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The effects of drugs on ciliary motility I. Decongestants

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Summary

The effects of some decongestants at different pHs on the ciliary beat frequency of chicken embryo tracheas have been investigated. Ephedrine, phenylephrine, xylometazoline and oxymetazoline exerted the smallest effect on the ciliary beat frequency at pH 7.4, whereas phenylpropanolamine, tramazoline and naphazoline had the smallest effect at pH 6. The decongestants investigated did not cause a 50% decrease in the ciliary beat frequency within 20 min at the pH at which the ciliotoxicity was minimal. The effects of all decongestants on the ciliary beat frequency at pH 7.4, after exposure for 20 min, were reversible. Phenylephrine and oxymetazoline appeared to be the least ciliotoxic.

Introduction

A large part of the respiratory tract is covered with ciliated epithelia which removes dust, allergens and microorganisms in the direction of the pharynx. If ciliary motility is impeded for a long time, recurrent infections often appear, as is known from the Immotile Cilia Syndrome (Afzelius, 1979). The effect of temporary ciliary arrest is unknown, but ciliodepression should be avoided especially in chronic therapy.

However, it is well-known that drugs can influence ciliary motility in a negative way. In former studies we described the effects of preservatives and nasal preparations on the ciliary beat frequency of chicken embryo tracheas (van de Donk et al., 1980b and 1981). We found a good correlation between the effects of drugs on the ciliary beat frequency of chicken embryo tracheas and human adenoids in vitro and

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also between these in vitro results and the in vivo effects of drugs on nasal clearance in volunteers (van de Donk et al., 1982a and 1982b).

The influence of alpha-sympathomimetic drugs on ciliary activity has received little attention until now. Hutcheon and Cullen (1955) investigated the effects of phenylephrine, ephedrine, naphazoline and tetrahydrozoline on rat tracheas. Verdugo et al. (1980) found a stimulating effect for isoproterenol. This compound has both alpha- and beta-sympathomimetic properties. The stimulation could be compensated according to Verdugo et al. with the beta-blocking agent propranolol, indicating that the stimulating effect of isoproterenol was merely caused by its beta-sympathomimetic effect. In this study the effects of decongestants, acting like alpha-sympathomimetics, at different pHs on the ciliary beat frequency of chicken embryo tracheas are described.

Methods and materials

The ciliary beat frequency was determined with a photo-electric registration device at 25°C in Locke Ringer (LR) solution (van de Donk et al., 1980a). The effects of each drug at a fixed pH were assayed 6 times. Reversibility was studied at pH 7.4 by washing the tissues with LR after 20 min contact with the decongestant. For each experiment a piece of tissue from the same trachea, and placed in pure LR, served as a reference. Table 1 lists the substances investigated and their lot numbers.

Results

The effects of the drugs at different pHs on the ciliary beat frequency of chicken embryo tracheas are shown in Table 2. The effects of rinsing with LR at pH 7.4 after 20 min contact have been assayed as well. The first column shows the pH, the next columns the ciliary beat frequency as a percentage of the initial beat frequency after 20, 40 and 60 min. The contact time necessary to reduce the beat frequency to 95% and 90% of the initial beat frequency are indicated by the last two columns.

TABLE 1

LIST OF INVESTIGATED DECONGESTANTS

Substance	Lot number	Manufacturer
Ephedrine-HCl	108635/79F26	Brocacef
Phenylephrine-HCl	110107/79F12	Brocacef
Phenylpropanolamine-HCl	19C-0559	Sigma
Xylometazoline-HCl	790717	Multipharma
Oxymetazoline-HCl	0080766	Merck
Tramazoline-HCl	11441	Karl Thomae gmbh
Naphazoline nitrate	111082/80D10	Brocacef

