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Assessing risks and adverse effects of naphazoline hydrochloride: a literature review (2013-2023)

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Abstract. This study examines the risks and harms associated with the use of naphazoline hydrochloride (NHC). The methodology involved a narrative literature review from 2013 to 2023 in Portuguese, English, and Spanish, which identified eleven relevant articles from Scielo, Medline Complete, PubMed, and Google Scholar. The guiding question was: What are the risks and potential adverse effects associated with the use of NHC? Results and Discussion: Pharmacists play a crucial role in educating against misuse and promoting responsible medication use. However, challenges arise due to the prevalence of self-medication and limited pharmacist involvement in prescribing. The Role of Pharmacists: Harms of Misuse: Key concerns identified include systemic effects, drug-induced rhinitis, and dependence. Overuse of NHC during pregnancy and in children can lead to serious consequences such as hypothermia, bradycardia, and nervous system depression. The abuse hazards of NHC include rebound effects, drug-induced rhinitis, and long-term health risks such as hypertension and heart problems. Conclusion: The study emphasizes the pressing need for enhanced pharmacist training to equip them to effectively counsel and prevent misuse. Additionally, increased public awareness campaigns should be implemented to promote responsible non-prescription healthcare (NHC) use. Stricter dispensing measures, such as regulations to restrict over-the-counter access, should also be put in place. It is essential to promote responsible NHC use. Pharmacists play a critical role in mitigating the risks associated with this widely used medication as public health educators and patient guides.
Keywords: Indiscriminate, naphazoline, self-medication, public health.

Introduction

Naphazoline is a drug of the naphthimidazoline class available in the form of eye drops or nasal drops. Naphazoline is widely used in Brazil due to its easy accessibility and low cost (Queiroz, T. C. et al. 2022).

According to ANVISA (Health Surveillance Agency), naphazoline is the predominant member of the imidazoline family available on the Brazilian market for the treatment of nasal congestion and is the most sought-after remedy for self-treatment (Lima M. I. M. de M. et al., 2021).

Due to their long-lasting action, imidazole compounds tend to cause a more pronounced rebound effect. The chemical structure of naphazoline contains an imidazole nucleus, which, in addition to adrenergic effects, also acts on cholinergic receptors, selectively blocking the activity of the parasympathetic system, i.e. inhibiting the action of acetylcholine (Borges A. S. S. et al., 2019).

The free prescription and lay sale of topical nasal decongestants in Brazilian pharmacies and drugstores attracts attention, especially because they disregard the adverse events that their inappropriate use can cause to health. In Brazil, nasal decongestants are one of the most sought-after drugs by patients who self-medicate (Rodrigues C. E. et al., 2017).

Nasal decongestants have contraindications, and some adverse effects can be induced in the long term, such as arrhythmia, headache, insomnia, nasal irritation, sneezing, restlessness, tachycardia, tremor, and even urinary retention (Lima, M. I. M. et al. 2021).

Approximately 25% of people living in industrialized regions who suffer from allergic rhinitis and other respiratory diseases often take these drugs uncontrollably because of the immediate relief they provide (Dionizio I.C. et al. 2020).

Thomseth et al, (2018) in their work highlight the possible risks of using eye drops containing naphazoline, especially the adverse systemic effects such as increased blood pressure and cardiac arrhythmias, the authors state that these are known complications of high-dose sympathomimetic eye drops.

Children, especially those under 3 years of age, exposed to naphazoline and agents in the same drug class show early signs of intoxication regardless of the route of exposure. Among the observed reactions are depression of the cardiovascular, respiratory, and nervous systems, leading to the possibility of short- and long-term damage (Queiroz T. C. et al. 2022).

Considering the irrational use of these medicines containing naphazoline and the fact that it is a public health problem, pharmacists have an important role to play in helping society by promoting health education on the use of medicines and their main adverse effects.

Therefore, based on the above, this study aimed to analyze the risks and potential adverse effects associated with the use of medicines containing naphazoline hydrochloride.

