Effects of Theophylline on Tolerance to the Bronchoprotective Actions of Salmeterol in Asthmatics In Vivo

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Long-term treatment with salmeterol produces tolerance for its protective effects against bronchoconstrictor stimuli in patients with asthma. There is human in vitro evidence that theophylline may prevent β2-adrenoceptor downregulation. Therefore, we investigated the effect of theophylline on the tolerance to the protective effect of salmeterol against histamine challenge in asthma in vivo. In a parallel 6-wk study, 25 asthmatics were treated with theophylline (mean serum level ± SEM: 9.9 ± 1.1 mg/L Days 1 to 40) or placebo, combined with inhaled salmeterol (50 μg twice daily, Days 8 to 36). Histamine challenges were carried out by tidal breathing method at entry, and at Days 4, 8, 22, 36, and 40. The response was measured by PC20. There was no significant change in PC20 after 4 d monotherapy with theophylline or placebo (mean difference ± SEM: 0.54 ± 0.39 and −0.02 ± 0.41 doubling dose [DD], respectively; p > 0.15). One hour after the first dose, salmeterol afforded significant protection against histamine, as shown by an increase in PC20 in both the theophylline and placebo group (by 3.49 ± 0.28 and 3.36 ± 0.32 DD, respectively; p < 0.001). However, after 2 and 4 wk salmeterol treatment, the improvements in PC20 by salmeterol were significantly reduced to 1.80 ± 0.35 and 1.69 ± 0.36 DD, respectively, in the theophylline group (p < 0.001), and to 1.55 ± 0.47 and 1.52 ± 0.56 DD, respectively, in the placebo group (p < 0.002). These changes were not significantly different between the groups (p > 0.80). After cessation of salmeterol treatment, PC20 was not significantly different from the values at entry in either group (p > 0.90). We conclude that regular theophylline treatment neither prevents, nor worsens, the development of tolerance to the bronchoprotective effect of salmeterol in asthmatics in vivo.


Inhaled β2-adrenoceptor agonists are very effective bronchodilators. The short-acting agonists, such as albuterol and terbutaline, are first choice for rapid relief of asthma symptoms (1). Recently, the long-acting β2-adrenoceptor agonists salmeterol and formoterol have been introduced, that provide bronchodilation for at least 12 h (2). While it is still controversial whether the bronchodilator action of both short- and long-acting inhaled β2-adrenoceptor agonists can be fully maintained with regular dosing (3, 4), it has generally been observed that their protective effect against provoked bronchoconstriction diminishes (3, 5–9). The clinical significance of this is not clear yet, but it is possible that tolerance to the protective effects of inhaled β2-adrenoceptor agonist may contribute to less effective control of asthma and an increased severity of asthma exacerbations (10, 11).

The mechanism for the development of tolerance to the bronchoprotective effects of inhaled β2-adrenoceptor agonists is not yet certain. Aimal studies indicate that chronic exposure to β2-adrenoceptor agonist results in downregulation of pulmonary β2-receptors, including β2-receptors in airway smooth muscle (12). Even though this can be prevented in vitro by glucocorticosteroids (13), it appears that concurrent treatment with inhaled steroids can not prevent the β2-adrenoceptor agonist-induced tolerance for protective effects in patients in vivo (14, 15).

There is some circumstantial evidence that theophylline might increase the density of β2-receptors on polymorphonuclear leukocytes in asthmatic children ex vivo, thereby counterpointing the tendency toward downregulation after exposure to β2-adrenoceptor agonists (16). This suggests that theophylline treatment may prevent the development of tolerance to the bronchoprotective effect of inhaled β2-adrenoceptor agonists in vivo.

Therefore, the objective of the present study was to investigate the effects of theophylline on the development of tolerance to the bronchoprotective effect of inhaled β2-adrenoceptor agonists in asthmatics in vivo. To that end we have examined the effect of regular treatment with theophylline, in individu-
alized dosage, on the protective effects of salmeterol against histamine challenge in mildly asthmatic subjects before and after 8 wk of salmeterol therapy.

