Pharmacokinetics and pharmacodynamics of topical decongestants xylometazoline and oxymetazoline: A literature review

ABSTRACT

Introduction. This article provides a review and detailed analysis of scientific publications on the pharmacokinetic and pharmacodynamic characteristics of xylometazoline and oxymetazoline. Xylometazoline and oxymetazoline are two commonly used nasal decongestants used to temporarily relieve nasal congestion caused by colds, allergies, and sinusitis. Both drugs narrow blood vessels in the nasal passages, reducing edema and rhinorrhea.

Aims. The aim of the study is to evaluate the pharmacokinetic and pharmacodynamic characteristics of xylometazoline and oxymetazoline based on a literature review.

Material and Methods.A retrospective review of literature data was performed using Scopus, Web of Science, PubMed, and ScienceDirect databases. Different keyword combinations, such as "topical decongestants", "xylometazoline", "oxymetazoline", "pharmacokinetics" and "pharmacodynamics", were used to search for information on the problem addressed. When processing search results, either the most recent publications (over the last 10 years) or the latest publications for this topic (regardless of their release) were chosen.

Results. After reviewing abstracts and getting acquainted with their full-text articles, 47 scientific sources that met the eligibility criteria were selected. Although there are minor differences between pharmacokinetics and pharmacodynamics of xylometazoline and oxymetazoline according to available literature sources, both drugs exhibit very low systemic exposure, thus reducing the number of side effects due to the lack of systemic action and producing a high local concentration of the drugs in areas of inflammation. Besides, because of its pharmacokinetic properties, xylometazoline has a faster onset of action and a shorter duration of therapeutic effect compared to oxymetazoline.

Keywords: topical decongestants; xylometazoline; oxymetazoline; pharmacokinetics; pharmacodynamics; review.

1. INTRODUCTION

“Oxymetazoline and xylometazoline are two commonly used nasal decongestants that provide temporary relief for nasal congestion caused by colds, allergies, and sinusitis” [18]. “Both drugs narrow blood vessels in the nasal passages, thus reducing edema and rhinorrhea. Xylometazoline and oxymetazoline are imidazoline derivatives that act as alpha-adrenoceptor agonists” [18]. “They stimulate alpha-adrenergic receptors in the blood vessels of the nasal mucosa, which results in vasoconstriction, thus shrinking swollen nasal passages and facilitating breathing” [10, 24, 25, 31, 39]. “Some studies suggest that

oxymetazoline is more potent and has a longer duration of action in comparison to xylometazoline" [16].

Xylometazoline demonstrates a slightly faster onset of action; its decongestant effect begins within 5–10 minutes of application [20, 36]. Oxymetazoline starts working in 10 minutes [7, 14, 37, 35]. The duration of oxymetazoline action is 8–12 hours, compared to 6–8 for xylometazoline [7, 14, 20, 36, 37, 35].

The difference in the mechanism of action of both drugs comes from their pharmacokinetic and pharmacodynamic characteristics.

The aim of the study is to evaluate the pharmacokinetic and pharmacodynamic characteristics of xylometazoline and oxymetazoline based on a literature review.

2. MATERIAL AND METHODS

A retrospective review of literature data was performed using Scopus, Web of Science, PubMed, and ScienceDirect databases. Different keyword combinations, such as "topical decongestants", "xylometazoline", "oxymetazoline", "pharmacokinetics" and "pharmacodynamics", were used to search for information on the problem addressed. When processing search results, either the most recent publications (over the last 10 years) or the latest publications for this topic (regardless of their release) were chosen. After reviewing abstracts and getting acquainted with their full-text articles, 47 scientific sources that met the eligibility criteria were selected. An overview and detailed analysis of scientific papers on the problem addressed are below.

3. RESULTS AND DISCUSSION

Pharmacokinetics

The comparison of the main pharmacokinetic properties of xylometazoline and oxymetazoline is somewhat difficult, as there exists only a limited number of papers dedicated to this topic in the scientific literature.

Absorption and distribution

Xylometazoline and oxymetazoline are rapidly absorbed after oral or intranasal administration. Drugs practically do not reach the systemic circulation following oral and intranasal administration.

The absolute bioavailability of xylometazoline after oral administration is about 33%, according to the literature data [34].

The results of an autoradiographic study demonstrated that the majority of 14C-xylometazoline remained in the nasal cavity after intranasal administration of 14C-xylometazoline to rats. However, a part of 14C-xylometazoline was absorbed and distributed into the tissues in a pattern similar to that observed after the intravenous administration.

