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Histamine and allergen induced changes in nasal airways resistance measured by anterior rhinomanometry: reproducibility of the technique and the effect of topically administered antihistaminic and anti-allergic drugs

O. J. CORRADO, S. OLLIER, M. J. PHILLIPS, J. M. THOMAS[1] & R. J. DAVIES
Academic Department of Respiratory Medicine and [1]Computer Services, St Bartholomew's Hospital, London EC1

1 Changes in nasal airways resistance (NAR) following the topical application of histamine and allergen solutions were measured by passive anterior rhinomanometry.
2 The repeatability of five consecutive measurements of resting NAR prior to provocation with histamine or allergen (expressed as the coefficient of variation) was 32.8% and following instillation of saline control solution 37.2%.
3 The repeatability of five consecutive measurements of NAR during the nasal obstruction produced by histamine and allergen was similar to that recorded prior to provocation; the coefficients of variation (median values) being 39.6% and 33.1% respectively. The degree of variability was not related to the dose of agonist or the degree of nasal obstruction.
4 The reproducibility of histamine or allergen induced changes in NAR on four separate weekly occasions showed no significant intra-subject differences.
5 The effects of sodium cromoglycate (SCG), clemastine and ketotifen administered to the nasal mucosa 30 min before provocation with histamine and allergen were compared in a random order, double-blind, placebo controlled study.
6 Clemastine and SCG, but not ketotifen, significantly inhibited the nasal response to increasing concentrations of histamine. None of the drugs administered in the concentrations used in this study significantly inhibited the nasal response to allergen.

Keywords rhinomanometry nasal airways resistance ketotifen sodium cromoglycate clemastine

Introduction

Allergic rhinitis is the most common allergic disease affecting up to 20% of the population (Mygind, 1981).

Many investigators have relied on subjective assessments of symptoms, often recorded in diaries, to evaluate therapeutic agents in the treatment of allergic rhinitis (Todd *et al.*, 1975; Wong *et al.*, 1981), whilst others have used objective measurements of changes in nasal patency after provocation with histamine and allergen (Taylor & Shivalkar, 1971; Britton *et al.*, 1978; Connell, 1979).

Although recent attempts have been made to improve the standardisation of techniques of nasal provocation and measurements of nasal patency (Kern, 1981; Clement, 1984) many dif-

Correspondence: Dr R. J. Davies, Academic Department of Respiratory Medicine, St Bartholomew's Hospital, London EC1A 7BE

derent methods remain in use (Graamans, 1981; Wihl, 1983) making comparisons of the results obtained from different laboratories difficult. Furthermore, the repeatability and reproducibility of these methods has rarely been the subject of detailed study. This situation is in total contrast to that existing for challenge procedures involving the lower airways where well standardised methods are in operation, and good reproducibility of measurements can be obtained (Parker *et al.*, 1965; Haynes *et al.*, 1976; Juniper *et al.*, 1978; SEPCR Working Group, 1984).

Anterior rhinomanometry is one method in which nasal airways resistance (NAR) can be measured, and has been used to determine the effects of drugs on nasal obstruction (Britton *et al.*, 1978). Many preparations are available for the treatment of allergic rhinitis including H_1-histamine receptor antagonists which have been in clinical use for over 40 years (Halpern, 1942) and have been a mainstay of the treatment of allergic rhinitis. They are generally considered to be highly effective for the relief of itching, sneezing and rhinorrhoea, but less so for nasal obstruction (Connell, 1979; Wong *et al.*, 1981). These agents have principally been administered orally and the effects of topical administration have been the subject of comparatively little study (Kirkegaard *et al.*, 1983). Clemastine is an H_1-receptor antagonist thought to have little or no anticholinergic effects (Nogrady & Bevan, 1981).

Sodium cromoglycate (SCG) has also been widely used in the treatment of allergic rhinitis both in powder form and as a 2% solution and has been shown to be effective in controlled clinical trials (Holopainen *et al.*, 1973; Blair & Illum, 1973). This drug is thought to exert its main therapeutic effect in man by mast cell stabilisation (Cox, 1971; Orange *et al.*, 1971), although more recent studies have suggested that it might possess additional properties (Stokes & Morley, 1981). Ketotifen is a benzocyclohepathiophene derivative shown to have antihistaminic properties in man (Martin & Roemer, 1978; Phillips *et al.*, 1983). It is also claimed that this drug might have an anti-allergic effect similar to SCG as it inhibits passive cutaneous anaphylaxis reactions in rats (Martin & Roemer, 1978), though we have been unable to demonstrate any 'anti-allergic' effect of ketotifen in human skin at least after single dose administration (Phillips *et al.*, 1983).

