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HISTAMINE CHALLENGE AND ANTERIOR NASAL RHINOMETRY: THEIR USE IN THE ASSESSMENT OF PSEUDOEPHEDRINE AND TRIPROLIDINE AS NASAL DECONGESTANTS IN SUBJECTS WITH HAYFEVER

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1 Nasal airway resistance (NAR) was measured by anterior rhinometry in ten volunteers with allergic rhinitis. Measurements before and after challenge with three concentrations of histamine diphosphate showed significant rises in NAR for each challenge.

2 In a double-blind, crossover study with the same patients triprolidine (2.5 mg) and pseudoephedrine (60 mg) were shown to be equally effective in reducing the rise in NAR produced by histamine challenge to one nostril; both were significantly better than placebo.

3 The rise in NAR of both nostrils after histamine challenge to one nostril was significantly reduced after pseudoephedrine compared with placebo. This suggests that pseudoephedrine is effective in preventing reflex mucosal congestion in the unchallenged nostril.

4 No increase in the pulse rate or blood pressure of the volunteers was detected after either drug.

Introduction

The nasal mucosa is a convenient and accessible site highly suitable for the assessment of anti-allergic or decongestant drugs. However, changes in nasal patency due to drug action alone are slight and the lack of a convenient, reliable and sensitive method for measuring these changes has limited this approach.

Histamine is an important mediator for the symptoms of asthma and allergic rhinitis (Stone, Merril & Meneely, 1955). Inhalation of histamine has been widely used in bronchial challenge studies (Empey, Laitinen, Jacobs, Gold & Nadel, 1976) but rarely applied to studies on the nose (Aschan, Drettner & Ronge, 1958).

Many methods for measuring the patency of the nasal airway have been described (Uddstroemer, 1940; Butler, 1960; Solomon, McLean, Cookingham, Ahronheim & DeMuth, 1965; Connell, 1966; Taylor, Macneil & Freed, 1973) but some are either complex, unreliable or actually produce major changes by stimulating the sensitive nasal mucosa. Triprolidine and pseudoephedrine have been shown to be useful clinically as nasal decongestants (Benson, 1971; Empey, Bye, Hodder & Hughes, 1975). In our study we have investigated the efficacy of these drugs in preventing the effects of nasal histamine challenge in a double-blind crossover study.

Measurement of nasal airway resistance was made by a new apparatus using a modification of the anterior rhinometry method initially described by Roth, Cantekin, Bluestone, Welch & Cho (1977). This method offers several distinct advantages in that it is a passive procedure, non-invasive, quick and measures NAR in each nostril separately.

Methods

Patients

Ten volunteers (age 24–35 years) with a clinical history of allergic rhinitis and positive skin tests to grass pollen and at least one other common allergen were selected for the study, and gave informed consent. They had no other medical condition which required any concurrent medication, and they had no nasal obstruction or deformity due to either operation or injury.

Drugs and their action

L(+)-pseudoephedrine is primarily an α-adrenoceptor stimulant with actions similar to D(—)-ephedrine, but has the advantage that it has less vasopressor action and causes less cerebral stimulation (Hughes & Benson, 1973; Bye, Dewsbury & Peck, 1974). Sympathomimetic drugs have long been known to reduce nasal blood flow by their vasoconstrictor properties, and are thus suitable as nasal decongestants.

Triprolidine has been shown to be a potent and effective anti-histamine (Fowle, Hughes & Knight, 1971).

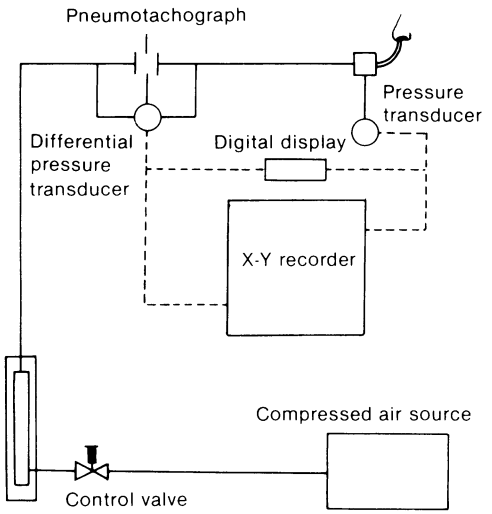

Figure 1 A schematic diagram of the apparatus used for measuring NAR.