TABLE 2

EFFECTS OF DECONGESTANTS ON THE CILIARY BEAT FREQUENCY

Compound	pH	Frequency [a]			$t_{95\%}$ [b]	$t_{90\%}$ [c]
		t = 0.33 h	t = 0.67 h	t = 1.00 h		
Ephedrine-HCl (0.5%)	7.4	82 [d]	95	98	0.09	0.18
	7.4	74	66	63	0.06	0.13
	6	56	44	51	0.04	0.08
	5	48	40	43	0.03	0.06
Phenylephrine-HCl (0.5%)	7.4	95 [d]	96	99	0.30	
	7.4	88	86	80	0.14	0.29
	6	77	64	62	0.07	0.14
	5	68	50	44	0.05	0.10
Phenylpropanolamine-HCl (0.75%)	7.4	50 [d]	89	95	0.03	0.07
	7.4	43	37	28	0.03	0.06
	6	61	54	48	0.04	0.09
Xylometazoline-HCl (0.05%)	7.4	78 [d]	101	100	0.08	0.15
	7.4	76	63	50	0.07	0.14
	6	65	55	42	0.05	0.10
	5	54	48	37	0.04	0.07
Oxymetazoline-HCl (0.05%)	7.4	84 [d]	96	99	0.11	0.21
	7.4	90	75	65	0.17	0.33
	6	64	59	52	0.05	0.09
	5	56	49	37	0.04	0.07
Tramazoline-HCl (0.117%)	7.4	18 [d]	34	75	0.02	0.04
	7.4	28	11	0	0.02	0.05
	6	62	59	53	0.04	0.09
	5	50	48	45	0.03	0.07
Naphazoline nitrate (0.1%)	7.4	48 [d]	79	92	0.03	0.06
	7.4	52	33	23	0.03	0.07
	6	50	58	51	0.03	0.07
	5	42	35	32	0.03	0.06

[a] Ciliary beat frequency as a percentage of the initial frequency, after 0.33, 0.67 and 1 h.

[b] Time necessary to decrease the ciliary beat frequency to 95% of the initial value.

[c] Time necessary to decrease the ciliary beat frequency to 90% of the initial value.

[d] After this measurement the tissue was rinsed with LR and the experiment was continued in LR.

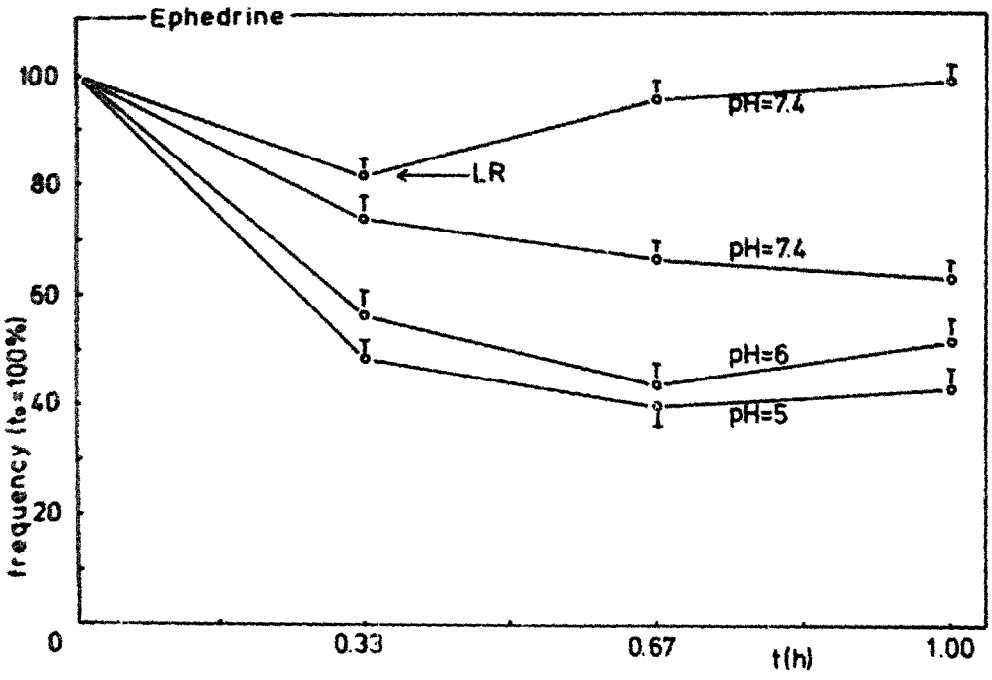

Fig. 1. Time versus frequency plot of ephedrine-HCl (0.5%) at pH 5, 6, 7.4 continuously, and at pH 7.4 washed after 20 min with LR.

