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The effects of nasal drops on the ciliary beat frequency of chicken embryo tracheas

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SUMMARY

The effects of proprietary preparations in the Netherlands and nasal preparations according to the F.N.A. (Formulary of the Netherlands' Pharmacists Association) on the ciliary beat frequency of chicken embryo tracheas have been determined. In general the preservatives, used in the nasal drops, turned out to have a more decisive influence on the ciliary motion than the pharmacologically active constituents.

The average time, necessary to decrease the frequency 50% with 1 = 5 diluted nasal drops (average $t_{50\%(1=5)}$) containing a mercury compound or chlorbutol, is 0.4 h. Quaternary ammonium compounds containing preparations, however, have less influence, average $t_{50\%(1=5)} > 1.22$ h. They are to be used preferably.

Nasal drops, used as decongestants, provided that they are preserved with quaternary ammonium compounds, have little influence on the ciliary motion (average $t_{50\%(1=5)} > 1.38$ h).

Nasal drops containing antihistamines, in contrast, inhibit the ciliary motion largely and almost independently of the preservatives (average $t_{50\%(1=5)} = 0.22$ h); the cromoglycate containing preparation, on the contrary, has only little effect in this respect ($t_{50\%(1=5)} > 2$ h).

Antimicrobial preparations are not preserved and have an intermediate ciliotoxic effect (average $t_{50\%(1=5)} = 0.7$ h).

INTRODUCTION

The extensive use of nasal drops and sprays is explained by the frequent occurence of nasal diseases, like the common cold. These preparations are easily available as "over the counter" drugs in most countries.

In the nasal cavity a mucociliary structure exists to remove particles, microorganisms, viruses and allergens.

Wanner (1977) called this capability "the nasal clearance". Most nasal medications influence the nasal clearance in a negative way. Dudley and Cherry (1978)

investigated the effects of dilutions of 10 proprietary preparations, registered in the U.S.A., on the ciliary movement after a contact of 5 minutes, three times a day. All the nasal drops showed, to some degree, ciliotoxicity, but the damaging component was not mentioned. Perrault et al. (1978) investigated some preparations containing preservatives like chlorbutol, thiomersal and p.hydroxybenzoates. They did not study quaternary ammonium compounds. So, the available literature does not offer a comprehensive survey of the ciliotoxic effects of nasal preparations and their common components.

In a former publication (Van de Donk et al., 1980b) we described the effects of preservatives on ciliary movement. In this study we want to elucidate the effects of proprietary preparations in the Netherlands and nasal preparations according to the F.N.A. (F.N.A. preparations) on ciliary movement.

The F.N.A. is the formulary of the Netherlands' Pharmacists Association.

Table I. Nasal preparations

names	lot-numbers	manufacturers
Argyrophedrine®	1490	Aron
Rhinamide®	776 81	Bailly
Rhinogutt®	78J25	Boehringer Ingelheim
Fenox®	3X	Boots
Chloramphenicol®	78K16	Bournonville-Pharma
Chloransulfa®	78C22	Bournonville-Pharma
Antistine-Privine®	78F02AF	Ciba
Otricorten®	78B27HH	Ciba
Otrivin® 0.1%	80A11AB	Ciba
Otrivin® 0.05%	80A10AB	Ciba
Privine® 0.1%	77H30AK	Ciba
Privine® 0.05%	747L	Ciba
Lomusol®	78K08	Fisons
Nasivin® 0.05%	78A10M205 1430	Merck
Nasivin® 0.025%	80B15U074 4362	Merck
Codelsol®	79A08NC0656	Merck, Sharp & Dohme
Rhinofral®	31489	Philips-Duphar
Sinex®	9E	Richardson-Merrell
Endrine®	78J06	Wyeth
Rhinoguttae antazolini 0.5%		FNA
Rh. antazolini et naphazolini		FNA
Rh. argenti nucleinici comp.		FNA
Rh. ephedrini 1%		FNA
Rh. ephedrini comp.		FNA
Rh. naphazolini 0.05%		FNA
Rh. phenylephrini 0.025%		FNA
Rh. xylometazolini 0.1%		FNA
Rh. xylometazolini 0.05%		FNA
Rh. xylometazolini 0.025%		FNA

MATERIALS AND METHODS

Names, lot-numbers and manufacturers' names of the investigated proprietary preparations are given in Table I. Some experiments were performed in the pure preparations, other experiments in dilutions: 20% of the preparation in Locke-Ringer solution. The ciliary beat frequency was assessed by a photo-electric registration device (Van de Donk et al., 1980a). The effects of diluted preparations and the effects of the reference (Locke-Ringer) were determined on six different chicken embryo tracheas. The effects of the pure preparations were determined on four different tracheas.

The concentrations of the quarternary ammonium compounds in the nasal preparations were determined with high performance liquid chromatography (HPLC), according to the method of Meyer (1980). Although with this method each homolog can be separated, concentrations of the benzalkonium homologs were listed as a total only.

The mercury concentrations were determined with atomic absorption spectrophotometry (AAS) after destruction with nitric acid.

RESULTS

Assays

Table II lists the concentrations of benzalkonium chloride, determined with the United States Pharmacopeia reference as a standard, and the concentrations of benzalkonium chloride as claimed by the manufacturer.