Nasal Airway Resistance Tester (NART®)

Nasal airway resistance was determined by a passive anterior rhinometric technique first devised by Roth *et al.* (1977). The principle of the method is illustrated in Figure 1.

Supply of clean air stored under a pressure of 140 kgf/cm^2 was controlled by a British Oxygen S 60 M.G. flowmeter. A gradually increasing flow of air (0–4 l min^{-1}) was passed through the system to the patient's right or left nostril, and then on through the nasal passages to the open mouth. The air flow rate was continuously monitored by a Fleisch pneumotachograph (size OO) linked with a Validyne Differential Pressure Transducer ($\pm$ 2 cm H_2O) and displayed on the Y axis of a Morgan-Bryants XY recorder.

The pressure created by the flow was sensed by a small bore sylastic tube emerging from a side arm on the head of the apparatus and positioned just inside the external nares. The changes in pressure were compared with atmospheric pressure by a Validyne differential pressure transducer (0–50 cms H_2O) which was displayed on the X axis of the recorder. Nasal airway resistance is derived from the slope of the line produced by plotting flow against pressure (example Figure 2).

An apparatus (NART®) suitable for making such measurements was made to our specification (P.K. Morgan Ltd, 10, Manor Road, Chatham, Kent ME4 6AL). This incorporated a digital display which automatically computed and displayed the resistance of the nostril in kPa l^{-1}s at a flow rate of 3 l min^{-1}; this flow rate was chosen because the flow-pressure trace was linear between 2 and 4 l min^{-1}.

Connection of the air line to the patient's nostril was achieved by means of an inverted tracheostomy tube with an inflatable cuff (Portex size No. 24) (Figure 3). The tracheostomy tube could be easily removed for sterilization by alcohol or to be replaced by a fresh one.

The apparatus was calibrated before use by an internal electronic calibration system, but this could be double checked by attaching a 'standard nose' to the tracheostomy tube, which provided a physical standard. The 'standard nose' was a fixed aperture with a known resistance.

Histamine challenge

A Rogers' Crystal Spray (Riddell Products Ltd) was used to deliver histamine to the nose as an aerosol. Each challenge consisted of three activations of the hand pump which delivered approximately 0.025 ml of solution. The spray was directed medially, centrally and laterally in succession in an attempt to obtain an even coating of the nasal mucosa.

The sterile histamine solutions (0.01%, 0.1% and 1%) were prepared as histamine diphosphate dissolved in normal saline in sealed ampoules.

Study design

The volunteers were studied on three mornings at weekly intervals outside the pollen season. They were starved from midnight and avoided blowing their noses during the study. After a short rest period, blood pressure and pulse readings were taken, followed by baseline measurements of NAR, taking five readings from each nostril. The subjects were then given either triprolidine 2.5 mg, pseudoephedrine 60 mg or an identical placebo, according to a randomized double-blind crossover design.

One hour later, blood pressure and pulse readings were repeated and five measurements of NAR from each nostril were made before and exactly 2 min after spraying 0.025 ml of 0.01% histamine diphosphate into one nostril. At further hourly intervals, the same nostril was challenged with 0.1% and then 1% solutions of histamine and similar measurements of blood pressure, pulse and of NAR were made.

Method of measurement

The volunteer was seated comfortably and the head of the tracheostomy tube was positioned so that the subject's neck was neither flexed nor hyperextended. The tube was gently inserted into the external nares so that just less than half of the deflated balloon was visible. A sparing application of KY jelly to the tip of the tube made this atraumatic. The balloon was then

