Thorax, 1978, 33, 700–704

Inhaled antihistamines—bronchodilatation and effects on histamine- and methacholine-induced bronchoconstriction

S G NOGRADY AND C BEVAN

From the Welsh National School of Medicine and MRC Pneumoconiosis Research Unit, Llandough Hospital, Nr Penarth, South Glamorgan CF6 1XX, UK

Nogrady, S G, and Bevan, C (1978). *Thorax*, **33**, 700–704. **Inhaled antihistamines—bronchodilatation and effects on histamine- and methacholine-induced bronchoconstriction.** To assess further the bronchodilator activity of inhaled antihistamines ten stable asthmatic subjects inhaled aerosols of clemastine, 1 mg/ml, and saline placebo administered double blind. Subjects underwent bronchial challenge with increasing concentrations of histamine and methacholine, and specific airways conductance was measured by whole body plethysmography at each concentration. There was a significant 21·9% increase in specific airways conductance after inhalation of clemastine. Subjects could tolerate significantly higher mean concentrations of histamine when treated with clemastine than with saline. The shift of the cumulative log histamine dose-response curve suggests that such protection is due to competitive antagonism to the inhaled clemastine. Clemastine did not protect subjects against methacholine-induced bronchoconstriction, which suggests that its bronchodilator properties are not related to any anticholinergic action.

The role of histamine in human bronchial asthma and the place of histamine antagonists in its management remains controversial. While histamine causes bronchoconstriction at significantly lower doses in asthmatic than in normal subjects (Curry, 1946), bronchial hyper-reactivity to a range of stimuli is seen in asthma (Curry, 1947; Mathé *et al*, 1973). Histamine is released in vitro from human asthmatic lung sections on appropriate allergen challenge (Schild *et al*, 1951), and in-vivo release of histamine after allergen, but not methacholine challenge, has also been shown (Bhat *et al*, 1976). Slightly raised plasma histamine concentrations have been noted in patients with acute exacerbations of asthma (Bruce *et al*, 1976), while more pronounced elevations correlating with the severity of the asthma attack have recently been described (Simons *et al*, 1977).

In theory, antihistamines ought to be effective in the management of asthma, but there is little evidence of therapeutic efficacy for this group of drugs (*Lancet*, 1955). Large doses, given by mouth or parenterally, cause some bronchodilatation (Popa, 1977), but dose-related systemic side effects limit their use in this way. Inhaled antihistamines cause bronchodilatation but have previously been found to be too irritating, and may, themselves, cause bronchoconstriction (Herxheimer, 1948, 1949; Hawkins, 1955).

In an earlier study (Nogrady *et al*, 1978) we showed that the H_1-receptor blocking antihistamine, clemastine, administered as an aerosol from a Wright nebuliser was a potent bronchodilator with a prolonged action, and without observed side effects. As most antihistamines have anticholinergic side effects the current study was undertaken to investigate the relative importance of anticholinergic and specific H_1-receptor blocking functions of clemastine inhalation in producing bronchodilatation.

Materials and methods

SUBJECTS

Ten stable asthmatic subjects (six men, four women: age range 24–38 years, mean 29) gave informed consent to the study after it had been approved by the hospital ethical committee. All

had previously shown a greater than 15% increase in peak expiratory flow rate or forced expiratory volume in one second (FEV_1) after inhaled salbutamol. All had positive prick skin tests to more than one allergen. The severity of their asthma ranged from currently asymptomatic to moderate incapacity with a work time loss, due to asthma, of up to four weeks a year. None was steroid dependent at the time of the study. They were asked to abstain from bronchodilators and inhaled corticosteroids for 12 hours before each study day. None had taken antihistamines within one week of each study. Only two were using disodium cromoglycate, and this was discontinued 12 hours before the study.

MEASUREMENT OF AIRWAYS OBSTRUCTION

Each study included measurement of airways resistance (AWR) and thoracic gas volume (VTG) by whole body plethysmography using a constant volume plethysmograph (Dubois *et al,* 1956). Specific airways conductance (sGaw) was determined according to the equation sGaw=1/(AWR $\times$VTG). The mean of the three most technically satisfactory recordings was obtained. FEV_1, forced vital capacity (FVC), and maximum expiratory flow rate at 50% of vital capacity (MEF_{50}) were measured using a McDermott spirometer, a stereo tape recorder, and a Hewlett Packard 9830 programmable calculator (McDermott *et al,* 1976; McDermott and McDermott, 1977). The means of the three most technically satisfactory results of each measurement were obtained.

