

Effect of the H₁ Antihistamine Chlorpheniramine Maleate on Histamine-Induced Symptoms in the Human Conjunctiva

Indirect Evidence for Nervous H₁ Receptors

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Earlier studies have shown that intranasal chlorpheniramine (0.77%) can inhibit histamine-induced tickling, sneezing, and hypersecretion by a local effect on nerve fibres. The aim of the present study was to examine whether this solution has local anaesthetic or parasympatholytic properties. If neither of these properties are present it suggests that the anti-pruritic effects of the solution are caused by inhibition of H₁ receptors, which in turn is indirect evidence for the presence of H₁ receptors on nerve fibres. In a double-blind design 15 normal subjects were provoked with histamine in the eye after pretreatment with chlorpheniramine or with a local anaesthetic, oxybuprocain. Both drugs inhibited itching, but the H₁ antihistamine was significantly more effective than the local anaesthetic ($P < 0.01$). Corneal sensitivity was measured by an esthesiometer, and pupil difference was used as a measure for atropine activity. Chlorpheniramine had neither a local anaesthetic nor a parasympatholytic effect. This study has therefore strengthened the hypothesis that there are nervous H₁ receptors in the mucous membranes of the eye and airways, and has extended its application in animals to also include man.

Key words: allergic conjunctivitis; allergic rhinitis; H₁ antihistamines; histamine provocation; nervous H₁ receptors.

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CLINICAL ASPECTS

In the treatment of allergic rhinitis there is a need for a symptomatic drug, which acts almost immediately but without risk of systemic side effects. In a series of studies we have therefore examined the effect of nasal sprays, containing H₁ and H₂ antihistamines, on histamine-induced symptoms. The results are: 1) the mode of action is local, and not via the CNS, 2) the H₁ and the H₂ antihistamines have an additive effect on blockage, and 3) only the H₁ antihistamine inhibits tickling, sneezing and hypersecretion. In conclusion, these studies have provided a rationale for topical antihistamine treatment, and suggest that further experiments might be worthwhile.

Exogenous histamine can imitate the immediate allergic symptoms in the eye, nose and bronchi (2, 10), and the therapeutic efficacy of H₁ receptor antagonists suggests that histamine and H₁ receptors play an important role in mediating type-1 allergic reactions in the eye and nose (12, 18). The lack of a clinically significant effect of antihistamines in asthma is usu-

ally considered as being due to the relatively greater importance of other mediators in the bronchi (1, 7), but also the possibility of a poor drug accessibility to receptor sites has been mentioned as a part of the explanation (5).

It is generally accepted that H₁ antihistamines counteract the histamine effect on smooth muscles in blood vessels and in the

bronchial wall by binding to specific, pharmacological H_1 cell receptors (5, 14). But histamine can also cause bronchoconstriction, itching in the eye and nose, and sneezing via action on the sensory nerves (17), and it is less obvious how the H_1 antihistamines inhibit these reflex-mediated symptoms.

In a series of studies of antihistamines' mode of action in the human airway (9, 16) we have recently shown that the H_1 antihistamine, chlorpheniramine maleate, inhibits histamine-induced nasal symptoms by a local effect in the mucous membrane and not by an effect on the central nervous system; it was concluded that the most likely explanation of the H_1 antihistamine inhibition of tickling, sneezing and hypersecretion is an effect on sensory nerve endings. It is not easy to account for this action, as pharmacological H_1 receptors on nerve fibres have not been demonstrated before, although their presence has been suggested in animal experiments (4, 15). Other possible explanations, often referred to in standard textbooks, are local anaesthetic and parasympatholytic effects of the antihistamine molecule (5, 14).

In our earlier studies we demonstrated a marked inhibition of the histamine effect on sensory nerves in the nose by pretreatment with a 0.77% solution of chlorpheniramine maleate (9, 16), and it was the aim of the present experiment to study whether this solution, which has anti-pruritic qualities, also possesses local anaesthetic and parasympatholytic characteristics. If this is not the case, it will provide us with indirect evidence for the presence of nervous H_1 receptors in man. For this purpose we found the conjunctival sac more suitable than the nasal mucosa, because sensitivity and atropine activities of the solution can be readily measured in the eye.

MATERIAL AND METHODS

Volunteers. Fifteen medical students with no history of allergic or chronic-recurrent diseases in the airways or eyes volunteered for the study. The mean age was 23.6 years (range 22–38); six were females and nine males. Consent was obtained after verbal and written information.

H_1 receptor antagonist. Chlorpheniramine maleate (in the remainder of this text, referred to as chlorpheniramine), which is a potent antihistamine, effective in a low dosage, had also been used in the earlier studies (9, 16). It was supplied as a powder from the Glaxo Group Ltd., Ware, Hertfordshire, U.K. A solution of 7.7 mg chlorpheniramine in 1 ml of saline was made up by the pharmacy at the Rigshospital. The osmolality was calculated to 325 mosm and pH measured to 4.8. No preservative was added. The chlorpheniramine solution, the local anaesthetic, and placebo (0.02% benzalkonium chloride) were filled in plain eyedrop bottles, which were coded by a technician not participating in the trial.