The table includes the contents of two commercially available brands of benzalkonium chloride. All assays resulted in roughly three quarters of the concentrations as claimed by the manufacturer. The assays of mercury and domiphen bromide (compared to domiphen bromide Lot 7002121, Ciba-Geigy) and all benzalkonium chloride concentrations are summarized in table III.

Table II. Concentrations of benzalkonium chloride in some nasal drops

	Benzalkonium chloride assayed	Benzalkonium chloride as claimed by the manufacturer
Rhinogutt®	0.0154%	0.02%
Lomusol®	0.0087%	0.01%
Nasivin® 0.05%	0.0074%	0.01%
Nasivin® 0.025%	0.0073%	0.01%
Sinex®	0.015%	–
Benzalkonium chloride[1]	0.006%	0.01%
Benzalkonium chloride[2]	0.009%	0.01%

[1] Used by Van de Donk et al., 1980b and in all the FNA preparations.
[2] Merck 9159612.

Tabel III. Composition of nasal drops

preparation	composition	
	preservative[1]	drug
Nasivin® 0.05%	benzalkonium chloride 0.0074%[2]	oxymetazoline HCl 0.05%
Nasivin® 0.025%	benzalkonium chloride 0.0073%[2]	oxymetazoline HCl 0.025%
Rhinogutt®	benzalkonium chloride 0.0154%[2]	tramazoline HCl 0.117%
Sinex®	benzalkonium chloride 0.015%[2]	oxymetazoline HCl 0.05%; menthol 0.025%; camphor 0.015%; eucalyptol 0.0075%
Lomusol®	benzalkonium chloride 0.0087%[2]	sodium cromoglycate 2%
Rhinoguttae antazolini 0.5%	benzalkonium chloride 0.006%; EDTA 0.1%	antazoline HCl 0.5%
Rh. antazolini et naphazolini	benzalkonium chloride 0.006%; EDTA 0.1%	antazoline HCl 0.5%; naphazoline nitrate 0.025%
Rh. ephedrini 1%	benzalkonium chloride 0.006%; EDTA 0.1%	ephedrine HCl 1%
Rh. ephedrini comp.	benzalkonium chloride 0.006%; EDTA 0.1%	ephedrine HCl 1%; menthol 0.015%; camphor 0.015%; eucalyptol 0.1%
Rh. naphazolini 0.05%	benzalkonium chloride 0.006%; EDTA 0.1%	naphazoline nitrate 0.05%
Rh. phenylephrini 0.25%	benzalkonium chloride 0.006%; EDTA 0.1%	phenylephrine HCl 0.25%
Rh. xylometazolini 0.1%	benzalkonium chloride 0.006%; EDTA 0.1%	xylometazoline HCl 0.1%
Rh. xylometazolini 0.05%	benzalkonium chloride 0.006%; EDTA 0.1%	xylometazoline HCl 0.05%
Rh. xylometazolini 0.025%	benzalkonium chloride 0.006%; EDTA 0.1%	xylometazoline HCl 0.025%
Endrine®	chlorbutol 0.25%	ephedrine HCl 0.5%; eucalyptol; menthol and camphor
Fenox®	chlorbutol 0.5%; cetrimide 0.02%	phenylephrine HCl 0.5%; menthol 0.025%; eucalyptol 0.025%
Otrivin® 0.1%	domiphen bromide 0.008%[2] a mercuric compound: 9.6 µg Hg/ml[3]	xylometazoline HCl 0.1%
Otrivin® 0.05%	domiphen bromide 0.008%[2] a mercuric compound: 9.6 µg Hg/ml[3]	xylometazoline HCl 0.05%
Privine® 0.1%	a mercuric compound: 7.0 µg Hg/ml[3]	naphazoline nitrate 0.1%
Privine®0.05%	a mercuric compound: 9.2 µg Hg/ml[3]	naphazoline nitrate 0.05%
Otricorten®	a mercuric compound: 10.0 µg Hg/ml[3]	xylometazoline HCl 0.05%; dexamethazone 0.01%
Antistine-Privine®	a mercuric compound: 8.0 µg Hg/ml[3]	naphazoline nitrate 0.02%; antazoline sulphate 0.5%
Codelsol®	phenylmercuric acetate 0.004%	prednisolone phosphate 0.1%; neomycin 0.35%; phenylephrine HCl 0.25%; phenylpropanolamine HCl 0.75%
Rhinofral®	aminacrine HCl 0.1%	naphazoline HCl 0.05%
Rhinamide®	benzalkonium chloride 0.0015%; benzoic acid 0.1%	sulphanilamide 0.4%; ephedrine HCl 1%; butacaine sulphate 0.03%
Argyrophedrine®	none	mild silver protein 0.5%; ephedrine laevulate 1%
Chloramphenicol®	none	chloramphenicol 0.4%
Chloransulfa®	none	chloramphenicol 0.5%; sulphacetamide 10%
Rhinoguttae argenti nucleinici comp.	none	mild silver protein 0.5%; ephedrine sulphate 1%

[1] Preservative content as claimed by the manufacturer with the exception of [2] and [3].
[2] Assayed with HPLC.
[3] Assayed with AAS.

