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Review

The Influence of Drugs on Nasal Ciliary Movement

Walter A. J. J. Hermens [1] and Frans W. H. M. Merkus[1,2]

Drugs in nasal preparations, for local use as well as for systemic use, should not interfere with the self-cleaning capacity of the nose, effectuated by the ciliary epithelium. Many drugs and additives, however, have a negative effect on nasal ciliary function. Examples of ciliotoxic agents are lipophilic and mercuric preservatives, local anesthetics, antihistamines, propranolol, and absorption enhancers such as the bile salts. Cholinergic drugs and β-adrenergic drugs exert a ciliostimulatory effect. It is the purpose of this review to summarize the present knowledge of ciliotoxicity of drugs and additives and to give recommendations for the use of ciliofriendly drugs in nasal preparations.

Key Words: ciliary movement; ciliotoxicity; nasal drug delivery.

INTRODUCTION

Nasal drops for local effect are extensively used, as they are often "over the counter" drugs and indicated for frequently occurring diseases such as the common cold and hay fever. The nasal mucosa is also a potential site for drug absorption, as the surface of the mucosa is large and well provided with blood vessels. With nasal drug delivery the first-pass effect and gastrointestinal degradation of drugs, occurring after oral administration, can be avoided (1). An important aspect of nasal drug delivery is the effect of drugs and additives on nasal ciliary function. Cilia are fingerlike protrusions of the nasal epithelial cells (Fig. 1). They were first described by De Heide and Leeuwenhoek in the seventeenth century, but it was not until the 1930s that Proetz (2) emphasized the importance of studying the ciliary function and physiology. Cilia move in a well-organized and coordinated way to propel the overlying mucus layer toward the throat. By mucus transport the inspired dust, allergens, and bacteria entrapped in the mucus are removed. It is the main defensive mechanism of the respiratory tract. Ciliostasis prevents the defensive barrier from functioning properly. From patients with immotile cilia syndrome it is known that chronic ciliary arrest leads to recurrent infections of the airways (3). Ciliary movement is the most important parameter in nasal mucociliary clearance in normal circumstances (4) and should therefore not be decreased by nasal medication.

To study the actions of drugs on ciliary movement, mucociliary clearance studies with marker substances deposited in the nose are described (5–8). These methods may be useful as an overall index of mucociliary clearance, but they lack specifity as an index of ciliary movement as such. Therefore methods have been developed to measure the *in vitro* effects of drugs on ciliary movement. The frequency of ciliary waves can be estimated with high-speed cinematography (9). A motion picture is recorded at high speed and afterward projected at low speed. This method is accurate but expensive and laborious. Another method uses stroboscopic light to illuminate the cilia (10). When the number of flashes per second of the light equals the ciliary beat frequency, the cilia are perceived as stationary. Cilia can also be illuminated with a laser beam (11). The spectrum of the scattered light can be analyzed and gives information about the ciliary beat frequency. Other methods involve the use of a photocell or a photomultiplier to measure the variations in the intensity of a light beam directed through a preparation of ciliary epithelial tissue (12–22). After amplification the signal can be visualized and the frequency can be measured. With these methods the influence of many drugs on ciliary movement has been studied. Other, more simple methods have been described, but an important disadvantage is the poor precision of these methods. (23,24).

PRESERVATIVES

To prevent microbial contamination of multidose nasal preparations, the presence of a preservative is required. Mercuric compounds, such as thiomersal, have been found to be extremely ciliotoxic in an irreversible way (25). Further, lipophilic preservatives such as chlorbutol are ciliotoxic, although the effects may be reversible. Polar preservatives such as benzalkonium chloride are less ciliotoxic. For preservation of nasal preparations the use of benzalkonium chloride (0.01%) with EDTA (0.05%) is recommended, because this combination appeared the least harmful (25).

NASAL DRUGS FOR LOCAL USE

Decongestants

Decongestant-containing nasal drops are extensively

[1] Center for Bio-Pharmaceutical Sciences, Leiden University, P.O. Box 9502, 2300 RA Leiden, The Netherlands.
[2] To whom correspondence should be addressed.

