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Review

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Influence of Intranasal Drugs on Human Nasal Mucociliary Clearance and Ciliary Beat Frequency

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ABSTRACT

The nasal mucociliary clearance system, which comprises epithelial cilia and mucus from goblet cells, is an important intrinsic defense mechanism of the upper respiratory tract. Intranasal drugs and additives can have a detrimental effect on ciliary activity and mucociliary clearance, and thus impact the integrity of nasal defense mechanisms. This article discusses the current literature on the effects of different classes of intranasal drugs including intranasal corticosteroids, antihistamines, decongestants, antimicrobials and antivirals, as well as various drug excipients and nasal irrigation solutions on human nasal mucociliary clearance and ciliary beat frequency. Available data indicate that some intranasal formulations tend to hamper nasal ciliary function and mucociliary clearance. Therefore, it is of great importance to assess the effects of intranasal drugs and additives on mucociliary function before they are recommended as therapy for different nasal conditions.

Keywords: Intranasal administration; excipients; nasal irrigations; mucociliary clearances; cilia

INTRODUCTION

Intranasal administration of drugs has generated much attention within pharmaceutical industry as a viable option for local or systemic delivery of diverse therapeutic compounds in recent years. The intranasal route provides several advantages for drug delivery due to the noninvasive nature of the process, a large nasal mucosa surface area, rapid onset of therapeutic effect, potential for direct-to-central nervous system delivery, avoidance of first-pass metabolism, and likelihood for maximal patient comfort and compliance.[1] A prerequisite for intranasal formulations, however, is that the drugs and additives should not interfere with normal nasal function, especially mucociliary clearance function.

The nasal mucociliary clearance system, which comprises epithelial cilia and mucus from goblet cells, is one of the most important nonspecific defense mechanisms of the respiratory tract. Under normal conditions, epithelial cilia beat in a coordinated and unidirectional fashion to transport mucus through the epithelium to various drainage sites, and thus remove inhaled particles and irritants such as dust, bacteria, viruses and air pollutants from the airway.[2] Inhibition of the mucociliary clearance system induces a longer contact time of nasal mucosa with entrapped particles and irritants, possibly leading to airway infection and

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damage to the nasal mucosa. Mathematical modeling shows that energy transferred by cilia to mucus blanket is proportional to the square of ciliary beat frequency (CBF). Additionally, experimental data have demonstrated that a relatively modest increase in CBF (16%) resulted in a 56% increase in surface liquid velocity, *i.e.*, mucociliary transport.[3] Thus, CBF is an important parameter for assessing ciliary function and mucociliary clearance.

Evidence-based international guidelines have recommended the use of intranasal corticosteroids, antihistamines, decongestants, anti-infective agents and nasal irrigation for the treatment of rhinitis, sinusitis, and related allergic or chronic nasal conditions.[4,5] Intranasal drug formulations are composed of active drugs and various formulation excipients such as preservatives and absorption enhancers, which may individually or in combination have harmful effects on nasal ciliary function or mucociliary clearance. This article reviews the current literature on the effects of different types of intranasal formulations on human nasal mucociliary clearance and CBF.

EFFECTS OF INTRANASAL CORTICOSTEROIDS

Intranasal corticosteroids are recommended as first-line therapy for the treatment of allergic rhinitis due to their efficacy, tolerability and ease of use. However, debates over the safety of intranasal corticosteroids and their potential side effects on nasal mucociliary function have been on-going for several years. Some of the current, widely used intranasal corticosteroids include budesonide, fluticasone propionate/furoate, triamcinolone acetonide and mometasone furoate[6] as well as newer non-aqueous intranasal corticosteroid aerosols beclomethasone dipropionate and ciclesonide.[7,8]

Several studies have investigated the influence of intranasal corticosteroids on mucociliary clearance. An early study by Holmberg and Pipkorn[9] reported that topical beclomethasone dipropionate suspension treatment did not change mucociliary clearance in healthy volunteers, as indicated by utilizing the saccharine-dye test.[9] Similarly, Klossek and colleagues[10] and Pata and colleagues[11] have employed the saccharine test to assess the effect of 6 months' treatment with triamcinolone acetonide or 1 month's treatment with mometasone furoate, respectively, and demonstrated that neither compound impaired mucociliary function in patients with perennial allergic rhinitis. Employing a radiotracer technique, Naclerio and colleagues[12] compared the influence of 2 weeks' treatment with either budesonide or mometasone on nasal mucociliary function and reported that neither drug impaired mucociliary clearance function[12] (**Table 1**).

