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The effects of drugs on ciliary motility III. Local anaesthetics and anti-allergic drugs

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Summary

The effects of local anaesthetics and anti-allergic drugs at different pHs on the ciliary beat frequency of chicken embryo tracheas have been investigated. The local anaesthetics arrested ciliary movement reversibly within 2.5 min at pH 7, whereas the antihistamines arrested ciliary movement irreversibly within 20 min at pH 7.4. Lowering the pH made both groups of drugs less ciliotoxic. The effects of a solution of prednisolone sodium phosphate are very limited, whereas solubilization of dexamethasone in polysorbate decreases the ciliary beat frequency more than 60% in 20 min. The latter effect was due largely to the polysorbate. Cromoglycate sodium was found to be only slightly ciliotoxic.

Introduction

This final part, which continues from part I 'decongestants' and part II 'antimicrobial agents' (van de Donk et al., 1982a and 1982b), describes the effects of local anaesthetics and anti-allergic drugs on the ciliary beat frequency of chicken embryo tracheas. Local anaesthetics can come into contact with ciliated epithelia when used before or during nasal surgery and bronchoscopy, when added in low concentrations to nasal drops or when injected into the spinal cord from which it may reach the ciliated ependymal lining of the brain and the spinal cord.

The drugs used in the therapy of allergic diseases are antihistamines, corticosteroids and sodium cromoglycate. Antihistamines are used in nasal drops often in combination with a decongestant; corticosteroids and sodium cromoglycate are used

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in preparations intended for the lower as well for the upper respiratory tract. These drugs have received little attention until now as far as their effects on ciliated epithelia are concerned. The effects of local anaesthetics (lignocaine and others) have been investigated by Manawadu et al. (1978) and Mastow et al. (1979). The study presented here describes the effects of lignocaine, cocaine and butacaine. The latter two were not included in the studies of Manawadu et al. and Mastow et al. The effect of only one antihistamine (antazoline) has been investigated by Mirimanoff (1969), the study presented here also reveals the effects of diphenhydramine, tripelennamine and antazoline. The effects of corticosteroids have not been investigated until now as far as we know. The effects of sodium cromoglycate have been investigated by Blair and Woods (1969).

Methods and materials

The ciliary beat frequency is determined with a photo-electric registration device at 25°C in Locke Ringer (LR) solution (van de Donk et al., 1980). The effects of each drug at a fixed pH were assayed 6 times. The local anaesthetics were dissolved in enough distilled water to obtain an iso-osmotic solution, which was diluted with a solution containing 2.5% dextrose and 0.45% NaCl, which also served as a reference. The local anaesthetics were investigated in a medium containing only NaCl and dextrose because the $CaCl_2$ of LR precipitates butacaine sulphate. Cocaine-HCl appeared to precipitate above pH 7. Reversibility was investigated by washing with LR or with a solution containing 0.45% NaCl and 2.5% dextrose (reference). Table I 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 at pH 7.4 of rinsing with LR after

TABLE I

LIST OF SUBSTANCES INVESTIGATED

Substance	Lot number	Manufacturer
Lignocaine-HCl	112015/80H30	Brocacef
Cocaine-HCl	111089/79J08	Brocacef
Butacaine sulphate	118C-0479	Sigma
Diphenhydramine-HCl	108814/78K24	Brocacef
Tripelennamine-HCl	103834/74H30	Brocacef
Antazoline-HCl	109380/79I10	Brocacef
Prednisolone sodium phosphate	5644 1111	Organon
Dexamethasone	109567/79F13	Brocacef
Sodium cromoglycate	025980P760	Fisons
Polysorbate	104215/74L30	Brocacef

