Protective effect of theophylline on histamine-induced bronchoconstriction in asthmatic children

S. LEVENE & S. A. McKENZIE

Department of Paediatrics, Oldchurch Hospital, Romford, Essex

1 The bronchial responsiveness of a group of asthmatic children was studied using histamine stimulation after a single dose of theophylline and after placebo.

2 Theophylline, when levels were greater than $10 \mu\text{g ml}^{-1}$ significantly reduced responsiveness but only by just over one doubling concentration of histamine ($P < 0.001$).

Keywords asthma theophylline

Introduction

Theophylline is widely used as a maintenance treatment for moderately severe asthma and has been repeatedly shown to reduce day to day symptoms and to improve pulmonary function by bronchodilatation (Weinberger & Bronsky, 1974; Hambleton *et al.*, 1977; Rachelefsy *et al.*, 1978; Wilson & Silverman, 1982). It has also been shown to block bronchoconstriction induced by exercise (Bierman *et al.*, 1977) and inhaled allergens (Falliers, 1979), and to give a small degree of protection to bronchoconstriction induced by inhaled histamine in a small number of adults who were highly responsive (Cockcroft *et al.*, 1977a).

The purpose of this study was to examine the protective effect of theophylline to bronchoconstriction by histamine in a group of asthmatic children of varying responsiveness, and to relate it to the serum theophylline level and degree of bronchodilatation.

Methods

Subjects were children attending hospital for management of asthma of varying severity in whom the diagnosis had been made on clinical grounds supplemented by exercise-testing and skin-testing. All could use a peak flow meter. Informed consent was obtained from parents and children and the study was approved by the local ethics committee.

Patients were studied on 2 days between 4 and 6 weeks apart during which time each continued his usual therapy. Before each study day all drugs were discontinued as follows: inhaled salbutamol 8 h; theophylline according to preparation, 18–36 h; inhaled steroids, disodium cromoglycate, antihistamines, 48 h.

On each study day patients were given either placebo or theophylline between 08.00 h and 09.00 h. Histamine provocation tests were carried out 1 h later. Blood was drawn for serum theophylline (ST) measurement immediately following each test. The preparation of theophylline used was that with which the patient was familiar, either a liquid or slow-release preparation, and placebos for each were available. The patients were randomly allocated into three groups.

Group 1: This group served as a control group to measure the variability of bronchial responsiveness over the period of the study:

- (a) Given placebo on both study days.
- (b) Given same dose of theophylline on both study days.

Group 2: Given placebo on one day and theophylline 5 mg kg^{-1} on the other.

Group 3: Given placebo on one day and theophylline on the other, 10 mg kg^{-1} .

Two different doses of theophylline were used in order to obtain a range of serum theophylline levels. The order in which placebo and drug were given was randomized.

Histamine stimulation provocation testing

The method of Cockcroft and colleagues (1977b) was used for bronchial provocation by histamine inhalation but since the subjects were children peak expiratory flow rate (PEFR) measurements were made instead of forced expiratory volume in 1 s (FEV₁) (Henry *et al.*, 1982). Aerosols of the test solution were produced by a paediatric jet nebuliser kit (Lifecare Ltd) calibrated to a delivery rate of 0.16 ml min⁻¹ (Ryan *et al.*, 1981). Children wore a nose-clip during the inhalation and breathed quietly for 1 min. After a control inhalation of phosphate buffered saline twofold increasing concentrations of buffered histamine phosphate (0.03–8 mg ml⁻¹) were administered at 5 min intervals. PEFR was measured using a Wright peak flow meter 30 and 90 s after the completion of each dose. Inhalations were discontinued when PEFR had fallen by at least 20% of that after the control inhalation. A log dose response curve was plotted for each test, and the concentration of histamine required to reduce PEFR by 20% of that after the control inhalation (PC₂₀) was obtained by interpolation. Variables known to influence the outcome of histamine inhalation tests (Spector, 1979; Hargreave *et al.*, 1981) were eliminated or matched for repeat tests on the same patient. These were recent upper respiratory tract infection, recent allergen exposure, time of day and previous drug exposure.

Values of PC₂₀ were expressed logarithmically for analysis. Paired *t*-tests, linear regression analyses and Kendall's rank correlation test were used for analysis of the results. A *P* value of < 0.05 was considered significant.

Results

Thirty-two children were studied on 41 pairs of occasions. The age range was 5 years 10 months to 13 years 9 months; the mean age was 9 years 9 months.

At the end of the study the patients were re-allocated according to the serum theophylline concentrations obtained into four groups as follows:

Group 1a: with undetectable serum theophylline concentrations on both days (eight patients).

