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Xylometazoline and oxymetazoline - unusual effects of everyday drugs (literature review)

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Abstract

The aim of the study is to systematize the knowledge about xylometazoline and oxymetazoline - commonly used nasal sprays with sympathicomimetic effect, mainly directly on α-adrenergic receptors [1]. A review of recent reports on possible side effects and new therapeutic options will be presented.

Results: Over several years, reports have been published regarding descriptions of unusual cases of side effects, such as angina attack [4], a case of respiratory failure in a newborn [5], ischemic stroke [6], or anaphylactic reaction during routine surgery.

In experiments using rats, on the other hand, it has been shown that these substances can also cause increased inflammation of the lower respiratory tract [7], as well as numerous ophthalmic problems [8].

Recent reports also suggest new uses for xylometazoline and oxymetazoline. In combination with lidocaine, an intranasal solution of xylometazoline has shown efficacy in the anesthesia of maxillary teeth in patients with minor carious lesions [9], and a beneficial therapeutic combination of oxymetazoline and dye laser (PDL) has also been reported for the treatment of rosacea, among others [10].

Conclusions: Although imidazoline derivatives were admitted to the drug list decades ago, still their pharmacological potential has not been fully exploited. Finding applications of these drugs in dermatology and dentistry may not only improve the efficacy and comfort of treatment, but also significantly reduce the costs of the whole therapy. The aforementioned reports on the side effects of xylometazoline and oxymetazoline should not be forgotten. It is possible that the presented examples will increase awareness to use these drugs with more respect, according to the recommendations on the leaflet.

Key words : xylometazoline, oxymetazoline, rosacea, anesthesia dental

INTRODUCTION

Xylometazoline and oxymetazoline are imidazole derivatives with sympathicomimetic effects. These drugs act directly on the α-adrenergic receptors. When applied topically as a nasal spray, they cause vasoconstriction and relieve the inflammatory reaction by reducing congestion, exudate and swelling of the nasopharyngeal mucosa [1]. They improve sinus drainage and facilitate nasal breathing. Because of their rapid resolution of nasal mucosal congestion, medications containing nasal decongestants are often used by both physicians and the patient [2].

Oxymetazoline reduces intraocular pressure by decreasing the rate of flow of the aqueous fluid and increasing choroidal and scleral outflow, and therefore shows clinical potential as an ocular hypotensive drug [3]. In ophthalmology, it has also been shown to be effective in the treatment of histamine-induced congestion [4].

It is important to note that prolonged use of these drugs adversely affects the patient's body. The strong stimulus-dependent vasodilatory action of beta receptors masks that effectively occurring with alpha receptor agents. The long-used negative feedback mechanism of imidazoline derivatives results in decreased norepinephrine production in the presynaptic region [2].

As a result, patients using the medication for a longer period of time are forced to use higher doses of the drug to achieve the same therapeutic effect, leading to nasal mucosal dependence on the preparation and the occurrence of side effects: increased rhinorrhea or nasal congestion, blurred vision, rapid irregular heartbeat, pain and dizziness [5].

The findings from the 1990s also showed that oxymetazoline nasal drops, commonly used for acute rhinitis and sinusitis, interfere with normal defense mechanisms during bacterially induced sinusitis, probably by reducing mucosal blood flow [6].

Despite the passage of decades since the introduction of xylomatezoline and oxymetazoline and the knowledge of their mechanism of action and common side effects, new reports of unique unwanted reactions and new applications of these preparations continue to emerge.

OBJECTIVES AND METHODS

The aim of this study is to systematize the knowledge about xylometazoline and oxymetazoline. A review of recent reports on possible side effects and new therapeutic options will be presented. In order to find the most recent information, a review of scientific papers using Google Scholar search engine covering articles from 2016-2021 was performed. More than a dozen scientific papers covering the scope of the publication were selected. Older review papers were used to provide preliminary information on drug mechanism.