However, the effects of intranasal corticosteroids on ciliary motility observed *in vitro* are different from those observed *in vivo*. Early studies have indicated that while budesonide appeared to decrease human nasal CBF only slightly *in vivo* [13]; beclomethasone dipropionate and flunisolide induced a dose-related, irreversible decrease in human nasal CBF *in vitro*.[14] Using cultured human nasal epithelial cells, Hofmann and colleagues[15] have reported that budesonide spray did not affect CBF at 10% dilution and induced moderate reversible decrease in CBF at 50% dilution. In contrast, fluticasone propionate and mometasone furoate sprays induced a reversible decrease in CBF at 10% dilution and a complete, irreversible ciliostasis at 50% dilution. Using primary human nasal epithelial culture models, we have previously demonstrated that budesonide induced a rapid but reversible ciliostasis at undiluted therapeutic concentrations and a gradual but fully reversible decrease in CBF

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Table 1. Effects of intranasal corticosteroids on human nasal mucociliary clearance and CBF

Compound	Indicator	Effect
Beclomethasone dipropionate	Mucociliary clearance	No effect[9]
	CBF	Decrease, irreversible[14]
Triamcinolone acetonide	Mucociliary clearance	No effect[10]
Mometasone furoate	Mucociliary clearance	No effect[11,12]
	CBF	Decrease, irreversible[15]
Budesonide	Mucociliary clearance	No effect[12]
	CBF	Decrease[13]/Decrease, reversible[15,16]
Fluticasone propionate	CBF	Decrease, irreversible [15,16]

CBF, ciliary beat frequency.

at 50% dilution, whereas no effect was observed on CBF at 10% dilution.[16] In contrast, fluticasone propionate induced irreversible ciliostasis when used undiluted and at up to 50% dilution of therapeutic concentration, whereas there was a reversible decrease of CBF at 10% dilution[16] (**Table 1**).

EFFECTS OF INTRANASAL ANTIHISTAMINES

Intranasal antihistamines, along with intranasal corticosteroids, are also proposed as first-line therapy in patients with allergic rhinitis.[4,5] In contrast to intranasal corticosteroids, intranasal antihistamines have a more rapid onset of action, ranging from 15 to 30 minutes, and are therefore especially useful in patients with episodic nasal symptoms or as a pretreatment before inhaled allergen exposure.[17] Antihistamines are functionally classified as first-or second-generation antihistamines according to whether or not they enter blood brain barrier readily and cause side effects such as sedation and mucosal dryness. Current widely used second-generation antihistamines, for example azelastine and levocabastine, cause fewer adverse side effects and are also highly potent and selective H1-receptor antagonists, with many of these compounds possessing additional antiallergic and anti-inflammatory properties.[18]

Studies investigating the influence of intranasal antihistamines on mucociliary clearance and ciliary function have provided contradictory results (**Table 2**). Some studies have demonstrated no adverse effects of intranasal formulations containing azelastine or levocabastine on mucociliary clearance and/or ciliary function, either *in vivo* or *in vitro*.[19,20] In contrast, others have reported that intranasal formulations containing azelastine and levocabastine do produce ciliotoxic effects on human nasal epithelium *in vitro*.[21,22] We have also assessed the effects of azelastine and levocabastine nasal sprays on CBF of human nasal epithelial cell cultures and demonstrated that while undiluted aqueous azelastine or levocabastine caused irreversible ciliostasis and a 10% dilution resulted in reversible decreases in CBF of these cultures, up to 5% dilution of these formulations had no effect on the CBF of these cultures.[16]

Table 2. Effects of intranasal antihistamines on human nasal mucociliary clearance and CBF

Compound	Indicator	Effect
Azelastine	CBF	No effect[19]/Decrease[22]/Decrease, irreversible[16,21]
Levocabastine	CBF	No effect[20]/Decrease, irreversible[16,21]
	Mucociliary clearance	No effect[20]

CBF, ciliary beat frequency.