Table IV. Effects of nasal drops on ciliary activity

		activity								
		undiluted		diluted (1=5)						
preservative	preparation	$t_{0\%}$(h)[1]	pH	freq.[2] $t=0.33$ h	freq.[3] $t=1$ h	freq.[4] $t=2$ h	$t_{50\%}$(h)[5]	$t_{0\%}$(h)[1]	pH	figure
benzalkonium chloride	Nasivin® 0.05%	0.58	6.8	95	92	59	>2	>2	6.9	3
	Nasivin® 0.025%	0.72	7.0	98	96	57	>2	>2	7.2	3
	Rhinogutt®	0.65	6.2	98	76	28	1.59	>2	6.6	3
	Sinex®	0.30	6.8	47	11	0	0.31	1.67	6.9	3
	Lomusol®	0.68	5.4	100	92	83	>2	>2	7.7	6
	Rhinoguttae antazolini 0.5%	0.43	4.7	20	0	0	0.21	0.67	7.2	6
	Rh. antazolini et naphazolini	0.37	4.8	12	0	0	0.19	0.67	7.2	6
	Rh. ephedrini 1%	0.99	4.7	82	45	10	0.90	>2	7.7	1
	Rh. ephedrini comp.	0.27	4.7	39	4	0	0.27	1.33	7.3	1
	Rh. naphazolini 0.05%	0.82	4.7	88	62	29	1.18	>2	7.2	4
	Rh. phenylephrini 0.25%	1.51	4.7	103	75	45	1.17	>2	7.2	1
	Rh. xylometazolini 0.1%	0.83	6.0	97	73	22	1.45	>2	7.1	2
	Rh. xylometazolini 0.05%	0.98	6.0	90	86	38	1.74	>2	7.1	2
	Rh. xylometazolini 0.025%	0.96	6.0	94	94	55	2	>2	7.1	2
chlorbutol	Endrine®	0.13	5.0	45	7	0	0.30	2	7.7	1
	Fenox®	0.07	5.2	31	5	0	0.24	1.33	7.6	1
mercury containing preservatives	Otrivin® 0.1%	0.25	6.4	60	29	0	0.54	2	6.9	2
	Otrivin® 0.05%	0.28	6.4	75	41	6	0.78	>2	6.9	2
	Privine® 0.1%	0.12	5.0	53	15	0	0.38	2	7.1	4
	Privine® 0.05%	0.13	4.9	50	24	0	0.33	1.67	7.4	4
	Otricorten®	0.07	5.0	39	0	0	0.27	1	5.3	6
	Antistine-Privine®	0.05	5.0	35	0	0	0.25	1	7.4	6
	Codelsol®	0.52	6.1	59	33	18	0.52	>2	7.3	6
others	Rhinofral®	0.13	6.5	33	0	0	0.25	1	7.3	4
	Rhinamide®	0.80	6.8	43	14	5	0.30	>2	7.7	5
none	Argyrophedrine®	0.22	8.1	85	50	0	1	2	8.0	5
	Chloramphenicol®	0.18	7.2	50	21	12	0.33	>2	7.6	5
	Chloransulfa®	0.01	7.7	67	20	0	0.54	2	7.7	5
	Rhinoguttae argenti nucleinici comp.	0.30	7.7	64	47	24	0.91	>2	7.8	5

[1] $t_{0\%}$(h) = time necessary to arrest ciliary movement in hours.
[2] freq. $t=0.33$ h = frequency of ciliary movement after a contact of 20 min.
[3] freq. $t=1$ h = frequency of ciliary movement after a contact of 1 h.
[4] freq. $t=2$ h = frequency of ciliary movement after a contact of 2 h.
[5] $t_{50\%}$(h) = time necessary to decrease the frequency of ciliary movement with 50% in hours.

Ciliary movement

The effects of some proprietary preparations and F.N.A. preparations on the ciliary beat frequency are demonstrated in Table IV.

The preparations are ranged according to their preservatives. Those containing more than one preservative are ranged according to the preservative with the strongest effect on ciliary movement, as published by Van de Donk et al. (1980b). Thiomersal and other mercury compounds appeared to have the strongest effect.

The first column shows the duration of movement in the case of undiluted preparations (mean of 4 experiments).

The second column gives the pH of these preparations.

The next columns reveal the effects of the preparations diluted with Locke-Ringer (1 = 5): the activity after a contact of 20 min, 1 h and 2 h.

The sixth column shows the time necessary to decrease the frequency 50% compared to the initial frequency, and the last two columns the duration of movement and the pH after the measurements.

The Figures 1-6 show the effects in detail. The S.E.M. values are indicated by vertical bars. The preparations are grouped, according to their indications.