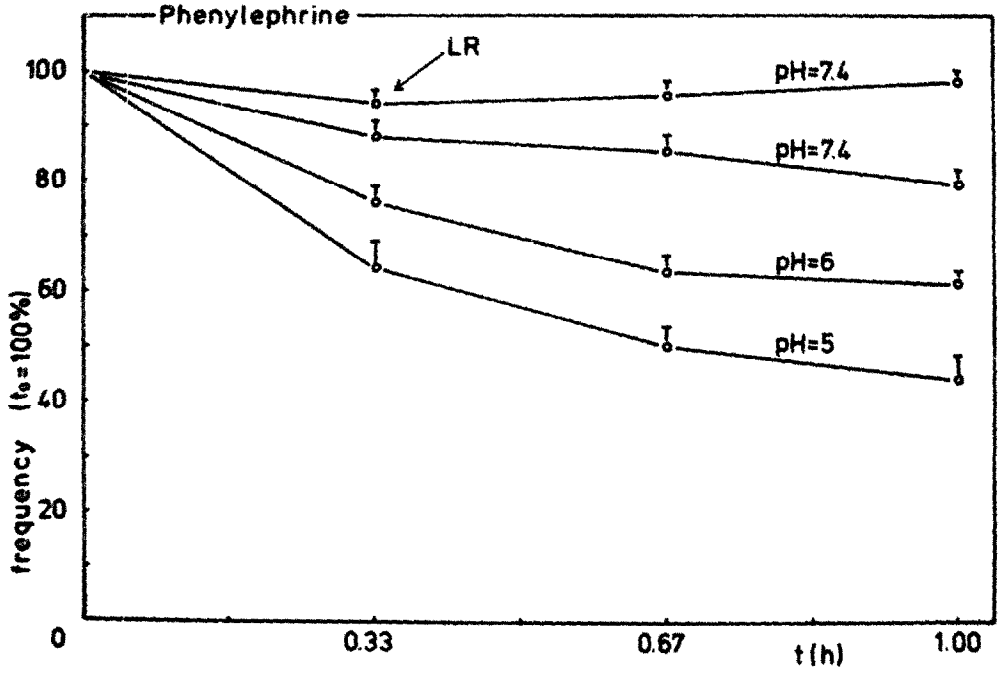

Fig. 2. Time versus frequency plot for phenylephrine-HCl (0.5%) at pH 5, 6, 7.4 continuously, and at pH 7.4 washed after 20 min with LR.

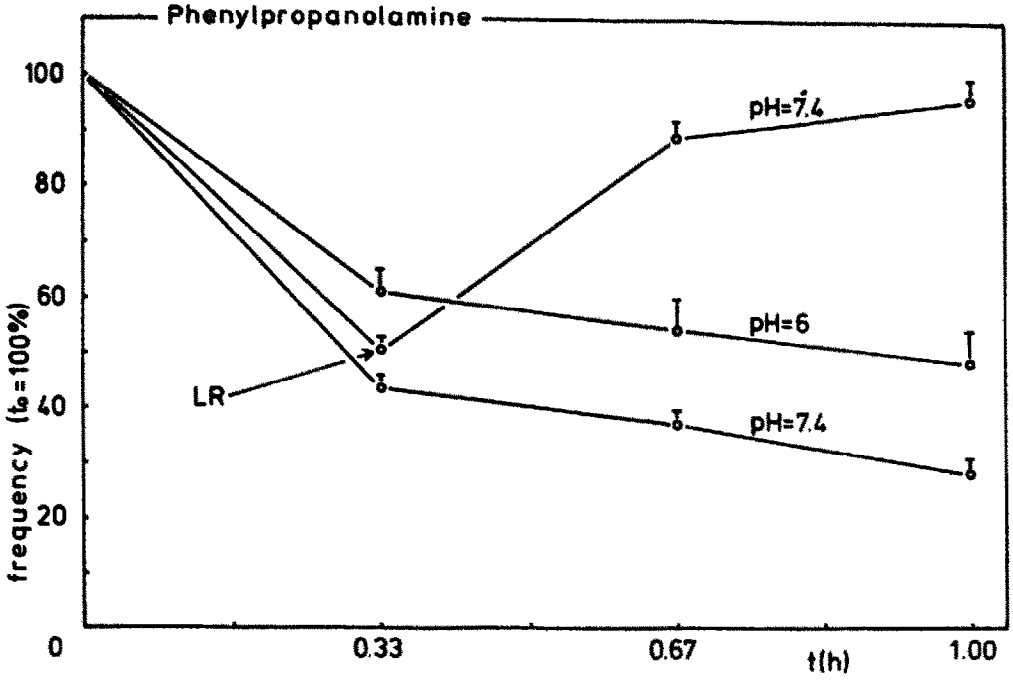

Fig. 3. Time versus frequency plot for phenylpropanolamine-HCl (0.75%) at pH 7.4 continuously, pH 7.4 washed after 20 min with LR and at pH 6.

