

From the Allergology Division and the Pulmonary Division of the Department of Internal Medicine, University Hospital, Groningen, The Netherlands.

EFFECTS OF SOME DRUGS APPLIED TOPICALLY TO THE NASAL MUCOSA BEFORE NASAL PROVOCATION TESTS WITH ALLERGEN

By

Z. PELIKAN & K. DE VRIES

The purpose of this clinical experiment was to investigate the possibility of some drugs having protective effects when applied topically to the nasal mucosa before nasal provocation tests with allergen.

By "protective effects" is meant the ability of these drugs to prevent or to decrease the development of nasal mucosa changes (swelling, hypersecretion) caused by an antigen-antibody reaction. The antigen-antibody reaction was represented in our trial by nasal provocation tests using the challenge of a known allergen in a known dose.

Two of these medicaments, i.e. an antihistaminic and an antiserotonic agent, were chosen as examples of antagonists to some mediators playing a possible role in an allergic reaction of the 1st type. Two others were representatives of sympathomimetic and corticosteroid drugs. An alpha-sympathomimetic agent was chosen as a known topical decongestant of the nasal mucosa. Corticosteroids may suppress some types of antigen-antibody reaction (7, 10) and one of their side-effects is topical decongestion.

The "protective effects" of these drugs could be compared with the protective effects of Disodium cromoglycate (Rynacrom®), demonstrated in our previous clinical experiments (16).

MATERIAL AND METHODS

Drugs

- a) *Alpha-sympathomimetic drug*: Xylometazoline hydrochloride (Otrivin®)¹⁾ in a 0.1 per cent solution.
- b) *Antihistaminic drug*: Pyranisamine hydrochloride (Mepyramine®, Antalergan®)²⁾ in a 2 per cent solution in "physiologic solution" (saline).
- c) *Antiserotonic drug*: Methysergide maleate (Deseril®)³⁾ in a 0.05 per cent solution.
- d) *Corticosteroid drug*: Dexamethasone 21-isonicotine (H 3a - H 111)⁴⁾ 0.125 mg of microcrystalline suspension in "Frigen-gas" per nasal inhalation (per one spray).

Allergen

House dust in a concentration of 5.0 mg of dry weight of dialysed and lyophilized extract per 1 ml of "Coca solution".⁵⁾

Apparatus and Equipment

This was the same as in our previous experiments (16, 17).

Principle of the Method

The nasal mucosa of an allergic individual reacts, when challenged topically by allergen, with changes such as swelling and hypersecretion. These changes influence the passage of air through the nose, resulting in changes in the pressure-differences between the nasopharyngeal cavity and the outside air. The pressure-differences, the so-called NPG (nasopharyngeal-nostril-pressure gradient), expressed in cm of H₂O, were recorded and considered as a parameter for the assessment of the reactivity of the nasal mucosa. The mean values of the NPG were always calculated during regular breathing over a time-period of 90-120 seconds (16, 17).

Design of the Experiment

In each patient the whole trial consisted of 3 parts, each of which was carried out on a separate day; between the 1st and the 2nd parts there was an interval of 1-2 days; between the 2nd and the 3rd parts there was an interval of 14 days.

Before each part of the experiment, a rubber balloon was introduced into the nasopharynx through one of the nasal cavities, and it was then filled with 2 ml of air and connected to the pressure transducer. During the investigation, the patient breathed only through the non-intubated nasal cavity with his mouth closed.

1) Ciba Co. 2) Specia Co. 3) Sandoz Co. 4) C. H. Boehringer Sohn Co.
5) prepared by Pharmacy "Diephuis" (Groningen).

The 1st Experimental Part

The 1st control test ("Initial test"). The mean NPG values were recorded at the 0, 5, 10, 20, 30, 45, and 60th min, for 90–120 sec in each instance (so-called "initial values").

The 2nd control test ("Coca test"). The Coca solution was applied for 3 min to the nasal mucosa of the non-intubated nasal cavity by means of a wad of cotton wool on a nasal probe. The mean NPG values were then recorded at the 0, 5, and 10th min.

Provocation test with allergen. The nasal mucosa was challenged with house dust for 3 min in the same way as with the Coca solution. The mean NPG values were then recorded at the 0, 5, 10, 20, 30, 45, and 60th min.

The 2nd Experimental Part

The 1st control test ("Initial values"). The mean NPG "initial" values were recorded at the 0, 5, and 10th min.

The 2nd control test ("Drug control test"). The drug was applied to the nasal mucosa for 3 min in the same way as the Coca solution. The mean NPG values were then recorded at the 0, 5, 10, 20, 30, 45, and 60th min.

A waiting interval of 30 min followed.

The protection test. The same drug was applied to the nasal mucosa for 3 min. Seven minutes after the drug challenge, the 3-min challenge with house dust was performed. The mean NPG values were then recorded at the 0, 5, 10, 20, 30, 45, and 60th min. Both challenges were carried out on the same site and in the same fashion as with the Coca solution.

The 3rd Experimental Part

After the 2nd experimental part, a 14-day period followed during which time the patient used 3×2 sprays of corticosteroids in each nostril per day; i.e. a total dose of 1.5 mg Dexamethasone 21-isonicotine per day.

The 1st and the 2nd control tests were carried out in the same way as those in the 2nd experimental part.