Figure 1 shows the effect of preparations with short acting decongestants: ephe-

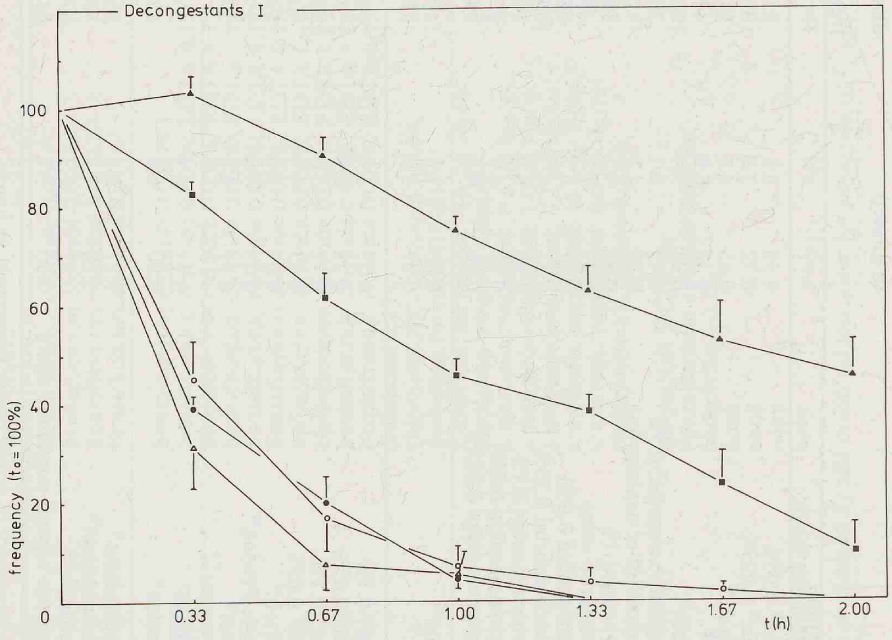

Figure 1. Time versus frequency plot for Rhinoguttae phenylephrini (FNA) 0.25% (▲), Rhinoguttae ephedrini (FNA) 1% (■), Endrine® (○), Rhinoguttae ephedrini compositae (FNA) (●) and Fenox® (△).

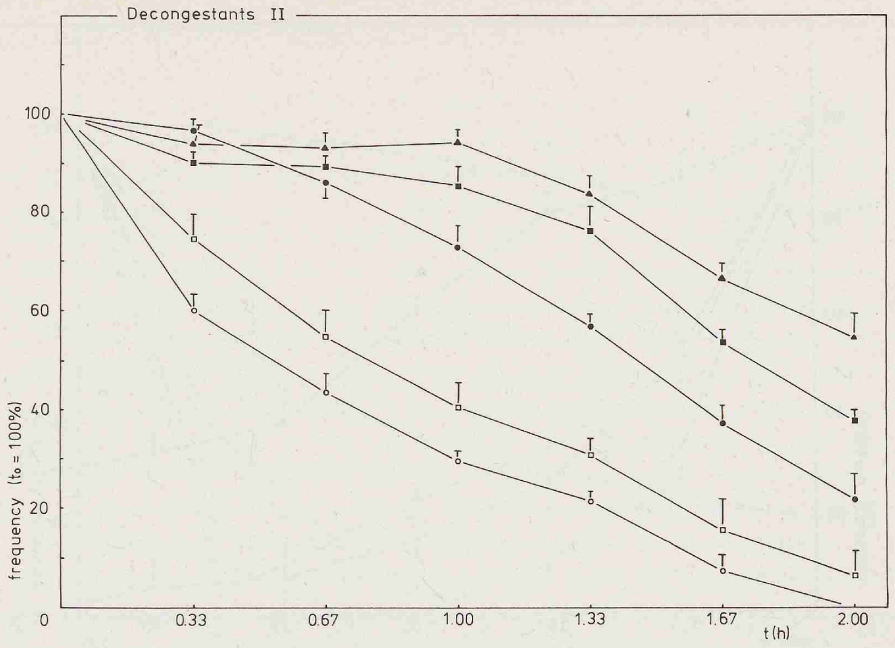

Figure 2. Time versus frequency plot for Rhinoguttae xylometazolini (FNA) 0.025% (▲), 0.05% (■) and 0.1% (●) and Otrivin® 0.05% (□) and 0.1% (○).

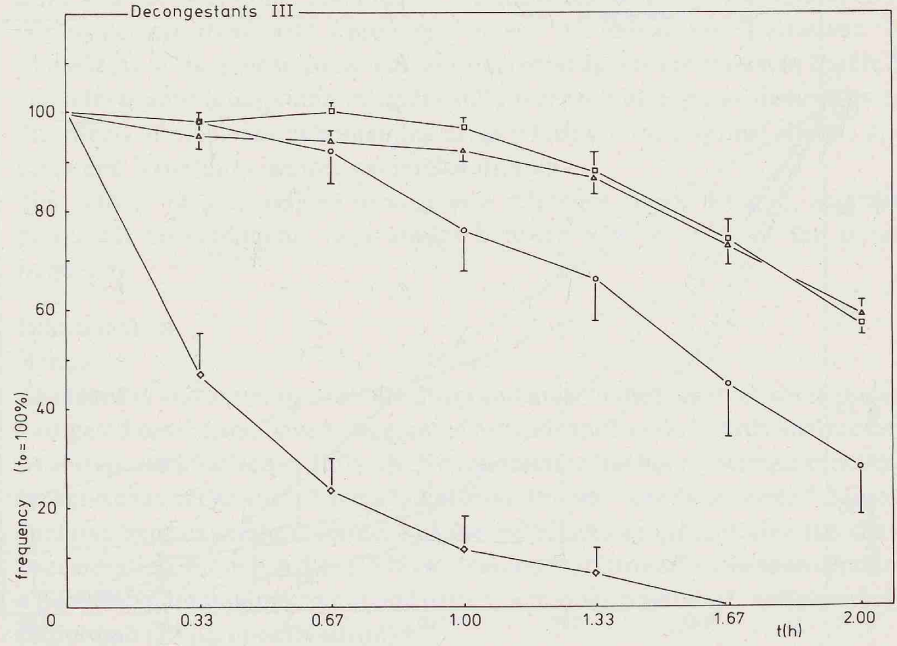

Figure 3. Time versus frequency plot for Nasivin® 0.025% (□) and 0.05% (△), Rhinogutt® (○) and Sinex® (◇).