Material and Methods

The scope of the review was determined by applying previous theoretical knowledge related to the topic and relevant concepts within the chosen research area. It was accompanied by the following guiding question "What are the risks and potential adverse effects associated with the use of drugs containing naphazoline hydrochloride?

A literature review was conducted in August 2023. It included articles in Portuguese, English, and Spanish published between 2013 and 2023. These articles were retrieved from the following databases: Scielo, Medline Complete, PubMed, and Google Scholar.

The descriptors used included terms such as "indiscriminate", "naphazoline", "self-medication", "public health", "and pharmaceutical", as well as their English equivalents: "indiscriminate", "naphazoline", "self-medication", "public health", "pharmaceutical". The Boolean operator "AND" was used to facilitate the intersection between the selected descriptors, while the operator "NOT" was used to exclude arguments not relevant to the thematic area in question. *Statistical analysis*

Results and discussion

Eleven articles were selected, published between 2013 and 2022, and divided into thematic categories for better understanding: three (3) related to the use of Naphazoline Hydrochloride by pregnant women and children; six (6) related to Naphazoline Abuse Hazards and Risks; and (2) related to The Role of the Pharmacist in the rational use of medicines and the fight against self-medication (Table 1).

Use of Naphazoline Hydrochloride by pregnant women and children

For ophthalmic use, naphazoline works by constricting blood vessels to relieve redness caused by minor eye irritation. In the nasal passages, it works by constricting blood vessels to relieve nasal congestion caused by colds, allergic rhinitis, or allergies. These products are safe when used as directed in the eyes or nose, but if ingested, they can cause serious and potentially fatal adverse events (U.S. Food & Drug Administration, 2016).

The use of naphazoline is widespread in Brazil due to its easy accessibility and low cost. Intoxication with this drug during pregnancy has implications for the pregnant woman and her children. In children, intoxication from oral ingestion of naphazoline occurs when the solution is greater than 0.1 mg/ml.

In addition, intoxication is associated with lower body weight and greater absorption capacity in children. In addition, ANVISA contraindicates the use of these substances in children, but they are widely used due to their easy availability in pharmacies (Queiroz, T. C. et al. 2022).

Classic symptoms of intoxication include hypothermia, pallor, and bradycardia associated with adrenergic receptor agonist mechanisms. In addition, symptoms such as tachycardia, sweating, and transient hypertension are associated with the activation of these receptors and are also observed as some of the symptoms resulting from this intoxication (U.S. Food & Drug Administration, 2016).

Ingestion of a small amount of eye drops or nasal spray can have serious adverse effects in young children, causing serious events such as coma, decreased heart rate, decreased respiratory rate, sedation (drowsiness), and requiring hospitalization. Most of these eye drops and nasal decongestant sprays to relieve redness currently come in bottles that are easy for children to handle and open, so they can accidentally ingest the medication (U.S. Food & Drug Administration, 2016).

To protect children from ingesting these products, the U.S. Consumer Product Safety Commission (CPSC) has issued a proposed rule that would require nasal decongestant sprays to come in bottles that children cannot open (U.S. Food & Drug Administration, 2016).

Dionizio et al (2020) highlight the importance of warning against the use of naphazoline in children and the elderly, as the risk of intoxication is higher. Díaz, Mariano, et al (2018) describe the case of a 4-year-old boy diagnosed with sinusopathy. A syrup containing dexamethasone was prescribed, but instead, the child received nasal decongestant drops containing naphazoline. A therapeutic error occurred at the time of administration, and after the second dose, the boy suffered from drug intoxication.

When he went to the pediatric emergency room, he was diagnosed with cardiac arrhythmia and started on life support. It is important to note that naphazoline in the form of a nasal decongestant is approved from 12 years of age (Díaz, Mariano et al, 2018).

It is important to take a medical history and assess the clinical condition of children who use nasal decongestants with naphazoline if they are in poor general condition and appear to be seriously ill, as the possibility of poisoning by the drug is worrying since there is no known antidote.