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EFFECTS OF INTRANASAL DECONGESTANTS

Intranasal decongestants are the most powerful drugs available for the reduction of nasal obstruction. These drugs cause vasoconstriction and reduce congestion of the mucosa in favour of the available volume of nasal cavities for air passage and conditioning, and are therefore widely used as an adjuvant for improving ventilation of sinuses in the treatment of allergic rhinitis and acute or chronic rhinitis. Intranasal decongestants can be divided into 2 groups: sympathomimetic amines (*e.g.*, adrenaline, phenylephrine, ephedrine and phenylpropanolamine) and imidazoline derivatives (*e.g.*, naphazoline, oxymetazoline and xylometazoline).[23] Serving as commonly used nasal decongestants; ephedrine is a nonselective α/β-adrenergic receptor agonist, while phenylephrine, naphazoline, oxymetazoline and xylometazoline are selective α-adrenergic receptor agonists.

The influence of intranasal decongestants on human nasal mucociliary clearance and CBF is summarized in **Table 3**. Teng and colleagues[24] demonstrated that ephedrine (0.5% and 1%) decreased the human mean nasal mucociliary transport rate in healthy volunteers.[24] In contrast to these findings, studies from our laboratory investigating the effects of ephedrine on the regulation of human nasal CBF have demonstrated ephedrine to induce instant and moderate increases in CBF followed by inhibitory responses.[25] Moreover, we demonstrated that the clinically used concentration of ephedrine (0.5%) induced the highest stimulatory effect, without any obvious inhibitory effect on human nasal CBF.[25] Phillips and colleagues[26] investigated the *in vivo* and *in vitro* effect of phenylephrine on nasal CBF and mucociliary transport of healthy volunteers and demonstrated that while phenylephrine had a cilio-stimulatory effect *in vivo* as well as at a low concentration (0.01%) *in vitro*, it also had a cilio-inhibitory effect at higher concentrations (0.25% and 0.5%) *in vitro*.[26] Similarly, Min and colleagues[27] reported that at concentrations of 0.125% to 2.5%, phenylephrine induced a significant decrease in human nasal CBF in a dose-dependent- and time-dependent manner.[27]

Oxymetazoline, xylometazoline and naphazoline have also been reported to inhibit ciliary movement and mucociliary transport in human nasal mucosa.[28-30] Mickenhagen and colleagues[31] have investigated the influence of different alpha-sympathomimetic drugs on the CBF of cultured human nasal mucosa cells *in vitro*. They demonstrated that while oxymetazoline was not ciliotoxic at concentrations of 0.01% and 0.001%, it did cause irreversible damage to cilia and a significant decrease in CBF, which was partially reversible, at a concentration of 0.1%. In contrast, naphazoline at concentrations ranging from 0.001% to 0.1% was not shown to significantly alter CBF.[31] We have also investigated the effects of oxymetazoline on CBF and mucociliary transport time in cultured nasal mucosal tissue of

Table 3. Effects of intranasal decongestants on human nasal mucociliary clearance and CBF

Compound	Indicator	Effect
Ephedrine	Mucociliary clearance	Decrease[24]
	CBF	Instant increase followed by decreas3[306]
Phenylephrine	Mucociliary clearance	Increase[26]
	CBF	Increase (low concentration), decrease (high concentration)[26]/ Decrease[27]
Oxymetazoline	Mucociliary clearance	Decrease, reversible[30]/Increase[32]/No effect (low concentration), decrease (high concentration)[24]
	CBF	Decrease[28]/No effect (low concentration), decrease (high concentration)[31,32]
Xylometazoline	CBF	Decrease[28]/Decrease, partially reversible[29]
Naphazoline	CBF	Decrease[28]/No effect[31]

CBF, ciliary beat frequency.

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healthy individuals and demonstrated that CBF was not significantly altered at concentrations of oxymetazoline 0.025% or 0.05%, but was significantly decreased at concentrations of oxymetazoline 0.10% and 0.20%. Additionally, 0.05% oxymetazoline increased the mean human nasal mucociliary transport time.[32] Another study has investigated the effects of nasal decongestants on the mucociliary transport rate and ciliary structure in the human nasal mucosa of healthy volunteers using the saccharine test and electron microscopy, respectively and reported that while 0.025% or 0.05% oxymetazoline neither affected mucociliary transport nor the ciliary structure in the nasal mucosa, higher concentrations of 0.5% and 1.0% ephedrine significantly decreased mucociliary transport as well as exfoliated the cilia in the nasal mucosa of these individuals.[24]