Local anaesthetic. Oxybuprocain hydrochloride (referred to as oxybuprocain) 0.2% was chosen, because for years it has been used by ophthalmologists as a non-irritating and effective surface-anaesthetic for short ophthalmological procedures.

Histamine provocation. Histamine chloride (referred to as histamine) was used in the same concentration (0.77 mg/ml distilled water) as in our studies of histamine provocation of the nose. Two drops of histamine, and of the other solutions were instilled in the conjunctival sac, while the student looked up at the ceiling.

Trial design. This was double-blind with each volunteer as his own control. The trial took place in December 1980 at the same time of day (1–3 p.m.). The students were provoked with histamine in both eyes on two occasions at 1–2 days' interval. Ten minutes earlier they had been pretreated in a random order with either antihistamine in one eye and placebo in the other, or with local anaesthetic in one eye and placebo in the other.

Statistical analysis. Wilcoxon's sign rank test for paired data was used, and $2\alpha \leq 0.05$ considered as significant.

Symptom recording. Irritancy from antihistamine, local anaesthetic and placebo was estimated by

the student as 0 (none), 1 (slight, of no significance for continuous use), 2 (moderate, of some significance for continuous use), and 3 (severe, not compatible with continuous use). Itching immediately after histamine provocation was also given a score from 0–3, and so was redness of the conjunctiva 5 min after provocation. Corneal sensitivity was measured by a corneal esthesiometer, described by Keeney (8). The instrument used consists of a single nylon filament which is inserted in a handle in such a way that the length of the filament can be changed and easily measured. With the filament extended, its tip is brought into perpendicular contact with cornea. If no sensation is evoked, the filament is progressive-

ly shortened, until the patient senses the contact. Sensitivity is then recorded as the length of the filament. Contact with the sensitive lashes is a source of error. Throughout the study we looked for divergence of pupil diameters, as this can detect the effect of atropine in a concentration of 1 µg/ml (6).

RESULTS

The results, depicted in the diagrams (Figs. 1–3) were as follows: 1) Only chlorpheniramine prevented redness. 2) This effect was almost complete. 3) Both chlorpheniramine and oxybuprocaine prevented itching, but the antihistamine was significantly better than the local

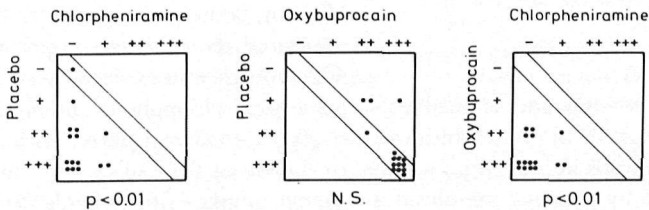


Fig. 1. Drug-prevention of histamine-induced redness of the eye in 15 normal subjects. –, ++ and +++ indicate increasing degrees of redness.

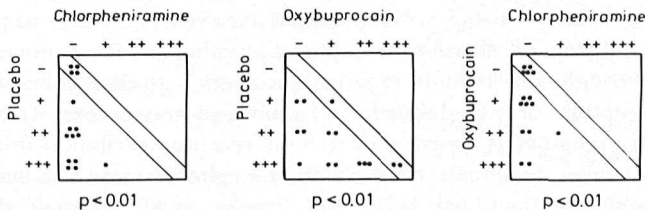


Fig. 2. Drug-prevention of histamine-induced itching in the eye in 15 normal subjects. –, ++ and +++ indicate increasing degrees of itching.

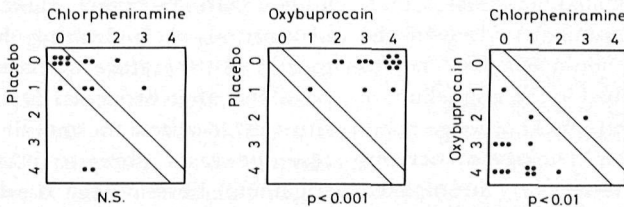


Fig. 3. Direct drug-effect on corneal sensitivity in 15 normal subjects. Scales indicate the reduction in length of the esthesiometer filament after use of the eyedrop. Thus, "4" indicates that the volunteer, after using the eyedrop, was only able to sense the nylon filament when it was 4 cm shorter than before medication.

Table 1
Immediate irritation after use of eyedrops
(no histamine provocation)

	Placebo (n = 30)	Chlorphenir- amine maleate (n = 15)	Oxybuprocain (n = 15)
None	24	2	10
Slight	6		3
Moderate		7	1
Severe		6	1

anaesthetic. 4) Only the latter had an effect on corneal sensitivity. 5) No divergence of pupil diameter was seen. 6) Chlorpheniramine in the given concentration was a moderate irritant in the normal eye (Table 1).