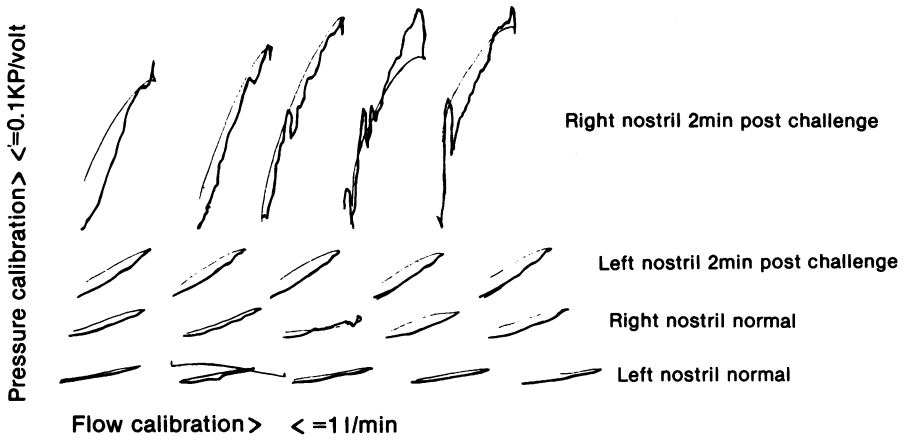

Figure 2 The flow-pressure tracings produced for measuring NAR. The two lower lines show five measurements from each nostril prior to challenging the right nostril with 1% histamine. The upper two lines are tracings showing the marked increase in resistance of the right nostril measured 2 min after the challenge, and some increase in the resistance of the left nostril due to reflex mucosal congestion.

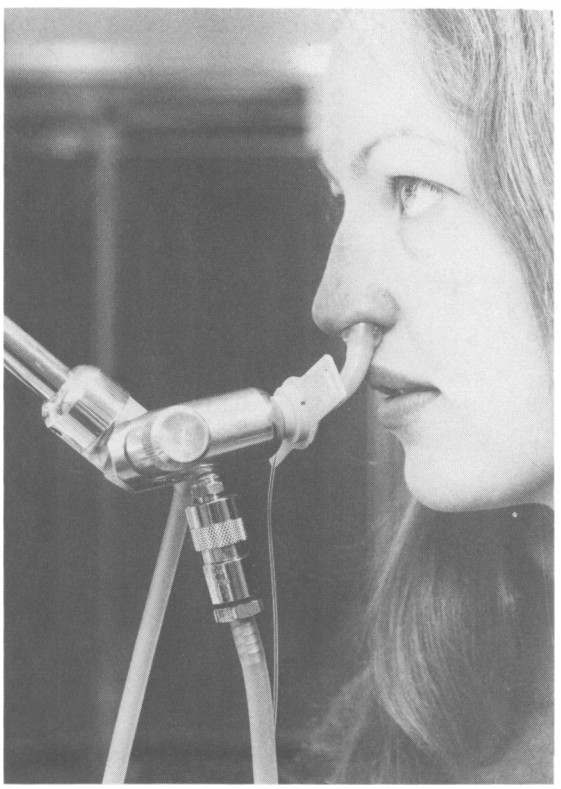

Figure 3 A patient with her mouth partially open and the inverted cuffed tracheostomy tube in position having measurements of NAR taken.

inflated by a syringe with just enough air to make an airtight seal with the nostril. The air was held in the cuff by a non-returnable valve, the volume was noted and the same amount was used on all occasions. Figure 3 shows the tube suitably placed in the nose of one of the volunteers.

The subjects were instructed to open their mouths slightly and then to stop breathing in a position of rest—inspiration and expiration caused movement of the pen of the XY recorder and could be easily monitored by the operator. When the pen was stationary the flow of air was uniformly increased to 4 l min^{-1}, by which time the digital display had lighted up, the flow was then promptly turned off and the reading taken.

The XY graph served as a permanent record and any irregularity in the curve clearly demonstrated a false resistance reading. False readings were mainly due to the subject failing to stop breathing throughout the short procedure or rarely due to a leak in the system. Each reading took about 5 s to complete and an example of the curves obtained is shown in Figure 2.

Statistics

The means of the five measurements of NAR at each time interval were calculated and the mean data were used in the analysis. The relationship between the standard deviations and the means was examined, and the standard deviation was found to vary directly with the mean indicating that a logarithmic transformation of the data should be performed. All subsequent analyses of NAR were, therefore, performed on the

transformed data; results were expressed both on the logarithmic scale and also after conversion back to the original scale (in terms of geometric means).

All the NAR data were analysed using three- and four-factor analyses of variance, as appropriate. Where indicated further examination of the data was performed using Duncan's multiple range test.

Results

The means of the five measurements of NAR taken at each time interval for each nostril and for the three occasions are shown in absolute values (i.e. before logarithmic transformation) in Table 1.