The purpose of this investigation was to measure changes in NAR induced by histamine and allergen by anterior rhinomanometry, to determine their repeatability and reproducibility, and to examine the effect of topically administered clemastine, ketotifen and SCG on these changes.

Methods

Patients

All patients studied had seasonal or perennial allergic rhinitis with clearly identifiable provoking allergens and the appropriate positive skin prick test. Patients with seasonal allergic rhinitis were tested out of the grass pollen season. None of the patients had evidence of nasal polyposis or deformity, and they took no medication during the study which might have affected their response to nasal provocation.

Reproducibility study Two groups of five patients were studied, one group undergoing nasal provocation with histamine, the other with allergen. The age range of the patients was 21–58 years (mean 29.4 years). Eight were female and two male. Allergen provocation was performed with an extract of *Dermatophagoides pteronyssinus* (*D. pteronysinnus*) in three patients and an extract of mixed grass pollens in two.

Drug study The study was approved by the Hospital Ethics Committee and all patients provided written informed consent. Two groups of ten patients were studied, one group undergoing nasal provocation with histamine, the other with allergen. The age range of the patients was 17–40 years (mean 25.8 years). Thirteen were female and seven male. Allergen provocation was performed with an extract of *D. pteronyssinus* in four patients, mixed grass pollens in four and cat fur in two.

Agonist solutions

Glycerinated allergen skin test solutions of *D. pteronyssinus* 1.2% weight to volume (w/v), grass pollen 2.5% w/v and cat fur extract 150% w/v (Bencard, Brentford, UK) were dialysed 0.5% phenol saline solution (0.4% w/v phenol, 0.275% sodium bicarbonate in 0.5% saline) and used for nasal provocation. The same batches of allergen solutions were used throughout the studies. Two allergen concentrations were used, the undiluted (stock) solution and a 10-fold dilution made up on each test day.

Solutions of histamine acid phosphate in isotonic saline (0.9% w/v) were made up each week. Concentrations from 4 to 32 mg ml^{-1} were used for the reproducibility study and from 4 to 16 mg ml^{-1} for the drug study.

Drugs

The drugs were used in the following concentrations: SCG 20 mg ml^{-1}, ketotifen 0.5 mg ml^{-1} and clemastine 1 mg ml^{-1}. Isotonic saline was administered as placebo.

Administration of solutions

Drugs and agonists in a volume of 100 μl were nebulised at an airflow rate of 7 l min^{-1} from a cuvette using a modified air brush (Humbrol, Hull, UK). In order to maximise the distribution of solutions over the nasal mucosa, the nostril with the lower initial NAR was chosen for provocation. Patients were instructed to breathhold in inspiration (for approximately 3 s) during nebulisation of solutions to minimise exposure of the lower airways to allergen.

Nasal provocation tests

Each nasal provocation test consisted of an initial instillation of phenol saline (control) solution followed by the topical application of increasing concentrations of histamine or allergen as appropriate. The agonists were given in a non-cumulative fashion with sufficient time allowed for any rise in NAR to subside by at least 80% between each administration. NAR was measured in each nostril separately using a technique of passive anterior rhinomanometry (Britton *et al.*, 1978). A cuffed tracheostomy tube was gently inserted into the external nares and the balloon inflated carefully to provide a comfortable airtight seal. Patients were instructed to breathhold with the mouth partially open whilst a current of air was passed through the tracheostomy tube into their nostril. Airflow was measured by a Fleisch pneumotachograph, and a Validyne differential pressure transducer was used to record pressure from a sampling catheter incorporated in the tracheostomy tube. NAR was computed at a flow rate of 3 l min^{-1} and shown on a digital display using a nasal airways resistance tester (NART) (P. K. Morgan Ltd, Chatham, UK). NAR was measured before nasal provocation, and at 2, 5, 10 and 15 min after provocation and every 5 min thereafter until the nasal reaction had subsided. At each time point five measurements of NAR were recorded within 1 min. NAR was measured in kPa $l^{-1}s$.