A waiting interval of 60 min followed.

The allergen provocation test with house dust was performed in the same way as in the 1st experimental part.

A waiting interval of 60 min followed.

The protection test with the drug was carried out in the same way as in the 2nd experimental part.

The provocation tests were considered to be positive when the mean NPG values increased within 30 min after the allergen challenge by at least 1.5 cm H₂O, with respect to the "initial values". The protection tests can be considered to be positive when the mean NPG values, recorded after the drug challenge followed by the allergen challenge, decreased distinctly compared to the mean NPG values measured after the single allergen challenge.

TABLE I
Characteristics of the Investigated Patients.

Group					Nasal complaints				Blood eosinophilic cells per mm ³	Allergen	Skin tests (mm)
	Patient	Sex	Age		obstruction	hypersecretion	sneezing	Lividity of nasal mucosa			
1	1	m	20		+++	+	+	+	209	HD	++
	2	f	36		—	—	+++	—	275	HD	+
	3	m	19		+++	+++	+++	+	264	HD	+++
	4	f	26		+++	++	++	—	187	HD	++
	5	m	23		++	+	+	+	330	HD	++
	6	m	35		+	++	+	—	286	HD	++
2	7	m	17		+	+	+	—	726	HD	++
	8	m	21		+	+	+	+	880	HD	++
	9	m	16		+++	++	+	+	572	HD	++
	10	m	16		—	—	+	—	506	HD	++
	11	m	17		+	+	+	+	638	HD	++
	12	m	21		+	++	—	+	264	HD	++
3	13	m	22		+++	++	+	+	1001	HD	++
	14	f	18		+++	+++	+++	+	209	HD	+
	15	m	12		+	—	+	+	737	HD	+
	16	m	60		+	+++	++	+	946	HD	++
	17	m	49		++	+	++	—	286	HD	++
	18	m	18		+	+	—	—	451	HD	++

Legends: m = male, f = female, HD = House dust (in the skin tests as well as in the nasal provocation tests).

Group 1 = patients challenged with Methysergide maleate (Deseril®).

Group 2 = patients challenged with Pyranisamine hydrochloride (Mepyramine®).

Group 3 = patients challenged with Xylometazoline hydrochloride (Otrivin®).

The evaluation of the intracutaneous tests:

— = normal skin appearance.

± = wheal not greater than original injected papule.

+

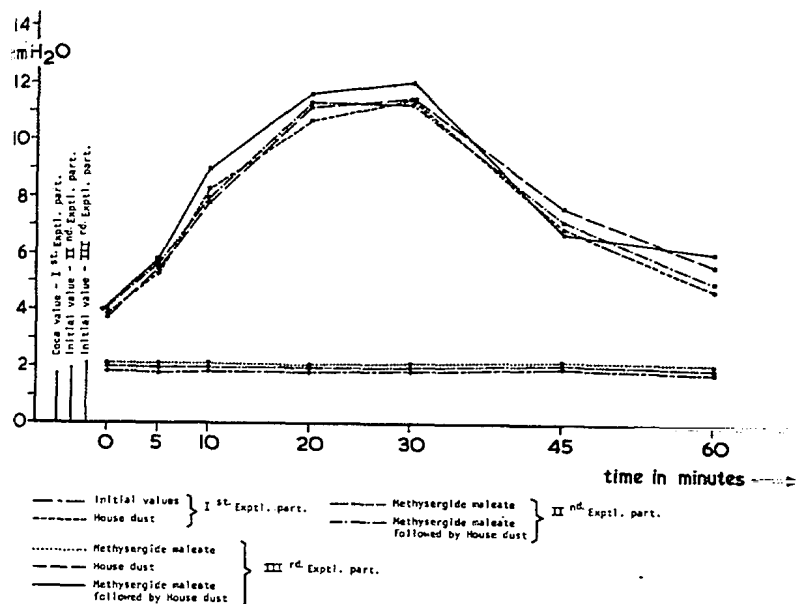


Fig. 1.

The mean NPG values of all patients in the group Methysergide maleate (Deseril®).

Patients

The 18 patients examined were either outpatients from the Pulmonary Division (Univ. Hospital, Groningen) or hospitalized patients from the Department for Asthmatic Diseases of "Beatrixoord" Sanatorium (Haren-Groningen).

All examined patients showed: a) positive intracutaneous tests with house dust; b) nasal complaints ("allergic rhinitis"), often combined with chronic non-specific lung diseases (CNSLD); and c) positive nasal provocation tests with house dust.

The patients were divided randomly into 3 groups, each group comprising 6 patients. Patients of any one group received only one of the 3 drugs tested. The characteristics of the patients investigated are given in Table 1.

The patients were investigated during a period when they were without manifest nasal complaints. No antihistaminics, anticholinergics, antiserotonics, sympathomimetics or corticosteroids were given to them during the 24-hour period before each part of the experiment. These patients were not treated with Disodium cromoglycate or with immunotherapy.