Analysis of the baselines

The first set of readings taken on each of the three trial days were considered to be controls and are referred to as baseline 1. The three sets of measurements recorded just before each of the three challenges of 0.01%, 0.1% and 1% histamine are referred to as baselines 2, 3 and 4 respectively.

Table 1 Mean data of five measurements of NAR (on original scale) for each subject or each occasion and for each challenge in kPa $l^{-1}s$.

			Control (Baseline 1)		+ 1 h (Baseline 2)			+ 2 min		+ 1 h (Baseline 3)	
Subject	*Occasion*	*Treatment*	*X*	*Y*	*X*	*Y*	*Challenge*	*X*	*Y*	*X*	*Y*
	2	A	0.35	0.72	0.21	0.33		0.45	0.27	0.29	0.25
1	1	B	0.50	0.43	0.47	0.37	0.01%	0.49	0.51	0.68	0.67
	3	C	0.35	0.39	0.58	0.41	histamine	0.39	1.02	0.45	0.57
	1	A	0.35	0.31	0.45	0.31		0.59	0.74	0.51	0.51
2	2	B	0.11	0.92	0.21	0.72		0.21	1.00	0.33	0.70
	3	C	0.17	0.13	0.21	0.61		0.23	4.02	0.41	2.13
	3	A	0.11	0.47	0.41	0.65		0.21	2.75	0.30	1.18
3	1	B	0.41	0.53	0.31	0.45		0.47	0.61	0.64	0.51
	2	C	0.11	0.73	0.21	0.55		0.23	2.12	0.21	1.08
	3	A	0.11	0.21	0.13	0.31		0.17	0.62	0.21	0.31
4	2	B	0.15	0.19	0.13	0.21		0.19	0.41	0.21	0.31
	1	C	0.31	0.21	0.41	0.27		0.21	0.57	0.21	0.35
	1	A	0.20	0.15	0.55	0.41		1.08	0.81	0.59	0.51
5	3	B	0.34	0.47	0.81	0.47		0.41	0.51	0.87	0.89
	2	C	0.39	0.39	0.68	0.43		1.10	0.79	0.51	0.57
	2	A	0.09	0.17	0.33	0.31		0.31	0.31	0.41	0.31
6	3	B	0.11	0.11	0.13	0.29		0.11	0.51	0.31	0.37
	1	C	0.21	0.13	0.29	0.21		0.31	0.31	0.21	0.31
	1	A	0.11	0.05	0.51	0.35		0.55	0.23	0.51	0.25
7	2	B	0.33	0.09	0.33	0.15		0.33	0.21	0.63	0.21
	3	C	0.19	0.21	1.63	0.10		0.76	0.31	1.44	0.07
	1	A	0.17	0.33	0.31	0.33		0.39	0.65	0.35	0.31
8	3	B	0.41	2.16	0.74	0.44		0.45	0.98	0.43	0.41
	2	C	0.21	0.21	0.49	0.81		0.41	1.89	0.31	2.16
	2	A	0.64	0.62	0.99	0.92		0.84	0.72	1.22	0.92
9	1	B	0.73	0.55	1.01	0.71		1.54	0.87	1.23	0.80
	3	C	0.98	0.78	1.12	0.81		1.51	1.18	1.27	1.00
	3	A	0.27	0.25	0.72	0.91		2.33	2.54	0.65	0.83
10	1	B	0.29	0.31	0.65	0.53		0.57	1.19	0.31	0.61
	2	C	0.15	0.13	0.41	0.39		0.76	1.41	0.59	0.92

A = Triprolidine, 2.5 mg
B = Pseudoephedrine, 60 mg
C = Placebo.

X unchallenged nostril
Y challenged nostril

The geometric means for each baseline and the 95% confidence intervals were as follows:

B.1 0.27 kPa $l^{-1}s$ (0.237, 0.303)
B.2 0.41 kPa $l^{-1}s$ (0.365, 0.468)
B.3 0.49 kPa $l^{-1}s$ (0.436, 0.558)
B.4 0.49 kPa $l^{-1}s$ (0.430, 0.551)

Duncan's multiple range test showed that baselines 2, 3 and 4 were not significantly different from each other and therefore comparisons between the three challenges are valid. However, all these baselines were significantly larger than baseline 1 ($P<0.01$). Presumably the initial measurement produced some increase in nasal mucosal congestion which persisted throughout the study.