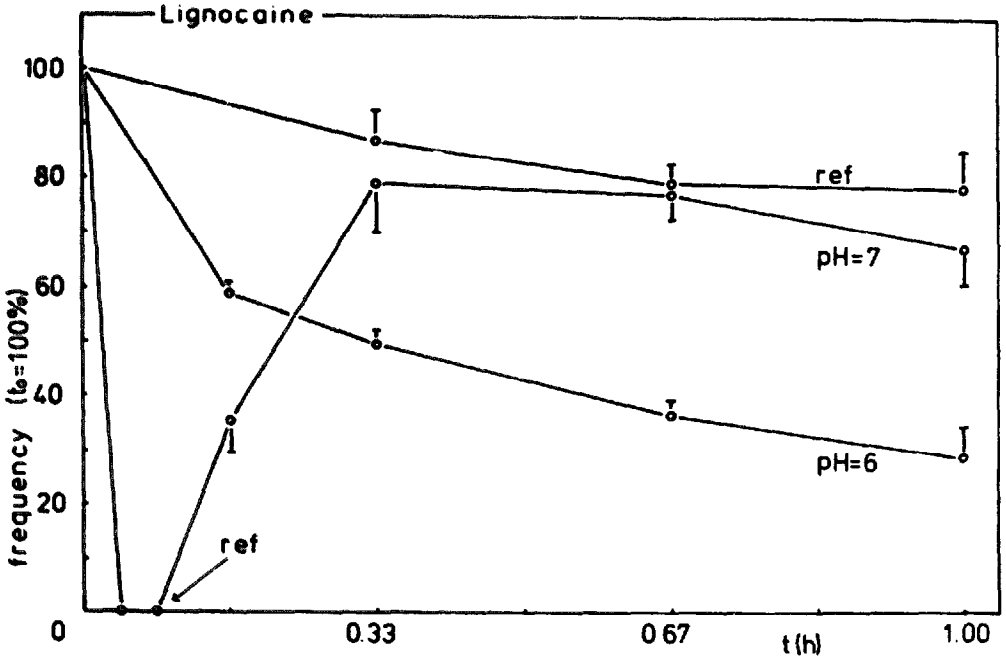

Fig. 1. Time versus frequency plot for lignocaine-HCl (2%); at pH 7, washed after 5 min with LR and at pH 6 and for the reference.

20 min contact (for the local anaesthetics, at pH 7 and rinsing with dextrose 2.5% + NaCl 0.45% after 5 min contact) have been assayed as well. The first column shows the pH, the next columns show the ciliary beat frequency as a percentage of

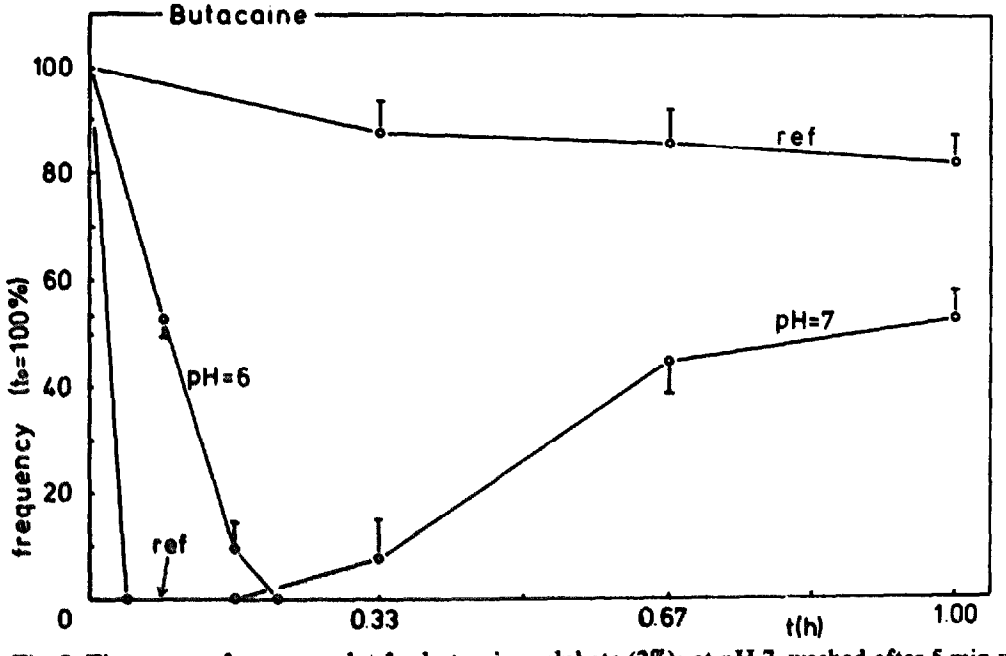

Fig. 2. Time versus frequency plot for butacaine sulphate (2%); at pH 7, washed after 5 min with LR and at pH 6 and for the reference.