DISCUSSION

There is ample experimental and clinical evidence for the importance of reflex-induced symptoms in allergic rhinitis and asthma, which are both characterized by mucous membranes which are hyperreactive to inhaled irritants, mechanical stimulation, and the chemical mediators released by the allergic reaction (11, 13). We usually consider the reflex-mediated symptoms to be due to stimulation of nervous receptors, i.e. "sneezing, cough and irritant receptors", but our conception of well-defined nerve fibre endings as receptors is based on electrical recording of action potentials from single nerve fibres in subhuman mammals (17), and not on direct evidence from human studies.

While there is indirect but good evidence that the irritant receptor in the bronchial tree is located to afferent myelinated nerve fibres, ending 1–2 μm from the luminal surface of the epithelium (17), only non-myelinated nerves have so far been described in the epithelium of the human nose (3), and our knowledge about the structure and neurophysiology of nervous receptors in the human nose is very incomplete.

In a series of studies of the human nose, we have indirectly tried to get information about the role played by nervous receptors in allergic

rhinitis by measuring the response to nasal histamine provocation. While both H_1 and H_2 antihistamines were necessary for maximum inhibition of the histamine-induced nasal blockage (16), only the H_1 antihistamine could, by a local mode of action, inhibit tickling, sneezing, and rhinorrhoea (9, 16). The present study suggests that this was not due to a local anaesthetic or parasympatholytic effect of the antihistamine, and provides therefore indirect evidence for the existence of nervous H_1 receptors in the airway mucosa of the human nose.

There are also other lines of evidence for the existence of nervous H_1 receptors in the airways. Sampson & Vidruk (15) examined the effects of H_1 and H_2 antagonists on histamine-provoked activity in fibres from airway receptors in dog lungs. While the H_2 antagonist, burimamide, was essentially without effect, the H_1 antagonist, chlorpheniramine, completely abolished the increase in activity of the rapidly adapting receptors. However, the suprapharmacological chlorpheniramine dosage given (5 mg/kg i.v. as compared with the usual single oral dose of 0.1 mg/kg used in hay fever treatment), makes it difficult to rule out non-selective effects, such as local anaesthetic properties or CNS depression. But these possibilities are unlikely, as the authors were unable to inhibit the excitatory effect of prostaglandin $F_{2\alpha}$ and of lung hyperinflation on nervous receptors with this very high chlorpheniramine dose.

Dixon and co-workers (4) could inhibit the irritant receptor excitation in the dog bronchi with chlorpheniramine at a much lower dosage (0.1 mg/kg i.v.). Although these results are highly suggestive of the existence of nervous H_1 receptors, the authors would not exclude the possibility that the histamine stimulation of lung irritant receptors could be attributed to contraction of underlying bronchial smooth muscle. It therefore remained a theoretical possibility that bronchial H_1 receptors are exclusively localized to smooth muscles. In that case the vagal fibres to bronchi differ from trigeminal fibres to the nasal mucosa, as histamine-induced tickling and sneezing occur almost instantaneously after provocation, before any nasal blockage can have affected the ner-

vous receptors. In conclusion, our studies with histamine provocation of the nose and eye have strengthened the hypothesis, advanced by Sampson & Vidruk (15) and by Dixon and co-workers (4), that sensory nerve fibres in the airways possess pharmacological H₁ receptors, and have extended the application of this theory in subhuman mammals to include man.

It now seems likely that histamine-provoked itching in the eye, tickling in the nose, sneezing and cough are all mediated via nervous H₁ receptors. It remains to be studied whether these receptors are neurophysiologically and histologically identical in the different mucous membranes, and also how the "sneeze receptor" in the nose compares with other nervous receptors, which mediate pain and irritation, when stimulated mechanically and by chemical irritants.

While serial histamine provocations at 5-min intervals in the nose resulted in development of tachyphylaxis with regard to tickling, sneezing and hypersecretion, this phenomenon was not observed for nasal blockage (16), suggesting basic differences in the responsiveness of nervous and vascular H₁ receptors in the same tissue. Our studies have also suggested a difference between various organs, regarding vascular histamine receptors; while both H₁ and H₂ antihistamines are necessary for optimal inhibition of the congestive response to histamine in the nose, the H₁ antihistamine alone could almost completely abolish the vasodilatation in the eye.

In conclusion, the recent interest in studies of antihistamine effects in airways and eye has contributed to our understanding of the basic mechanisms in allergic inflammation, and also seems to provide us with a rationale for topical use in the future, but at present we know too little about compounds of choice, dose-time-response relationships, clinical efficacy, patient compliance, irritancy and risk of sensitization.

Finally, the present study has indicated that the antihistamine compound is an important part of the combined antihistamine-vasoconstrictor eyedrops, used in allergic conjunctivitis; an assumption which has been supported by a controlled clinical trial (12).

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