At the same time, the absence of systemic effects following intranasal administration of xylometazoline to test dogs at a concentration 1000 times greater than the minimum effective dose (1,65 μg) demonstrates a very low absorption of xylometazoline [43].

The bioavailability of oxymetazoline following intranasal administration (40 μg/dose) to rats was 6,8% [19].

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The peroral absorption and in vitro steady-state intestinal permeability coefficients were determined for oxymetazoline in the paper by Dowty et. al. [12]. Rats were administered either an oral or intravenous dose of 91,2 μg/kg 14C-oxymetazoline to determine absorption parameters. The fraction of orally absorbed oxymetazoline was 43%.

Duzman et al. studied oxymetazoline absorption after its ocular administration in rabbits [15]. Rabbits received binocular topical applications of 50 μL of 0,025% (12,5 μg/eye) 14C-oxymetazoline. The measurements of the exposure to radioactivity in the different compartments of the eye were performed at 30 minutes, 1, 3, and 6 hours post-administration. Oxymetazoline was poorly absorbed into the cornea (0,405% of the dose was recovered at 30 minutes). Only 0,006% of the radioactive dose was present in the aqueous humor 30 minutes after drug administration, which increased to approximately 0,02% of the dose 3 and 6 hours after drug administration. Radioactivity was also low in other ocular tissues, including the choroid/retina, ciliary body, iris, lens, and vitreous humor.

The total amount of radioactivity found in all tissues was only 0,084% of the dose at 30 minutes, 0,091% at 1 hour, 0,127% at 3 hours, and 0,107% at 6 hours. The highest concentrations were found in the external ocular tissues, such as the cornea, conjunctiva, sclera, and nictitating membrane.

Metabolism and elimination

There is practically no data on the metabolism and elimination of xylometazoline in the scientific literature. Xylometazoline undergoes extensive first-pass metabolism in the liver. It is mainly metabolized by oxidation and conjugation to form several metabolites, which are then excreted in the urine. The elimination half-life of xylometazoline is approximately 2–3 hours. Only a small amount of the drug is excreted in the feces [43].

No information on oxymetazoline metabolism in the liver was found due to its low systemic absorption and bioavailability. Mahajan et al. paper [32] studied the in vitro metabolism of oxymetazoline. As a result, the authors found 11 metabolites (M1–M11) in the post-mitochondrial supernatant fraction from homogenized tissue fractions and their microsomes supplemented with nicotinamide adenine dinucleotide phosphate (NADPH). M6 and M7 were not detected without NADPH. Only M6 had significant pharmacokinetic consequences as it affected CYP2C19 function. Researchers concluded that such low concentrations of the drug in the systemic circulation were not clinically significant.

In the study conducted in rabbits, radioactivity excreted in the urine during the first 48 hours was 23% for intranasal 14C-oxymetazoline administration and 48% for IV 14C-oxymetazoline administration [15].

Pharmacodynamics

Nasal obstruction induced by acute infective or allergic rhinitis is characterized by swelling of the nasal mucosa and rhinorrhea due to the dilation and increased permeability of cavernous venous plexuses and their overfilling with blood [13].

The vascular smooth muscle of the nasal mucosa is believed to be the only tissue that has the ability to contract in response to vasoconstrictor sympathomimetic agents, imidazole derivatives (oxymetazoline) [22]. Previous studies demonstrated that α1- and α2-adrenoceptors were present in the nasal mucosa of dogs [6], pigs [9, 29], and humans [3, 8], and their stimulation led to vasoconstriction in the nasal mucosa [9, 8, 29], whereas stimulation of β-adrenergic receptors had the opposite effect (vasodilation) [28, 30].

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Xylometazoline is a direct-acting alpha-adrenergic agonist with affinity to both α1- and α2-adrenoceptors [18]. Stimulation of α1-adrenoceptors through Gq/11-proteins leads to the activation of phospholipase C, generation of inositol-1,4,5-triphosphate, which facilitates the release of Ca2+ from the sarcoplasmic reticulum. Ca2+ interaction with calmodulin activates myosin light chain kinase. Phosphorylation of the myosin light chain and their interaction with actin result in smooth muscle contraction [11, 33]. At the same time, activation of α2-adrenoceptors through Gq/11-proteins inhibits adenylyl cyclases and, therefore, decreases cAMP production and protein kinase A activity. The inhibitory effect of protein kinase A on myosin light chain kinase is decreased. Phospholamban inhibits sarcoplasmic reticulum Ca2+-ATPase, which transports Ca2+ from cytoplasm to sarcoplasmic reticulum, thus increasing Ca2+ concentration in the cytoplasm and resulting in smooth muscle and vessel contraction [2, 42, 27, 33]. The extracellular fluid that contributes to congestion and rhinorrhea, as well as nasal mucosa, are reduced as a result of vasoconstriction and a decrease in the blood flow to cavernous venous plexus vessels, which facilitates nasal breathing.