TABLE II

EFFECTS ON CILIARY BEAT FREQUENCY

Compound	pH	Frequency [a]							$t_{95\%}$ [b]	$t_{90\%}$ [c]
		2.5	5	10	20	40	60	(min)		
		0.04	0.08	0.16	0.33	0.67	1.00	(h)		
Lignocaine-HCl (2%)	7	0	[d]	36	79	77	67		0.00	0.00
	6			59	50	37	29		0.02	0.05
Butacaine sulphate (2%)	7	0	[d]	0	8	45	53		0.00	0.00
	6		51	10	0				0.01	0.02
Cocaine-HCl (5%)	7	0	[d]	27	50	67	65		0.00	0.00
	6			66	49	39	20		0.02	0.05
Reference	7				87	81	78		0.13	0.26
Antazoline-HCl (0.5%)	7.4				0 [e]	0	0		0.02	0.03
	6				29	19	0		0.02	0.03
	5				31	26	20		0.02	0.05
Diphenhydramine-HCl (2%)	7.4	0	[e]		0 [e]	0	0		0.00	0.00
	6	0							0.00	0.00
	5	3	0						0.00	0.00
Tripelennamine-HCl (2%)	7.4	2	[e]		0 [e]	0	0		0.00	0.00
	6	0							0.00	0.00
	5			58	14				0.02	0.04

Prednisolone sodium phosphate (0.1%)	7.4	93[e]	102	105	0.24	–
	7.4	91	87	86	0.19	0.43
	8	97	99	98	–	–
	9	95	93	94	0.35	–
Dexamethasone (0.01%)+polysorbate (0.4%)	7.4	39[e]	75	89	0.03	0.05
	7.4	36	33	26	0.03	0.05
	6	34	33	16	0.03	0.05
	5	32	23	14	0.02	0.05
Polysorbate (0.4%)	7.4	48	39	37	0.03	0.06
Cromoglycate sodium (2%)	7.4	98[e]	107	109	–	–
	7.4	96	93	84	0.47	0.77
	8	85	88	81	0.11	0.22
	6	65	61	67	0.05	0.10
Locke Ringer solution	7–10	103	104	103	–	–
	6	93	82	74	0.24	0.42
	5	82	62	54	0.09	0.19

[a] Ciliary beat frequency as a percentage of the initial frequency, after 2.5, 5, 10, 20, 40 and 60 min.
[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] The tissue was rinsed with NaCl (0.45%)+dextrose (2.5%) after 5 min and the experiment was continued in this medium.
[e] The tissue was rinsed with LR at the indicated time and the experiment was continued in LR.

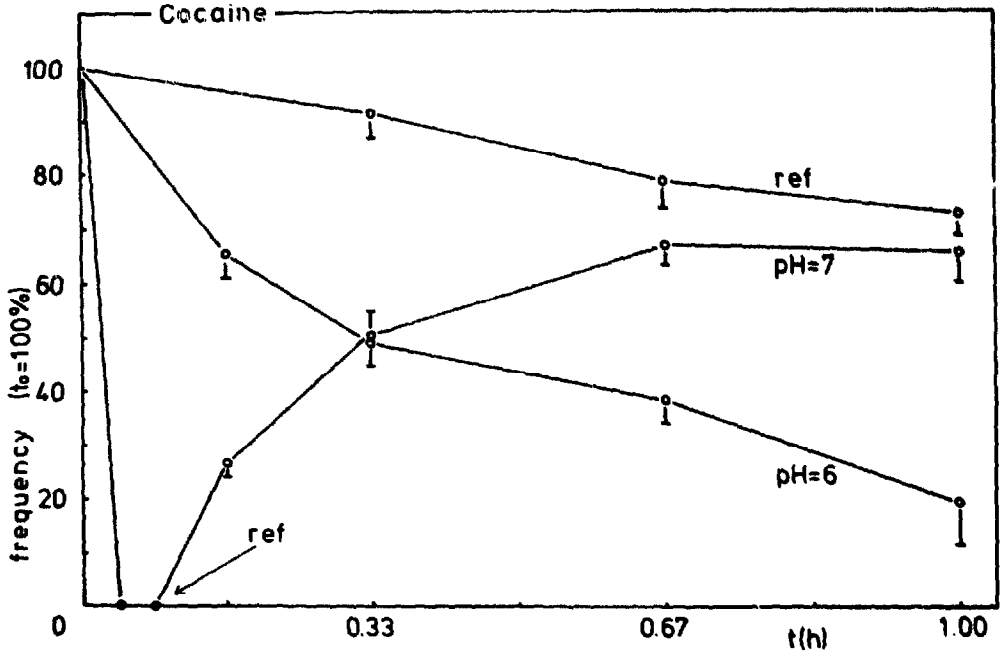

Fig. 3. Time versus frequency plot for cocaine-HCl (5%); at pH 7, washed after 5 min with LR and at pH 6 and for the reference.