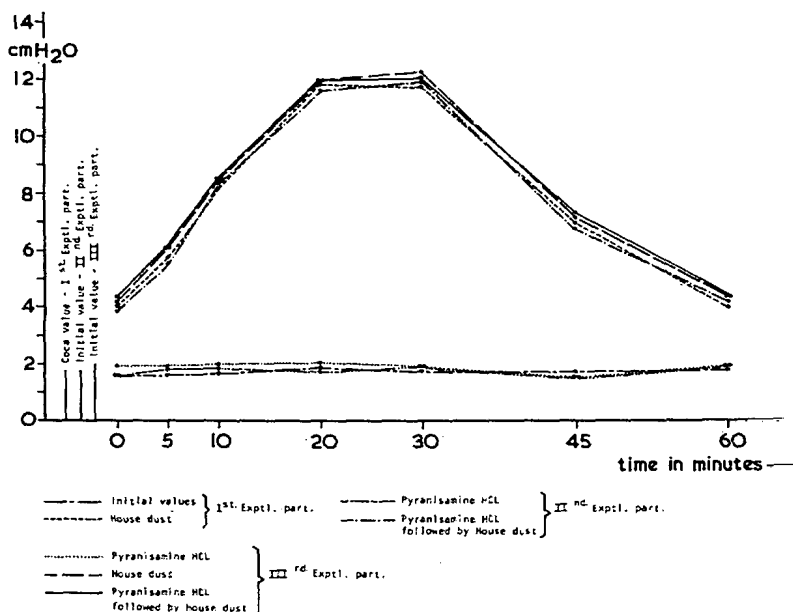


Fig. 2.

The mean NPG values of all patients in the group Pyranisamine hydrochloride (Mepyramine®).

RESULTS

The NPG values measured in all parts of the experiment in each of the patients are summarized in the Table 2, and their mean values are given in Figs. 1, 2 and 3.

The provocation effects of house dust in a concentration of 5.0 mg/ml, applied topically to the nasal mucosa in both the 1st and 3rd parts of the experiment, were significantly positive with respect to the "initial curve" as well as to the "Coca solution" values. The provocation effects of house dust started within 5 min in most patients, reached their maximum within 30 min, and did not disappear completely during the 60 min after the allergen challenge. The time taken for

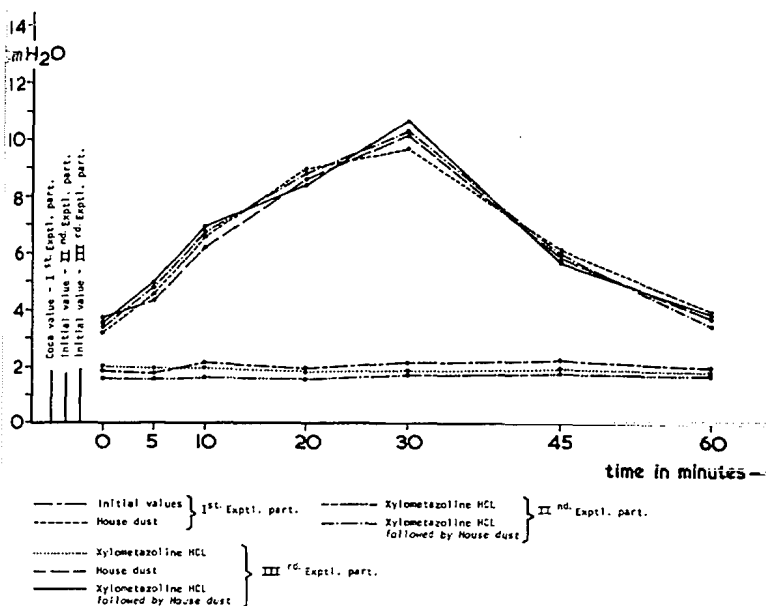


Fig. 3.

The mean NPG values of all patients in the group Xylometazoline hydrochloride (Otrivin®).

recovery to the "initial" NPG values depended on the degree of response.

The time-course of the mean NPG values measured during the "initial test" in the 1st part of the experiment in the same patient, did not show any significant differences during a 60-min period. The "initial values" in the 2nd and 3rd parts were identical to the "initial test" values in the 1st part for the same patient.

The mean NPG values recorded after the challenge with the Coca solution, as well as after the application of each of the drugs tested, did not differ significantly with respect to the "initial test".

The time-course of the mean NPG values recorded during

TABLE 2

Survey of the Nasopharynx-Nostril-Pressure Gradient Values (in cm H₂O) Measured in the Individual Patients at Different Time Intervals during all Experimental Parts.

