 to 36 hours[4]. Central α agonists are not detectable in standard urine drug screening and specific drug concentrations. Concentrations can be obtained through specialized laboratories but are usually not indicated and involve a mail-in process that can take days to weeks to obtain results[3]. No tests prove poisoning; therefore, the diagnosis is clinical, making it difficult to detect the possibility of the condition early. A detailed anamnesis, with questions directed at the use of medications and a physical examination with suggestive findings, is essential to raise the hypothesis of poisoning.

As observed in the clinical case described here, the patient initially presented symptoms due to drug overdose with catecholaminergic depletion by activation of presynaptic a_2-adrenergic receptors leading to bradycardia and paradoxically by stimulation of postsynaptic a_2-adrenergic receptors, induced by persistent use of NA during hospitalization because the patient had an associated hypertensive condition. The diagnosis was proposed by observing the use of medication in the hospital.

An important point that deserves to be highlighted in the present discussion involves prior bariatric surgery with subsequent significant weight loss. A controlled study observed that the reduction in body weight induced by bariatric surgery was associated with substantial changes in heart rate variability (HRV). The observed changes were consistent with an increase in parasympathetic and a reduction in sympathetic modulation of the sinus node[6]. In the case presented here, such weight loss may have been an additional component for the bradyarrhythmia presented by the patient, adding

such vagal predominance to the effects of NA. It is also worth noting that weight loss, even after a short period, determines typically favorable changes in the autonomic control mechanisms, with improved HRV6.

Unlike most cases that we have observed, which show spontaneous improvement with supportive measures between 24 and 36 hours, and 68.4% of patients are asymptomatic after 24 hours of exposure (2,3,5), the patient remained hypertensive and had bradycardia.

After a literature review reporting the possibility of using Naloxone as a reverser of the adverse effects of NA, a therapeutic test was chosen with a good response, adding to the possibility of drug therapy in refractory cases, which do not show improvement of symptoms with supportive measures.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: Dreckmann MV, Lima PF, Amaral FB, Ramos VS, Linhares M, Schulz JC, Gardenghi G; **Data analysis and interpretation:** Amaral FB, Ramos VS, Linhares M, Schulz JC; Writing: Dreckmann MV, Lima PF, Cruz E, Gardenghi G; **Critical review:** Gardenghi G; **Final approval:** Dreckmann MV, Lima PF, Cruz E, Amaral FB, Ramos VS, Linhares M, Schulz JC, Gardenghi G.

DATA AVAILABILITY STATEMENT

Not applicable.

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