the initial frequency after 2.5, 5, 10, 20, 40 and 60 min. The contact time necessary to reduce the beat frequency to 95% and to 90% of the initial beat frequency are indicated in the last two columns. Figs. 1–8 show the effects in more detail. The

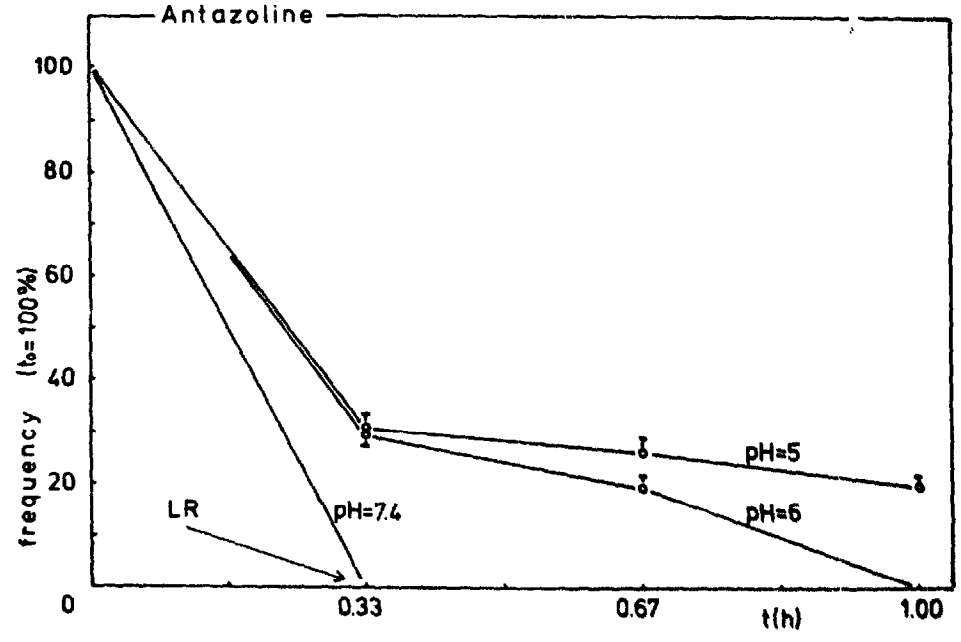

Fig. 4. Time versus frequency plot for antazoline-HCl (0.5%); at pH 7.4, washed after 20 min with LR, at pH 6 and 5.