Group	Patient	Initial values						1st experimental part						House dust										
		0'	5'	10'	20'	30'	45'	60'	Coca solution			Time in minutes after the challenge			0'			5'	10'	20'	30'	45'	60'	
Methysergide maleate	1	2.1	2.1	2.3	2.3	2.1	2.3	2.1	2.1	2.2	2.1				3.6	5.5	8.4	10.3	13.0					
	2	1.9	1.9	1.9	1.7	1.7	1.7	1.9	1.7	1.7	1.8				3.2	4.2	5.7	8.9	13.4					
	3	1.6	1.6	1.4	1.6	1.8	1.8	1.6	1.8	1.6	1.7				3.8	5.5	9.0	11.7	13.8					
	4	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.1				2.7	3.2	7.6	11.9	7.6					
	5	2.7	2.7	2.7	3.2	3.2	3.2	3.0	2.7	2.8	2.8				7.9	10.3	13.3	14.3	12.5					
	6	1.8	1.5	1.5	1.7	1.6	1.6	1.6	1.5	1.7	1.5				2.5	3.1	5.4	6.9	8.5					
Mean value		1.9	1.8	1.8	1.9	1.9	2.0	1.9	1.8	1.9	1.8				4.0	5.3	8.2	10.6	11.5					
HCL	1	1.4	1.4	1.6	1.6	1.6	1.6	1.6	1.4	1.5	1.5				6.6	8.5	12.4	15.2	17.1					
	2	1.9	2.1	1.9	1.7	1.7	1.9	2.1	2.1	2.0	2.1				3.3	4.5	6.1	10.4	8.9					
	3	1.6	1.6	1.6	1.7	1.6	1.7	1.7	1.8	1.8	1.7				4.3	6.3	9.2	9.9	10.4					
	4	1.5	1.5	1.5	1.6	1.5	1.6	1.6	1.6	1.6	1.6				2.7	3.9	7.3	9.8	9.8					
	5	1.7	1.7	1.7	2.1	1.9	1.9	1.9	1.8	1.9	1.9				3.7	4.8	5.6	11.7	12.5					
	6	1.8	1.6	1.8	1.8	1.6	1.6	1.6	1.6	1.7	1.7				3.4	6.1	8.7	13.7	11.4					
Mean value		1.7	1.7	1.7	1.8	1.7	1.7	1.8	1.7	1.8	1.8				4.0	5.7	8.2	11.8	11.7					
Pyranisamine HCL	1	1.8	1.8	2.1	2.1	2.3	2.5	2.1	2.1	2.3	2.2				4.1	4.3	5.5	6.9	5.3					
	2	1.3	1.1	1.5	1.5	1.3	1.3	1.3	1.5	1.4	1.4				2.4	3.3	7.5	9.9	13.9					
	3	2.2	2.4	2.4	2.2	2.2	2.2	1.8	1.7	1.9	2.0				2.4	3.7	5.0	6.9	6.4					
	4	2.7	2.7	2.7	2.7	2.9	2.9	2.0	2.5	2.8	2.8				4.9	9.2	11.7	14.9	14.1					
	5	2.9	2.6	2.9	2.6	2.9	2.9	2.9	2.6	2.8	2.7				4.2	4.6	5.9	7.7	11.0					
	6	0.8	0.7	0.7	0.7	0.8	0.8	0.8	0.8	0.8	0.8				1.9	2.4	3.7	6.9	7.1					
Mean value		1.7	1.7	1.7	1.8	1.7	1.7	1.8	1.7	1.8	1.8				4.0	5.7	8.2	11.8	11.7					
HCL	1	1.8	1.8	2.1	2.1	2.3	2.5	2.1	2.1	2.3	2.2				4.1	4.3	5.5	6.9	5.3					
	2	1.3	1.1	1.5	1.5	1.3	1.3	1.3	1.5	1.4	1.4				2.4	3.3	7.5	9.9	13.9					
	3	2.2	2.4	2.4	2.2	2.2	2.2	1.8	1.7	1.9	2.0				2.4	3.7	5.0	6.9	6.4					
	4	2.7	2.7	2.7	2.7	2.9	2.9	2.0	2.5	2.8	2.8				4.9	9.2	11.7	14.9	14.1					
	5	2.9	2.6	2.9	2.6	2.9	2.9	2.9	2.6	2.8	2.7				4.2	4.6	5.9	7.7	11.0					
	6	0.8	0.7	0.7	0.7	0.8	0.8	0.8	0.8	0.8	0.8				1.9	2.4	3.7	6.9	7.1					
Mean value		1.7	1.7	1.7	1.8	1.7	1.7	1.8	1.7	1.8	1.8				4.0	5.7	8.2	11.8	11.7					