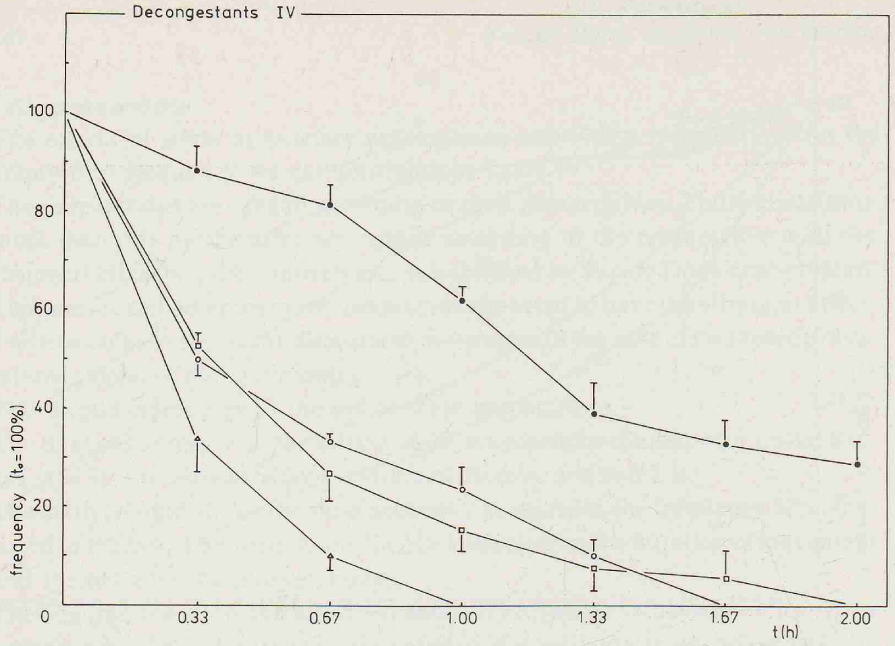

Figure 4. Time versus frequency plot for Rhinoguttae naphazolini (FNA) 0.05% (●), Privine® 0.1% (□) and 0.05% (○) and Rhinofral® (△).

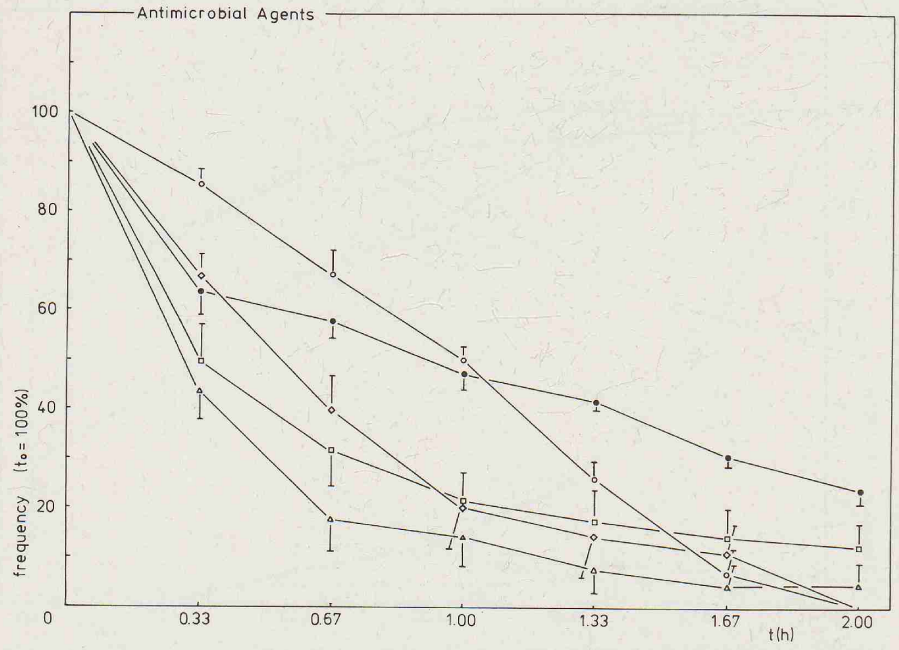

Figure 5. Time versus frequency plot for Argyrophedrine® (○), Chloransulfa® (◇), Rhinoguttae nucleinici compositae (FNA) (●), Chloramphenicol® (□) and Rhinamide® (△).

