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Analysis of adverse effects of nitrates and nitrites with particular emphasis on methemoglobinemia and maculopathy based on clinical cases and publicly available literature

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Abstract

Background: Nitrates are currently one of the most commonly used drug classes in medical practice. The usefulness of nitroglycerin in the treatment of coronary artery disease is invaluable. Nitrates have also been used in other cardiac, gynecological, and gastrointestinal diseases.

Aim: To draw attention to the problem of inappropriate recreational use of nitrates and nitrites by analyzing extreme cases and adverse reactions resulting from the use of these preparations.

Materials and Methods: This article is a review of the publicly available literature from recent years (including case reports) regarding nitrates, their mechanisms of action, and adverse reactions, particularly maculopathy and methemoglobinemia.

Results: Alkyl nitrites are a specific group of inhalant drugs that are readily available and legal in Poland. They have a similar mechanism of action to nitrates used in the treatment of the previously mentioned diseases, involving the supply of nitric oxide. In addition to mild reactions, adverse reactions such as dizziness and headache, may lead to maculopathy or methemoglobinemia in severe cases. Although the exact mechanism of action is unknown, it is thought to result from oxidative stress and vascular epithelium damage.

Conclusions: The widespread availability of nitrite preparations on the market and the underestimated prevalence of recreational nitrite use should prompt primary care physicians to rapidly diagnose and initiate treatment when characteristic symptoms of nitrate toxicity occur.

Keywords: maculopathy; methemoglobinemia; nitrates; nitrites; poppers,

1. Introduction

Nitrates are a group of prodrugs whose common mechanism is the supply of nitric oxide (NO), which dilates blood vessels [1,2]. They are currently used to treat angina pectoris, a condition associated with myocardial ischemia, manifested by chest pain [1]. Their vasodilatory action primarily affects venous vessels and increases blood flow to the heart, alleviating ischemic symptoms [2,3]. Nitrates include nitroglycerin, isosorbide mononitrate, isosorbide dinitrate, and alkyl nitrates [2,3,4,5]. Volatile alkyl nitrites include amyl and butyl nitrites, among others, commonly known as "poppers," which are often inhaled recreationally due to their relaxing and psychoactive effects [6,7]. Nitrates and nitrites exert their effect through the release of NO [1,2,3,8]. These transformations result in the formation of free NO and an inactive metabolite [1]. In the body, NO exerts its effects by activating the soluble guanylate cyclase (sGC) pathway, leading to the formation of guanosine-5'-monophosphate (cGMP), which activates subsequent dependent pathways [3]. The observed effects of nitrate use include smooth muscle relaxation and venous and arterial vasodilation. This increases vascular capacity, increases preload, and reduces end-diastolic pressure, all of which contribute to the reduction of symptoms associated with coronary artery disease [2]. Nitrates can be administered via inhalation, oral, transdermal, and intravenous routes [3]. Recreational nitrates are most commonly inhaled, although cases were reported in which patients swallowed the substance or administered it intravenously [4,7].

2. Materials and methods

This article reviews the publicly available literature from recent years on nitrates, nitrites, poppers, their mechanisms of action, adverse effects, methemoglobinemia and maculopathy.

3. Results

Surveys and trials from recent years in the UK indicate that the lifetime prevalence of popper use among people aged 16-59 is 8.3%, rendering it a relatively common drug use problem. The rate of popper use has increased compared with previous years, with the estimated number of lifetime users reaching into millions. It is difficult to assess how many people today take poppers regularly. Data show that individuals aged 25-34 are the most likely to use poppers in their lifetime (14.8%). Approximately 2.7% of people aged 15-24 reported taking poppers within the last year. Rates tend to be higher among males than females. These products are often labeled as other types of merchandise such as leather cleaners, deodorizers

or polish removers – in order to evade anti-drug regulations. It should be noted that those substances are not safe to be inhaled, ingested or administered in any form [8,9].