Group	Patient	Initial value	2nd experimental part							Drug followed by house dust						
			Drug							Time in minutes after the challenge						
			0'	5'	10'	20'	30'	45'	60'	0'	5'	10'	20'	30'	45'	60'
Methysergide maleate	1	2.0	2.0	2.0	2.0	2.0	2.0	2.0	2.2	3.3	5.1	8.4	11.2	12.5	6.7	5.6
	2	2.5	2.1	2.1	2.1	2.1	2.1	2.1	2.1	3.8	5.7	7.6	12.6	14.2	8.5	4.7
	3	1.5	1.5	1.5	1.5	1.5	1.7	1.8	1.5	3.5	5.2	8.1	11.7	13.6	7.8	5.5
	3	1.7	1.5	1.7	1.7	1.7	1.9	1.9	1.7	3.6	4.4	8.0	11.8	7.4	4.0	3.8
	5	2.4	2.6	2.5	2.4	2.4	2.4	2.6	2.4	7.2	9.9	11.0	14.1	11.5	9.7	6.2
	6	1.8	2.0	2.0	1.8	1.7	1.8	1.8	1.6	2.6	3.0	4.1	6.8	9.4	6.3	3.9
Mean value		2.0	2.0	1.9	2.0	1.9	2.0	2.0	1.9	4.0	5.6	7.9	11.4	11.4	7.2	5.0
HCL	1	1.5	1.5	1.7	1.7	1.5	1.5	1.7	1.9	6.3	8.6	12.0	14.8	17.1	9.3	5.8
	2	1.7	1.9	1.9	1.9	1.9	2.1	1.9	2.1	3.4	4.4	6.7	10.8	9.1	6.5	4.0
	3	1.8	1.8	1.6	1.8	1.8	1.8	1.8	1.8	4.6	6.4	10.0	10.7	10.9	6.1	3.3
	4	1.5	1.5	1.5	1.5	1.6	1.6	1.5	1.5	2.5	3.8	7.4	10.0	9.7	7.8	5.0
	5	1.7	1.6	1.7	1.8	1.8	1.7	1.7	1.7	3.1	4.3	5.6	10.5	12.8	5.0	3.5
	6	2.0	1.8	2.0	1.5	1.8	1.8	1.8	1.8	4.0	7.0	8.4	13.2	11.4	7.0	4.1
Mean value		1.7	1.7	1.7	1.7	1.7	1.8	1.7	1.8	4.0	5.8	8.4	11.7	11.8	7.0	4.3
Pyranisamine HCL	1	1.6	1.6	1.6	1.5	1.6	1.5	1.4	1.6	3.4	4.3	5.2	7.1	6.9	4.0	2.4
	2	1.6	1.5	1.5	1.5	1.3	1.5	1.5	1.6	2.5	3.6	7.6	10.5	13.9	4.2	2.0
	3	1.8	1.2	1.2	1.2	1.2	1.4	1.4	1.4	2.1	3.2	4.4	5.8	6.5	4.9	2.3
	4	2.4	2.2	2.2	2.2	2.0	2.0	2.2	2.0	6.6	9.2	11.9	14.2	15.1	12.6	6.4
	5	2.3	2.4	2.6	2.4	2.4	2.8	2.6	2.6	4.0	5.2	6.7	8.5	12.2	8.1	5.6
	6	0.7	0.8	0.7	0.7	0.8	0.7	0.8	0.8	2.0	2.7	3.7	6.3	6.9	2.7	1.9
Mean value		1.7	1.6	1.6	1.6	1.6	1.7	1.7	1.7	3.4	4.7	6.6	8.7	10.3	6.1	3.4
Xylometazoline HCL	1	1.7	1.7	1.7	1.7	1.7	1.8	1.7	1.8	4.0	5.8	8.4	11.7	11.8	7.0	4.3
	2	1.6	1.6	1.6	1.5	1.6	1.5	1.4	1.6	3.4	4.3	5.2	7.1	6.9	4.0	2.4
	3	1.8	1.5	1.5	1.5	1.3	1.5	1.5	1.6	2.5	3.6	7.6	10.5	13.9	4.2	2.0
	4	2.4	2.2	2.2	2.2	2.0	2.0	2.2	2.0	6.6	9.2	11.9	14.2	15.1	12.6	6.4
	5	2.3	2.4	2.6	2.4	2.4	2.8	2.6	2.6	4.0	5.2	6.7	8.5	12.2	8.1	5.6
	6	0.7	0.8	0.7	0.7	0.8	0.7	0.8	0.8	2.0	2.7	3.7	6.3	6.9	2.7	1.9
Mean value		1.7	1.6	1.6	1.6	1.6	1.7	1.7	1.7	3.4	4.7	6.6	8.7	10.3	6.1	3.4

TABLE 2 (continued)