HISTAMINE CHALLENGE STUDY

Subjects were investigated on two separate days. Baseline measurements of sGaw, FEV_1, FVC, and MEF_{50} were obtained on each day. Subjects then inhaled 1·5 ml of clemastine (1 mg/ml) on one day, and 1·5 ml of physiological saline on the other, administered from a Hudson 1700 nebuliser: 1·0 ml of each dose was delivered with 0·5 ml being left to the dead space of the apparatus. Each test substance was administered double blind and in a random sequence. SGaw, FEV_1, FVC, and MEF_{50} were measured 30 minutes after the inhalation to assess bronchodilatation.

Increasing concentrations of histamine were then inhaled at three-minute intervals from another Hudson 1700 nebuliser. The concentrations were 0·1, 0·25, 0·5, 1·0, 2·5, 5·0, 10, 25, 50, 100, 250, and 325 mg/ml. Five tidal breaths of each concentration were taken and sGaw was measured before each concentration increment (Chai *et al,* 1975). This was continued for the whole concentration range, or until there was a 50% fall in sGaw from the post-treatment baseline. At the end of the challenge sequence relief of bronchospasm was provided by the inhalation of salbutamol aerosol 200 μg.

METHACHOLINE CHALLENGE STUDY

On two separate days baseline measurements of sGaw, FEV_1, FVC, and MEF_{50} were obtained before and 30 minutes after inhalation of clemastine 1 mg/ml and physiological saline. This was administered as outlined above. Subjects then inhaled five tidal breaths of increasing concentrations of methacholine at three-minute intervals administered as described above. SGaw was measured at each concentration increment, and the sequence ended when sGaw had fallen by 50% from the post-treatment baseline. Fresh solutions of methacholine, 0·05, 0·1, 0·25, 1·0, 2·5, 5 0, 10, 25, 50, 100, and 250 mg/ml, were prepared no more than 30 minutes before challenge. Relief of bronchospasm was provided at the end of the challenge sequence by the inhalation of salbutamol aerosol 200 μg.

ANALYSIS

Cumulative log dose response curves were constructed for each challenge, and the slope of the regression line was calculated for the fall in sGaw in each patient. Results on clemastine and saline treatment days were compared by Student's *t* test for paired observations.

Results

INITIAL BRONCHODILATATION (table 1)

There was no significant difference between mean baseline values of sGaw, FEV_1, FVC, or MEF_{50} on the clemastine and saline treatment days. Thirty minutes after clemastine inhalation there was a mean percentage increase in sGaw of 21·9%. FEV_1, FVC, and MEF_{50} rose by 7·4%, 4·5%, and 12·2% respectively. The mean percentage increase in sGaw, FEV_1, FVC, and MEF_{50} produced by clemastine was significantly better than with saline ($P<0.002$, $P<0.002$, $P<0.05$, and $P<0.002$, respectively).

HISTAMINE CHALLENGE

Onset of bronchoconstriction (table 2)

After starting the histamine challenge sequence there was an initial period where sGaw remained unchanged despite the inhalation of increasing concentrations of histamine. Bronchoconstriction, as shown by a sudden fall in sGaw, was seen in all patients on saline treatment days, but clemas-

Table 1 *Baseline and percentage change in FEV_1, FVC, MEF_{50} and sGaw with saline and clemastine inhalations*

	FEV_1 (l)		FVC (l)		MEF_{50} (l/min)		SGaw (l/sec^{-1} cn H_2O^{-1})	
	Baseline	Mean % increase	Baseline	Mean % increase	Baseline	Mean % increase	Baseline	Mean % increase
Saline	2·97±1·12	−0·70±9·04	4·14±1·32	−0·50±11·40	2·99±1·36	−3·12±12·57	0·100±0·049	−1·00±15·86
Clemastine	2·91±1·14	7·44±8·83	4·06±1·28	4·50± 9·75	2·91±1·45	12·16±14·75	0·100±0·045	21·92±21·72
P	NS	<0·002	NS	<0·05	NS	<0·002	NS	<0·002