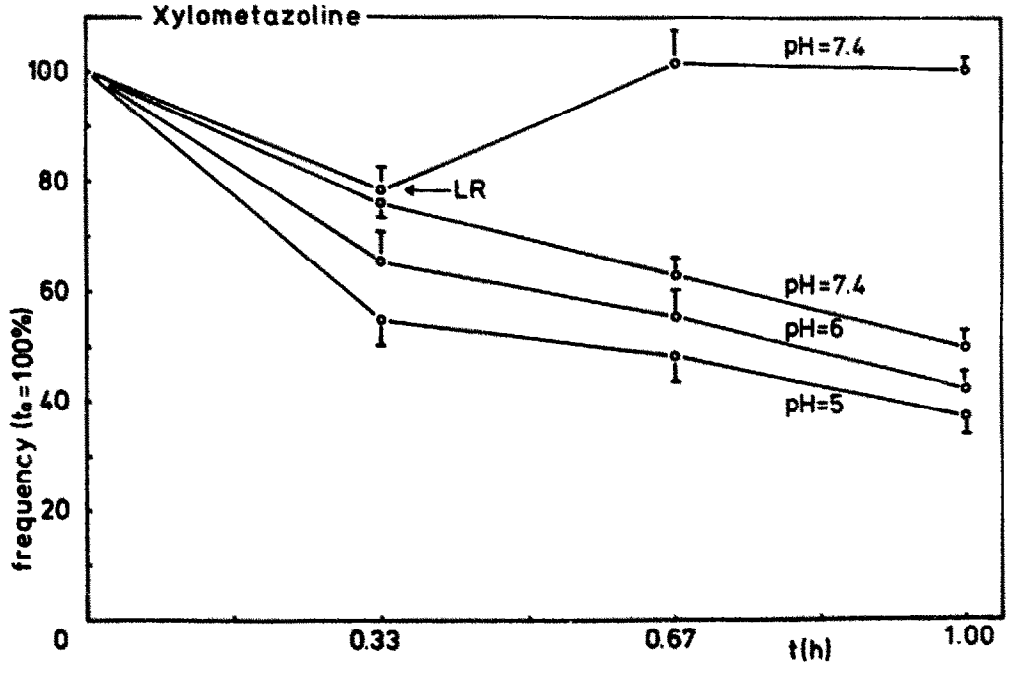

Fig. 4. Time versus frequency plot for xylometazoline-HCl (0.05%) at pH 5, 6, 7.4 continuously, and at pH 7.4 washed after 20 min with LR.

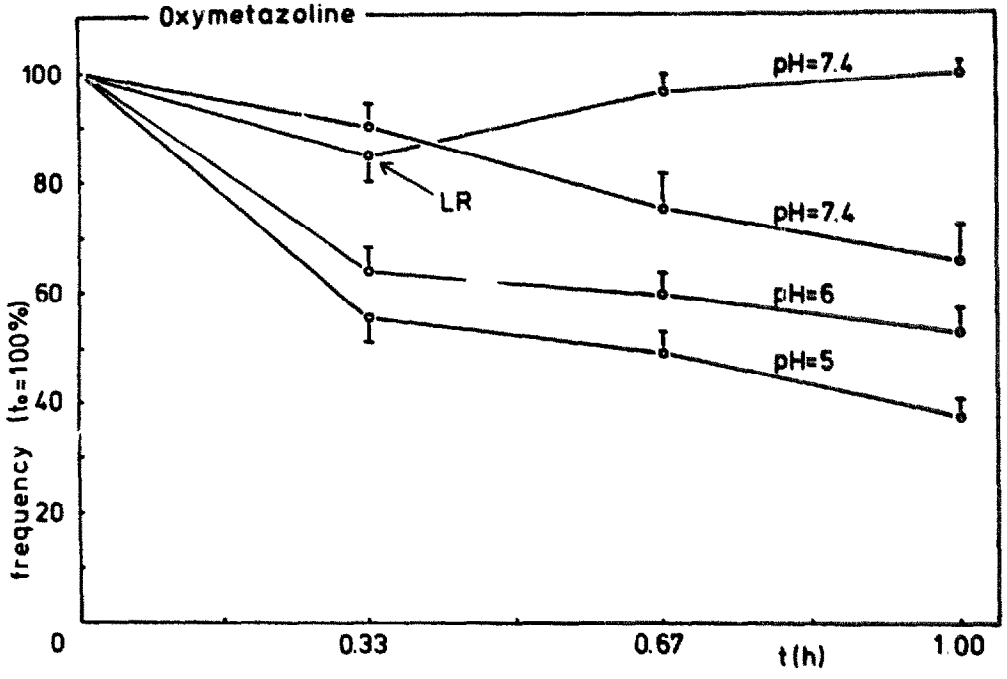

Fig. 5. Time versus frequency plot for oxymetazoline-HCl (0.05%) at pH 5, 6, 7.4 washed after 20 min with LR, and at pH 7.4 continuously.