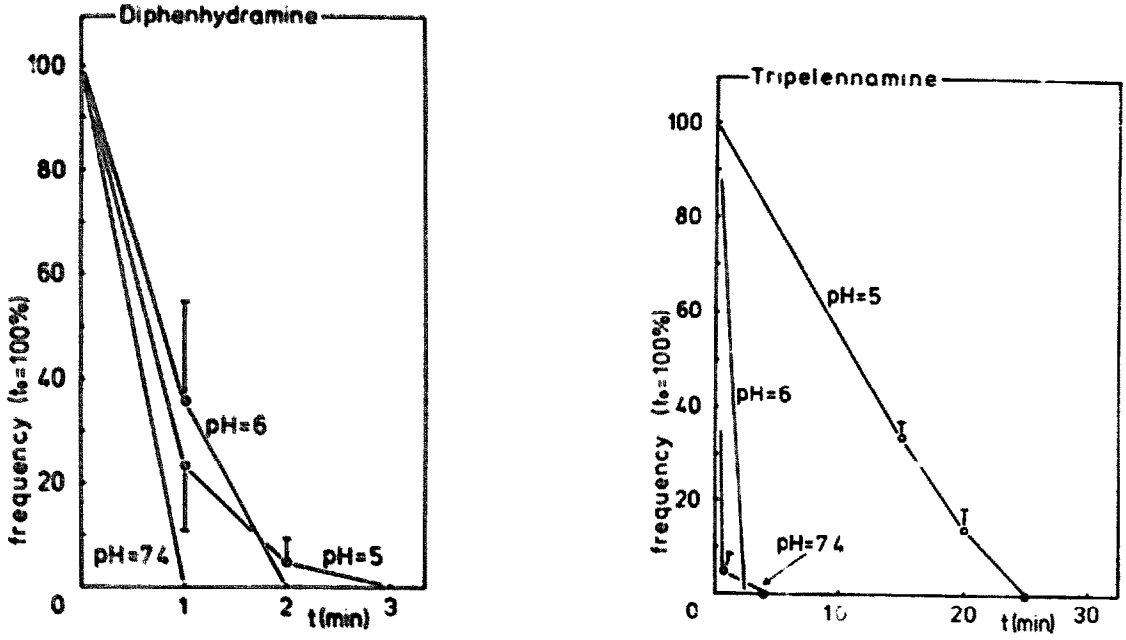

Fig. 5. Time versus frequency plot for diphenhydramine-HCl (2%); at pH 7.4, 5 and 6.

Fig. 6. Time versus frequency plot for tripelennamine-HCl (2%); at pH 7.4, 6 and 5.

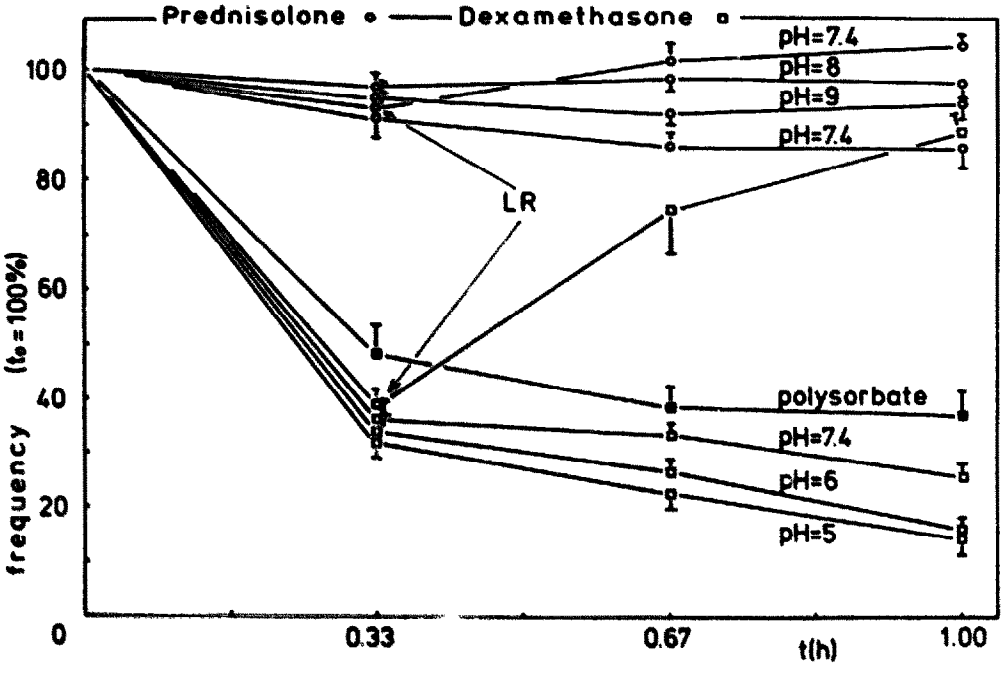

Fig. 7. Time versus frequency plot for prednisolone sodium phosphate (○) 0.1% at pH 7.4 continuously and at pH 7.4 washed after 20 min with LR and at pH 9 and 8 and for dexamethasone (0.01%) + polysorbate (0.4%) (□) at pH 5, 6 and 7.4 continuously and pH 7.4 washed after 20 min and for polysorbate 0.4% (■) at pH 7.4.