METHODS

Subjects

Twenty-five nonsmoking, asthmatic adults (mean age 29.6 yr; range 19 to 59 yr), who met the diagnostic criteria of the American Thoracic Society for asthma (17), volunteered to participate in this study (Table 1). On entry, the FEV₁ without bronchodilator was > 70% of predicted value (18). They had mild to moderate airway hyperresponsiveness as indicated by a lowered provocative concentration of histamine to cause a 20% fall in FEV₁ (PC₂₀ < 8 mg/ml) (19). The subjects had not used corticosteroids, theophyllines, antihistamines, sodium cromoglicate, or nedocromil sodium for at least 6 wk preceding the study. Symptoms of asthma were controlled by on-demand usage ofinhaled albuterol alone and not more than 200 µg per day, that was withheld for at least 12 h before the measurements. There was no history of upper respiratory tract infection or relevant exposure to allergens during the 2 wk before the experiments in any subject. The study was approved by the hospital’s medical ethics committee, and informed consent was obtained from all participants.

Study Design

The study had a double-blind, placebo-controlled parallel design. It was divided into a baseline period and a treatment period during which the patients were randomly allocated to two groups receiving regular treatment with either theophylline or placebo from Days 0 to 40. The baseline period was divided into a screening day, an entry day, and a day on which the individual theophylline dose was determined. From Day 0 until Day 36 of the treatment period, inhaled salmeterol (2 puffs of 25 µg salmeterol, twice a day) was added in both groups using a metered-dose inhaler attached to an aerosol chamber (Aerochamber; Trudell Medical, London, ON, Canada). During the study the subjects attended the laboratory on entry day in the baseline period, and on Days 8, 22, 36, and 40 of the treatment period. At each visit a dose-response curve to inhaled histamine was recorded at the same time of the day for each subject. In the baseline period and on Days 4 and 40 of the treatment period, the histamine challenges were carried out without any pretreatment. On Days 8, 22, and 36 of the treatment period, the histamine challenges were carried out 1 h after inhalation of 50 µg salmeterol administered by the investigator in the laboratory. To allow an adequate washout of the salmeterol medication, the patients interrupted their inhaled treatment 36 h before Days 22 and 36 (5). A part from the test medication, the subjects were allowed to use inhaled albuterol as required (up to 400 µg per day) as rescue medication. Theophylline was given orally in a dose of 250, 375, or 500 mg twice daily (Euphylong; Byk Gulden, Konstanz, Germany). Serum theophylline level was determined with a particle-enhanced turbidimetric inhibition immunosassay (Synchron CX system; Beckman Instruments, High Wycombe, UK). In the baseline period a theophylline serum level was obtained after 4-d treatment with theophylline 375 mg twice daily. If the theophylline serum level ranged between 8 and 15 mg/L, the same theophylline dosage was used during the treatment period. In case of higher or lower serum levels, the dosage was individually adjusted to 250 or 500 mg twice daily, respectively. The theophylline serum level was again measured doubleblindly at Day 40 of the treatment period in all subjects.

Inhalation Challenge Tests

The inhalation challenge tests were performed according to a validated method (19), using histamine diphosphate in phosphate-buffered saline. The solutions were prepared by the Pharmacy of the Leiden University Medical Centre. Histamine was stored at 4°C and warmed up to room temperature before nebulization. Serial doubling concentrations ranging from 0.06 to 32 mg/ml were used. The aerosols were generated by a DeVilbiss 646 nebulizer (DeVilbiss Co., Somerset, PA) operated by oxygen (output 0.13 ml/min) and were inhaled by tidal breathing for 2 min at 5-min intervals with the nose clipped.

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* Bronchial responsiveness to histamine measured on screening day in the baseline period.
† Serum theophylline level measured at Day 40 of the treatment period.
During the histamine challenge tests, measurements of FEV₁ were obtained at 30 and 90 s after each dose from which the lowest technical satisfactory value was used in the analysis (19). The tests were discontinued if FEV₁ dropped > 20% from baseline or when 32 mg/ml histamine had been administered. After the test, the patient inhaled 200 μg salbutamol from a metered-dose inhaler in order to provide adequate bronchodilation.

**Analysis**

The response of FEV₁ to histamine was expressed in percentage fall from (post-pretreatment) baseline value (19) and was plotted against log nebulized noncumulative concentration in mg/ml. The dose–response curves were characterized by their position and expressed as the provocative concentration causing a > 20% fall in FEV₁ from baseline (PC₂₀), which was calculated by log-linear interpolation between the two adjacent data points (19). The logarithm of PC₂₀ was used in the analyses, and changes in PC₂₀ were expressed in doubling doses (D.D.).