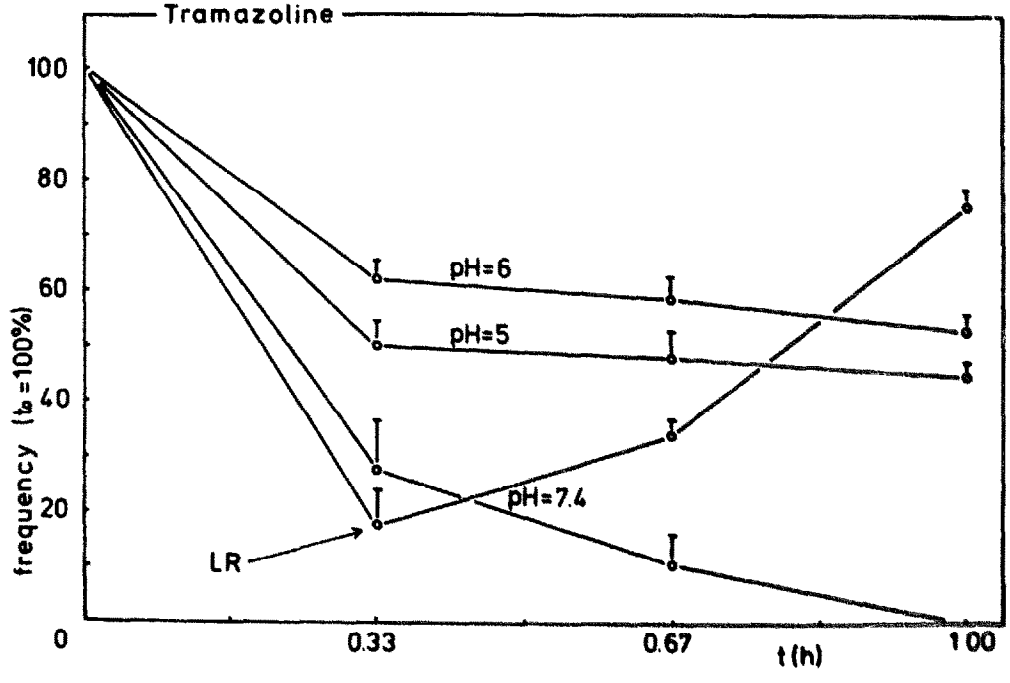

Fig. 6. Time versus frequency plot for tramazoline-HCl (0.117%) at pH 7.4 washed after 20 min with LR, at pH 7.4 continuously, pH 5 and at pH 6.