Table 2 *Histamine challenge: sGaw (mean±SE)*

	Saline	Clemastine
Baseline	0·099±0·017	0·086±0·014
Post-treatment baseline	0·096±0·015	0·103±0·015
Histamine (mg/ml)		
0·1	0·092±0·013	0·106±0·016
0·25	0·095±0·013	0·106±0·015
0·5	0·095±0·013	0·107±0·017
1·0	0·093±0·013	0·109±0·016
2·5	0·093±0·014	0·107±0·014
5·0	0·085±0·014	0·113±0·017
10·0	0·086±0·015	0·109±0·016
25·0	0·081±0·015	0·110±0·015
50·0	0·057±0·013	0·106±0·018
100·0	0·051±0·017	0·096±0·021
250·0		0·087±0·020
325·0		0·070±0·022

tine gave complete protection in four subjects, in that no bronchoconstriction was caused by the highest available histamine concentration. The remaining six patients did exhibit bronchoconstriction despite clemastine, but at significantly higher concentrations of histamine. The mean histamine concentration causing a 20% fall in sGaw from the post-treatment baseline was 18·5±18·7 mg/ml with saline, compared to 178·6±117·6 mg/ml when treated with clemastine ($P<0·01$). The degree of protection would be very much greater than this if one could take into account the four patients in whom no bronchoconstriction could be elicited when treated with clemastine.

The cumulative log histamine dose response curve (fig 1)

Inhalation of clemastine caused a parallel shift to the right of the cumulative log histamine dose response curve when compared with the curve after saline. Regression lines were calculated for the fall in sGaw on each treatment for the six patients in whom bronchoconstriction occurred on both treatments. The slope of these regression lines was obtained and compared by Student's *t* test for paired observations. There was no significant difference in the slopes between the saline and clemastine treatment days.

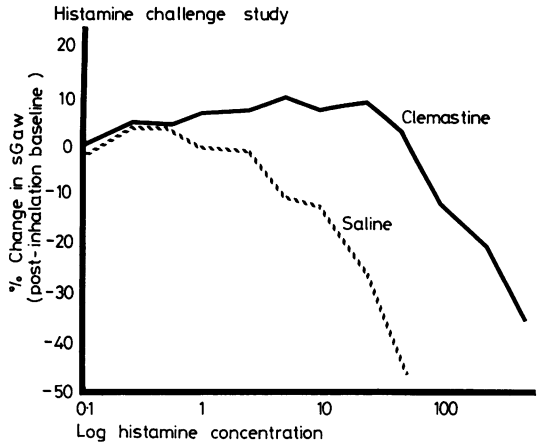

Fig 1 *Mean cumulative log dose response curves for histamine.*

Methacholine challenge (fig 2, table 3)

Methacholine challenge produced a rapid fall in sGaw in all patients on both treatment days. The mean concentration of methacholine causing a 20% fall in sGaw from post-treatment baseline

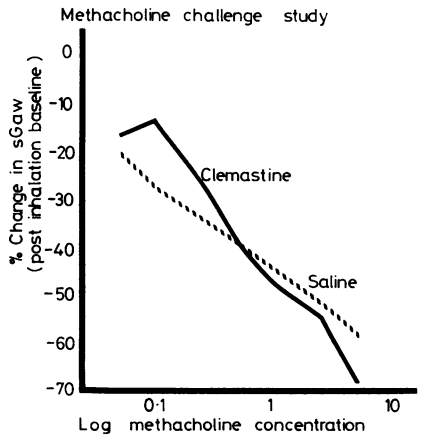

Fig 2 *Mean cumulative log dose response curves for methacholine.*

Table 3 *Methacholine challenge: sGaw (mean±SE)*

	Saline	*Clemastine*
Baseline	0·103±0·016	0·115±0·014
Post-treatment baseline	0·101±0·016	0·131±0·015
Methacholine (mg/ml)		
0·05	0·085±0·013	0·107±0·013
0·1	0·072±0·014	0·111±0·015
0·25	0·071±0·014	0·095±0·015
0·5	0·066±0·015	0·080±0·015
1·0	0·070±0·017	0·069±0·016
2·5	0·060±0·013	0·064±0·011

was 0·66±1·00 mg/ml when treated with saline, and 0·71±0·96 mg/ml when treated with clemastine (no significant difference). The inhalation of clemastine appeared to give no protection against methacholine-induced bronchoconstriction.