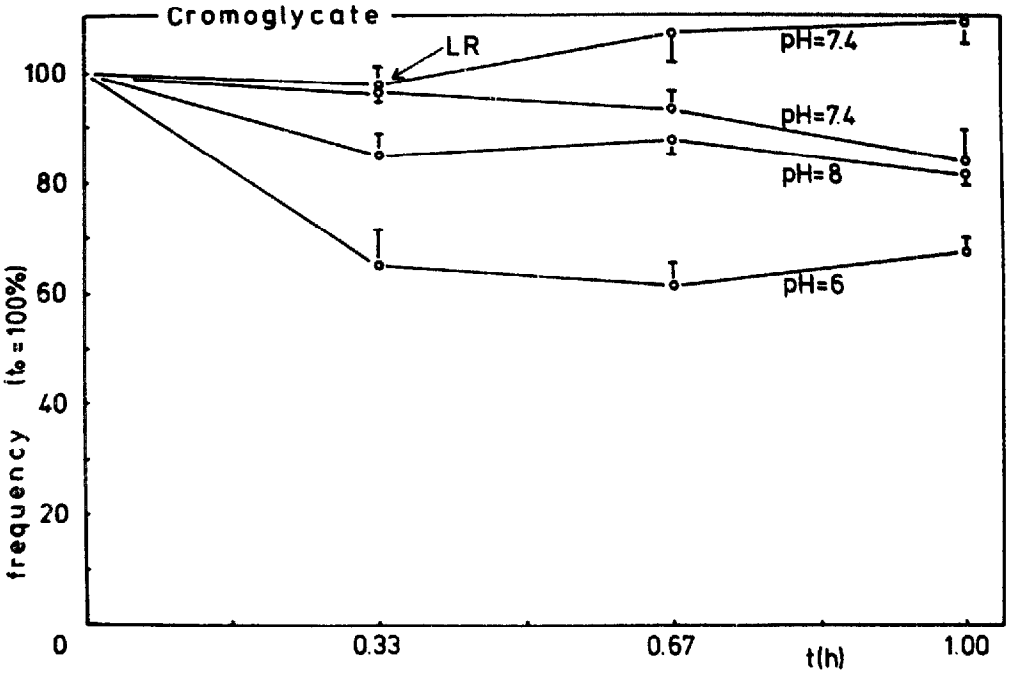

Fig. 8. Time versus frequency plot for cromoglycate (2%) at pH 6, 8 and pH 7.4 continuously, and at pH 7.4 washed after 20 min with LR.

S.E.M. values are indicated by vertical bars. The effects of the pH of pure LR have been added to Table 2 (van de Donk et al., 1980). The ciliary beat frequency of the trachea rings in LR remained between 96% and 106% during all experiments.

Discussion

The effects on the ciliary beat frequency of the local anaesthetics were quite severe but they were reversible; the reversibility diminished from lignocaine, cocaine to butacaine. The effects at pH 6 were small compared to the effects at pH 7. However, the effects of butacaine were still much more severe than those of lignocaine and cocaine.

The antihistamines were all very ciliotoxic and irreversible. Diphenhydramine appeared to have the strongest effects, whereas antazoline was the least ciliotoxic of the 3 antihistamines investigated. Lowering the pH diminished the effects on the ciliary beat frequency, as was found for the local anaesthetics. This can be explained by the fact that in both groups of drugs pK_a values range from 8 to 10. Under such conditions it applies that the lower the pH, the larger the protonated fraction and the smaller the fraction of the drug that diffuses through the cell membranes. Both Manawadu et al. (1978) and Mastow et al. (1979) found irreversible ciliary arrest within 30 min for 2% lignocaine on ferret tracheal rings. However, Mastow et al. performed their experiments at pH 6.5–7. Manawadu et al. do not give information on the pH. In both studies the rings were not washed earlier than after 1 h contact,

whereas we washed the tissues after 5 min contact. Mirimanoff (1969) found an immediate decrease in frequency for a gel containing 0.5% antazoline (pH 6.9) on guinea pig tracheas, but even after 1 h contact ciliary arrest appeared in only 3 of 10 experiments. Probably the high viscosity prevented intensive contact between the drug and the tissue. The benefit of administering antihistamines intranasally is doubtful. Cirillo and Tempero (1976) reported the occurrence of severe irritative rhinitis and allergic reactions. Moreover, no information on the therapeutic effects of such preparations can be found. This, added to their ciliotoxicity, indicates that the intranasal application of antihistamines should be discouraged.

The corticosteroids have a very modest and reversible effect on the ciliary beat frequency. In comparison with the soluble salts (prednisolone sodium phosphate, dexamethasone sodium phosphate), the effects on ciliary motility of the pure corticosteroids solubilizated in polysorbate 80 are much worse. This difference, however, is caused largely by the polysorbate (Fig. 7). The polysorbate effect is reversible. Solubilization of corticosteroids is often used because the salts tend to precipitate at pH < 7.5. This makes the combination of a corticosteroid salt and a decongestant impossible. The effects on ciliary motility at different pHs are almost equal.

Sodium cromoglycate exerts at different pHs very little influence on the ciliary beat frequency and the effects are reversible. Also, Blair and Woods (1969) found hardly any effect for sodium cromoglycate on the ciliary beat frequency of cat trachea.

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