Nitrates have a wide range of side effects. These symptoms vary from mild, resulting from their vasodilatory effects, to reduced afterload and blood pressure. A possible mechanism underlying these effects may also be explained by reflex activation of the sympathetic nervous system in response to vasodilation. Such symptoms include headache (in more than 10% of patients, described as persistent and throbbing), reflex tachycardia, hypotension, nausea, vomiting, cutaneous flushing, lightheadedness, dizziness, and syncope (all occurring in fewer than 10% of patients) [3,10,11,12]. The most dangerous of these described adverse effects is syncope, as it can lead to falls and subsequent secondary injuries. The risk of syncope and other hypotensive reactions is significantly increased when nitrates are co-administered with phosphodiesterase-5 (PDE-5) inhibitor such as sildenafil and it is absolutely contraindicated. Nitrates are also contraindicated in patients with a right coronary artery occlusion as they reduce preload, which may lead to a severe hypotension, even resulting in a cardiogenic shock. Other contraindications include right-sided myocardial infarction, increased intercranial pressure, severe anemia and allergic reaction, which are extremely rare, although such cases exist [11]. Nitrates require particularly cautious use in groups of patients, such as older adults with autonomic dysfunction, due to the increased risk of orthostatic hypotension. Caution is also advised in individuals taking diuretics, as their blood volume is decreased, potentially leading to much more severe hypotension [3,10]. Topical use of nitroglycerin in nursing mothers caused side effects - which included headache, dizziness and lightheadedness - in 78% of the patients, yet it had no apparent adverse effect on their infants. Nitrates should not be applied on the nipples during breastfeeding. Sublingual and intravenous administration of nitroglycerin has not been studied in this group of patients, however infants should be observed for adverse effects such as flushing or discomfort after breastfeeding[13]. Nitroglycerin is classified as pregnancy category C and must be used with caution in breastfeeding mothers - it is not known whether it is excreted into breast milk [11]. Nitrates also decrease lower esophageal sphincter pressure (LESP) and impair esophageal clearance, potentially leading to gastroesophageal reflux disease (GERD). A double-blind placebo-controlled trial proved that isosorbide dinitrate reduced LESP more than placebo [14]. Serious complications associated with nitrate use also include cardiac hypertrophy, methemoglobinemia, maculopathy, vision loss, or serious hypotensive complications caused by interactions with other drugs (e.g., sildenafil) [9,12,15,16]. The toxic effects of nitrates on

the liver remain unclear [2,8]. In this article we would like to highlight rare adverse effects of nitrate and nitrite use, such as maculopathy, methemoglobinemia and bronchiolitis.

Twenty-one cases of patients presenting with maculopathy or methemoglobinemia and concomitant nitrate or nitrite use were analyzed. Five of these cases involved maculopathy, and sixteen involved methemoglobinemia. The group of nineteen patients were men aged 18 to 68, while two cases concerned women aged 23 and 25. In twenty cases, the individuals took alkyl or propyl nitrate "poppers" and in one case nitroglycerin (GTN) in 0.2% ointment [16].

4. Adverse effects of nitrate and nitrite use

4.1 Maculopathy

Poppers-induced maculopathy is characterized by impaired retinal photoreceptor function, particularly in the outer segments, accompanied with bilateral central visual impairment [15]. The exact mechanism of retinal damage remains unknown, but it has been attributed to oxidative stress and ocular perfusion pressure [17].

In the group of five patients presenting with maculopathy, the main complaints on admission were blurred vision, inability to focus on objects, and scotomas. The vision loss was described as central with minor peripheral changes. Patients did not report pain or discomfort.

Four of the patients presented to the hospital due to overuse of inhaled poppers, while one patient was treated with 0.2% GTN ointment three times daily for the preceding two months. Reported comorbidities included type 2 diabetes, hypertension, depression, human immunodeficiency virus (HIV), and hearing loss. Medications taken concomitantly by these patients included antiviral agents, antidiabetic drugs, antidepressants, and commonly used nonsteroidal analgesics. None of the patients had a previous ophthalmological or family history of maculopathy.

All patients were examined and diagnosed. Normal intraocular pressure was observed, with reduced visual acuity despite best correction. Extraocular movements, confrontational visual fields, and color vision were within normal limits.

Four patients underwent fundus examination. Two of them demonstrated abnormalities in the form of venous dilatation, scattered hemorrhagic spots, macular hyperreflectivity, retinal

epithelial changes consistent with a central foveal xanthelasma, and subtle parafoveal whitish peripheral changes. Fundus examination revealed no other pathology.

Imaging methods, including optical coherence tomography (OCT), optical coherence tomography-angiography (OCT-A), and fluorescein angiography (FA), revealed focal retinal defects, disruption of the inner and outer segment layers limited to the fovea, loss of pigment epithelium, hypoautofluorescence in the fovea, focal hyperreflectivity and irregularity of the ellipsoidal zone in the fovea, and diffuse hyperreflective changes at the level of the inner plexiform layer, inner nuclear layer, and outer plexiform layer. No other clinically significant changes were observed. In four cases, the changes were bilateral, and in one case, unilateral. Patients were advised to immediately discontinue the substance which caused the symptoms. In three cases, the patients returned for a follow-up visit; their symptoms resolved, and post-correction visual acuity improved minimally [15,16,17,18,19].