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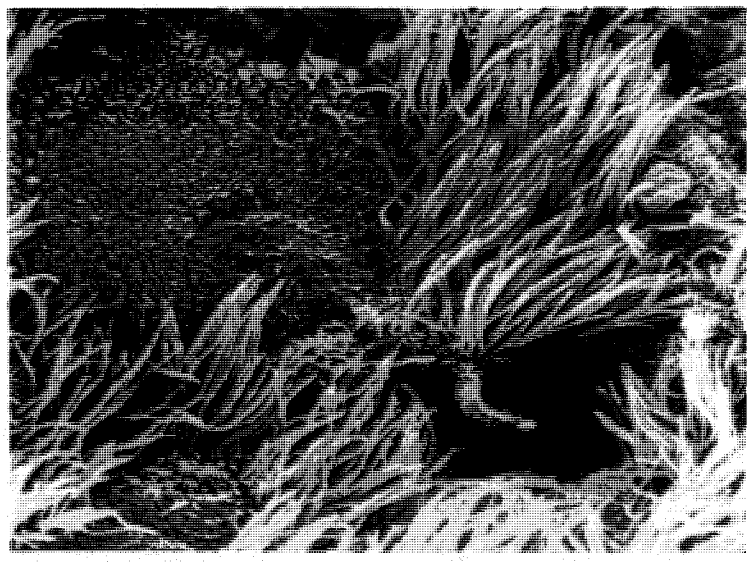

Fig. 1. Scanning electron micrograph of human nasal ciliated epithelium. Fixed in glutaraldehyde, × 4,300. (Courtesy of Dr. E. Rijntjes.)

used for frequently occurring diseases such as the common cold. Although ciliotoxicity for all topical nasal decongestants except for phenylephrine has been reported (26), the ciliotoxic effects of imidazolines are usually considered to be small (27,28). Like the preservatives, the effect of the more lipophilic compounds was larger, but not unacceptably large, and reversible within a 20-min contact. From a comparison among the effects of decongestants, preservatives, and commercial decongestant preparations, it appeared that the ciliotoxicity of the commercial preparations investigated was due mainly to the effect of the preservatives used (28).

General and Local Anesthetics

Suppression of ciliary activity by inhalation anesthetics has long been recognized. In 1928 Hill (29) reported that ether and chloroform inhibited ciliary activity.

A dose-dependent suppression of the ciliary beat frequency of a moderate degree after exposure of tracheal segments to warmed and humidified vapors of halothane and enflurane has been observed. No suppression, however, was noted after exposure to nitrous oxide (30).

Local anesthetics are used in, for example, small nose operations and during bronchoscopy. Their effects on the ciliary beat frequency are severe but reversible to some extent. The reversibility diminishes from lidocaine to cocaine to butacaine (31). Bupivacaine is considered to be particularly harmful for the ciliated epithelium, because of its strong and irreversible ciliotoxicity (32). Fortunately long-term nasal treatment with these drugs is rare.

Antimicrobial Agents

The advantages of local application of antimicrobial agents are the possibility of limiting adverse reactions of the drug to a small area of the body and possibility of using antibiotics that are too toxic for systemic administration. The ciliotoxic effects of most antimicrobial agents at normal therapeutic concentrations are modest (33–35). Penicillins show little ciliotoxicity (33,34). The effects of the sulfonamides are more pronounced, but even at high concentrations (e.g. 10% sulfacetamide sodium) there is a reversal of the effect. Neomycin is not ciliotoxic, probably because this drug hardly passes through cell membranes. Chloramphenicol is more ciliotoxic than neomycin. Bacitracin depresses ciliary activity dramatically and irreversibly (33). The use of an antimicrobial drug on ciliated epithelia should be based on the antimicrobial action of the drug, but the ciliotoxicity of chloramphenicol and bacitracin has to be taken into account (33).

Antiallergic Drugs

Of the antiallergic drugs, antihistamines, corticosteroids, and sodium cromoglycate are frequently used in allergic diseases of the airways. Local antihistamines are all very ciliotoxic in an irreversible way (31). Both diphenhydramine and tripelennamine arrest ciliary movement within 1 min. Their local use should therefore be discouraged. The ciliotoxic effects of prednisolone sodium phosphate (31) and budesonide (36) are very limited, whereas a solubilization of dexamethasone in polysorbate decreases the ciliary beat frequency more than 60% within 20 min. This effect is due largely to the polysorbate (31). Cromoglycate sodium has been found to be only slightly ciliotoxic (31,37).