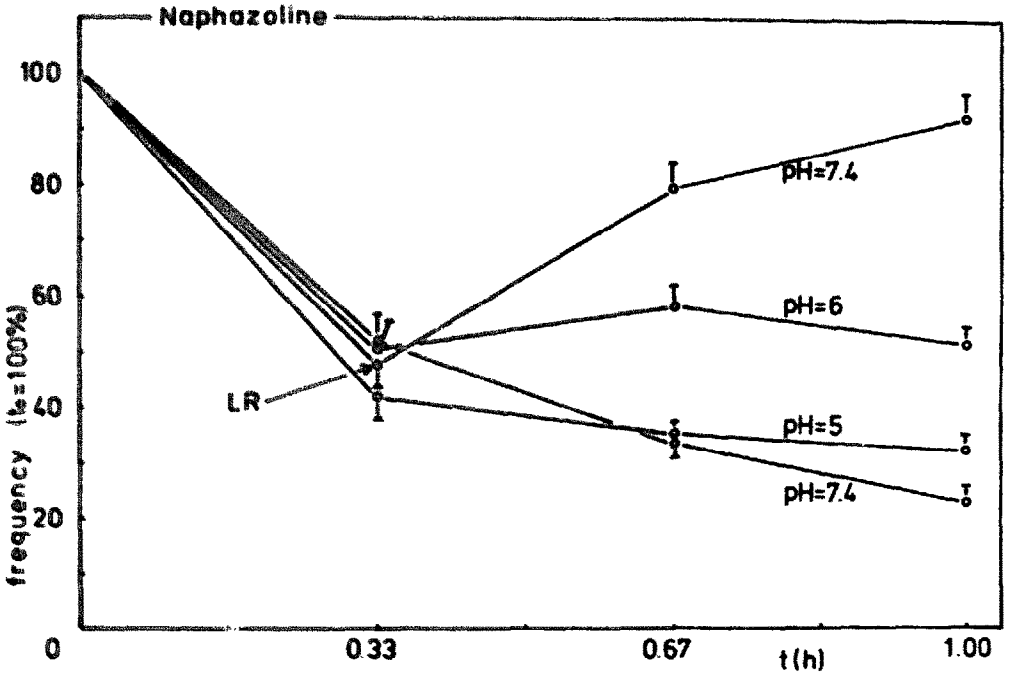

Fig. 7. Time versus frequency plot for naphazoline nitrate (0.1%) at pH 5, pH 7.4 washed after 20 min with LR, at pH 6 and at pH 7.4 continuously.

The effects of the decongestants appeared to be reversible because the ciliary beat frequency was restored by washing with LR after 20 min contact. Figs. 1–7 show the effects in more detail. The S.E.M. is indicated by vertical bars.

The ciliary beat frequency of the references remained between 98% and 109% during all experiments.

Discussion

The effects of the decongestants were investigated at only one concentration. Table 3 shows the concentrations that have been investigated and those that are

TABLE 3

INVESTIGATED AND THERAPEUTIC CONCENTRATIONS

Compound	Concentration investigated	Concentration for adults
Ephedrine-HCl	0.5%	0.5–2%
Phenylephrine-HCl	0.5%	0.25–0.5%
Phenylpropanolamine-HCl	0.75%	1–3%
Xylometazoline-HCl	0.05%	0.1%
Oxymetazoline-HCl	0.05%	0.05%
Tramazoline-HCl	0.117%	0.117%
Naphazoline nitrate	0.1%	0.05–0.1%

recommended for adults by Martindale (1977). Tramazoline-HCl was investigated at its concentration in Rhinogutt as Martindale gives no data.

The concentrations chosen were close to those normally used for adults, and in such a way that the effects of chemically similar substances could be compared. Therefore, the same concentrations were used for ephedrine-HCl and phenylephrine-HCl (0.5%) and for xylometazoline-HCl and oxymetazoline-HCl (0.05%). In the Netherlands phenylpropanolamine-HCl is not used as a single agent but only in combination with a corticosteroid. Its concentration in Codelsol is 0.75% which was the concentration used in this investigation. Naphazoline nitrate was investigated at the concentration normally used.

From Table 2 it appears that phenylephrine is less ciliotoxic than epherine. Phenylephrine-HCl is more hydrophilic than ephedrine-HCl; the Merck Index (1976) states that phenylephrine-HCl is freely soluble and ephedrine-HCl 1:4 in water. Also, oxymetazoline-HCl (freely soluble in water) is more hydrophilic than xylometazoline-HCl (1:33 in water). The hydrophilic substances are less ciliotoxic than their more lipophilic counterparts, which is in agreement with our former results that lipophilic preservatives damage ciliary motility faster than polar preservatives (van de Donk et al., 1980b). We also found that polar preservatives decrease ciliary movement irreversibly. However, the effects of the decongestants, regardless of lipophilicity, were found to be reversible.

The effects on ciliary motility at pH lower than 7.4 can be expected to increase, since lowering the pH of LR resulted in a decrease in the frequency (van de Donk et al., 1980a). This phenomenon is reversed for the naphthyl derivatives (naphazoline and tramazoline) and for phenylpropanolamine. This reversed pH-dependency could not be explained.

Hutcheon and Cullen (1955) found that at therapeutic concentrations phenylephrine was far less ciliotoxic than ephedrine, and ephedrine was to a limited extent less ciliotoxic than naphazoline at pH 7.2. The results of our study indicate that at equal concentrations phenylephrine is less ciliotoxic than ephedrine, and since phenylephrine is used at lower concentrations than ephedrine, this difference in effect on ciliary movement will be more pronounced at therapeutic concentrations. This study shows that 0.1% naphazoline nitrate is slightly more ciliotoxic than 0.5% ephedrine-HCl but as ephedrine-HCl is often used at a concentration of 1% the difference in ciliotoxicity at therapeutic concentrations will be very small.

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