EFFECTS OF INTRANASAL ANTIMICROBIALS AND ANTIVIRALS

Topical anti-infective therapy is a promising addition to chronic rhinosinusitis treatment, particularly for patients with persistent or recurrent disease. Current anti-infective therapy includes antibacterials, antifungals, antivirals, *etc*. Mallants and colleagues[33] investigated the effects of different antibiotics on CBF of human nasal epithelial cells and demonstrated that clarithromycin and neomycin did not influence ciliary activity, while bacitracin, clindamycin, gramicidin and roxithromycin significantly increased CBF. However, another investigation of the effects of some protease inhibitors on human nasal CBF reported that bacitracin (8 mM), as well as puromycin (135 mM) had no effect on CBF after acute exposure, but significantly reduced the CBF following 15-minute daily exposure for 1 week.[34] Indeed, several other antibacterials, including ofloxacin, betadine and mupirocin, have also been reported to decrease ciliary activity in human nasal epithelial cells.[35-37] A recent study investigating the influence of nebulized drugs on nasal ciliary activity reported that nebulization of tobramycin, colistimethate, ceftazidime and aztreonam did not affect CBF, while a tobramycin-containing solution manufactured for intravenous use had a negative effect on CBF.[38]

With respect to the influence of antivirals on ciliary function and mucociliary clearance, Han and colleagues[39] have reported that although 20 mg/mL ribavirin, a broad spectrum antiviral agent, did not influence ciliary activity *in vitro*; 50 mg/mL ribavirin slowed ciliary beating significantly and 60 mg/mL caused ciliostasis. Nasal inhalation of ribavirin at 60 mg/mL for up to 20 minutes, however, neither slowed mucociliary clearance, nor affect the ciliary beat of nasal epithelium examined *in vitro* immediately after inhalation.[39] Another study investigating the effect of ribavirin on ciliary activity, however, showed that a concentration of 500 mg/mL ribavirin did not affect ciliary beating of nasal epithelial cells collected from either individuals with symptomatic colds or healthy volunteers.[40] Dimova and colleagues[41] investigated the effects of 5,7,3′,4′-tetrahydroxy-3-O-methylflavone (3-MQ), an anti-rhinoviral compound for nasal application, on CBF of human nasal epithelial cells and demonstrated that 3-MQ at 2 mg/mL and 10 mg/mL had a reversible cilio-stimulatory effect, without any observable ciliotoxic effect at even higher concentrations up to 20 mg/mL.

Several antifungal drugs, including amphotericin B (AMB), clotrimazole and itraconazole, have also been reported to have an inhibitory effect on human nasal CBF.[35,42,43] However, a study on the safety of a novel formulation of nanodisc (ND) containing super aggregated AMB (ND-AMB) for sinonasal delivery has recently demonstrated apically administered 75

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Table 4. Effects of intranasal antimicrobials and antivirals on human nasal mucociliary clearance and CBF

Compound	Indicator	Effect
Clarithromycin	CBF	No effect[33]
Neomycin	CBF	No effect[33]
Bacitracin	CBF	Increase[33]/No effect (acute exposure), decrease (1-week exposure)[34]
Clindamycin	CBF	Increase[33]
Gramicidin	CBF	Increase[33]
Roxithromycin	CBF	Increase[33]
Puromycin	CBF	No effect (acute exposure), decrease (1-week exposure)[34]
Ofloxacin	CBF	Decrease[35]
Betadine	CBF	Decrease[35,37]
Mupirocin	CBF	Decrease[36]
Tobramycin	CBF	No effect[38]
Colistimethate	CBF	No effect[38]
Ceftazidime	CBF	No effect[38]
Aztreonam	CBF	No effect[38]
Ribavirin	CBF	No effect (low concentration), decrease (high concentration)[39]/No effect[40]
	Mucociliary clearance	No effect[39]
5,7,3′,4′-tetrahydroxy-3-O-methylflavone	CBF	Increase, reversible (low concentration), no effect (high concentration)[41]
Amphotericin B	CBF	Decrease[35,42,43]/No effect[44]
	Mucociliary clearance	No effect[45]
Clotrimazole	CBF	Decrease[35]
Itraconazole	CBF	Decrease[35,42]

CBF, ciliary beat frequency.