3rd experimental part																							
Group		Patient	Drug						House dust						Drug followed by House dust								
			Time in minutes after challenge						Time in minutes after challenge						Time in minutes after challenge								
		Initial value	0'	5'	10'	20'	30'	45'	60'	0'	5'	10'	20'	30'	45'	60'	0'	5'	10'	20'	30'	45'	60'
Methysergide maleate	1	2.9	2.5	2.5	2.5	2.3	2.3	2.3	2.3	3.3	4.3	7.2	10.5	13.0	9.2	3.9	3.8	5.8	9.4	12.8	11.8	6.7	4.8
	2	2.4	2.4	2.6	2.4	1.8	1.7	2.0	2.2	3.6	4.9	6.6	10.1	14.1	11.8	6.5	3.5	4.5	7.5	11.3	14.3	7.8	6.4
	3	2.3	2.7	2.5	2.1	2.3	2.3	2.3	2.5	4.4	6.3	9.5	13.1	14.7	9.3	5.5	4.4	6.5	10.7	13.0	15.3	9.0	5.9
	4	1.3	1.5	1.3	1.5	1.8	2.0	1.8		3.1	3.4	7.9	12.3	6.8	4.5	3.5	3.1	4.0	8.1	12.1	7.9	4.2	3.5
	5	2.6	2.6	2.6	2.5	2.6	2.5	2.6	2.6	6.8	9.6	10.5	13.8	10.7	6.4	6.0	6.8	9.8	12.6	12.6	13.2	8.7	7.5
	6	1.6	1.4	1.6	1.6	1.6	1.6	1.6	1.6	2.5	3.6	5.2	7.6	9.2	4.7	2.3	2.4	3.6	5.5	7.6	9.5	4.8	2.5
	Mean value	2.2	2.2	2.1	2.0	2.1	2.1	2.1	2.2	4.0	5.4	7.8	11.2	11.4	7.7	4.6	4.0	5.7	9.0	11.6	12.0	6.9	5.1
Pyranisamine HCL	1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1	7.2	8.7	12.0	16.1	18.3	10.3	5.2	7.6	8.7	10.5	15.9	18.5	10.7	6.0
	2	2.2	2.0	1.5	2.0	2.0	2.0	2.0	2.0	3.3	5.1	6.6	10.3	9.2	6.4	4.0	3.4	4.6	6.2	10.1	9.1	6.7	4.4
	3	1.9	1.9	2.0	1.9	2.0	2.0	2.0	1.9	4.4	6.9	10.9	10.9	10.5	6.3	3.7	4.4	6.7	10.1	11.4	10.8	6.4	3.6
	4	1.6	1.6	1.7	1.5	1.6	1.5	1.6	1.6	2.6	4.0	7.2	10.0	9.5	8.1	4.7	2.5	4.1	7.4	9.8	9.6	8.0	4.7
	5	2.0	2.0	2.0	2.2	2.0	2.0	2.0	2.2	3.3	4.4	6.0	10.3	13.5	5.0	4.0	3.3	5.7	8.4	10.6	12.2	5.5	3.7
	6	2.2	1.9	1.9	1.9	2.2	2.2	1.9	2.1	3.7	7.2	8.4	13.9	12.3	7.2	4.4	3.7	6.7	8.5	14.0	11.8	6.6	3.9
	Mean value	2.0	1.9	1.9	1.9	2.0	2.0	1.9	2.0	4.1	6.1	8.5	11.9	12.2	7.2	4.3	4.2	6.1	8.5	12.0	12.0	7.3	4.4
X-metazoline HCL	1	1.9	1.9	1.7	1.9	1.9	1.9	1.7	1.7	4.2	4.7	5.3	7.2	6.5	5.7	4.2	3.8	4.3	5.7	7.8	6.8	5.3	4.2
	2	1.7	1.4	1.4	1.4	1.4	1.4	1.4	1.8	2.8	3.5	8.0	10.1	13.9	5.2	3.1	2.6	4.0	8.2	10.6	14.1	4.7	2.8
	3	1.5	1.7	1.5	1.6	1.6	1.3	1.5	1.3	3.0	3.3	4.1	6.4	5.5	4.1	2.0	1.9	3.3	4.5	7.3	5.9	4.5	2.0
	4	3.8	3.5	3.7	3.6	3.6	3.2	3.4	3.1	6.7	8.1	10.3	13.6	17.0	9.2	6.2	6.7	10.0	13.9	16.1	17.0	9.1	6.2
	5	2.0	2.1	2.1	2.3	2.1	2.1	2.1	2.1	3.3	4.1	5.9	7.0	11.8	8.6	5.1	3.7	4.3	5.4	7.7	12.3	8.3	5.1
	6	0.8	0.8	0.8	0.8	0.8	0.8	0.8	0.8	2.0	2.6	4.0	6.6	7.3	2.8	1.9	1.7	3.0	3.8	7.1	7.6	2.8	1.9
	Mean value	2.0	1.9	1.9	1.9	1.9	1.9	1.9	1.9	4.1	4.7	6.1	8.5	11.9	12.2	7.2	4.3	4.2	6.1	8.5	12.0	12.0	7.3

the protection tests with the individual drugs in the 2nd and 3rd parts, did not differ significantly between themselves, or with respect to the mean NPG values measured during the provocation tests in the 1st and 3rd experimental parts.

From the data obtained in this clinical experiment the following conclusions can be drawn: None of the drugs (Methysergide maleate, Pyranisamine hydrochloride and Xylometazoline hydrochloride) was found, when applied topically, to be able to decrease or to prevent the changes of the nasal mucosa caused by a challenge with house dust in a concentration of 5.0 mg/ml (Cf: /drug + house dust/ from the 2nd experimental part with house dust provocation from the 1st part). These drugs did not exhibit any protective effects against a following house dust provocation of the nasal mucosa.

Using a Dexamethasone 21-isonicotine nasal spray for 14 days did not decrease or prevent the provocation effects of the house dust on the nasal mucosa (Cf: the house dust provocation from the 3rd experimental part with that from the 1st part).

Combining the above-mentioned drugs individually with Dexamethasone 21-isonicotine did not lead to a decrease in, nor to a prevention of the changes in the nasal mucosa due to a subsequent challenge with house dust (Cf: /drug + house dust/ from the 3rd experimental part with the identical test from the 2nd part). The combination of these drugs with the corticosteroid nasal spray did not demonstrate any protective effects against a following challenge of house dust on the nasal mucosa.

All patients showed one or more nasal complaints (obstruction, sneezing, hypersecretion) after the house dust challenge during the provocation as well as during the protection tests. The degree of the nasal complaints was similar in both kinds of test in the same patient.

DISCUSSION

The arrangement of this clinical experiment, as well as the method used, were chosen to allow comparison of the actual results with those from our previous investigations on Disodium cromoglycate (Rynacrom®, Lomudal®) (16). This compound demonstrated distinct protective effects against nasal mucosa changes caused by provocation with allergen.