Analysis of variance showed that there were significant differences between the ten subjects ($P<0.01$), but no significant differences were found between treatments or the nostrils. Two interactions were found to be significant:

Subject x Nostril $P<0.01$
Subject x Treatment x Nostril $P<0.05$

These can be explained by wide subject variation, and the fact that only one nostril was challenged.

Challenge	*+2 min*		*+1 h (Baseline 4)*		*Challenge*	*+2 min*	
	X	*Y*	*X*	*Y*		*X*	*Y*
	0.70	0.57	0.51	0.45		0.45	1.43
0.1%	1.13	0.79	0.76	0.89	1.0%	0.33	1.04
histamine	0.91	0.95	0.45	0.59	histamine	0.49	5.39
	0.47	0.55	0.43	0.49		0.72	1.87
	0.27	1.48	0.33	0.60		0.25	4.18
	0.95	10.52	0.41	1.79		0.43	13.14
	0.63	1.90	0.31	0.39		0.49	2.05
	1.00	0.77	0.41	0.41		0.38	0.98
	0.17	1.16	0.23	1.13		0.31	7.39
	0.25	0.65	0.21	0.41		0.21	1.50
	0.21	0.93	0.23	0.39		0.21	1.81
	0.21	0.59	0.21	0.31		0.35	5.52
	0.94	0.72	0.59	0.51		3.86	1.22
	2.73	0.89	0.73	0.57		7.45	1.97
	0.87	0.70	0.57	0.47		8.38	4.28
	0.43	0.63	0.31	0.41		0.47	2.50
	0.12	0.79	0.10	0.37		0.10	6.55
	0.21	1.30	0.23	1.83		0.21	12.46
	0.49	0.33	0.51	0.31		0.51	1.13
	0.59	0.21	1.51	0.23		0.81	0.26
	0.47	0.10	0.67	0.10		0.51	0.21
	0.31	1.16	0.43	0.43		0.45	3.47
	0.47	1.93	0.33	0.64		0.33	9.07
	0.33	2.82	0.68	0.68		0.55	6.69
	0.99	0.84	0.92	0.83		5.51	1.95
	1.06	0.68	1.09	0.72		9.42	2.31
	1.18	1.12	0.67	0.66		1.84	2.54
	1.00	1.22	0.65	0.57		0.65	5.79
	0.31	1.85	0.31	0.95		0.35	6.14
	1.30	2.19	0.41	0.90		0.57	11.63

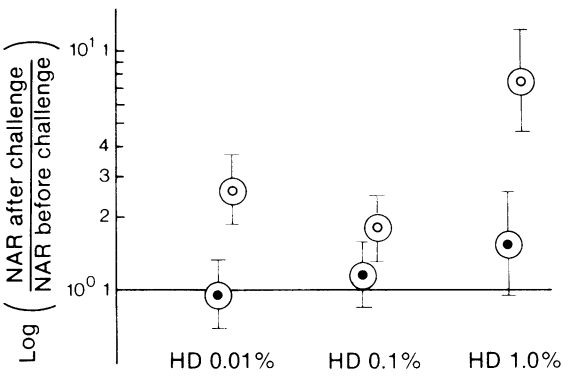

Figure 4 Combined data from all ten subjects showing the rise in NAR after each histamine challenge. ⊙ unchallenged nostrils; ◉ challenged nostrils.

Analysis of response to histamine challenge

To determine whether the three challenges of histamine diphosphate had any effect on NAR, the data recorded on the day the subjects received the placebo tablet were studied.

These data were analysed using a three-factor analysis of variance, and the *rises* in NAR for each challenge and for each nostril were then calculated. They are shown in terms of geometric means with the 95% confidence intervals in Figure 4. Values of one indicate no change following challenge, values of greater than one a rise in resistance, and values of less than one a fall.

The rises in NAR for the challenged nostrils were significant ($P<0.01$) on all three occasions and they were all significantly different from each other ($P<0.05$). None of the changes in the unchallenged nostrils reached statistical significance.