Expectorants

Somewhat conflicting reports are given as to the effect of expectorants on ciliary movement, which may be due to a concentration dependence of the effect. An increase in ciliary beat frequency has been observed for low concentrations of *N*-acetylcysteine, ethylcysteine, and *S*-carboxymethylcysteine (38,39). At high concentrations these drugs cause a progressive reduction in ciliary beat frequency, but the inhibitory effect seems fully reversible (40,41). It is suggested that the increase in ciliary activity produced by these mucolytic drugs at low concentrations is due not to a direct effect on the ciliated cells, but rather to a mucolytic effect on the mucus around the cilia (39). It is thought that *N*-acetyl-

cysteine induces its ciliotoxic effect via the sulfhydryl group, and prolonged use may impair mucociliary clearance (42).

β-Adrenergic Drugs

Several drugs cause cilioexcitation. Among these, β-adrenergic drugs have been reported to stimulate ciliary movement (43–49). The effect is thought to be mediated by β-adrenoceptors, via the intracellular AMP system (43). The effect can be reduced by propranolol (47,49). An increased mucociliary clearance following aerosolized isoprenaline has been found to be independent of bronchial vasodilation, aqueous aerosol droplets, reflex parasympatic activation, or bronchodilation, and the effect can therefore be attributed to an increase in the ciliary beat frequency (48). Drugs isoprenaline and terbutaline may be beneficial in asthma bronchiale, in addition to their bronchodilationary action, because of this excitatory cilio effect (45).

Cholinergic Drugs

Cholinergic compounds, such as acetylcholine, methacholine, and pilocarpine, also have a significant ciliostimulatory effect at therapeutic concentrations (44,50). This effect can be blocked by atropine. Atropine alone does not influence basal mucociliary activity (50).

Methylxanthines

Theophylline and aminophylline have been found to increase the ciliary beat frequency slightly (16,43,44,51), probably because the methylxanthines have the ability to inhibit phosphodiesterase, thereby raising intracellular cyclic AMP levels (43,51).

NASAL DRUGS FOR SYSTEMIC USE

Recent investigations have demonstrated that the nasal mucosa can be very effective for drug absorption (1). When nasal administration of a drug is considered for systemic action, it is important to investigate the effect of the drug and additives on ciliary movement at an early stage. For example, some years ago the intranasal administration of propranolol was suggested in order to avoid a first-pass effect, occurring after oral administration. Nasal bioavailability was reported to be as high as 100% (53). Propranolol, however, turned out to be extremely cilitoxic in *in vitro* experiments (54,55) (Fig. 2). Even a 50-fold dilution of the proposed nasal drop arrested ciliary movement irreversibly within 20 min, and the authors comment that chronic use should therefore be discouraged (54).

Recently the absorption of the morphine derivatives naloxon and buprenorphine has been studied (56). A bioavailability of 101% for buprenorphine was found, implicating complete absorption. Nasal administration of morphine or potent morphinomimetics may be an effective route of drug delivery for preoperative sedation and postoperative analgesia and for the treatment of chronic severe pain. The effect of morphine, fentanyl, and sufentanil on the ciliary beat frequency of human nasal epithelial tissue has been investigated (57). These substances have a very low ciliotoxic potency (Fig. 3.), which therefore does not present a drawback for nasal administration of these drugs.

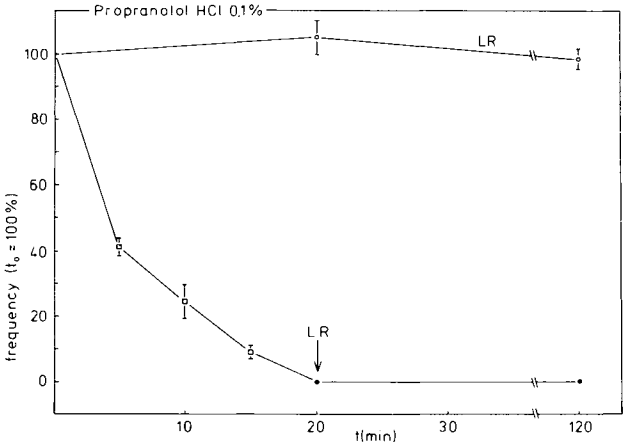

Fig. 2. Time versus ciliary beat frequency plot: effect of 0.1% propranolol-HCl on the cilia of human adenoids. LR, Locke-Ringer (control). (Reproduced from Ref. 54 with permission)