Cardoso D. S. (2022) shows that the main problems that led parents to self-medicate their children were: flu, cold, runny nose, fever, diarrhea, sore throat, and cough. This study also found that other factors contribute to this behavior on the part of parents, such as difficulty or lack of mobility, distance between health services and the home, overcrowding, and long waiting times in queues for care at health facilities.

A study in Denmark followed a national sample of women who had normal births between 1997 and 2011 and identified those who had used antazoline-naphazoline eye drops at least once during the first 84 days of pregnancy. The study compared the risk of malformations in babies exposed to the eye drops with those not exposed. There was no association between antazoline-naphazoline use in the first trimester and major congenital malformations in general or any specific type. The number of times the eye drops were used did not change in any trimester of pregnancy compared with the period before or after pregnancy. The use of antazoline-naphazoline eye drops in early pregnancy does not appear to increase the risk of teratogenicity (Thomseth, et al. 2018).

According to Queiroz (2022), the effects of this medication favor the improvement of nasal obstruction, but when used in excess, it can have systemic effects. systemic effects. This relationship is no different for pregnant women. In addition to the various adverse effects on the health of the woman, this substance can cause serious disturbances in the cardiorespiratory system.

Naphazoline Abuse Hazards and Risks

Rodrigues, C. E. et al (2017) report the existence of three hypotheses that attempt to explain the rebound effect associated with decongestants. The first states that the frequent constriction of the vessels causes an oxygen deficiency in the nasal mucosa and, consequently, an increase in blood flow with intense vasodilation. The second argues that continuous use of the substance leads to a reduction in natural norepinephrine and, after the decongestant wears off, there is a rebound dilation of the vessels. The third proposes that excessive use results in the stimulation of parasympathetic activity, leading to an increase in vascular permeability and the formation of swelling.

Rodrigues, C. E. et al (2017) highlight one of the adverse effects of prolonged use of nasal decongestants containing naphazoline: drug-induced rhinitis, a form of non-allergic rhinitis. The nasal mucosa becomes more sensitized and new sores may appear, as well as existing sores, which may worsen). The authors also explain that excessive doses of decongestants make the mucosa less responsive to the medication, which can lead the individual to use more and more of the drug, leading to dependence on the medication.

According to Martins, T. R. et al. (2022), it was possible to observe some of the health risks that can be associated with nasal decongestants when they are abused and used for a prolonged period, with emphasis on heart problems, severe headaches, loss of sleep, irritation in the nasal area, acceleration of the heart, urinary incontinence, as well as a tendency to develop hypertension, with a risk of stroke, in addition to a decrease in neurological and respiratory frequency.

Martins, T. R. (2022) believes that one way to prevent these events is to avoid misuse for longer than necessary so that the patient does not become dependent on the drug.

According to other authors, given the irrational use of nasal medicines containing naphazoline and the fact that this is a public health problem, pharmacists have an important role to play in helping society by promoting health education on the use of medicines and their main adverse effects (Borges, A. S. S., 2019).

The role of the pharmacist in the rational use of medicines and the fight against self-medication.

Lima, et al (2021) warn that self-medication continues to be a serious health problem due to the sale of medicines without the guidance of a qualified professional, supervision, and medical prescription. The consequences of this practice can lead to poisoning, masking of other diseases, overdose, dependence on the substance, resistance to microorganisms, and, in more critical cases, death.

A comprehensive survey on self-medication in Brazil found that 77% of citizens practice self-medication, with 47% of them doing so at least once a month and 25% doing so daily or at least once a week (Conselho Federal de Farmácia, 2019). According to the World Health Organization (WHO), about half of the users of medicines use them inappropriately. ANVISA (Health Surveillance Agency) also estimates that 18% of poisoning deaths in Brazil are related to self-medication (ANVISA, 2021).