Group 1b: similar serum theophylline concentrations (within 2 µg ml⁻¹ of each other) on both days (six patients).

Group 2: with undetectable serum theophylline concentrations on one day and 5–10 µg ml⁻¹ on the other day (13 patients).

Group 3: with undetectable concentrations on one day and > 10 µg ml⁻¹ on the other day (14 patients).

Results are shown in Figure 1. For Groups 1a, 1b and 2 there was no significant difference in bronchial responsiveness between the two occasions. In Group 3 when the serum theophylline concentration was unrecordable on one day and > 10 µg ml⁻¹ on the other the improvement in PC₂₀ was significant (*P* < 0.001). The mean improvement in this group was just over 1 doubling concentration of histamine (mean ± s.e. mean = 1.18 ± 0.32 doubling concentrations of histamine).

There was no significant difference between the mean baseline PC₂₀ measurements on placebo for Groups 2 and 3. The fall in bronchial responsiveness (ΔPC₂₀) and PC₂₀ on placebo correlated significantly for Group 3 (*n* = 14, *r* = -0.52, *P* < 0.05).

The mean change in baseline PEFR was significant only when serum theophylline concentrations were > 10 µg ml⁻¹ (mean Δ PEFR = +15.5% expected for height: *P* < 0.001). The change in PC₂₀ and change in baseline PEFR between the 2 study days (Figure 2) correlated significantly (*n* = 14, *r* = 0.54, *P* < 0.05).

Discussion

Bronchial hyper-responsiveness to non-specific stimuli is a characteristic of asthma, the more severe the asthma the more responsive the airways (Hargreave *et al.*, 1981; Juniper *et al.*, 1981) and so reduction in responsiveness, as well as bronchodilatation, may be considered as one of the aims of treatment.

This study expands the work of Cockcroft *et al.* (1977a). It has shown that when serum theophylline concentrations rise from unrecordable levels to > 10 µg ml⁻¹ there is a significant reduction in bronchial responsiveness to histamine. By comparison the control groups who had either unrecordable or similar serum theophylline concentrations on the 2 study days showed no significant change in responsiveness. The degree of improvement was however extremely small, just over one doubling concentration of histamine. This is likely to be of little clinical importance; a study of Hariparsad and colleagues (Hariparsad *et al.*, 1982), using the same method, has shown that the responsiveness in a group of asthmatic children on no treatment can vary by about 1.5 doubling concentrations over a period of a day (95% confidence limits).

The lower the values of PC₂₀ on placebo the more likely children were to show improvement when serum theophylline levels changed from unrecordable to > 10 µg ml⁻¹. This suggests that the most severely affected patients were most

Figure 1 PC_{20} values on the 2 study days. For Groups 1a and 1b PC_{20} values are paired for each subject with the result on the first occasion plotted first. For Groups 2 and 3 PC_{20} values are paired with the result on placebo plotted first, and that on theophylline second.

likely to be afforded best protection by theophylline, although no child who had a PC_{20} value on placebo of less than 0.12 mg histamine ml^{-1} improved on treatment to reach PC_{20} values similar to those expected in normal or even mildly affected subjects (Juniper *et al.*, 1981).

It has been suggested that airway calibre influences the measurement of bronchial responsiveness (Benson, 1979). Our present study which has shown that the degree of improvement in responsiveness has a weak positive correlation with improvement in PEFR would tend to support the view that reactivity relates directly to starting airways calibre. Nevertheless for the group with serum theophylline levels $> 10 \mu g\%$ the mean improvement in PEFR was 15%—a good clinical response—whereas the mean improvement in bronchial responsiveness was only one doubling dilution of histamine.

Thus theophylline although an efficient bronchodilator affects bronchial responsiveness very

little. This is of some interest with regard to nocturnal asthma. Airway calibre decreases in the early hours of the morning and it has been suggested that the exaggerated fall in airway calibre in the asthmatic at this time is a manifestation of increased bronchial responsiveness (Barnes, 1984). Both theophylline and β -adrenoceptor agonists given orally have been recommended for the management of nocturnal asthma and both result in improved PEFR measurements on waking in the morning (Fairfax *et al.*, 1980). Oral β -adrenoceptor agonists, however, have little effect on bronchial responsiveness (Cockcroft *et al.*, 1977a) and our present study has shown that the effect of theophylline is similarly small.

Dr Levene was supported by a grant from Napp Laboratories Ltd.

Figure 2 Change in PC_{20} (ΔPC_{20}) and PEFR ($\Delta PEFR$) in patients in Group 3.

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(Received 29 May 1985,
accepted 17 November 1985)