Study design

Reproducibility study Nasal provocation with either histamine or allergen was performed on each subject on four occasions separated by intervals of 1 week.

Drug study Drug or placebo solutions were administered to the nasal mucosa 30 min before provocation with histamine or allergen at intervals of 1 week. Drugs and placebo were administered double-blind and in random order.

In both studies provocation testing was carried out at the same time of day (± 2 h) to minimise the effect of nasal cycles.

Statistical analyses

Each nostril can be considered as a resistance in parallel and a value for total NAR can be obtained from the formula

$$\frac{1}{R} = \frac{1}{r_l} + \frac{1}{r_r}$$

(where R is the total NAR, and r_l and r_r the NAR of each separate nostril (Kern, 1981). We found that the changes in total NAR were small, probably because reflex mechanisms lead to dilatation of the unchallenged nostril as the challenged nostril became obstructed. For this reason only the changes in the challenged nostril were considered for analysis in this study. In all statistical analyses a 5% significance level was used.

Reproducibility study The repeatability of measurements of NAR was determined by calculating the coefficient of variation of the five consecutive measurements of NAR before provocation, and at the height of the nasal obstruction produced by instillation of the control solution and each concentration of agonist. The means of the five measurements of NAR were used in subsequent analyses as described by Britton and co-workers (1978). Examination of NAR measurements at each point of the dose response curves showed that s.d.s varied directly with the mean and that the results were skewed to the right indicating a non-normal distribution. This indicated that logarithmic transformation of the results would be appropriate as suggested by Britton *et al.* (1978).

The reproducibility of dose-response curves on four separate occasions with each agonist was also studied. NAR measurements on each of the four test days were compared using a two-way analysis of variance on the logarithmically transformed values: both for levels of NAR before provocation, and following the administration of the control solution. In this way a global comparison of the differences between days is possible. This is important since it is not necessary to know where any differences might lie but rather that they exist. To compare the dose-

response curves on the four test days analysis of covariance was used. The change in NAR produced by agonist administration was related to that produced by the control solution which was used as a covariate. Patients, agonist concentrations and the separate days were treated as independent variables.

Drug study The analyses were performed on the means of five consecutive measurements of NAR recorded before provocation and at the height of the nasal obstruction produced by the administration of the control solution and each concentration of agonist. To compare the effects of the administration of different drugs with placebo in preventing histamine and allergen induced nasal obstruction, analysis of covariance was used on the logarithmically transformed data. The change in NAR produced by the control solution was used as the covariate. Patients, agonist concentrations, and the three drugs and placebo were treated as independent variables, thus allowing estimation of the dosage effect as well as the effect of different treatment days.

Results

The maximum increase in NAR occurred 2 min after topical administration of histamine and returned to pre-provocation levels after approximately 10 min. Changes which occurred after allergen instillation followed a longer time course, the maximum increase occurring between 5 and 15 min, returning to pre-provocation levels by 30 min.

Reproducibility study

The measurements of NAR recorded before nasal provocation and after the administration of the control solution and increasing doses of histamine and allergen are shown for each patient in Table 1 (histamine) and Table 2 (allergen). One patient (patient 5 in Table 1) failed to attend for the final histamine provocation test. In two patients (patient 2 in Table 1 and patient 10 in Table 2) total nasal obstruction resulted from the administration of a low agonist concentration and the rise in NAR failed to return to pre-provocation levels preventing the administration of higher concentrations. Where this occurred, the mean NAR value produced by administration of the last agonist concentration was used to complete the dose-response curves in the analysis. This value represented total nasal obstruction and administration of higher agonist concentrations would not have produced a greater change in nasal patency.

The mean coefficient of variation of five consecutive measurements of resting NAR prior to provocation with histamine or allergen was 32.8% and 37.2% following the instillation of saline control solution. Following instillation of agonist the repeatability of five consecutive measurements of NAR ranged from 10.8 to 123.6% (median 39.6%) for histamine, and 1.1 to 80.2% (median 33.1%) for allergen. The degree of variability was not related to the dose of agonist or the degree of nasal obstruction.