In this study, the authors also point out that nasal decongestants, in addition to being an over-the-counter medication, are sought after because they have an immediate effect. The low cost, the inconvenience of nasal obstruction and congestion combined with the proven efficacy, especially of naphazoline, contribute to the reduction of these symptoms, increasing the demand and the rampant use of the drug (Lima, M. I. M. de M, et al 2021). Azeredo Soterio, K. (2016) reports that the ease of purchase is an aggravating factor, coupled with the

information available on the Internet that can be accessed at any time, generating a lack of concern about seeking a competent professional. In this way, self-medication ends up being the choice to "treat" or "alleviate" any illness or pain.

In this context, pharmaceutical care is an essential method for reducing self-medication and thus acting on behalf of society. Direct contact with the patient, willingness to listen and answer questions, correct guidance on medicines, and taking an anamnesis are indispensable acts for the protection and well-being of the individual (Azeredo Soterio, K, 2016).

Over-the-counter (OTC) medications are used for self-limiting health problems to relieve, treat, and prevent symptoms that are considered minor, such as headaches, cramps, colds, diarrhea, dry cough, muscle aches, and others. Although these drugs are non-prescription, they can cause adverse reactions, side effects, drug interactions, and other problems (Cardoso. D.S. et al, 2022).

The use of pharmacists' knowledge and their contribution to multidisciplinary teams increases the efficacy of drugs and advocates the rational use of drugs through pharmacotherapy. Therefore, it is necessary to provide health education to the population to avoid the unnecessary purchase of MIPS and to educate about the harm that the chronic use of a drug can cause despite its benefits (Lima, M. I. M. de M, et al 2021).

Martins, T.R. (2022) believes that pharmacists play a fundamental role in guiding the use of medicines for the population, so they have attributions and obligations in their daily routine, given that they can act to guide and advise patients who seek medicines in pharmacies, enlightening them on the correct way to take medication, explaining the risks and contraindications of drugs.

The dispensing of medicines involves not only handing the product to the patient, but also providing information on the correct use of the medicine and following guidelines on drug interactions. These teachings should take into account factors such as diet and laboratory tests, as well as knowledge of adverse reactions and the proper way to store products (Lima, M. I. M. de M, et al 2021).

Still about pharmacists, Martins, T.R(2022) states that being present in pharmacies and drugstores, they have the ability and duty to inform and make decisions based on technical-scientific knowledge and current legislation and to take a proactive stance in dispensing practice, without waiting for signals from the patient as to the understanding of their treatment, the guidance of this professional is necessary to avoid allergic, adverse reactions, drug interactions or even being contraindicated for the patient in question.

The prescription of medicines is an act that allows the pharmacist to get closer to the patient and to demonstrate his importance in this relationship since he carries out the prescription at the time of the consultation. However, this service is still rare in pharmacies and drugstores in Brazil, since there are some obstacles to its practice, such as financial difficulties, interest in the establishment, lack of adequate space, and lack of training. (Cardoso, D.S. 2022).

Further research on the use of naphazoline is urgently needed to provide substantial information to train pharmacists in the approach to self-medication and to support stricter measures for dispensing the drug.

Table 1. List of articles selected by topic category.

Topic related: Use of Nafazoline Hydrochloride by pregnant women and children
Queiroz et al. Uso de Cloridrato de Nafazolina em pacientes gestantes e seus malefícios. CPAH Science Journal of Health, v. 5 n. 2, 2022. **Considerations topics**: Demonstrate that naphazoline can be harmful to the central nervous system and the cardiorespiratory system. Intoxication with this drug in pregnancy has repercussions for the pregnant woman and the child.
Thomseth et al. Exposure to antazoline naphazoline eye drops during pregnancy and the risk congenital malformation: a Danish Nationwide cohort study. Acta Ophtalmologica v. 97, n. 5, p. 505-509, 2018. **Considerations topics**: The purpose of this study was to determine whether antazoline-naphazoline eye drop exposure during first-trimester pregnancy is associated with increased teratogenic risk of malformations in humans.
U.S. Food & Drug Administration, 2016. Comunicado de la FDA sobre la seguridad de los medicamentos: Sucesos adversos graves resultantes de ingestión acidental por niños de colírios (gotas para los ojos) y aerosoles nasales de venta libre **Considerations topics**: Insurance of medicaments
Topic related: Naphazoline Abuse Hazards and Risks
Rodrigues, C. E.; Piloto, J. A. D. R.; Tiyo, R. Rinite medicamentosa e o consumo indiscriminado de vasoconstritores nasais tópicos. Uningá Review, v. 29, n. 1, 2017. **Considerations topics:** To review the adverse effects of vasoconstrictive nasal decongestants, especially drug-induced rhinitis, and to warn of the risks of these drugs
Dionizio et al. A dependência de descongestionantes nasais e seus efeitos colaterais. Revista Esfera Saúde, v. 5, n.2, 2020. **Considerations topics:** To warn of the risks of indiscriminate use of decongestants and their relationship to addiction