μg/mL ND-AMB or AMB solution for 15 minutes to insignificantly alter the CBF of human nasal epithelial cells grown as air-liquid interface cultures.[44] More recently, Jiang and colleagues[45] evaluated the efficacy of AMB nasal irrigation as adjuvant therapy after functional endoscopic sinus surgery (ESS) on chronic rhinosinusitis patients, and demonstrated that nasal irrigation with 200 μg/mL AMB for 2 months did not significantly alter saccharine transit time, compared to pre-irrigation. The influence of different antimicrobials and antivirals on human nasal mucociliary clearance and CBF is summarized in **Table 4**.

EFFECTS OF INTRANASAL DRUG EXCIPIENTS

Absorption enhancers and preservatives are commonly used drug excipients and indispensable components of intranasal drugs. Intranasal absorption enhancers are used to increase nasal membrane permeability so as to enhance efficient nasal absorption of the active drugs, while preservatives are essential for preventing microbial contamination, which could result as a consequence of repeated administration of the aqueous nasal formulation. Despite their effectiveness, some of these excipients have been reported to be toxic to the nasal epithelium and may interfere with mucociliary clearance and ciliary function. Thus, it is necessary to choose safe and effective excipients for intranasal drug delivery.

Many compounds of widely varying chemical structures, including bile acids, fusidate derivatives, fatty acids, phospholipids, cyclodextrins and chitosans, have been investigated as potential nasal absorption enhancers.[46] Ideally absorption enhancers should not interfere with the normal mucociliary function of nasal mucosa; however, early studies demonstrated

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several absorption enhancers, such as polysorbate 80 and LPC, had a cilio-inhibitory effect *in vitro*.[41,47] Various chitosans with different molecular weights were also reported to inhibit the mucociliary transport rate in human nasal tissue *ex vivo*, while once daily application of 0.25% chitosan solution for 7 days had no effect on saccharin clearance times *in vivo*.[48] In contrast to these earlier compounds, cyclodextrins are now preferred absorption enhancers because of advantageous properties for improved drug solubilization, protection against physicochemical and enzymatic degradation, and the potential for improved absorption. Uchenna and colleagues[46] assessed the effects of a series of cyclodextrins, including gamma-cyclodextrin, hydroxypropyl-beta-cyclodextrin, anionic-beta-cyclodextrin polymer, dimethyl-beta-cyclodextrin and alpha-cyclodextrin, on CBF using human nasal epithelial cell suspension cultures. They demonstrated that irreversible cilio-inhibition by cyclodextrins occurred only at concentrations exceeding those used in pharmaceutical formulations and/or after unusual exposure times in this model. Considering that dilution and mucociliary clearance contribute to a further decrease in local drug concentration *in vivo*, they proposed that cyclodextrins were safe nasal absorption enhancers[46] (**Table 5**).

Thiolization of well-established polymers such as poly(acrylates) or chitosans by immobilization of sulfhydryl bearing ligands on the polymeric backbone results in production of "thiomers" with significantly improved mucoadhesive enzyme- and efflux-pump inhibiting, as well as permeation-enhancing properties.[49] Palmberger and colleagues[50] investigated the effects of gel formulations of thiomers on CBF in human nasal epithelial cells and found that Poly(acrylic acid) 450 kDa-cysteine (PAA-cys), alginate-cysteine (alg-cys) and chitosan-thiobutylamidine (chito-TBA) exhibited a concentration-dependent and partially reversible cilio-inhibitory effect. Thus, they suggested that thiomers were likely to be suitable excipients for nasal drug delivery systems, taking into account that dilution after application and cilio-modifying effects are usually more pronounced under *in vitro* conditions.[50]

A variety of preservatives have been used in aqueous nasal formulations, such as benzalkonium chloride (BKC), potassium sorbate (PS), phenylethyl alcohol, chlorbutol, thiomersal, methylparaben and propylparaben. BKC is by far the most commonly used preservative in aqueous nasal formulations. However, the safety concerns about BKC remain controversial, particularly as some studies have shown that BKC caused impairment of CBF,

Table 5. Effects of intranasal drug excipients on human nasal mucociliary clearance and CBF