Comparison of the NAR on the four test days prior to administration of the control solution showed no significant differences. Similarly, there was no significant difference in NAR measurements on the four test days after administration of the control solution. However, instillation of control solution did result in a significant rise in mean NAR from resting levels on each test day both in subjects subsequently tested with allergen (from 0.1 to 0.18 $kPal^{-1}s$; $P < 0.05$) and in those subsequently tested with histamine (from 0.07 to 0.135 $kPal^{-1}s$; $P < 0.05$) (Wilcoxon signed rank pairs test).

Increases in NAR in response to both histamine and allergen were significantly related to dose, $P < 0.02$ and $P < 0.001$ respectively (see Tables 1 and 2). Although differences were found in the responses of patients to nasal provocation when tested on different days these were not statistically significant.

Drug study

Comparison of the NAR on the four test days both before and after administration of the nebulised drugs showed no significant differences. Neither was there a significant difference in levels of NAR attained on the four test days after administration of control solution.

The change in NAR following the administration of histamine and allergen after premedication with placebo and the three drugs are shown as means and standard errors of the logarithmically transformed values of the groups of 10 patients in Figure 1 and 2. Two of the drugs tested were significantly more effective than placebo in inhibiting the rise in NAR produced by the topical administration of histamine, namely clemastine ($P < 0.01$) and SCG ($P < 0.05$). Although there was a trend for ketotifen to inhibit histamine induced nasal obstruction this was not statistically significant. None of the three drugs tested differed significantly from placebo in preventing the rise in NAR induced by allergen.

Table 1 The five consecutive measurements of NAR, made before provocation and after the administration of the control solution and increasing concentrations of histamine on the four test days for the five patients