Discussion

H_1-receptor blocking antihistamines have been shown to have bronchodilator properties, but when given by mouth or parenterally in sufficient dose to cause bronchodilatation they produce unacceptable anticholinergic side effects and sedation (Popa, 1977). When given by inhalation they are more effective but can cause cough, throat irritation, and occasionally, bronchoconstriction (Herxheimer, 1948, 1949; Hawkins, 1955). Inhalation of clemastine causes bronchodilatation comparable to that produced by salbutamol aerosol and is without observed side effects (Nogrady *et al,* 1978).

Most antihistamines have anticholinergic properties, and any bronchodilatation produced could be mediated by blockade of vagal reflex bronchoconstrictor mechanisms. Clemastine is a potent, highly specific, H_1-receptor antagonist, giving virtually no protection against bronchoconstriction induced in guinea pigs by aerosols of acetylcholine and serotonin (Kallós, 1971). In this study we have shown that clemastine causes highly significant protection against histamine-induced bronchoconstriction in asthmatic subjects. The parallel shift of the cumulative log dose response curve to the right suggests that this protection is due to clemastine acting as a competitive antagonist to histamine (Popa, 1976). While causing bronchodilatation, its failure to protect against methacholine-induced bronchoconstriction supports the suggestion that its bronchodilator action is not related to anticholinergic properties. There is no information available regarding antagonism to the effects of prostaglandins, kinins, or slow reacting substance of anaphylaxis (SRSA). Similarly, it is not known if clemastine has any beta agonist or phosphodiesterase inhibiting activity, to which its bronchodilator properties could be attributed. Clearly, further studies need to be undertaken in this direction.

The mechanism of histamine-induced bronchoconstriction is not clear. While some authors have reported some protection against histamine-induced bronchoconstriction by atropine (Drazen and Austen, 1975), most workers have found the protection to be of minor importance (Itkin and Anand, 1970; Casterline *et al,* 1976; Casterline and Evans, 1977). Histamine, however, does increase the rate of firing of bronchial irritant receptors, and this effect is blocked by atropine (Mills *et al,* 1969). These findings suggest that histamine-induced bronchoconstriction is due more to a direct action on the airways and to a lesser extent to stimulation of vagally mediated bronchoconstrictor reflexes. The failure of clemastine to block methacholine-induced bronchoconstriction suggests that vagal mechanisms may act directly on bronchial smooth muscle and are not mediated by local histamine release.

The findings that inhaled clemastine causes bronchodilatation in stable asthmatic subjects, and that this action may be related to specific competitive antagonism of the H_1-receptor, suggest that histamine is constantly present in the vicinity of the H_1-receptor and that such low grade mediator release is present even in remission. Free histamine could cause airways obstruction by direct action on bronchial smooth muscle, or by a mucosal inflammatory response, leading to oedema, mucosal swelling, and the formation of an inflammatory exudate. Such low grade histamine release might not be measurable in the systemic circulation, but in asthmatic exacerbations excessive release, related to large-scale degranulation of mast cells, may cause a rise in plasma histamine concentrations (Simons *et al,* 1977).

We believe that inhaled antihistamines, such as clemastine, will gain a place in the management of bronchial asthma, and their actions again raise the question of the relative importance of mediator and reflex mechanisms in human bronchial asthma.

We would like to thank Dr J Cotes and Mr G Berry of the MRC Pneumoconiosis Research Unit, Llandough Hospital, for advice and criticism, and Dr G S Kilpatrick, Dr B H Davies, and Dr A P Smith for their permission to study their patients.

