Short reports

Effect of preservative on the efficacy of terbutaline nebuliser solution in atopic asthma

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Abstract

The efficacy of bronchodilator nebuliser solutions may be influenced by the presence of preservatives. In a double blind, randomised, crossover study the effect of preservatives in determining the airway responses to 5 mg of terbutaline was studied in a group of 21 atopic asthmatic patients. The presence of preservatives affected neither the bronchodilator action of terbutaline nor its protection against bronchoconstriction induced by histamine.

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The presence of preservatives in bronchodilator nebuliser solutions may cause bronchoconstriction or diminish the effectiveness of the drug constituents.[1] Although paradoxical bronchoconstriction has not been reported with terbutaline nebuliser solution, this formulation contains two preservatives—EDTA and chlorbutol—both of which have the capacity to cause bronchoconstriction.[2,3] A preservative free formulation of terbutaline nebuliser solution has recently been introduced as unit dose vials, each 2 ml vial containing 5 mg terbutaline. In this study we have compared the efficacy of these two formulations (with and without preservatives) by examining their effects on airway calibre and histamine induced bronchoconstriction in a group of atopic asthmatic subjects.

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Methods

SUBJECTS

Twenty one non-smoking patients (16 men) of mean (SE) age 35·2 (2·6) years with mild to moderate atopic asthma were studied. They had a mean (SE) baseline forced expiratory volume in one second (FEV_1) of 1·92 (0·13) l or 59·2% (2·5%) predicted and were bronchial hyperresponsive with a provocation concentration of histamine causing a 20% fall in FEV_1 (PC_{20}) which ranged from 0·06 to 7·2 mg/ml (geometric mean 0·4 mg/ml). They all received regular inhaled corticosteroids and inhaled β_2 agonists on demand. Informed consent was obtained from each patient and the study was approved by the hospital ethical committee.

STUDY DESIGN

Subjects attended the laboratory at the same time of day on four separate occasions at least 48 hours apart. At each visit inhaled bronchodilators were withheld for 12 hours and inhaled steroid for 24 hours. Baseline FEV_1 was measured on each visit by a dry wedge spirometer (Vitalograph, Buckingham, UK). On the first visit this was followed by a histamine concentration-response study[4] and skin prick tests to assess the degree of non-specific airway responsiveness and atopic state. On subsequent visits one of the three 2 ml solutions—preservative free terbutaline (PFT, 2·5 mg/ml), preservative containing terbutaline (PT, 0·5 ml of 10 mg/ml solution + 1·5 ml saline), or placebo (2 ml saline)—was inhaled in a random, double blind fashion via a face mask attached to a Hudson nebuliser driven by oxygen at a flow rate of 8 l/min. The inhalation was continued until nebulisation to dryness was achieved which generally took about seven minutes. FEV_1 was measured immediately and at 2, 5, 10, 15, and 30 minutes after nebulisation. This was then followed by a histamine concentration-response study.

DATA ANALYSIS

The airway response for the two formulations of terbutaline solution and placebo was determined by comparing the maximum and minimum values of FEV_1 achieved, the areas under the FEV_1-time response curves (AUC) calculated by trapezoid integration, and the values of histamine PC_{20} obtained after the nebulised solutions. Two way analysis of variance was used to compare baseline FEV_1 values and the four indices of airway response between visits 2, 3, and 4. Any significance was further sought by the Newman Keuls' procedure. Least squares linear regression analysis was used to investigate the relationships between the bronchodilator effect of the active drugs and their ability to protect against histamine provoked bronchoconstric-

Table 1 Mean (SE) baseline FEV_1 values (l) on the three treatment days

	Placebo	*PFT*	*PT*
Before treatment	1·92 (0·14)	1·88 (0·13)	1·80 (0·13)
Before histamine	1·85 (0·13)	2·22 (0·13)*	2·20 (0·13)*

PFT—preservative free terbutaline; PT—preservative containing terbutaline.
*$p < 0·0001$ *v* placebo day (two way analysis of variance).