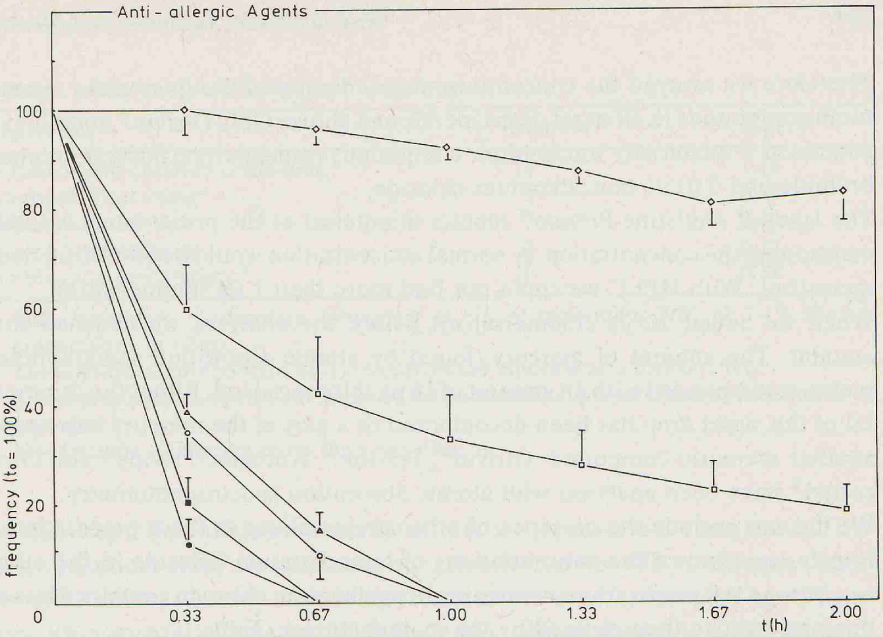

Figure 6. Time versus frequency plot for Lomusol® (◇), Codelsol® (□), Otricorten® (△), Antistine-Privine® (○), Rhinoguttae antazolini (FNA) 0.5% (■) and Rhinoguttae antazolini et naphazolini (FNA) (●).

drine and phenylephrine. The Figures 2, 3 and 4 deal with the preparations containing decongestants with a prolonged action: the imidazoline derivatives.
The effects of the preparations with antimicrobial agents are shown in Figure 5 and refer to antibiotics, sulphonamides and silver protein. Figure 6 demonstrates the effects of preparations containing drugs which are used against allergic diseases and sometimes against vasomotor rhinitis.
The activity of preparations serving as a reference (Locke-Ringer), assessed during all measurements, was always between 97% to 107% of the initial frequency.

DISCUSSSION

Assays

The identity and amounts of all the drugs and most of the preservatives in the investigated nasal drops have been granted by the manufacturer, partly analyzed by us and are summarized in Table III. No information has been obtained about the preservatives of Otrivin®, Privine®, Antistine-Privine® and Octricorten®. Sinex® contains benzalkonium chloride, but the manufacturer did not give the exact concentration. From F.A.S.S. (1978) we learned that Otrivin® in Sweden contains a quaternary ammonium compound (0.01% domiphen bromide)* and a mercury compound (20 µg thiomersal/ml).*

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* This has recently been confirmed by Ciba with respect to the Netherlands' market.

Therefore we assayed the concentration and identity of the quaternary ammonium compounds in all nasal drops mentioned above. Only Otrivin® and Sinex® contained a quaternary ammonium compound: respectivily 0.008% domiphen bromide and 0.015% benzalkonium chloride.
The label of Antistine-Privine® reports thiomersal as the preservative without mentioning the concentration. A normal concentration would be 50–200 µg thiomersal/ml. With HPLC we could not find more than 1 µg thiomersal/ml.
When we added 20 µg thiomersal/ml before the analysis, we detected this amount. The amount of mercury, found by atomic absorption spectrophotometry, corresponded with an amount of 16 µg thiomersal/ml. Either the thiomersal of this nasal drop has been decomposed or a part of the mercury belongs to another mercuric compound. Otrivin®, Privine®, Antistine-Privine® and Otricorten® have been analysed with atomic absorption spectrophotometry.
We did not exclude the presence of other preservatives in these preparations.
Finally, we essayed the concentrations of benzalkonium chloride in the other nasal drops. All preparations containing benzalkonium chloride contained less of this preservative than claimed by the manufacturers (Table II).
The Extra Pharmacopoeia (Martindale, 1977) demands that benzalkonium chloride contains not more than 15% of water. Benzalkonium chloride is highly hygroscopic. After storage the water content may exceed 15%, which explains the rather low benzalkonium chloride concentrations.

Ciliary movement
It turned out that all preparations decreased the ciliary beat frequency though to a very different extent.
Some undiluted preparations arrested ciliary movement very fast ($t_{0\%} < 0.2$ h). These results were less reproducible than the effects of the diluted preparations. Moreover, the nasal drops will be diluted by the nasal mucus after application. Therefore we focussed our investigations on the diluted preparations and assessed the effects of undiluted preparations only in fourfold.
A good parameter to evaluate the effects of the nasal drops on ciliary movement is the time necessary to decrease the frequency 50% ($t_{50\%}$, table IV) in the case of fivefold dilutions.
Relating the effects of nasal drops to the preservatives which they contain, it appears that the chlorbutol or mercury containing products have a strong effect on ciliary movement in contrast to the preparations which contain only benzalkonium chloride as a preservative (Table V).
These results are in agreement with our former publication (Van de Donk et al., 1980b). Table V compares average $t_{50\%}$ of nasal drops with a specific preservative or a specific drug regardless other components of the nasal drops. The preparations with chlorbutol as a preservative contain more than one drug, which makes

Table V. Effects of some groups of nasal drops

preparation	number	$\bar{t}_{50\%(1=5)}$ [1]
benzalkonium chloride containing[2]	14	1.22
chlorbutol containing[3]	2	0.27
mercury containing	7	0.44
antazoline containing	3	0.22
combination preparations[4]	10	0.38

[1] Time necessary to decrease frequency of ciliary movement 50% of 1=5 diluted preparations in hours.
[2] These preparations contain only benzalkonium chloride as a preservative.
[3] These preparations form a subgroup of the combination preparations as mentioned in foot-note 4.
[4] Preparations containing more than one drug.

it difficult to differentiate between the effects of the preservative and those of the drugs. In a next study we will focus our attention on the effects of single drugs. The effects of the mercury containing preservatives is more obvious. The preparations Rhinoguttae xylometazolini 0.1%, 0.05%; Rh. naphazolini 0.05% (average $t_{50\%} = 1.46$ h) and the preparations Otrivin® 0.1%, 0.05%; Privine® 0.05% (average $t_{50\%} = 0.55$ h) are quite comparable as to their composition, but the latter three contain a mercury compound.