“Messenger ribonucleic acid (mRNA) expression in the nasal mucosa of the six α-adrenoceptor subtypes was explored in one of the studies” [18]. “Furthermore, the affinity and potency of the imidazolines oxymetazoline and xylometazoline at these α-adrenoceptor subtypes were examined in transfected HEK293 cells (Human Embryonic Kidney 293). The rank order of mRNA levels of α-adrenoceptor subtypes in human nasal mucosa was: α2A > α1A > α2B > α1D > α2C > α1B. Oxymetazoline and xylometazoline showed a greater affinity for the most α-adrenoceptor subtypes than adrenaline and noradrenaline. Compared to xylometazoline, oxymetazoline displayed a significantly higher affinity for at α1A and also exhibited a lower affinity for α2B-adrenoceptors. In functional studies in which adrenoceptor-mediated Ca2+ signals were measured, both oxymetazoline and xylometazoline displayed full antagonist properties at α2B-adrenoceptors but oxymetazoline was more potent than xylometazoline. Besides, oxymetazoline was also an α1A-adrenoceptor partial agonist; however, its potency and affinity were low”. [18]

The highest affinity of oxymetazoline at α1A-adrenoceptors was confirmed in the study by Horie et al. [21].

“The effect of topical oxymetazoline hydrochloride on the blood flow of the nasal and sinus mucosa of the rabbits measured by laser-Doppler flowmetry was studied in another research. The results of the study demonstrated that oxymetazoline induced a dose-dependent decrease in nasal mucosal blood flow. Furthermore, oxymetazoline induced a dose-dependent decrease in mucosal blood flow in the maxillary sinus following intranasal administration. A vasoconstrictor effect of oxymetazoline on the arteries penetrating the maxillary sinus ostium is a possible explanation” [1].

“Besides, the Bende et al. study showed that oxymetazoline contributed to a decrease in vascular permeability of the nasal mucosa in rabbits after provocation with leukotriene B4” [5].

Increased nitric oxide (NO) levels in exhaled air are observed in patients with upper respiratory tract infections [26]. Furthermore, elevated nitric oxide metabolite levels are present in the nasal lavage fluid of patients allergic to house dust mites [17], and nasal polyps contain higher levels of NO synthase (NOS) than normal nasal mucosa [38]. “NOS plays a role in the regulation of vascular permeability and nasal cavity volume” [40, 23]. Also, NO, upon reacting with the superoxide anion radical and producing peroxynitrite, acts as a potent cytotoxic effector molecule [45]. Both functions may lead to nasal inflammation and indicate the involvement of NO in the pathogenesis of upper respiratory tract inflammation.

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Suggesting that the NO system is involved in the pathogenesis of upper respiratory tract inflammation, the effects of xylometazoline on NOS and inducible NO (iNOS) activity and expression were investigated in vitro. Besides, the direct scavenging properties of xylometazoline towards nitric oxide were studied.

“Xylometazoline was reported to have a dose-dependent inhibitory effect on total iNOS activity determined by nitrite/nitrate formation in the Griess test. This effect was found to be due to an inhibition of induction of the enzyme rather than inhibition of enzyme activity. Inhibition of constitutive NOS (cNOS) was moderate and had the same mechanism as inhibition of enzymatic iNOS activity. No direct scavenging properties of xylometazoline towards NO were detected” [46].

“As cNOS plays a crucial role in physiological processes and iNOS may exacerbate the inflammatory process, the pharmacological effect on the nitric oxide-generating system should be focused on the inhibition of iNOS alone. The specific characteristics of xylometazoline in vitro suggest its suitability for this application and may indicate an additional beneficial effect in the treatment of upper respiratory tract inflammation” [46].

“The antioxidant effects of xylometazoline were investigated by measuring the inhibition of microsomal lipid peroxidation and hydroxyl radical activity” [45]. It was reported that xylometazoline did not influence microsomal lipid peroxidation but significantly decreased hydroxyl radical levels. The mechanism of hydroxyl radical absorbance is still unclear. As oxidants play a role in tissue damage in inflammation, it is assumed that xylometazoline may have a beneficial effect thanks to its antioxidant effects in the topical treatment of nasal inflammation.