References

Bhat, K N, Arroyave, C M, Marney, S R, Stevenson, D D, and Tan, E M (1976). Plasma histamine

changes during provoked bronchospasm in asthmatic patients. *Journal of Allergy*, **58**, 647–656.
Bruce, C, Weatherstone, R, Seaton, A, and Taylor, W H (1976). Histamine levels in plasma, blood, and urine in severe asthma, and the effect of corticosteroid treatment. *Thorax*, **31**, 724–729.
Casterline, C L, Evans, R, and Ward, G W (1976). The effect of atopine and albuterol aerosols on the human bronchial response to histamine. *Journal of Allergy and Clinical Immunology*, **58**, 607–613.
Casterline, C L, and Evans, R (1977). Further studies on the mechanism of human histamine-induced asthma. *Journal of Allergy and Clinical Allergy and Clinical Immunology*, **59**, 420–424.
Chai, H, Farr, R S, Froehlich, L A, Mathison, D A, McLean, J A, Rosenthal, R R, Sheffer, A L, Spector, S. L., and Townley, R G (1975). Standardisation of bronchial inhalation challenge procedures. *Journal of Allergy and Clinical Immunology*, **56**, 323–327.
Curry, J J (1946). The action of histamine on the respiratory tract in normal and asthmatic subjects. *Journal of Clinical Investigation*, **25**, 785–791.
Curry, J J (1947). Comparative action of acetyl-beta-methylcholine and histamine on the respiratory tract in normals, patients with hay fever and subjects with bronchial asthma. *Journal of Clinical Investigation*, **26**, 430–438.
Drazen, J M, and Austen, K F (1975). Atropine modification of the pulmonary effects of chemical mediators in the guinea pig. *Journal of Applied Physiology*, **38**, 834–838.
DuBois, A B, Botelho, S Y, and Comroe, J H (1956). A new method for measuring airway resistance using a body plethysmograph. *Journal of Clinical Investigation*, **35**, 327–335.
Hawkins, D F (1955). Bronchoconstrictor and bronchodilator actions of antihistamine drugs. *British Journal of Pharmacology*, **10**, 230–234.
Herxheimer, H (1948). Aleudrine and Anthisan in bronchial spasm. *Lancet*, **1**, 667–671.
Herxheimer, H (1949). Antihistamines in bronchial asthma. *British Medical Journal*, **2**, 901–904.
Itkin, I H, and Anand, S C (1970). The role of atropine as a mediator blocker of induced bronchial obstruction. *Journal of Allergy*, **45**, 178–186.
Kallós, P (1971). Laboratory and clinical investigations of the antihistamine clemastine. *Clinical Trials Journal*, **8**, No 3, 23–26.
Lancet (1955). Antihistamines and asthma, **2**, 1182.
Mathé, A A, Hedqvist, P, Holmgren, A, Svanborg, N (1973). Bronchial hyper-reactivity to prostaglandin $F_2\alpha$ and histamine in patients with asthma. *British Medical Journal*, **1**, 193–196.
McDermott, M, Bevan, M M, and James, P J (1976). Incremental digital techniques for recording and processing flow volume curves. *Bulletin Européen de Physiopathologie Respiratoire*, **12**, 110–111P.
McDermott, M, and McDermott, T J (1977). Digital incremental techniques applied to spirometry. *Proceedings of the Royal Society of Medicine*, **70**, 169–171.
Mills, J E, Sellick, H, and Widdicombe, J G (1969). Activity of lung irritant receptors in pulmonary micro-embolism anaphylaxis and drug-induced bronchoconstriction. *Journal of Physiology*, **203**, 337–357.
Nogrady, S G, Hartley, J P R, Handslip, P D J, and Hurst, N P (1978). Bronchodilatation following inhalation of the antihistamine, clemastine. *Thorax*, **33**, 479–482.
Popa, V T (1976). Beta blockade of the bronchial smooth muscle in asthmatic subjects: Audi et alteram partem. *Journal of Allergy and Clinical Immunology*, **58**, 351–355.
Popa, V T (1977). Bronchodilating activity of an H_1 blocker, chlorpheniramine. *Journal of Allergy and Clinical Immunology*, **59**, 54–63.
Schild, H O, Hawkins, D F, Mongar, J L, and Herxheimer, H (1951). Reactions of isolated human asthmatic lung and bronchial tissue to a specific antigen: histamine release and muscular contraction. *Lancet*, **2**, 376–382.
Simon, R A, Stevenson, D D, Arroyave, C M, and Tan, E (1977). The relationship of plasma histamine to the activity of bronchial asthma. *Journal of Allergy and Clinical Immunology*, **60**, 312–316.

Requests for reprints to: Dr S G Nogrady, Welsh National School of Medicine, Llandough Hospital, Nr Penarth, S Glamorgan CF6 1XX.