The preservatives aminacrine and benzoic acid probably have a strong effect on ciliary movement, regarding the effects of Rhinofral® ($t_{50\%} = 0.25$ h) and Rhinamide® ($t_{50\%} = 0.3$ h). The effects of these preservatives have not been investigated separately in our former study as they are seldomly used in nasal drops.

In Table V the average $t_{50\%}$ of antazoline containing preparations is given as well. This drug is mentioned separately since the two nasal drops containing both antazoline and benzalkonium chloride (Rhinoguttae antazolini 0.5% and Rhinoguttae antazolini et naphazolini) appeared to be an exception in the group of nasal drops, preserved with benzalkonium chloride in showing a marked decrease of ciliary motion.

The mercury containing Antistine-Privine® has a smaller effect than Rhinoguttae antazolini and Rhinoguttae antazolini et naphazolini (after dilution with Locke-Ringer).

This can be explained by the fact that the two last mentioned products contain 20% more antazoline than Antistine-Privine®. The dilution moderates the effects of mercury containing preparations fairly, but the effects of antazoline hardly. This is in agreement with our recent findings that antazoline has a weaker effect at pH = 5 than at pH = 7.4 (to be published) and that the pH rises after dilution.

Generally, the combination preparations (nasal drops, containing more than one drug) have a worse effect on ciliary movement than the single drug containing

preparations. The effects of Fenox®, Endrine®, Sinex® and Rhinoguttae ephedrini compositae may, at least partially, be explained by the effects of drugs like menthol, camphor and eucalyptol, which are added to the main drugs in these preparations. The differences in effect between Rhinoguttae ephedrini 1% ($t_{50\%} = 0.9$ h) and Rhinoguttae ephedrini compositae ($t_{50\%} = 0.27$ h) indicate that the combination menthol 0.015%, camphor 0.015% and eucalyptol 0.1% has a strong effect on ciliary movement. Proetz (1953) found no effect for camphor 1% or menthol 1% on ciliary activity of human and rabbit tissues. But this author performed these experiments in liquid paraffin from which medium the penetration into the tissues is very limited. Secondly, mineral oils should never be used in nasal preparations as they have often been reported to cause oil-inspiration pneumonia.

The strong effect of Chloransulfa® is a.o. explained by the large drug concentration, which is about three times the isotonic concentration. This effect is very sensitive to dilution.
Many preparations had a more physiological pH after dilution than before, but their effect on ciliary movement diminished little. Sometimes the pH exceeds 7.4 after dilution of an acid preparation, which is due to the loss of carbon dioxide during the experiments.

Table VI reports the results of other authors. Only Schleppy and Blaser (1978) revealed the exact composition of their nasal drops. The preservatives of 4 nasal drops investigated by Dudley and Cherry (1978) are listed in the P.D.R. (1979). Hutcheon and Cullen (1955) assayed the concentrations of phenylephrine, naphazoline and ephedrine, that resulted in the same ciliotoxicity. These drugs are present in the nasal drops Rhinoguttae phenylephrini 0.25%, Rhinoguttae naphazolini 0.05% and Rhinoguttae ephedrini 1%. These concentrations are respectively 17.2, 8 and 2.4 times lower than the concentrations in the publication of Hutcheon and Cullen. This means that phenylephrine has the least and ephedrine the largest ciliotoxic effect, which is in agreement with the effects of the related nasal drops.
The effects of Privine® as reported by Bos and Jongkees (1966) are in agreement with our results.
In contrast with our results Bos and Jongkees (1966) did not find frequency decrease for Otrivin®. The composition of Otrivin® in 1965 in the Netherlands however is not known. Possibly this preparation did not contain a mercury compound at the time of their experiments, as it is still the case in the United States.
Like Hutcheon and Cullen, Mirimanoff (1969) studied drugs instead of nasal drops and found a strong effect for antazoline HCl 0.5% and a very slight effect for ephedrine HCl 1%. These effects are in agreement with the effects of Antistine-

Table VI. Comparison of the results from other "in vitro" studies

author	preparation	drug	preservative	activity of the cilia	dilution	tissue
Hutcheon and Cullen (1955)		ephedrine 2.4%	none	50% of the ring dead after 15 min	1=1	trachea, rat
		naphazoline 0.4%	none		1=1	trachea, rat
		phenylephrine 4.3%	none		1=1	trachea, rat
Bos and Jongkees (1966)	Privine®	naphazoline 0.1%	unknown	<5 min	1=1	adenoid, human
	Otrivin®	xylometazoline 0.1%	unknown	>1 h	1=1	adenoid, human
	Ephedrine HCl 1%	ephedrine HCl 1%	unknown	>1 h	1=1	adenoid, human
	Rhinospray®[1]	tramazoline HCl 0.1%	unknown	>1 h	1=1	adenoid, human
Mirimanoff (1969)		antazoline HCl 0.5%	none	immediate frequency decrease	1=1	trachea, guinea pig.
		ephedrine HCl 1%	none	modest decrease after one hour	1=1	trachea, guinea pig.
Schleppy and Blaser (1978)	Rhinapan®	phenylephrine HCl 0.25%	chlorhexidine gluconate 0.01% dequalinium acetate 0.01%	>20 min	1=1	trachea, mouse
Dudley and Cherry (1978)	Privine®	naphazoline HCl 0.05%	benzalk. chl. 0.02%	50% of the act. after 12 h[2]	1=6	trachea, chicken embryo
	Otrivin®	xylometazoline HCl 0.1%	benzalk. chl. 0.02%	50% of the act. after 12 h[2]	1=6	
	NTZ®	phenylephrine HCl 0.1% thenyldiamine HCl 0.1%	benzalk. chl. 0.02%	50% of the act. after 3 h[2]	1=6	
	Afrin®	oxymetazoline HCl 0.05%	phenylmercuric ac. 0.002%	50% of the act. within 1 h[2]	1=6	
			benzalk. chl. 0.02%		1=6	

