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Bronchodilatation after inhalation of the antihistamine clemastine

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Bronchodilatation after inhalation of the antihistamine clemastine. H_1 receptor blocking antihistamines administered by mouth have not found a clear place in the management of bronchial asthma. We investigated the possibility that higher concentrations of these drugs, administered directly to the bronchial tree, might produce bronchodilatation.

Twelve asthmatic patients inhaled aerosols generated from solutions of clemastine (0·05%), salbutamol (0·5%), and placebo. Bronchodilatation was assessed by changes in the forced expiratory volume in one second (FEV_1) and peak expiratory flow rate (PEFR) over four hours.

Both clemastine and salbutamol caused significant bronchodilatation. The mean maximum percentage increases in FEV_1 for clemastine and salbutamol were 21·1% and 29·2% respectively. The mean maximum percentage increases in PEFR were 31·2% and 35·2% respectively. There was no significant difference in the maximum bronchodilatation produced by the two drugs.

Clemastine, when administered by aerosol inhalation, appears to be an effective bronchodilator.

The role of histamine in the production of acute asthma is controversial. There is evidence that histamine is released in allergic reactions in the lung (Schild *et al*, 1951), and challenge studies have shown that the bronchi of asthmatics are more sensitive to histamine than those of non-asthmatics (Curry, 1947; Tiffenau, 1958; Townley *et al*, 1965). Oral antihistamine drugs have not found a place in treating asthma, however, and are widely thought to be ineffective (*Lancet*, 1955).

Assuming that histamine plays a role in asthma, the therapeutic failure of antihistamines could be due either to the failure to block the H_2 receptor sites or to incomplete H_1 receptor blockade caused by inadequate local concentrations of drugs. Indeed, higher doses of antihistamines, given by mouth or parenterally, have caused bronchodilatation (Popa, 1977), but central nervous system depression limits their use by this route.

We have attempted to assess whether the administration of an H_1 receptor blocking antihistamine, clemastine, given directly to the bronchi as an aerosol, could cause therapeutically useful bronchodilatation.

Patients

Twelve patients (age range 29–70, mean 46) gave informed consent. All were in hospital having recovered from a severe exacerbation of bronchial asthma and were in a relatively stable clinical state. All had previously shown reversibility of airways obstruction by a greater than 15% increase in peak expiratory flow rate (PEFR) after inhaling salbutamol aerosol 200 μg. Six of the twelve patients were atopic by prick skin testing.

On three consecutive mornings each patient had baseline measurements of PEFR (the best of three recordings) using a Wright peak flow meter and forced expiratory volume in one second (FEV_1) using a dry wedge spirometer (Vitalograph). Each subject then inhaled from a Wright's nebuliser 1 ml each of either clemastine 0·05% in saline, salbutamol 0·5%, or physiological saline as

placebo. Each drug was administered double blind and in a sequence determined by the extended latin square design. PEFR and FEV_1 were measured at 5, 15, 30, 45, 60, 90, 120, 180, and 240 minutes after the inhalation. Results were analysed using Students "*t*" test for paired samples.

Results

PEFR

All patients experienced an increase in PEFR with clemastine and salbutamol (fig 1 and tables 1 and 2). The mean baseline PEFR was 282±100 l/min with no significant difference between the three treatment days. After inhalation of salbutamol there was a mean maximum percentage increase over each baseline of 35·2% at 45 minutes. After clemastine inhalation there was a mean maximum increase of 31·2% at 60 minutes. There was no significant difference between the maximum changes obtained with the two drugs. The onset of bronchodilatation was slower with clemastine than with salbutamol, but while with the latter there was only a 12% increase in PEFR at 240 minutes, with clemastine it was maintained at 20·2%. Salbutamol became significantly better than placebo ($P<0·05$) after five minutes; clemastine took longer.

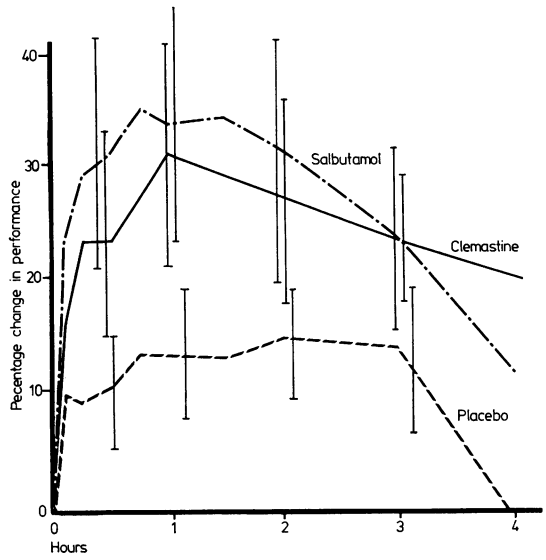

Fig 1 *Percentage change ±SE in peak flow rate with inhaled salbutamol, clemastine, and placebo.*