Díaz et al. Intoxicación grave com nafazoliua: puesta al día a partir de um error terapéutico. Archivos argentinos de pediatría, Buenos Aires, v. 116, n. 4, p. 626-629, 2018. **Considerations topics:** Describes a clinical case of a 4-year-old boy who suffered severe intoxication after accidentally ingesting a nasal decongestant containing naphazoline

Martins et al. Os riscos causados pelo uso indiscriminado de descongestionantes nasais derivados da nafazolina. Revista Multidisciplinar do Nordeste Mineiro, v. 8, n. 1, 2022. **Considerations topics:** The risks of indiscriminate use of nasal decongestants containing naphazoline hydrochloride to patient health are analyzed. There is a description of the role of the pharmacist in their use.

Cardoso et al. Uso indiscriminado de medicamentos isentos de prescrição no Brasil. Research, Society, and Development, v. 11, n. 9, 2022. **Considerations topics:** Discussion of PIMs and the importance of pharmaceutical guidelines in their use.

Borges et al. Riscos associados ao uso irracional do descongestionante nasal: Cloridrato de Nafazolina. Revista Uniabeu, v. 12, n. 31, p. 245-257, 2019. **Considerations topics:** Description of the risks associated with the use of the nasal decongestant naphazoline hydrochloride.

Topic related: The role of the pharmacist in the rational use of medicines and the fight against self-medication**.**

Lima et al. Riscos associados a automedicação de Cloridrato de Nafazolina e ao farmacêutico como protagonista da utilização racional dos medicamentos. Research Society and Development, v. 10, n. 15, 2021. **Considerations topics:** Exploring the risks of self-medication and the inappropriate use of nasal decongestants containing Hydrochloride, emphasizing the essential role of pharmacists in promoting the rational use of medicines.
medicines.

Azeredo Soterio, K.; Araújo dos Santos, M. A. A automedicação no Brasil e a importância do Farmacêutico na orientação do uso racional de medicamentos: uma revisão. Revista da Graduação, v. 9, n. 2, 2016.
Considerations topics: To evaluate the prevalence of self-medication in different locations in Brazil. To highlight the role of pharmacists in promoting the appropriate use of medicines.

Conclusion

This study focused on the use of naphazoline hydrochloride, emphasizing its use as a nasal and ophthalmic decongestant. Although safe when used correctly, accidental ingestion can have serious consequences. This is exacerbated by its easy availability and low cost in Brazil, despite ANVISA's contraindications for children.

Naphazoline intoxication has been associated with severe symptoms and no known antidote, highlighting the need for clinical vigilance. Inappropriate use may lead to dependence, rebound effects, and drug rhinitis, with consequences such as heart problems, severe headaches, and risk of stroke.

Self-medication without proper guidance and irrational use of medicines posed a public health challenge, driven by the search for nasal decongestants because of their immediate efficacy and low cost. The crucial role of pharmacists in guiding and preventing self-medication was highlighted.

Health education was identified as fundamental to avoid unnecessary purchases and to understand the risks of chronic use. Despite the challenges, prescribing was seen as a promising strategy to promote appropriate use of medicines.

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