NEW APPLICATIONS - A REVIEW

In addition to the traditional use of xylometazoline and oxymetazoline, recent scientific reports have demonstrated the possibility of their new use. Attention was drawn to the use of lidocaine solution with xylometazoline as an intranasal spray in the anesthesia of maxillary anterior and premolar teeth in dental procedures. We found that the spray was quite effective

in anesthetizing maxillary teeth with less carious lesions for restorative procedures in patients with a stable history. This method of anesthesia may be a great alternative for anesthesia in patients with fear of needles. [7] Although the formulation has been approved by the FDA, its clinical field of application is still narrow. Another study noted that studies are needed to evaluate its safety and efficacy in young children and in patients with systemic complications. Nevertheless, the concept of intranasal anesthesia opens new horizons in needle-free anesthesia for restorative procedures of single teeth in the maxillary arch, especially in the anterior segment. [8]

Among the novel trials of xylometazoline, it is worth mentioning the case of 2 patients with a history of long-term, uncontrolled, and unsupervised topical steroid use on the face. After applying xylometazoline to the face once daily for 2 weeks, improvement in redness and erythema was observed. Transient tingling and prickling sensations were reported adverse reactions. [9] Xylometazoline, which is an alpha-adrenergic receptor agonist, is an effective new treatment option for patients with redness and erythema resulting from long-term topical steroid use on the face.

Similar to the aforementioned cases, the property of imidazole derivatives is being attempted in the treatment of rosacea, telangiectasias and port-wine stains [10]. Another study, this time on the combination of oxymetazoline and pulsed dye laser (PDL), showed a higher rate of vascular closure when using oxymetazoline +PDL (66.7%) compared to saline +PDL alone (16.7%). Such an effect offers the possibility of using this treatment in cutaneous vascular diseases such as rosacea and port-wine stain. [10] [11] In addition, the application of oxymetazoline in cream form as adjunctive therapy has been evaluated as safe and well tolerated, and reduces facial erythema in patients with moderate to severe facial erythema associated with rosacea. [12]

Based on current research, topical alpha-adrenergic receptor agonist therapies have been shown to be safe and effective and are currently the only agents offered specifically for facial erythema associated with rosacea. Topical 1% oxymetazoline should now be included in the arsenal of medications for facial erythema in rosacea, as data suggest that it is an effective alternative with minimal side effects compared to previously approved topical medications. [13]

Additionally, there are data to suggest that xylometazoline does not affect Eustachian tube function. Using a battery of tests to obtain objective measurements of passive and active Eustachian tube function, the results of the cited study suggest that the baseline rate of Eustachian tube opening in healthy subjects and subjects reporting symptoms of obstructive Eustachian tube dysfunction is not altered after xylometazoline is applied to the anterior nasal cavity. There is little or no evidence that topical agents that reduce nasal mucosal congestion improve Eustachian tube function, and clinicians should inform patients of this when offering treatment. [14]

Studies have also been undertaken to determine the usefulness of intranasal xylometazoline during flexible bronchoscopy. However, it was shown that the operator's assessment of the ease of bronchoscope movement through the nose on a visual analog scale (Negotiation VAS) was similar to that of patients who received placebo. In addition, there were no differences in the secondary objectives of the study (facial pain score on an assistant's scale, patient-rated nasal pain score (Pain VAS)), time to reach the vocal cords after bronchoscope insertion, operator-rated nasal mucosal trauma score (Trauma VAS), hemodynamic changes, and complications between the groups; therefore, the results of the study do not support this use of xylometazoline as an anesthetic for bronchoscopy. [15]

ADVERSE SIDE EFFECTS - A REVIEW OF CLINICAL CASES

The use of xylometazoline and oxymetazoline is a silent, hidden health problem. Despite the fact that the combination is relatively rare, the association of the described side effects and alpha sympathicomimetic drugs is increasingly noted in the epidemiological description, which may also be related to the wide availability of such pharmaceuticals. Single cases found in the literature suggest that nor/epinephrine-based congestion-reducing drugs may cause acute coronary syndrome or ischemic stroke, leading to guidelines mandating that patients with cardiovascular risk factors not use these drugs. [16] These OTC sympathicomimetic drugs may also be considered as an independent risk factor for ischemic and hemorrhagic stroke. A potential mechanism for hemorrhagic stroke reported in the literature as a consequence of the use of sympathicomimetic drugs is cerebral arteritis and

hypertensive breakthrough, which can lead to intracerebral and/or subarachnoid hemorrhage. [17]