		Patient 1				*Patient 2*				*Patient 3*				*Patient 4*				*Patient 5*				Geometric mean ±
Day of test		1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4	s.e. mean
NAR before provocation ($kPa\,l^{-1}\,s$)	1	0.04	0.16	0.08	0.05	0.02	0.01	0.09	0.12	0.07	0.07	0.03	0.06	0.15	0.05	0.14	0.12	0.10	0.01	0.03	—	
	2	0.06	0.09	0.03	0.05	0.04	0.01	0.11	0.07	0.17	0.04	0.09	0.05	0.15	0.06	0.12	0.11	0.16	0.09	0.05	—	
	3	0.04	0.06	0.04	0.04	0.05	0.01	0.08	0.11	0.15	0.06	0.07	0.07	0.16	0.05	0.13	0.08	0.14	0.08	0.06	—	
	4	0.09	0.08	0.07	0.04	0.02	0.01	0.10	0.03	0.15	0.08	0.03	0.08	0.17	0.05	0.11	0.13	0.09	0.13	0.09	—	
	5	0.11	0.11	0.03	0.04	0.06	0.04	0.07	0.02	0.07	0.08	0.05	0.09	0.18	0.05	0.12	0.07	0.09	0.08	0.03	—	+ 0.009
Mean		0.07	0.10	0.05	0.04	0.04	0.02	0.09	0.07	0.12	0.07	0.06	0.07	0.16	0.05	0.12	0.10	0.12	0.08	0.05	—	0.070
CV		45.8	38.1	46.9	12.4	47.1	83.9	17.6	64.7	39.5	25.4	48.3	22.6	8.0	8.6	9.2	25.4	27.7	55.4	47.9	—	− 0.008
NAR after control solution	1	0.03	0.17	0.01	0.06	0.25	0.06	0.05	0.15	0.27	0.16	0.13	0.76	0.21	0.20	0.31	0.08	0.16	0.16	0.14	—	
	2	0.10	0.14	0.10	0.09	0.18	0.20	0.06	0.03	0.23	0.36	0.04	0.70	0.19	0.10	0.31	0.14	0.20	0.15	0.05	—	
	3	0.06	0.29	0.03	0.07	0.17	0.12	0.08	0.01	0.17	0.12	0.13	0.74	0.21	0.09	0.22	0.17	0.21	0.11	0.11	—	
	4	0.06	0.31	0.02	0.09	0.15	0.19	0.11	0.14	0.24	0.13	0.02	0.60	0.16	0.05	0.19	0.02	0.22	0.13	0.15	—	
	5	0.19	0.16	0.03	0.04	0.12	0.07	0.06	0.11	0.33	0.07	0.13	0.08	0.20	0.06	0.23	0.22	0.22	0.15	0.07	—	+ 0.021
Mean		0.09	0.21	0.04	0.07	0.17	0.13	0.07	0.09	0.27	0.17	0.09	0.58	0.19	0.10	0.25	0.13	0.20	0.14	0.10	—	0.135
CV		70.7	37.2	93.8	30.3	38.2	51.1	33.2	68.0	14.5	66.7	61.4	49.3	10.7	59.6	21.8	61.9	12.3	14.3	41.7	—	− 0.018
NAR after histamine 4 mg ml^{-1}																						+ 0.159
Mean		3.99	6.10	0.09	0.23	0.15	10.42*	1.03	0.21	0.23	0.18	0.15	0.43	0.37	0.09	0.92	0.25	0.28	0.28	0.18	—	0.412
CV		78.1	38.2	47.6	64.6	35.4	60.0	31.0	48.2	33.0	21.3	77.1	51.3	10.8	36.9	32.6	57.7	23.3	22.9	37.5	—	− 0.114
NAR after histamine 8 mg ml^{-1}																						+ 0.445
Mean		12.38	3.95	0.09	7.91	1.64	10.42*	2.57	1.66	0.30	0.10	1.80	1.03	0.67	0.08	1.76	0.95	0.56	0.88	0.45	—	1.056
CV		32.3	54.8	47.6	57.5	65.7		76.2	80.9	25.8	104.3	38.8	40.0	29.9	55.0	31.3	42.7	39.0	17.2	26.4	—	− 0.313
NAR after histamine 16 mg ml^{-1}																						+ 0.759
Mean		10.26	0.95	6.92	0.98	2.03	10.42*	7.01	3.32	4.49	7.58	3.34	2.33	1.09	0.12	1.62	1.12	3.90	4.81	2.13	—	2.609
CV		34.6	59.1	30.4	25.1	52.6	—	32.3	56.9	26.8	39.6	53.8	56.6	20.6	70.4	19.9	24.8	11.8	27.4	81.9	—	− 0.588
NAR after histamine 32 mg ml^{-1}																						+ 1.278
Mean		12.19	0.27	11.47	2.30	8.07	10.42*	9.07	7.61	4.12	7.07	6.56	7.52	1.19	0.04	1.77	2.48	5.37	2.91	1.35	—	3.164
CV		12.4	123.6	32.5	63.4	67.1	—	52.3	41.3	32.6	65.0	64.7	52.0	19.5	60.9	13.0	48.2	17.4	51.1	23.4	—	− 0.911

The mean and coefficient of variation (CV, %) of these five measurements are also shown. — Denotes a missing value. * Denotes substituted mean value used in analysis.

Table 2 The five consecutive measurements of NAR, made before provocation and after the administration of the control solution and the two concentrations of allergen on the four test days for the five patients