4.2 Methemoglobinemia

Methemoglobinemia is a pathological condition in which the iron in hemoglobin is oxidized to +3 oxidation state, preventing proper oxygen binding and oxygen distribution throughout the body. The reference range for methemoglobin in blood is <1%. Symptoms include hypoxia, cyanosis, dyspnea, tachycardia, headache, blurred vision, and syncope. The severity of these symptoms correlates with the concentration of oxygenated hemoglobin in the blood. Nitrates and nitrites are one of the causes of acquired methemoglobinemia [3,4,9,10,11,16,17].

A total of 16 cases were analyzed in the group of patients with methemoglobinemia. All patients had a recent history of nitrate or poppers use. In three cases, nitrites were administered by inhalation, in ten cases orally (variable amounts of liquid), and in one case intravenously. In two cases, the route of administration remained unknown, although the use of poppers was confirmed. Patients presented with central or peripheral cyanosis, hypoxia, respiratory failure, altered consciousness, tachycardia, vomiting, headache, and syncope. Comorbidities reported by these patients included HIV infection, type 2 diabetes, hypertension, hyperlipidemia, non-insulin-dependent diabetes, and atrial flutter. Patients also reported concurrent substance use, including tobacco, ethanol, bupropion, valproate, cocaine, and amphetamines. Oxygen saturation levels measured in the study patients ranged from 70 to 90%. Patients received oxygen therapy, primarily using a mask without a respirator or a mask with a bag valve, with oxygen flow rates of 10-15 L/min. Eight patients presented with

tachycardia exceeding 100 beats per minute. Two patients with high blood pressure on admission (150/78 mmHg and 155/93 mmHg). Two other patients lost consciousness after swallowing poppers (Glasgow coma scale (GCS) = 4 and GCS = 5). In two cases, blood pressure was low - 88/50 mmHg and 96/54 mmHg. The most important laboratory finding in all the mentioned cases was a significantly elevated methemoglobin level (MetHb %), ranging from 12% to 75.4%. In one case, due to confirmed use of poppers and a characteristic clinical presentation, methemoglobinemia was hypothesized and the patient was treated empirically. The percentage methemoglobin levels (earliest measured on admission) are presented in the table (Table 1).

Table 1. Summary of patients admitted with methemoglobinemia

No.	Age	MetHb(%)	Comorbidities	Sex	SpO2	Administration	Substance
1[4]	62	> 20%	non-insulin-dependent diabetes, hyperlipidemia and atrial flutter	M	87%	Ingestion	Popper “Jungle Juice”
2[5]	46	-	hypertension	M	74%	Unknown	popper "Rush"
3[6]	23	>30%	-	F	70%	Ingestion	uknown popper
4[7]	34	40%	-	M	82%	Intravenous	popper "boooster"
5[20]	42	19.8%	hypertension	M	88%	Inhalation	popper "Rush"
6[21]	51	> 30%	prediabetes, gastritis	M	77.0%	Ingestion	popper "Rush"
7[22]	25	75.4%	-	F	89%	Ingestion	uknown popper
8[23]	39	23.5%	-	M	85%	Ingestion	uknown popper
9[23]	40	46.0%	-	M	90%	Ingestion	popper "Buzz"
10[24]	40	30.3%	-	M	90%	Ingestion	uknown popper
11[25]	37	30.3%	-	M	70%	Ingestion	popper "Tiger"
12[26]	38	35.2%	cocaine and tobacco addiction	M	72%	Unknown	uknown popper
13[27]	43	12%	uncontrolled type 2 diabetes and hypertension	M	85%	Inhalation	popper "Rush"
14[28]	23	25.6%	asthma and depression	M	-	Inhalation	uknknown poppers (multiple)
15[29]	18	36%	-	M	90%	Ingestion	uknknown popper
16[30]	50	36.7%	type 2 diabetes, hypertension, hyperlipidemia, and human immunodeficiency virus (HIV)	M	87%	Ingestion	uknknown popper

Source: Prepared by the author.

All patients received treatment. Fourteen patients received intravenous methylene blue (typically at a dose of 1 mg/kg), one patient received toluidine blue at a dose of 3 mg/kg, and in one case, treatment for methemoglobinemia was abandoned because the patient did not require oxygen and was treated with intravenous fluids instead. This treatment proved effective, reducing methemoglobin levels to normal and resolving associated symptoms within 2–24 hours [4,5,6,7,20,21,22,23,24,25,26,27,28,29,30].