Ischemic stroke in these patients may result from a phenomenon called reversible cerebral vasospasm syndrome (RCVS). [18] The etiopathogenesis is traced to vascular tone abnormalities secondary to central adrenergic receptor stimulation via drugs such as xylometazoline. The literature describes the case of a 54-year-old man with symptoms suggestive of ischemic stroke. [18] He had no risk factors that contribute to stroke: diabetes, hypertension, dyslipidemia, use of stimulants such as tobacco or alcohol, and no positive family history. MRI images were suggestive of an ischemic stroke. On review of the patient's history, he had used xylometazoline nasal spray (1 mg/mL) 3-4 times a day for the past 5-6 years. The use of the described OTC drugs may also cause hypertension due to systemic vasoconstriction. Vasoconstriction further decreases the ratio of myocardial oxygen supply to demand, which potentiates the risk of angina or myocardial infarction, in patients at cardiovascular risk, in this case with impaired coronary circulation. To our knowledge, only a few cases of angina or acute coronary artery disease after oxymetazoline have been described. [16, 17, 19] Interestingly, acute coronary syndrome occurred in a patient without cardiovascular risk factors reported after the use of nasal drops containing the substances described in this review. The systemic dissemination of this drug even by the intranasal route can result in suspected unstable angina with new-onset chest pain as early as 3 hours after application. [19]

Also, anesthesiologists should be aware of a possible complication: anaphylactic shock associated with the use of nasal drops and should inquire about sensitization to xylometazoline nasal drop formulations during the preoperative evaluation. Haldar et al. describe the case of a 23-year-old patient referred for adenotomy who developed severe anaphylactic shock after applying 2 drops to each nostril of a commercially available xylometazoline preparation to reduce nasal mucosal congestion. [20] The patient required prompt intervention to stabilize baseline parameters as there was tachycardia (135 beats/min), hypotension (96/56 mmHg), and a decrease in oxygen saturation (92% for room air). Lung auscultation examination indicated bilateral wheezing. [20] Xylometazoline hydrochloride (0.1%) as an active ingredient and benzalkonium chloride (BAC) (0.011%) having antiseptic properties, which is known for adverse effects such as anaphylaxis and angioedema, are

suspected to be the main cause of the above mentioned symptoms. [20] After observing the aforementioned symptoms and correlating them with a positive skin test, as well as elevated serum tryptase levels-a marker of immune activation-it was concluded that the incident was an anaphylactic reaction to a xylometazoline-containing preparation. [20]

Because of the poorly formed blood-brain barrier, neonates and infants are more sensitive to the central side effects of sympathicomimetics. Inadvertent use of these drugs in children under 6 years of age is common and can cause adverse effects, including life-threatening ones. [21] A case of a male neonate born at 34 weeks gestation, weighing 1600 g, delivered by cesarean section due to severe maternal preeclampsia was reported in the literature. [22] At approximately 60 hours of age, the neonate developed an apneic episode that required tactile stimulation.

[22] A review of the medication chart revealed the use of oxymetazoline nasal drops by a nurse on night duty, 30 min before the apnea. [22]

In contrast, experiments using rats have shown that these substances can cause increased inflammation of the lower airways as well, exfoliation of the respiratory epithelium and hypertrophy of the airway smooth muscle [23], as well as numerous ophthalmic problems (dry eyes, corneal edema, cataracts or vascular damage) [24].

CONCLUSIONS

Although imidazoline derivatives were admitted to the list of drugs several decades ago still their pharmacological potential has not been fully exploited. Finding applications of these drugs in dermatology and dentistry may not only improve the efficacy and comfort of treatment, but also significantly reduce the cost of the whole therapy. We do not exclude that also other commonly used OTC drugs may show satisfactory but not yet discovered therapeutic effect in less common diseases or may be successfully used during treatments.

The aforementioned reports on the side effects of xylometazoline and oxymetazoline should not be forgotten, as we know from recent reports the potential risk of ischemic stroke, anaphylactic shock, or angina attack. It is possible that a combination of health care professionals' knowledge of the most common side effects of these drugs together with obtaining It is possible that the combination of health care professionals' knowledge of the

most common adverse effects of these drugs together with information about newly discovered side effects will help educate patients to use these drugs with greater respect, as recommended in the package leaflet.

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