[1] New name is Rhinogutt®.
[2] 5 min contact every 8 hours.

Privine®, Rhinoguttae antazolini 0.5% and Rhinoguttae antazolini et naphazolini, resp. Rhinoguttae ephedrini 1% in our experiments.
The effect of Rhinipan® is moderate and comparable with Rhinoguttae phenylephrini 0.25% (Schleppy and Blaser, 1978). This is in agreement with the weak effects found for chlorhexidine gluconate and quaternary ammonium compounds (Van de Donk et al., 1980b). Dudley and Cherry (1978) assessed the effects of nasal drops after 5 min. contact every 8 hours. After each contact the rings were rinced and stored in a rich medium (HEPES-BME).
It appears that the nasal drops containing quaternary ammonium compounds have a moderate effect, e.g. Privine® and Otrivin®.
The addition of the antihistamine thenyldiamine HCl makes the effect worse, e.g. NTZ®. the mercury compound in Afrin® is likely the cause of the very strong effect of this preparation.

To reduce the adverse reactions of locally applicated nasal drops three possibilities exist: (1) preservatives are omitted and to avoid microbial contamination of the nasal drop sterilized single dose units are used; (2) drugs and additives are selected according to their effects on ciliary acticity; (3) the drug is administered otherwise, e.g.: orally.
The first will be rather expensive, whereas the third might give systemic adverse reactions. Empey et al. (1980) reports a good decrease of the nasal airway resistance for 60 mg pseudo-ephedrine orally without increasing pulse and systolic blood pressure. After pseudo-ephedrine 120 mg orally significant increases in pulse and systolic blood pressure occurred. Benson (1971) found approximately the same effect for pseudo-ephedrine (60 mg, oral) and one drop ephedrine 1% on the maximal nasal inspiratory flow rate. The onset of action of the nasal drop was faster.
It is however, unlikely that systemic administration will ever be preferable to local administration. It is more reasonable to advise the use of the most harmless preparation within a therapeutical group.

CONCLUSION

Realizing the limitations of our "in vitro" model with a single application, it is possible to draw some preliminary conclusions. Some of our results will be checked in an "in vivo" model and described in a next study.

- For the preservation of nasal drops quaternary ammonium compounds should be preferred to mercury compounds. As appeared from our previous study (Van de Donk et al., 1980b), these compounds can be combined with EDTA. Nasal drops containing a mercury compound should not be used.
- The ciliotoxic effects of decongestants are moderate, provided that they are preserved with a quaternary ammonium compound and contain one drug only.

- The anti-allergic agents have different effects. Sodium cromoglycate hardly influences the ciliary motion, whereas antihistamines are likely to be very ciliotoxic (Figure 6). They need further study, especially while this group of drugs is often used in chronic diseases.

RÉSUMÉ

Les effets des gouttes nasales, sous forme de spécialités pharmaceutiques ainsi que de préparations magistrales, conformes à l'F.N.A. (Formulaire de l'Association des Pharmaciens Néerlandais), sur la fréquence du battement ciliaire de la trachea de l'embryon de poulet sont déterminés.

En général l'influence sur le battement ciliaire des conservateurs utilisés dans les gouttes nasales se réléva beaucoup plus forte que celle des éléments pharmacologiquement actifs. Le temps moyen, nécessaire à diminuer la frequence avec 50% en cas de gouttes nasales délayées 1 = 5 (le moyen $t_{50\%(1=5)}$) et contenantes des composés mercuriels ou du chlorobutanol est 0,4 h.

Les préparations contenants des composés d'ammonium quaternaire montrent cet effet à un moindre degré, le moyen $t_{50\%(1=5)} > 1{,}22$ h. Elles sont par conséquent à préférer.

Les gouttes nasales décongestives, à moins que conservées à l'ammonium quaternaire, ont peu d'influence sur le battement ciliaire, le moyen $t_{50\%(1=5)} > 1{,}38$ h.

Les gouttes nasales antihistaminiques ont, par contre, un effet inhibiteur prononcé sur le mouvement ciliaire, indépendent des conservateurs utilisés, le moyen $t_{50\%(1=5)} = 0{,}22$ h.

D'autre part l'effet faible à cet égard de la préparation de cromoglycate est remarquable, le $t_{50\%(1=5)} > 2$ h.

Les préparations antimicrobiennes ne sont pas préservées et retardent le mouvement ciliaire intermédiairement, le moyen $t_{50\%(1=5)} = 0{,}7$ h.

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