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Table 2 Airway response to nebulised PFT, preservative containing PT, and placebo in atopic asthmatic subjects

	Placebo	*PFT*	*PT*
Mean (SE) maximum FEV_1 (% of baseline)	3·01 (1·42)	23·64 (3·52)*	27·98 (3·85)*
Mean (SE) minimum FEV_1 (% of baseline)	−7·32 (1·20)	13·18 (2·96)*	13·19 (2·60)*
Mean (SE) AUC‡ (mm^2)	−55·6 (39·5)	571·0 (94·5)*	657·0 (92·3)*
Geometric mean (range) PC_{20} (mg/ml)	0·44 (0·068–11)	2·04* (0·27–64)	1·39† (0·14–64)

*p < 0·0001 *v* placebo (two way analysis of variance); †p < 0·001 *v* placebo.
‡Area under the FEV_1–time response curve from 0 to 30 minutes.

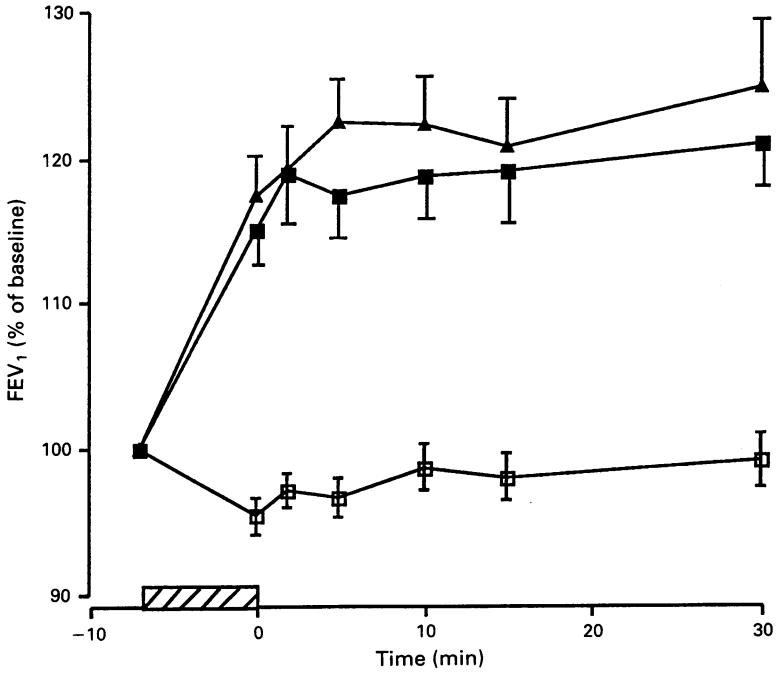
tion, and between this and baseline histamine airway responsiveness.

Results

All subjects completed the study. There was no significant difference between baseline FEV_1 on all treatment days; FEV_1 levels before histamine challenge on the placebo day was, however, significantly lower than on both active treatment days, but values on these latter days were not different (table 1).

Compared with placebo, inhalation of either PFT or PT resulted in significant bronchodilatation whether data were analysed as maximum or minimum values of FEV_1 or AUC (table 2, fig). This bronchodilator response was rapid and sustained for at least 30 minutes (fig). No significant difference was observed, however, between the effects of PFT and PT on airway calibre (table 2, fig). None of the subjects developed any significant bronchoconstriction (more than 6% fall in FEV_1) after inhalation of either preparation of terbutaline.

Bronchial responsiveness to histamine was significantly reduced after inhalation of PFT or PT compared with that after placebo (table 2). Expressed as concentration ratios with placebo, PFT and PT afforded a geometric mean protection of the airways of 4·6 (range 0·4–51) fold and 3·1 (0·4–27·2) fold respectively against bronchoconstriction provoked by histamine. Although there was a trend for a greater protection with PFT than PT, this was not significant (table 2). No significant correlation was observed between the histamine concentration ratio and the degree of bronchodilatation after inhalation of either preparation, or between the former and baseline histamine responsiveness. A significant correlation was found, however, between the ability of the two preparations of terbutaline to protect against histamine induced bronchoconstriction ($r = 0·49$, $p < 0·05$)



Mean (SE) changes in FEV_1 values in 21 atopic asthmatic subjects after preservative free terbutaline (PFT; closed squares), preservative containing terbutaline (PT; closed triangles), and saline placebo (open squares).