Compound	Indicator	Effect
Polysorbate 80	CBF	Decrease, reversible[41]
LPC	CBF	Decrease[47]
Chitosans	Mucociliary clearance	No effect[48]
Gamma-cyclodextrin	CBF	No effect[46]
Hydroxypropyl-beta-cyclodextrin	CBF	No effect[46]
Alpha-cyclodextrin	CBF	No effect (30-minute exposure), decrease (high concentration, after 45-minute exposure), partially reversible[46]
Dimethyl-beta-cyclodextrin	CBF	No effect (30-minute exposure), decrease (high concentration, after 45-minute exposure), irreversible[46]
Poly(acrylic acid) 450 kDa-cysteine	CBF	Decrease, partially reversible[50]
Alginate-cysteine	CBF	Decrease, partially reversible[50]
Chitosan-thiobutylamidine	CBF	Decrease, partially reversible[50]
Benzalkonium chloride	CBF	Decrease, irreversible[16,31,51]
	Mucociliary clearance	Decrease[52]/No effect[54]
Potassium sorbate	CBF	No effect[15,16]

CBF, ciliary beat frequency.

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mucociliary clearance or degenerative changes in nasal mucosa,[16,31,51,52] whereas others have reported BKC to have no toxic effects on the nasal mucosa.[53,54] Nevertheless, it is important to note that while data generated *in vitro* raises concerns regarding the safety of BKC, *in vivo* data generally indicates BKC to be safe. Taking into account that the toxic effect of BKC *in vitro* may be partially attenuated by absorption and dilution of respiratory mucus *in vivo*, the use of BKC in intranasal formulations has therefore generally been considered to be safe. Similarly, PS is another commonly used preservative in nasal formulations. In contrast to BKC, studies on the effects of PS have not found the cilio-toxic effect of this compound at clinically used concentrations.[15] Indeed, studies from our laboratory have also confirmed the safety of PS on CBF in human nasal ciliated cells.[16] Thus, like BKC, PS can also be considered as a safe preservative for use in intranasal formulations (**Table 5**).

EFFECTS OF NASAL IRRIGATION

Nasal irrigation is a simple, safe, effective therapeutic procedure that has been used in the treatment of nasal diseases for many years. Together with corticosteroid/pharmacological treatment, nasal irrigation is also recommended as first-line treatment in acute and chronic rhinosinusitis and after sinonasal surgery as well as adjunctive treatment for allergic rhinitis, acute upper respiratory tract infections, rhinitis in pregnancy, *etc*.[55] Nasal irrigation may be effective in reducing nasal congestion and mucopurulent secretion, stimulating cleansing of the nasal and paranasal cavities, and in preventing crusting and moisturizing the mucosa after endonasal surgery. Nasal irrigation also appears to improve the mucociliary transport function of the nasal mucosa.[56]

Different kinds of nasal irrigation solutions, such as normal saline as well as various concentrations of hypertonic saline, Ringer-Lactate solution, isotonic and hypertonic seawater solution have been used in clinical practice (**Table 6**). Saline solutions have been widely used in nasal irrigation for many years and are recommended for the treatment of various nasal diseases by several international expert groups.[55,57] While the majority of studies on the effects of saline solution of different osmolarities on mucociliary clearance have reported hypertonic saline to be more effective than normal saline in improving mucociliary clearance,[56,58,59] few studies have found no difference between hypertonic and normal saline.[60,61] Interestingly, a study by Ural and colleagues[62] has reported that irrigation with hypertonic saline restored impaired mucociliary clearance in chronic sinusitis patients, while isotonic saline improved mucociliary clearance in allergic rhinitis and acute sinusitis patients, suggesting that nasal irrigation with isotonic or hypertonic saline may improve mucociliary clearance time in various nasal pathologies.[62] Studies on the effects of saline

Table 6. Effects of nasal irrigation on human nasal mucociliary clearance and CBF

Compound	Indicator	Effect
Hypertonic saline	Mucociliary clearance	Increase[56,58-60,62]/No effect[61,66]
	CBF	Decrease[63,64]
Isotonic saline	Mucociliary clearance	Increase[56,60,62]/No effect[61,66]
	CBF	Decrease[63]/No effect[64]
Ringer-Lactate solution	Mucociliary clearance	Increase[65]/No effect[66]
Hypertonic seawater	Mucociliary clearance	Increase[67]
	CBF	Decrease[70]
Isotonic seawater	CBF	Increase[69]
Dexpanthenol in seawater	Mucociliary clearance	Increase[68]

CBF, ciliary beat frequency.