The drugs tested in the present investigation were chosen as being representative of some pharmacological groups which can theoretically influence either the antigen-antibody reaction (antihistaminics, antiserotonics, corticosteroids), or the changes of the nasal mucosa due to this reaction (alpha-sympathomimetics). Pyranisamine hydrochloride and Methysergide maleate are antagonists to histamine and serotonin, compounds which are presumed to be mediators released by the 1st type of antigen-antibody reaction and which play a part in the development of the nasal mucosa changes due to this reaction. Xylometazoline hydrochloride possesses a topical decongestant effect on the nasal mucosa (8). The corticosteroid drug, Dexamethasone 21-isonicotine, can possibly suppress some types of antigen-antibody reaction (7, 10), and one of its side-effects is topical decongestion of the mucosa. However, the whole role and the details of the mode of action of corticosteroids on the various types of the antigen-antibody reaction are not yet fully known.

These drugs were also chosen with respect to the previous studies carried out in our department. The effects of some of the above-mentioned drugs on the bronchial tree challenges with inhaled allergen were investigated, as possible means for investigating the pathophysiologic mechanism of certain types of allergic reaction (2, 3). The antihistaminics, as well as the antiserotonics, demonstrated only partial protection against the bronchoconstriction due to the allergen challenge (2).

Antihistaminics, sympathomimetics and corticosteroids are often used in daily practice in the treatment of nasal complaints of various origins. A number of authors have reported

the various therapeutical values of these drugs in the treatment of nasal complaints which have already developed (1, 4, 9, 11, 13, 15, 18, 19, 21, 22, 23). However most of them did not analyse exactly the different pathophysiological mechanisms (e.g. antigen-antibody reaction, non-specific hyperreactivity, possible reflex-reaction etc.), all resulting in the same spectrum of nasal complaints. In addition, the exact action of these drugs on the individual pathophysiological changes of the nasal mucosa is not yet fully known. Therefore we examined the possibility of the protective effects of these drugs on the changes of the nasal mucosa caused by a known allergen in a known dose.

The results of our investigation show that the drugs tested, when they are applied topically on the nasal mucosa before the house dust, cannot prevent or decrease the nasal mucosa changes caused by the subsequent challenge of house dust.

These results could be explained in various ways. Firstly, it could be suggested that the degree of effectiveness of the antihistaminic and antiserotonic drugs is dependent on various factors concerning the method, e.g. route of application, dose, time of challenge, kind and dose of allergen, and degree of hypersensitivity of patient. With respect to these factors, is it possible that the drugs do not reach specific receptor sites of the nasal mucosa in a sufficient and effective amount? Because the route of administration may be a relevant factor, we have started complementary experiments using an antihistaminic drug in another similar group of patients. Pyranisamine hydrochloride has been given to patients either topically on the nasal mucosa or injected intramuscularly (25 mg), and its protective effects in the nasal provocation tests with histamine or with house dust were observed. The results showed that when this drug is applied either topically to the nasal mucosa or injected intramuscularly, it demonstrates excellent protective effects in the nasal provocation tests with histamine. No protective effects of this drug, whether applied topically or intramuscularly, have been observed in the same person during the provocation tests with house dust. These results make it un-

likely that the route of administration of these drugs can influence significantly their effects on the nasal mucosa.

Secondly, with regard to the effector organ (nasal mucosa) and to the origin of histamine, Dolowitz (6) suggested that antihistaminics applied "intranasally" have better effects against the directly (outside) applied histamine than against that which is released by an antigen-antibody reaction. He said that the difference occurs because cellular liberation of histamine by proximity can tie up the cellular receptors before they become filled with a competing antihistamine. This suggestion is in accordance with our results demonstrating the protective effects of antihistaminics against the histamine challenge but not against the allergen nasal challenge. Weder (23) and Sheldon et al. (21) have also found distinct differences among various antihistaminics with respect to their effects on nasal complaints.

Lastly, other factors or mechanisms which are not influenced by the drugs investigated cannot be excluded as playing a role either during the antigen-antibody reaction in the nasal mucosa or during the development of the nasal mucosa changes. As examples of such factors could be considered: a) some mediators different from histamine and serotonin, e.g. SRS-A, bradykinine, kinine-like substances (5, 12, 14), b) the influence of the anatomical structure of the nasal mucosa on the course of the antigen-antibody reaction (e.g. lack of smooth muscles, a very rich vascular system (20), presence of various secretory elements etc.).

In various clinical investigations, Xylometazoline hydrochloride has been found to be a successful decongestant and vasoconstrictor of the nasal mucosa (1, 4, 9, 11, 13, 18, 19, 22). However the cause of the oedema of the nasal mucosa was not analyzed in detail in these papers. This nasal mucosa swelling can also have a different origin than the antigen-antibody reaction (e.g. non-specific hyperreactivity, common cold etc.). In the literature available we have not found reports on the possible protective effects of this drug on the nasal allergen provocation tests. With regard to our results,

we suggest that Xylometazoline hydrochloride may produce therapeutical effects on the already swollen nasal mucosa, but this drug is not able to prevent the swelling of the nasal mucosa due to the antigen-antibody reaction.

The lack of protective effects of the corticosteroid drug, observed in our experiment, could perhaps be explained by the action of corticosteroids being mainly against the IIIrd and the IVth type of the allergic reaction and not against the Ist type. The corticosteroids are perhaps more successful where an inflammatory component also occurs, or where the swelling of the nasal mucosa is caused by some mechanism other than the Ist type of the allergic reaction.