In none of the cases was the concurrent occurrence of maculopathy and methemoglobinemia observed. Acquired methemoglobinemia can also be caused by other medications. The most common agents include local aneathetics such as lidocaine, antibiotics such a dapsone or sulfonamide and other drugs including rifampicin, clofazimine, phenytoin, chloroquine, silver nitrate, phenacetin, nitrofuran [4]. That is why all clinicians should conduct differential diagnosis of acquired methemoglobinemia.

4.3 Bronchiolitis

A case of bronchiolitis developing after inhaling 'The New Amsterdam' poppers (Isoamyl nitrite) has been described. A 23-year-old female patient was admitted with an acute onset respiratory symptoms consisting of chest discomfort, breathlessness, and dry cough. The patient had no chronic illnesses, was not taking any medications or any other recreational drugs. The measured oxygen saturation (SpO2) was 91% on room air. Laboratory tests revealed a C-reactive protein (CRP) level of 35.3 mg·dL−1 (N<5 mg·dL−1) and oxygen tension of 66 mmHg (N=85–95 mmHg). Other laboratory parameters were not significant. High-resolution computed tomography (HRCT) without contrast enhancement was performed, which revealed nonspecific, diffuse inflammatory changes, thickening of the bronchiole walls, and the presence of secretions in the respiratory tract. Spirometry revealed reduced forced expiratory volume in the first second (FEV1), decreased total lung capacity (TLC), and forced vital capacity, which led to a conclusion of bronchial obstruction. The patient was administered 400 μg of salbutamol with spirometry performed afterwards, which resulted in reversion of the obstruction. Bronchoscopy did not reveal any significant findings. The patient was treated with methylprednisolone for 5 days, with significant improvement in his clinical condit

ion [31].

5. Monitoring

Since the half-life of nitroglycerin is approximately 2-3 minutes and the drug is rapidly metabolized in the liver, direct monitoring of its blood concentration is impossible. Therefore, patient evaluation should be based on changes measured blood pressure and the resolution of symptoms (angina, hypertension, heart failure). In cases of overdose and potential severe adverse effects monitoring of blood pressure, heart rate, respiratory rate and oxygen saturation is recommended [11]. Beta-blockers may be used to prevent reflex tachycardia, hydralazine may be used in conjunction with nitrates to improve mortality in heart failure patients [3]. Symptomatic treatment including efforts to increase central fluid volume, such as intravenous saline administration, prove effective since some side effects are lined to hypotension and decreased blood pressure. Adrenaline is not recommended in nitrate hypotension [11]. Possible nitrate interactions may include heparin, tricyclic antidepressants, anticholinergic drugs and alteplase. Patients should abstain from alcohol consumption. No medication is known to directly counteract the vasodilatory effect of nitrates [11]. Methylene blue may be useful in the treatment of methemoglobinemia, and methyloprednisone may be beneficial in managing inflammation caused by poppers [3,4,5,6,7,11,20,21,22,23,24,25,26,27,28,29,30]. In case of adverse effects immediate cessation of drug intake is recommended, however rebound angina may occur from nitrate withdrawal [3,15,16,17,18,19,31]. In contrast, patients may also develop nitrate tolerance after as little as 12-24 hours of repeated use, with substantial reduction in clinical effects. This creates the necessity of a drug-free interval of approximately 12 hours a day. It should be noted that anginal episodes may occur during the nitrate-free period [10]. There is no evidence of teratogenic or carcinogenic potential of nitrates [3].

6. Conclusions

Nitrates are well-known and long-used medications prescribed by primary care physicians. They are used to treat many conditions, especially cardiovascular diseases, and to alleviate their symptoms. Alkyl nitrites, widely available and used as narcotics, exert their effects in organisms as nitric oxide (NO) donors, similar to conventional nitrates. As described, the effects of prolonged, excessive or inappropriate use of these agents can lead to serious complications. Despite the widespread use of nitrates and nitrites, diagnosis of complications can be difficult due to nonspecific symptoms. Patients presenting with seemingly trivial symptoms, such as slight skin bruising, decreased vision, or cough, may be dismissed by

healthcare providers. Symptoms of nitrate toxicity can occur at any age, so it is crucial to identify risk factors as early as possible, confirm a history of nitrate use, whether medicinal or recreational, and implement specific treatment. Oxygen saturation measurements, blood methemoglobin levels, and eye fundus examination are relatively simple and inexpensive tests that can be used to diagnose nitrate abuse. Prompt implementation of targeted therapy is equally important, as severe cases involving loss of consciousness and the need for intubation have been reported. It should also be emphasized that in cases involving recreational use, immediate cessation of substance use is paramount. We encourage all clinicians and healthcare workers to evaluate the risk of nitrate adverse effects based on patient interviews, medical history, and laboratory findings.

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