FEV_1

An increase in FEV_1 was seen in all patients after inhalation of clemastine and salbutamol (fig 2 and tables 3 and 4). The mean baseline FEV_1 was 1·99±0·78 l with no significant difference between

Table 1 *Mean percentage change in PEFR (±SD)*

Time	*Salbutamol*	*P<0·05*	*Placebo*	*P<0·05*	*Clemastine*
5	23·3±27·7	*	10·0±20·9		16·2±25·5
15	29·3±34·0	*	9·3±20·4		23·6±27·2
30	31·4±32·8	*	10·6±21·3		23·5±30·0
45	35·2±37·3	*	13·8±15·4		27·5±33·2
60	34·1±35·3	*	13·7±18·0	*	31·2±31·6
90	34·5±34·5	*	13·3±19·6	*	29·2±33·0
120	31·8±32·9	*	15·0±15·4		27·6±27·4
180	23·9±26·8		14·2±19·3	*	23·5±15·4
240	12·0±18·4	*	−1·5±10·0	*	20·2±12·8

Table 2 *Individual baseline and peak values of PEFR with salbutamol, clemastine, and placebo*

	Salbutamol		*Clemastine*		*Placebo*	
Patients	*Baseline*	*Peak*	*Baseline*	*Peak*	*Baseline*	*Peak*
1	230	275	195	255	220	245
2	135	270	150	265	125	210
3	290	435	400	480	460	525
4	265	340	300	325	230	300
5	270	310	260	300	240	300
6	380	460	300	400	410	465
7	90	200	110	235	100	200
8	365	445	360	435	365	450
9	340	400	350	390	360	410
10	240	270	230	270	250	250
11	320	440	260	365	320	375
12	400	520	450	545	415	490

Table 3 *Mean percentage change in FEV_1 (±SD)*

Time	*Salbutamol*	*P<0·05*	*Placebo*	*P<0·05*	*Clemastine*
5	19·7±25·0	*	4·8±21·2		9·1±17·3
15	21·2±23·1	*	6·6±21·8		13·3±22·4
30	27·3±23·3	*	8·4±20·7	*	18·1±18·7
45	23·2±24·8	*	7·3±16·5	*	20·4±21·5
60	26·4±26·5	*	7·7±22·5	*	21·1±22·3
90	29·2±26·1	*	9·1±20·5	*	21·1±20·6
120	20·6±18·2		13·1±16·2		17·8±20·2
180	11·8±19·3		9·8±21·1		15·2±17·8
240	4·31±14·8		0·13±11·4	*	10·4±16·4

Table 4 *Individual baseline and peak values of FEV_1 with salbutamol, clemastine, and placebo*

	Salbutamol		*Clemastine*		*Placebo*	
Patients	*Baseline*	*Peak*	*Baseline*	*Peak*	*Baseline*	*Peak*
1	1·75	1·83	1·50	1·70	1·60	1·65
2	1·10	2·05	1·20	2·00	0·95	1·60
3	2·65	3·30	3·85	3·85	3·80	4·00
4	1·50	1·85	1·60	1·95	1·25	1·65
5	2·45	2·95	2·45	2·75	2·60	2·75
6	3·50	4·15	2·50	3·50	3·30	4·00
7	0·75	1·45	1·00	1·50	1·15	1·18
8	2·55	2·90	2·60	2·80	2·40	2·75
9	2·10	2·50	2·15	2·40	2·10	2·35
10	1·54	1·68	1·65	1·80	1·48	1·48
11	1·75	2·35	1·40	1·90	1·60	1·90
12	1·90	2·60	2·20	2·95	1·83	2·36

the three treatment days. After salbutamol inhalation there was a mean maximum percentage increase over each baseline of 29·2% at 90 minutes. With clemastine there was a mean maximum increase of 21·1% between 60 and 90 minutes. There was no significant difference between the maximum changes obtained with the two drugs. Salbutamol remained significantly better than placebo until 120 minutes. Clemastine remained significantly better than placebo until the end of the observation period at 240 minutes.