The ability of oxymetazoline to model pro- and anti-inflammatory and oxidative stress responses was evaluated in cell-free systems, including 5-lipoxygenase (5-LO) as proinflammatory and 15-lipoxygenase (15-LO) as anti-inflammatory enzymes. The oxidation of methionine by agglomerates of ultrafine carbon particles (UCPs), indicating oxidative stress, was studied. In a cellular system using canine alveolar macrophages, the impact of oxymetazoline on phospholipase A2 (PLA2) activity, respiratory burst, and synthesis of prostaglandin E2 (PGE2), 15(S)-hydroxy-eicosatetraenoic acid (15-HETE), leukotriene B(4) (LTB4), and 8-isoprostane was measured in the absence and presence of UCP or opsonized zymosan as particulate stimulants. In cell-free systems, oxymetazoline (0.4-1 mM) inhibited 5-LO but not 15-LO activity and did not alter UCP-induced oxidation of methionine.

“In alveolar macrophages oxymetazoline induced PLA2 activity and 15-HETE at 1 mM, enhanced PGE2 at 0,1 mM, strongly inhibited LTB4 and respiratory burst at 0,4/0,1 mM ($p < 0,05$), but did not affect 8-isoprostane formation. Oxymetazoline did not alter UCP-induced PLA2 activity and PGE2 and 15-HETE formation in alveolar macrophages but inhibited UCP-induced LTB4 formation and respiratory burst at 0,1 mM and 8-isoprostane formation at 0,001 mM. In opsonized zymosan-stimulated alveolar macrophages, oxymetazoline inhibited LTB4 formation and respiratory burst (0,1 mM)”. [4]

“Thus, in canine alveolar macrophages, oxymetazoline suppressed proinflammatory reactions including 5-LO activity, LTB4 formation, and respiratory burst, and prevented oxidative stress, whereas PLA2 activity and synthesis of immune-modulating PGE2 and 15-HETE were not affected” [4].

Schoeffter et al. [41] in their study, using American opossum kidney epithelium cells, demonstrated that oxymetazoline was a potent agonist at 5-hydroxytryptamine (5-HT, serotonin) 1A, 1B, and 1D, and a partial agonist at 5-HTP 1C receptors.

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Another study explored the effect of oxymetazoline on isolated rat's tracheal smooth muscles. A rat trachea of 5 mm in length was immersed in 30ml Krebs-Ringer solution at 37°C. Administration of oxymetazoline caused significant tracheal relaxation in a dose-dependent manner, even in the presence of a cholinergic agent. The effects of oxymetazoline on the basal tension of the trachea were insignificant. The study indicated that high concentrations of oxymetazoline might actually antagonize cholinergic receptors of the trachea [44].

The other study [47] showed that oxymetazoline following intravenous administration at 0,2-1,7 mmol/kg decreased basal gastric motor activity. After stimulation of the motility by insulin (5 IU/rat, i.v.), both clonidine (1,9-3.8 mmol/kg, i.v.) and oxymetazoline (0,1-3,4 mmol/kg, i.v.) inhibited the gastric motor activity. However, while the effect of clonidine was antagonized by the non-selective α2-adrenoceptor antagonist yohimbine (5 mmol/kg, i.v.) and the α2-adrenoceptor selective antagonist BRL 44408 (3 mmol/kg, i.v.), the effect of oxymetazoline was only partially affected. Prazosin (α1- and α2B-adrenoceptor antagonist, 0,07-0,28 mmol/kg, i.v.) also failed to reverse the effect of oxymetazoline. Furthermore, when gastric motility was stimulated peripherally by activation of postsynaptic cholinergic muscarinic receptors by the combination of carbachol (0,14 mmol/kg, i.v.) and hexamethonium (37 mmol/kg, i.v.), clonidine (3,8 mmol/kg, i.v.) failed to affect the increased motor activity; however, oxymetazoline (0,8-3,4 mmol/kg, i.v.) exerted a pronounced inhibition. These results suggest that different mechanisms may be involved in the inhibitory effects of clonidine and oxymetazoline; while clonidine reduces gastric motility by activating presynaptic α2-adrenoceptors, a postsynaptic component in the effect of oxymetazoline has also been observed.

4. CONCLUSION

Although, according to the available scientific data, there are minor differences between the pharmacokinetics and pharmacodynamics of xylometazoline and oxymetazoline. Both drugs have very low systemic exposure, while creating high local concentrations in areas of inflammation. Such properties of these drugs allow them to achieve high efficiency with a small number of systemic side effects.

In addition, due to its pharmacokinetic properties, xylometazoline has a faster onset of action and a shorter duration of therapeutic effect compared to oxymetazoline.

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