Day of test		*Patient 1* 1	2	3	4	*Patient 2* 1	2	3	4	*Patient 3* 1	2	3	4	*Patient 4* 1	2	3	4	*Patient 5* 1	2	3	4	Geometric mean ± s.e. mean
NAR before provocation ($kPa\,l^{-1}\,s$)	1	0.03	0.12	0.00	0.07	0.19	0.59	0.26	0.03	0.22	0.23	0.09	0.01	0.53	0.24	0.17	0.16	0.04	0.09	0.17	0.12	
	2	0.05	0.11	0.01	0.03	0.12	0.65	0.24	0.08	0.23	0.17	0.08	0.10	0.28	0.19	0.15	0.11	0.00	0.09	0.17	0.08	
	3	0.02	0.06	0.02	0.02	0.30	0.60	0.18	0.08	0.20	0.15	0.18	0.57	0.44	0.17	0.11	0.11	0.01	0.07	0.19	0.09	
	4	0.01	0.11	0.04	0.03	—	0.70	0.26	0.07	0.21	0.10	0.15	0.07	0.18	0.13	0.21	0.18	0.00	0.08	0.16	0.10	
	5	0.03	—	0.03	0.03	—	0.48	0.35	0.09	0.17	0.16	—	0.03	0.18	0.16	0.29	0.27	0.07	0.08	0.17	0.09	+ 0.027
Mean		0.03	0.10	0.02	0.04	0.24	0.37	0.26	0.07	0.21	0.17	0.12	0.01	0.35	0.23	0.20	0.17	0.02	0.08	0.17	0.10	0.101
CV		53.0	27.1	79.1	54.1	23.1	13.6	23.6	32.8	11.2	28.3	32.1	85.7	54.5	53.1	28.2	39.6	127.1	69.5	6.4	15.8	− 0.021
NAR after control solution	1	0.04	0.07	0.04	0.01	0.29	0.34	0.31	0.26	0.39	0.43	1.03	0.14	0.24	0.28	0.81	0.53	0.11	0.10	0.22	0.17	
	2	0.04	0.09	0.03	0.12	0.27	0.61	0.29	0.20	0.17	0.13	0.70	0.01	0.37	0.32	0.90	0.26	0.07	0.10	0.22	0.07	
	3	0.04	0.10	0.03	0.06	0.30	0.32	0.29	0.15	0.28	0.18	0.42	0.12	0.50	0.41	0.84	0.34	0.07	0.10	0.19	0.15	
	4	0.04	0.06	0.04	0.10	0.31	0.33	0.31	0.08	0.51	0.11	0.43	0.01	0.42	0.33	0.63	0.33	0.14	0.09	0.20	0.03	
	5	0.08	0.07	0.03	0.08	0.32	0.32	0.24	0.24	1.47	0.20	0.43	0.12	0.38	0.28	0.50	0.34	0.07	0.09	0.17	0.03	+ 0.042
Mean		0.05	0.08	0.03	0.07	0.30	0.38	0.29	0.19	0.56	0.21	0.60	0.08	0.38	0.32	0.74	0.36	0.09	0.10	0.20	0.09	0.182
CV		37.3	21.1	16.1	57.0	6.50	28.3	9.9	39.1	92.6	61.1	44.3	75.4	24.7	16.4	22.5	28.0	34.7	5.7	10.6	73.7	− 0.034
NAR after allergen 10^{-1} dilution																						+ 0.306
Mean		3.70	1.97	0.28	0.17	0.29	0.87	2.51	1.76	0.54	0.18	12.07	0.40	1.02	1.15	1.19	0.19	0.55	16.31	0.45	0.39	0.879
CV		22.5	64.2	38.8	68.5	3.0	17.2	60.8	34.2	14.1	39.3	28.5	45.9	13.0	18.4	37.1	48.4	80.2	13.8	21.6	64.2	− 0.227
NAR after allergen stock solution																						+ 1.482
Mean		15.44	5.91	4.32	14.97	9.08	5.23	2.23	1.04	12.18	5.28	16.65	9.61	3.72	1.57	2.34	0.75	14.29	16.31*	15.58	0.43	5.029
CV		38.9	33.6	36.3	25.4	28.2	41.5	33.1	76.3	24.8	27.4	14.0	35.0	28.2	40.5	12.1	21.8	1.08	—	22.3	37.0	− 1.139

The mean and coefficient of variation (CV, %) of the five measurements are also shown. — Denotes a missing value. * Denotes substituted mean value used in analysis.

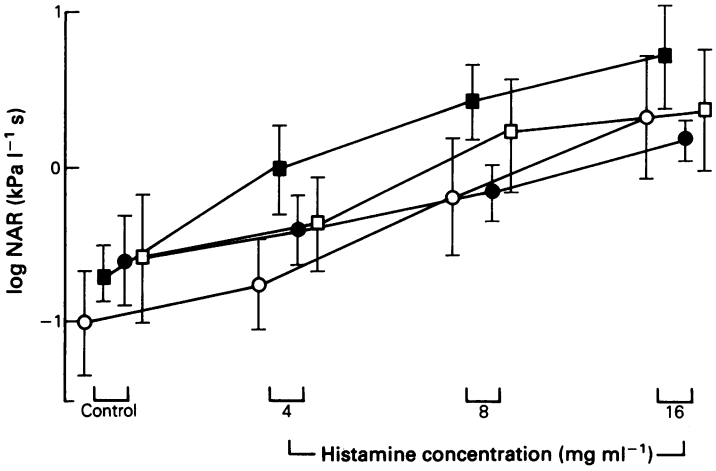

Figure 1 The effect of clemastine (○), ketotifen (□), SCG (●) and placebo (■) on histamine induced changes in NAR. The mean and s.e. mean of the logarithmically transformed values of NAR for the group of 10 patients are shown.