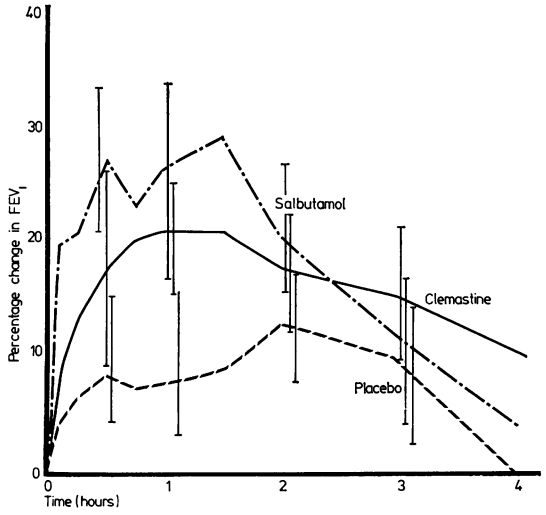

Fig 2 *Percentage change ±SE in forced expiratory volume in 1 second with inhaled salbutamol, clemastine, and placebo.*

ATOPIC STATUS

The mean maximum percentage increase in PEFR and FEV_1 did not significantly differ between the atopic and non-atopic groups for either salbutamol or clemastine.

SIDE EFFECTS

No patient complained of any degree of irritation of the throat, nor of any other side effects.

Discussion

Histamine, along with other mediators of the allergic reaction, has been shown to be released from previous sensitised lung tissue on appropriate allergen challenge (Schild *et al,* 1951). Asthmatic patients show an increased bronchial reactivity to inhaled histamine (Curry, 1947; Townley *et al,* 1965), and this reactivity is more pronounced in symptomatic than in asymptomatic patients (Cockcroft *et al,* 1977). Bhat *et al* (1976) showed a significant twofold rise in serum histamine concentration five minutes after allergen-induced bronchoconstriction, but not after methacholine-induced bronchoconstriction. Bruce *et al* (1976) found a higher plasma histamine concentration in subjects with acute severe asthma than in normal controls, though raised concentrations were also found in patients with other, less acute, chest illnesses.

In-vitro studies with the H_1 receptor antagonist mepyramine, (Dunlop *et al,* 1977), have shown that complete receptor blockade in isolated bronchial muscle can cause relaxation, even in the presence of histamine. Mepyramine also significantly reduced the contraction of sensitised bronchial muscle in allergen challenge. Oral antihistamines have been recommended for treating asthma but have been found to be relatively ineffective and have failed to find a clear place in its management (*Lancet,* 1955). Herxheimer (1948 and 1949) showed that inhalation of mepyramine caused a slight increase in vital capacity in five asthmatic patients, and that inhalation of pyribenzamine and promethazine gave some protection against mild histamine, methacholine, and allergen-induced bronchoconstriction. Pyribenzamine aerosol also caused bronchodilatation in patients with spontaneous asthma. Feinberg *et al* (1948) showed that aerosols of several antihistamines could prevent histamine-induced bronchoconstriction in guinea pigs. Recent work has shown that inhaled diphenhydramine can prevent histamine-induced bronchoconstriction in asthmatic patients (Casterline and Evans, 1977). On the other hand, aerosols of antihistamines were found to be irritating, and in concentrations of greater than 2% could themselves cause bronchoconstriction in animals (Hawkins, 1955).

Clemastine is one of the benzhydrylether group of antihistamine compounds. It is a highly specific H_1 receptor antagonist, and has no significant protective effect against bronchoconstriction induced by aerosols of acetylcholine or serotonin (Kallós, 1971). It causes little central nervous system depression as measured by critical flicker frequency depression (Hedges *et al,* 1971) and hand-eye co-ordination (Day *et al,* 1972). As an H_1 receptor antagonist it is considerably more potent than promethazine and chlorpheniramine in preventing wheal formation after intradermal injection of histamine and histamine-induced bronchoconstriction in guinea pigs (Hedges *et al,* 1971). Our choice of a 0·05% solution was made after pilot studies, as the highest concentration that did not cause throat irritation with the

delivery system used. At this concentration patients were aware of the characteristic taste, but it provoked neither complaints nor problems with cough or throat irritation. No side effects were observed during the study.

The finding that a specific H_1 receptor antagonist is an effective bronchodilator with a prolonged action raises again the question of the role of histamine in asthma. While it is possible that part of the bronchodilator effect may be due to anticholinergic properties, the specificity of the compound suggests otherwise. Further studies in histamine and methacholine-induced bronchoconstriction are in hand to resolve this question. Because the onset of bronchodilatation with inhaled clemastine is slower than with salbutamol, clemastine is likely to be of more use for the maintenance management of asthma than for the relief of acute attacks. Its use in conjunction with sympathomimetics and its role in the prevention of exercise-induced asthma are being investigated.

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