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solutions of different osmolarities on CBF *in vitro* have indicated that while 0.9% normal saline did not affect or had a moderately negative effect on CBF of human nasal epithelium, an increase in saline tonicity was associated with increased inhibition of CBF, reversible ciliostasis or irreversible ciliostatic effect, depending on saline hypertonicity.[63,64] Considering the findings from both *in vivo* and *in vitro* studies, isotonic or hypertonic saline solutions at concentrations of 2%–3% may be most appropriate for nasal irrigation.

Some studies have compared the effects of Ringer-Lactate solution with saline solution for nasal irrigation (**Table 6**). One study by Unal and colleagues[65] found that patients who used Ringer-Lactate solution for irrigation after nasal septal surgery had a significantly better mucociliary transport time than patients using isotonic saline solution.[65] In a more recent study by Low and colleagues[66] conducted a double-blind, randomized controlled trial to investigate the effects of normal saline, lactated Ringer's and hypertonic saline nasal douching solutions for 6-weeks after ESS. They reported that there was no significant improvement in mucociliary clearance with either of these solutions; however, irrigation with Ringer-Lactate solution resulted in significantly better improvement in sinonasal symptoms scores compared to normal or hypertonic saline solutions.[66] They suggest that nasal irrigation with lactated Ringer's solution after ESS may be better than irrigation with saline.

In recent years, isotonic or hypertonic seawater solution has commonly been used for nasal irrigation because of high levels of minerals and trace elements, such as calcium, potassium, magnesium and zinc ions, which can assist in epithelial wound repair and ciliary beat regulation. Indeed, Süslü and colleagues[67] have reported that in patients who underwent septoplasty, 20 days' nasal irrigation with hypertonic seawater significantly improved mucociliary clearance to a greater extent than isotonic saline irrigation, as indicated using the saccharine test.[67] Similarly, Fooanant and colleagues[68] have shown that dexpanthenol in seawater spray resulted in better mucociliary clearance than saline irrigation in sinusitis patients following ESS.[68] More recently, Bonnomet and colleagues[69] conducted a randomized, controlled, blinded, *in vitro* study to assess the effect of normal saline and diluted or non-diluted seawater on CBF and epithelial wound repair speed (WRS) in airway epithelial cells from 13 nasal polyps explants. They demonstrated that non-diluted seawater enhanced the CBF and WRS of nasal epithelial cells when compared to normal saline and diluted seawater.[69] Furthermore, undiluted seawater significantly enhanced CBF and slightly improved WRS compared to control medium. However, contrary to these findings, Laberko and colleagues[70] have demonstrated that hypertonic seawater solution had a strong ciliotoxic effect on nasal ciliary epithelium *in vitro*[70] (**Table 6**).

CONCLUSIONS

Nasal mucociliary clearance is an important intrinsic defense mechanism of the respiratory tract. A review of the published literature indicates that intranasal drugs including corticosteroids, antihistamines, decongestants, antimicrobials and antivirals, and various drug excipients such as preservatives and absorption enhancers as well as different nasal irrigation solutions may influence nasal mucociliary clearance or nasal mucosal ciliary function. Depending on whether intranasal drugs speed up, slow down or block mucociliary clearance or ciliary function, they subsequently influence different aspects of clinical activity. Thus, increased mucociliary clearance could lead to the drug being rapidly cleared and may result in much shorter duration and lower nasal bioavailability, whereas slowing down or

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blockage of normal mucociliary clearance would result in longer contact of the nasal mucosa with entrapped viruses and bacteria, possibly leading to airway infection and damage to the mucosa. Therefore, it is of great importance to assess the effects of nasal drugs and additives on nasal ciliary function and mucociliary clearance in the development of new nasal drugs and the selection of appropriate safe excipients. However, it should be noted that some of the observed effects of drugs on CBF *in vitro* are different and more pronounced than their actual effects on ciliary activity and mucociliary clearance *in vivo*. Thus, if a compound does not affect mucociliary clearance *in vivo* or is shown to have no effect or only a mild effect *in vitro*, it can be considered safe for *in vivo* use.

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