The effect of theophylline and placebo treatment on the bronchodilatory and bronchoprotective effects of salmeterol was evaluated from the pre- and postsalmeterol levels of FEV₁, and from the changes in PC₂₀ during the course of the study. Repeated measures analysis of variance (ANOVA) was used to explore the data, with therapy as a between-group factor and time as a within-group factor (20). Significant ANOVA effects were analyzed with Student t tests. The differences in the variables within the groups between the study days were examined using two-tailed paired t tests, and differences between the groups were analyzed using unpaired t tests. p values less than 0.05 were considered statistically significant. The summary statistics were expressed as mean difference ± SEM.

**RESULTS**

All subjects completed the study. The two treatment groups were not significantly different with respect to age, sex, FEV₁, and PC₂₀ in the baseline period (p = 0.15). The mean ± SEM level of serum theophylline at Day 40 in the treatment period in the theophylline group was 9.9 ± 1.1 mg/L.

**Baseline Lung Function**

The mean values of baseline FEV₁ in the placebo and the theophylline group are shown in Figure 1. There was no significant change in FEV₁ (before salmeterol was given) during the treatment period as compared with the value at entry in both groups (p = 0.30). These changes in FEV₁ were not significantly different between the placebo and theophylline group (p = 0.80).

**Acute Bronchodilation**

There was a significant increase in FEV₁ after inhalation of salmeterol at Days 8, 22, and 36 during the treatment period in the placebo and theophylline group (Figure 1). The increase in FEV₁ after salmeterol was 7.6 ± 2.0 (p < 0.003), 8.4 ± 1.9 (p < 0.001), and 6.6 ± 2.4 (p = 0.006) percent predicted on Days 8, 22, and 36, respectively, in the theophylline group. In the placebo group the increase in FEV₁ after salmeterol was 11.0 ± 1.8 (p < 0.001), 9.7 ± 2.1 (p < 0.001), and 10.1 ± 2.2 (p = 0.001) percent predicted on Days 8, 22, and 36, respectively. The improvement in FEV₁ by salmeterol was not significantly different between these three time points during the treatment period in both groups (p = 0.80), nor were these changes significantly different between the groups (p > 0.72) (Figure 1).

**Histamine Dose–Response Curves**

There was no significant change in PC₂₀ after 4 d monotherapy with theophylline or placebo treatment as compared with the values at entry (mean difference ± SEM: 0.54 ± 0.39 and −0.02 ± 0.41 doubling dose D.D., respectively; p > 0.15) (Figure 2). Nor were these changes significantly different between the groups (p > 0.05). At the first dose, salmeterol afforded significant protection against histamine, as shown by an increase in PC₂₀ in both the theophylline and placebo groups (by 3.49 ± 0.28 and 3.36 ± 0.32 D.D., respectively; p < 0.001) (Figure 2). However, after 2 and 4 wk salmeterol treatment, the improvements in PC₂₀ by salmeterol were significantly reduced to 1.80 ± 0.35 and 1.69 ± 0.36 D.D., respectively, in the theophylline group (p < 0.001), and to 1.55 ± 0.47 and 1.52 ± 0.56 D.D., respectively, in the placebo group (p < 0.002) (Figure 2). These changes were not significantly different between the groups (p > 0.80). Nor were these changes significantly correlated with the serum theophylline level in the theophylline group (r = −0.23, p > 0.45 and r = −0.41, p > 0.18, respectively) (Table 1).

After cessation of salmeterol at Day 40, PC₂₀ was not significantly different from the values at entry in the theophylline or placebo group (0.06 ± 0.50 and 0.02 ± 0.34 D.D., respectively; p > 0.90) (Figure 2).

**DISCUSSION**

The results of this study confirm that there is a significant loss of the bronchoprotective effect by salmeterol after 2 and 4 wk of regular salmeterol treatment, despite the well maintained bronchodilatory effect in patients with asthma. The use of regular theophylline at clinically recommended dosage did not change FEV₁ or PC₂₀ to histamine significantly, nor did it affect the loss of bronchoprotection as occurred during salmeterol treatment. This indicates that theophylline cannot be used to preserve the physiological responses to long-acting β₂-adrenoceptor agonists in asthma.