Nasal absorption may be useful for the administration of peptide hormones. Hormone substitution therapies require repeated injections for long periods. The high potency of most peptides makes these substances very suitable for intranasal administration, as the amount per dose can be very small. On the other hand, the sometimes large molecular size and hydrophilic properties at physiologic pH make absorption through the hydrophobic membranes difficult. The absorption efficiency of intranasally administered peptides can be improved with the aid of absorption promoters such as bile salts. However, these compounds are very ciliotoxic (58). Ciliotoxicity appeared to increase with an increase in hydrophobicity. Dihydroxy bile salts are more ciliotoxic than trihydroxy bile salts. Unfortunately, dihydroxy bile salts appeared to be more potent in the insulin absorption promoting effect (59).

Recently, hydroxyalkyl derivatives of β-cyclodextrin have been described for use in drug solubilization for preparations used on mucus membranes. These compounds are likely to become important additives in the intranasal application of drugs. A 10% solution of hydroxypropyl-β-cyclodextrin in water turned out to influence the ciliary beat frequency only slightly (60).

CONCLUSION

Investigations on the effect of drugs on nasal cilia are becoming increasingly important. Ideally, nasal drug formulations should not disturb ciliary movement and therefore leave the patient's respiratory defense mechanism intact. Nasal drug preparations for local use often appear to be ciliotoxic. Physicians should be aware of this when prescribing these preparations. It is often possible to choose a comparable formulation with a lower ciliotoxic potency (e.g., by altering the preservative). The use of a local symptomatic therapy that causes serious side effects on nasal cilia, counterbalancing the therapeutic effect, should be discouraged.

The investigation of the effect of drugs on nasal cilia may become even more important in the future because of the increasing design of nasal drug formulations for systemic effects. Therapy with these preparations will often be a

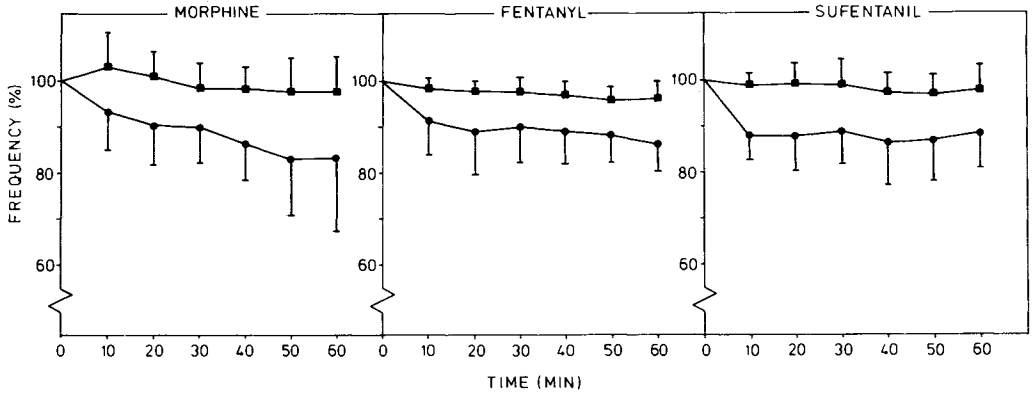

Fig. 3. Time versus ciliary beat frequency plots (mean ± SD) of cilia in solutions of drug and Locke-Ringer (control) (●) Drug; (■) Locke-Ringer. (Reprinted from reference 57 with permission.)

long-term treatment, as, for instance, insulin substitution therapy. Additives, necessary for absorption promotion of the active drug, should be carefully judged to be devoid of any serious ciliotoxicity. The feasibility of nasal drug administration will depend in large part on the effects on the ciliated epithelium. These effects will determine the acceptability of the formulation by the patient and thus the success of long-term nasal drug delivery.

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