Discussion

In this study we have shown that the presence of preservatives in terbutaline nebuliser solution does not appear to influence its effects on the asthmatic airways, whether assessed as bronchodilatation or as protection against histamine provoked bronchoconstriction. Our data are in accord with the absence of any report of paradoxical bronchoconstriction provoked by nebulised terbutaline. The apparent lack of effect of these preservatives could be related to their relatively weak bronchoconstrictor action: indeed bronchoconstriction did not occur in a group of asthmatic subjects after inhalation of chlorbutol.[5]

The ability to protect against a bronchoconstrictor agonist may be a more sensitive means of comparing the efficacy of bronchodilators[6,7] as maximum bronchodilatation may be achieved even with different doses of the same drug.[8] The lack of correlation between the extent of bronchodilatation produced by the active drugs and their ability to protect against bronchoconstriction by histamine in our subjects suggests that different mechanisms may underlie these two airway responses. This hypothesis is further supported by the finding that bronchodilatation after inhaled β_2 agonists[7,8] lasted longer than protection against histamine. Inhaled salbutamol produced a greater increase in the baseline value of specific airway conductance than atropine but afforded less protection against methacholine challenge[9] and, although similar degrees of bronchodilatation were attained with different drugs, varying degrees of protection against histamine were observed.[10] Despite the use of this sensitive index of airway function, we have failed to show a significant difference between the efficacy of these two preparations of nebulised terbutaline. Our observation is unlikely to represent a type II error as the power of our study had a 90% chance of detecting a 10% difference in FEV_1 and a greater than 1·5 doubling

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dilution difference in histamine PC_{20} at the 5% level of significance.

We have failed to show any adverse effect of preservatives on the airway response to nebulised terbutaline. Although it is more convenient to use the unit dose vials, the lack of evidence to suggest greater efficacy than the older preparation, together with the relatively high cost, may preclude its use as a first line treatment in asthma except in patients with well documented adverse reactions to the preservative containing preparation.

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Mediastinal mass caused by syphilitic aortitis

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Abstract

A 47 year old man presented with hoarseness and chest pain found to be due to proliferative syphilitic aortitis. The case is unusual as the syphilitic aortitis caused a mediastinal mass without affecting the lumen of the aorta.

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Syphilitic aortitis, the hallmark of cardiovascular syphilis, has become rare and is hardly considered by today's clinicians in their differential diagnosis. We describe a patient with a recurrent laryngeal nerve palsy resulting from a mediastinal mass caused by cardiovascular syphilis.

Case report

A 47 year old man was admitted to Karl Franzens University Medical Centre because of progressive hoarseness and angina like chest pain over the previous six months. The patient's past medical history included two episodes of syphilis at the age of 20 and 22 which, according to the patient, had both been treated with penicillin. The presence of coronary artery heart disease (NYHA II-III) had been verified by coronary angiography one year previously but the patient had refused treatment.

Upon admission the patient was in good general health, with hoarseness being the only abnormality on physical examination. There was no evidence of any syphilitic stigmata such as aortic incompetence, Argyll Robertson pupils, tabes dorsalis, or gummas. Laboratory tests revealed a normal haemoglobin, white blood cell and differential count, and platelets. C-reactive protein and sedimentation rate were both elevated. Other routine laboratory tests were within normal limits. Serum VRDL and IgM SPHA (solid phase haemadsorption) test results were negative; TPHA (*Treponema pallidum* haemagglutination) test results were positive at a low dilution, and FTA-ABS (fluorescence-*Treponema pallidum* antibody-absorption) test results were also positive, both consistent with previous syphilis.

Laryngoscopy revealed paresis of the left vocal cord and chest radiography showed enlargement of the aortic knuckle with tracheal deviation suggesting an aortic dissection. Computed tomography of the mediastinum revealed a mass which extended from the aortic knuckle down to the bifurcation of the trachea (fig 1). Magnetic resonance imaging showed a mass extending from the carina to 3 cm above the aortic arch which suggested a lymphoma or thymoma. An aneurysm of the aorta was ruled out by these imaging procedures.

In order to identify the nature of this mass, exploratory thoracotomy was planned. Coronary angiography performed before thoracotomy showed progression of his coronary artery disease so coronary artery bypass surgery was planned for the same operation. Further preoperative examinations such as bronchoscopy, carotid artery sonography, bone scan, and angiography of the aortic arch showed nothing remarkable.

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