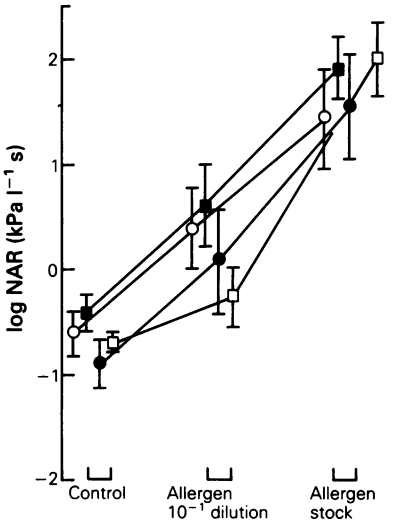

Figure 2 The effect of clemastine (○), ketotifen (□), SCG (●) and placebo (■) on allergen induced changes in NAR. The mean and s.e. mean of the logarithmically transformed values of NAR for the group of 10 patients are shown.

Discussion

Allergen and histamine induced increases in NAR were measured by a technique of passive anterior rhinomanometry which was quick, easy to perform and well tolerated by patients. Five measurements of NAR recorded consecutively within a short period of time in the same subject showed a substantial degree of variability (with a coefficient of variation of approximately 35%). However, no significant intra-subject variation was found for either histamine or allergen dose related changes in NAR when nasal provocation was repeated on four separate weekly occasions. Both clemastine and SCG were significantly more effective than placebo in preventing the rise in NAR induced by histamine. Ketotifen appeared to be ineffective. None of the three drugs tested inhibited allergen induced nasal obstruction.

Measurements of NAR reflect vascular changes in the nasal mucosa and the presence of secretions within the airway. The substantial variation noted in measurements recorded in one nostril, probably resulted from the presence of copious secretion which would have had varying effects on nasal airflow depending on position within the nasal cavity. This may be further influenced by our measurement technique in which air blown into the nostril is likely to dislodge secretions. The degree of variability of individual measurements of NAR following unilateral provocation with histamine or allergen diminishes the value of the technique. However, recent advances in the technical specifications of the Nasal Airways Resistance Tester, to incorporate a flow regulating device, have led to encouraging reports of much lower coefficients of variation of approximately 8% (Shelton *et al.*, 1986). Despite marked differences in consecutive measurements of NAR we found no significant intra-subject differences in response to histamine or allergen induced changes in NAR measured on four weekly

occasions, suggesting that passive anterior rhinomanometry may be a useful technique for evaluating pharmacological agents used in the treatment of nasal obstruction.

It has been previously demonstrated in clinical studies that oral H_1 antihistamines have a greater effect on the symptoms of sneezing and rhinorrhoea than on nasal obstruction in patients with allergic rhinitis (Connell, 1979; Wong *et al.*, 1981; Howarth & Holgate, 1984). Using the technique of anterior rhinomanometry, we have demonstrated a significant inhibitory effect of the H_1-histamine receptor antagonist clemastine against histamine induced nasal *obstruction* when topically administered. Britton *et al.* in 1978, using a technique identical to our own have also shown *oral* administration of an H_1-antihistamine (triprolidine) to be effective in inhibiting nasal obstruction experimentally induced by histamine

However, Kirkegaard and co-workers (1983) studying the effects of a topically administered antihistamine (chlorpheniramine maleate) failed to show an inhibitory effect on histamine induced nasal obstruction.

These conflicting findings are likely to result from differing doses, potencies and methods of administration. Indeed we have previously shown that clemastine and ketotifen are more potent antihistamines than chlorpheniramine at least in human skin (Phillips *et al.*, 1983).

This is the first study in which ketotifen has been administered topically on to the nasal mucosa. This drug has been shown to possess powerful antihistaminic effects both *in vitro* and *in vivo* (Martin & Roemer, 1978; Phillips *et al.*, 1983). The lack of a significant inhibitory effect of ketotifen against histamine provocation therefore requires explanation. It is certainly possible that a higher concentration or a different time interval of administration before histamine provocation may have been required, although under similar circumstances clemastine proved effective and in studies in human skin ketotifen is at least as effective as an antihistamine (Phillips *et al.*, 1983).