Analysis of response to histamine challenge following pseudoephedrine and triprolidine

The four-factor analysis of variance was performed upon rises in NAR from the respective baselines for each challenge.

The rise in NAR was calculated on transformed data as follows:

$$\text{If } X = \text{NAR before challenge}$$
$$Y = \text{NAR after challenge}$$

$$\text{Rise in NAR} = Y - X$$

$$\text{Rise in NAR (transformed)} = \log Y - \log X = \log (Y/X) = \log \frac{\text{NAR after challenge}}{\text{NAR before challenge}}$$

As the data consist of differences between logarithms, the resulting geometric means are ratios and have no units.

Significant differences were found between subjects ($P<0.01$), between the three challenges ($P<0.01$), between treatments ($P<0.05$) and between nostrils ($P<0.01$). The following six interactions were also significant:

1. Subject × Challenge ($P<0.01$)
2. Subject × Nostril ($P<0.01$)
3. Challenge × Nostril ($P<0.01$)
4. Treatment × Nostril ($P<0.05$)
5. Subject × Challenge × Treatment ($P<0.05$)
6. Subject × Challenge × Nostril ($P<0.01$)

These interactions are not surprising as there was wide variation in the subject responses to challenge, and one would expect the three challenges to affect the challenged and unchallenged nostrils differently.

The differences between the three treatments and the relevant interactions were studied more closely using Duncan's multiple range test as follows:

i. Treatments The geometric means and 95% confidence limits for each treatment are shown in Figure 5.

The rise in NAR of both nostrils after challenge following pseudoephedrine was significantly lower ($P<0.05$) than after placebo. Triprolidine was found to have an effect not significantly different from either that of pseudoephedrine or that of placebo.

ii. Treatment × Nostril interaction The results expressed as geometric means and the 95% confidence limits are also shown in Figure 5.

Table 2 Mean pulse rates for each baseline and for each treatment

	Pulse rate (beats/min)			
	Triprolidine	*Pseudoephedrine*	*Placebo*	*Mean*
Baseline 1	75.0	69.4	73.8	72.7
2	65.4	69.8	66.2	67.1
3	64.2	68.6	63.6	65.5
4	64.2	68.4	63.2	65.3

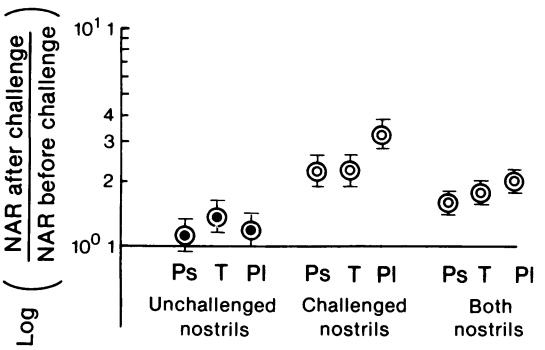

Figure 5 Combined data from all three challenges showing the rise in NAR in relation to treatment. Ps pseudoephedrine 60 mg; T triprolidine 2.5 mg; Pl placebo.

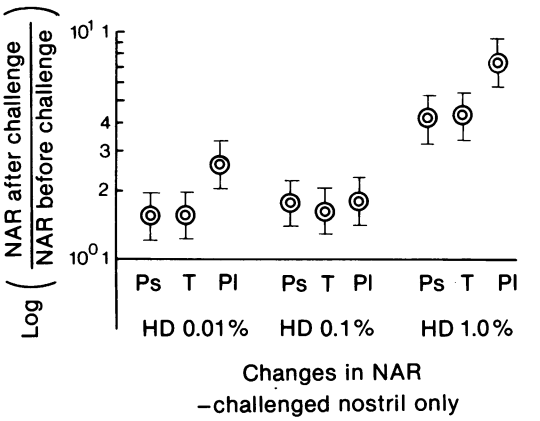

Figure 6 Rise in NAR for each challenge showing the effect of treatment. Ps pseudoephedrine 60 mg; T triprolidine 2.5 mg; Pl placebo.

(a) In the unchallenged nostril there were no significant differences in the rises of NAR between the three treatments, although pseudoephedrine appeared to have a greater protective effect than the others.