SUMMARY

The possibility of protective effects of the topically applied Xylometazoline hydrochloride (Otrivin®), Pyranisamine hydrochloride (Mepyramine®, Antallergan®) and Methysergide maleate (Deseril®), and of their combination with Dexamethasone 21-isonicotine, on the changes of the nasal mucosa caused by house dust challenge, was investigated in patients suffering from allergic rhinitis. These drugs did not demonstrate any protective effects in the nasal provocation tests with house dust.

ACKNOWLEDGEMENTS

We wish to thank Professor Dr. N. G. M. Orie and Professor Dr. H. J. Sluiter for their useful comments on this communication.

REFERENCES

1. Biesalski, P. & Marquardt, K. (1959): Zur Behandlung der Rhinitis im frühen Kinderalter. *Schweiz. med. Wschr.* 89, 510-512.
2. Booij-Noord, H., Orie, N. G. M., Berg, Ch. W. & de Vries, K. (1970): Results of provocation of human bronchial airways with allergic and non-allergic stimuli and of drug protection tests. In Orie, N. G. M. & Van der

- Lende, R. (eds.): *Bronchitis III, Third International Symposium*, p. 316-331. Royal Van Gorcum Publisher, Assen, Netherlands.
3. Booij-Noord, H., Orie, N. G. M. & de Vries, K. (1969): Serotonin inhalation in patients with chronic non-specific lung disease. *Scand. J. resp. Dis.* 50, 301-308.
 4. De Blasio, S. (1960): Analysis of a new decongestant in office rhinology. *E. E. N. T. Digest* 22, 22.
 5. Dolovich, J., Back, N. & Arbesman, C. E. (1970): Kinin-like activity in nasal secretions of allergic patients. *Int. Arch. Allergy* 38, 337-344.
 6. Dolowitz, D. A. (1971): Drug treatment in allergic disorders. *Otolaryngologic Clinics of North America* 4, 591-598.
 7. Gell, P. G. H. & Coombs, R. R. A. (1964): *Clinical aspects of immunology*. Blackwell Sci. Publ., Oxford.
 8. Goodman, L. S. & Gilman, A. (1970): *The pharmacological basis of therapeutics*, (4th ed.). MacMillan Co., New York, London, Toronto.
 9. Hagen, W. J. & Trelles, M. G. (1960): A new local decongestant of unusually low toxicity. *Eye, Ear, Nose, Thr. Monthly* 39, 56.
 10. Jasani, M. K. (1972): Possible modes of action of ACTH and glucocorticoids in allergic diseases. *Clin. Allergy* 2, 1-41.
 11. Lewison, E. (1970): Comparison of the effectiveness of topical and oral nasal decongestants. *Eye, Ear, Nose, Thr. Monthly* 44, 16.
 12. Logan, G. B. (1962): Chemical mediators of acute allergic reaction. *Amer. J. Dis. Child* 104, 185.
 13. Messek, H. (1962): Die Wirkung verschiedener Vasokonstriktoria auf eigene Qualitäten der Nasenschleimhaut. *Msschr. Ohrenheilk.* 96, 294-306.
 14. Mongar, J. L. & Schild, H. O. (1962): Cellular mechanism in anaphylaxis. *Physiol. Rev.* 42, 226-270.
 15. Mujic, M. & Van Rossum, J. M. (1965): Comparative pharmacodynamics of sympathomimetic imidazolines. *Arch. int. Pharmacodyn.* 155, 432-449.
 16. Pelikan, Z., Snoek, W. J., Booij-Noord, H., Orie, N. G. M. & de Vries, K. (1970): Protective effect of Disodium cromoglycate on the allergen provocation of the nasal mucosa. *Ann. Allergy* 28, 548-553.
 17. Pelikan, Z. & de Vries, K. (1972): Comparison of the nasal mucosa response on challenge of house dust and mites (*Dermatophagoides pteronyssinus*) allergens. *Acta allerg. (Kbh.)* 27, 167-178.
 18. Pelz, H. (1963): Zur Behandlung mit Nasentropfen. *Med. Welt (Berl.)* 32, 1603-1605.
 19. Sählbrandt, H. D. (1960): Klinische Erfahrungen mit Otriven. *Med. Klin.* 55, 842-844.
 20. Salvaggio, J. E., Cavanaugh, J. J. A., Lowell, F. C. & Leskowitz, S. (1964): A comparison of the immunologic response of normal and atopic individuals to intranasally administered antigen. *J. Allergy* 35, 62-69.
 21. Sheldon, J. M., Lovell, R. G. & Mathews, K. P. (1967): *A manual of clinical allergy*, (2nd ed.). W. J. Saunders Co., Philadelphia and London.

22. Toyoda, Y. & Ishikawa, K. (1968): Clinical experiences with Otrivin in diseases of the nasal cavity. *Jibi Inkoka Rinsho* (Oto-rhino-laryng. Clin. Jap.) *61*, 319-324.
23. Weder, A. (1962): Diagnostik und Therapie der allergischen und extra-allergischen vasomotorischen Rhinopathie. *Pract. oto-rhino-laryng.* (Basel), Suppl. ad Vol. 24.

Address of author:

Dr. Z. Pelikan,
Allergology Div.,
Dept. of Internal Medicine,
University Hospital,
59 Oostersingel,
Groningen,
The Netherlands.

This document is a scanned copy of a printed document. No warranty is given about the accuracy of the copy. Users should refer to the original published version of the material.