The fact that SCG had a significant inhibitory effect in preventing histamine induced nasal obstruction is perhaps surprising. Although several investigators have studied the effect of SCG on nasal provocation with allergen little is known about the effect of this drug on histamine induced nasal obstruction. Okuda and co-workers (1983) found no significant difference between SCG and placebo in preventing the rise in NAR induced by histamine. The administration of SCG to the lower airways has been shown by some investigators to inhibit histamine induced bronchoconstriction (Inoue, 1969; Kerr *et al.*, 1970) and also in selected patients by other investigators (Pegelow, 1974; Woenne *et al.*, 1979) which has led to the recommendation that SCG should be omitted for at least 8 h before routine bronchial provocation (SEPCR Working Group, 1983). However, this has not been a consistent finding, and in many more studies no such protective effect was found (Cockcroft *et al.*, 1977; Kang *et al.*, 1976; Ryo *et al.*, 1971; Lemire *et al.*, 1984; Phillips *et al.*, 1984).

In addition to histamine there are many other putative mediators of the nasal response to allergen provocation which may have important vasoactive and inflammatory properties. These chemicals may be of great importance in the development of allergen induced nasal obstruction (Shaw *et al.*, 1985). Compounds which are thought to act by inhibiting mast cell degranulation might be therefore expected to be of greater benefit than antihistamines. Although ketotifen is thought to possess such activity (Martin & Roemer, 1978) this could not be demonstrated in the present study. SCG, thought to act as a mast cell stabilising agent, has been investigated in several studies of nasal provocation with allergen when administered topically to the nasal mucosa both in powder form and as a 2% solution. Pelikan and co-workers (1970) demonstrated a protective effect of this drug against allergen provocation, although this study was not placebo controlled. Jenssen (1973) claimed that allergen induced nasal obstruction was inhibited to a greater extent by prior instillation of SCG than placebo in eight out of ten patients. However, no statistical analysis of changes in NAR was carried out. Taylor & Shivalkar (1971) also showed that SCG inhibited allergen induced nasal blockage but insufficient information is reported to allow us to compare our results in detail.

In the present study we have failed to show a significant inhibitory effect of clemastine, ketotifen or SCG on the increase in NAR which followed the topical administration of allergen. There are several possible explanations for this. Firstly, the concentrations of allergen used in this study may have been too high, overwhelming any possible antagonistic effect of these drugs. It is also possible that the time interval between administration of the drugs and provocation testing was of crucial importance. In our study all drugs were administered 30 min before provocation. It is conceivable that during this period the drugs may have been cleared from the nose by mucociliary action. If this were the case however, it is unlikely that we would have been able to show a significant inhibitory effect of clemastine against histamine induced increases in NAR.

Differences in the administration or deposition of drugs and agonists are also unlikely to explain the ineffectiveness of the therapies since all were administered in an identical fashion. In this study the effect of a single concentration of each of the drugs was tested. SCG was administered in a concentration of 20 mg ml^{-1}, the concentration used in clinical practice for the treatment of allergic rhinitis. The concentration of clemastine 1 mg ml^{-1} was chosen as this had previously been shown to inhibit the bronchial response to inhaled histamine (Nogrady & Bevan, 1978). We have previously shown in studies in human skin that ketotifen was twice as potent as clemastine, and we therefore chose to administer ketotifen at a dose theoretically equipotent to clemastine, namely 0.5 mg ml^{-1}. Since all the preparations tested have been previously shown to be useful in clinical practice (Todd *et al.*, 1975; Warner & Goldsworthy, 1982; Blainey *et al.*, 1983) it is possible that the topical administration of higher doses of the drugs would have inhibited allergen induced increases in NAR. This being so it is not possible to draw firm conclusions about the clinical efficacy of the compounds tested from the present study.

In conclusion, although the repeatability of measurement of NAR by passive anterior rhinomanometry shows considerable variability the technique proved reproducible for measurements of the nasal response to both histamine and allergen and may be of value in the initial assessment of drugs designed for the treatment of allergic rhinitis.

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