(b) In the challenged nostril, both triprolidine and pseudoephedrine were found to be significantly more protective than placebo ($P < 0.01$). No significant difference was found between the effects of triprolidine and pseudoephedrine.

iii. Challenge x Treatment x Nostril interaction (a) All comparisons made for the unchallenged nostril were found to be non-significant.

(b) For the challenged nostril pseudoephedrine and triprolidine were found to produce significantly greater protection ($P < 0.01$) than placebo for both the 0.01% and 1% challenges, but the differences were not significant for the 0.1% challenge. The results for the challenged nostril only are shown in Figure 6.

Analysis of pulse, blood pressure and side effects

(a) Pulse In the analysis of pulse rate, there were no significant differences between treatments. However, there were significant differences between subjects ($P < 0.01$). The pulse measurements for baselines 2, 3 and 4 were found to be significantly lower than baseline 1 after placebo and triprolidine; this was presumably due to rest.

The mean values for pulse rate for each baseline and for each challenge are shown in Table 2.

(b) Blood pressure In the analysis of systolic and diastolic blood pressure, there were differences between subjects ($P < 0.01$), but there were no significant differences between treatments nor baselines.

(c) Side effects Six subjects felt drowsy at the end of the study period following triprolidine, two felt drowsy following pseudoephedrine and there were no complaints following placebo. No other side effects were noted on any of the three occasions.

Discussion

The nasal mucosa is a very sensitive organ, and changes in nasal patency result from the slightest of stimuli (Solomon, 1966; Takagi, Proctor, Salnau & Evering, 1969) making research difficult.

Many techniques for measuring nasal airway resistance (NAR) have been described (see introduction); however, these necessitate the patients being fitted with face masks, nostril or oropharangeal catheters, or depend upon forced respiratory manoeuvres through the nose. These procedures may distort the nasal passage architecture or increase nasal mucosal congestion either directly or reflexly. Also techniques which measure the resistance to airflow of both nostrils in parallel produce results which are difficult to interpret.

Determination of NAR by the passive anterior rhinometric technique employed in this study offers several advantages. It requires the minimum of patient training and co-operation, patient contact with the machine is minimal, and there is no discomfort associated with the procedure. The flow of air through the nostril at the maximum of four litres per minute is considerably less than the air flow rates experienced during normal tidal breathing of up to 30 l min^{-1} (Proctor, 1977), and therefore unlikely to be an adverse stimulus. The apparatus was satisfactorily sensitive and consistent, and it also allowed us to measure the changes in each nostril separately.

We believe that NART® has many further applications for the assessment of drug action on the nose with or without histamine or antigen challenge. Also it may prove useful in providing objective assessment of nasal obstruction before and after corrective surgical procedures or in the ear, nose and throat clinic.

The dose response relationship we expected to see following challenge with increasing concentrations of histamine was only partially shown for the challenged nostril and there was a non-significant trend with the unchallenged nostril. The initial challenge with 0.01% histamine diphosphate (HD) produced a significantly greater rise in NAR than the second challenge with 0.1% HD 1 h later ($P < 0.05$). Possible explanations for this finding are that either the initial challenge of the day produced a super-added non-specific reflex response on top of the direct effect of the histamine which was not produced with subsequent challenges; otherwise the initial challenge may have produced changes, for example an increase in the thickness of the mucous layer, which partially protected the nasal mucosa from subsequent challenges. The 1% solution presumably had sufficient pharmacological action to overcome such effects.

The most interesting results are in the degree of protection provided by the prior administration of the drugs. Triprolidine reduced the rise in NAR of the nostril which was challenged with histamine, whereas it had little non-specific decongestant effect on the opposite nostril. Pseudoephedrine, on the other hand, is a decongestant rather than an anti-histamine and was therefore able to reduce the reflexly-produced mucosal congestion in the unchallenged nostril. These effects were produced without any effect upon the pulse or blood pressure.

These results lend support to the rational use of pseudoephedrine 60 mg and triprolidine 2.5 mg orally as effective treatments for hayfever in which histamine release and mucosal congestion are important causes of symptoms. Also we conclude that this modification of anterior nasal rhinometry is a valuable method for assessing drug action on the nasal mucosa and represents an advance on previously available techniques.

Reprint requests should be addressed to D.T.D.H., Wellcome Research Laboratories, Beckenham, Kent.

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