To our knowledge, this is the first study on the effects of regular theophylline on the development of tolerance for the bronchoprotective effects of a long-acting β₂-adrenoceptor ag-
PC20 after 4 d theophylline or placebo (p

Figure 2. Airway responsiveness to histamine (PC20, geometric mean ± SEM) in the baseline period, during monotherapy with theophylline or placebo (Day 4), and 1 h after inhalation of the salmeterol (arrow) at Days 8, 22, and 36 during the addition of regular salmeterol to theophylline or placebo treatment, and during theophylline or placebo treatment after cessation of regular salmeterol treatment (Day 40). Placebo group (open circles) and theophylline group (closed circles). There was no significant change in PC20 after 4 d theophylline or placebo (p > 0.15). Single-dose salmeterol led to a significant increase in PC20 in both groups at Day 8. However, there was a significant reduction in the protective effect of salmeterol on the PC20 to histamine after 2 and 4 wk of regular salmeterol treatment in either group (p < 0.002). However, these changes were not significantly different between the groups (p > 0.80).

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Our findings confirm that regular use of β2-adrenoceptor agonists in asthmatic subjects in vivo. Our findings confirm that regular use of β2-adrenoceptor agonists in asthmatic subjects results in a tolerance to the degree of protection against bronchoconstrictor stimuli, without affecting the bronchodilatory properties (3, 5). They also confirm that regular theophylline alone does not change airway responsiveness to histamine (21–24). A parently, the functional antagonism (25) and/or the potentially anti-inflammatory properties by theophylline (26) are insufficient to provide for acute or long-term protection against exogenous histamine. The absence of interaction of theophylline and salmeterol on bronchoprotective effects in vivo is a new finding, and resembles the observations with the combination of inhaled corticosteroids and long-acting β2-adrenoceptor agonists (14, 15, 27).

Our findings might have been influenced by the present methodology, such as subject selection, study design, and methods of measurements. First, as others we purposely selected asthmatics with mild to moderate airway hyperresponsiveness (3, 5–9). They were controlled by inhaled short-acting β2-agonist on demand only, which is considered not to modify disease severity (28). This patient selection enabled us to document the interaction between the two study drugs on airway hyperresponsiveness, without conflicting other drugs. Second, the present results were obtained using validated methodology (5). The study design was developed in order to allow inferences on any acute or sustained effects of theophylline and their interaction with the previously established tolerance to salmeterol. The dose of theophylline was chosen to obtain serum levels (around 10 mg/L) within the therapeutic range regarding its bronchodilatory and/or presumed anti-inflammatory effects (26, 29). The failure to prevent tolerance does not seem to be due to the dose of theophylline because there was no significant correlation between the theophylline dose and the decline in protection afforded by salmeterol. Similarly, the dose of salmeterol was comparable to previous studies (5, 7, 8). To be sure that FEV1 and PC20 were not influenced by remaining pharmacologic activity of the regular medication with salmeterol in the treatment period, salmeterol treatment was interrupted before each measurement (5) for at least its known duration of action on lung function and airway responsiveness (30). In addition, the acute effects of salmeterol were always measured after administration by the investigator in the laboratory.

Several studies have shown that tolerance develops to the protective effects of β2-adrenoceptor agonist against bronchoconstrictor stimuli with both short-acting and long-acting β2-adrenoceptor agonist (3, 5–9). This occurs to stimuli acting directly on airway smooth muscle, such as histamine (8), or methacholine (5), as well as to indirectly acting stimuli such as allergen (6), exercise (7), or adenosine monophosphate (3). This is likely to be due to β2-adrenoceptor uncoupling or downregulation (31, 32). There are indications that the longer duration of receptor occupancy produced by a long-acting β2-adrenoceptor agonist induces greater β2-adrenoceptor dysfunction (3). In a cross-sectional study without intervention, it appeared that asthmatic children treated with β2-adrenoceptor agonists alone had reduced density with unaltered affinity of β2-adrenoceptors on their polymorphonuclear leukocytes ex vivo (16). In those children with concurrent theophylline treatment such reduction in β2-adrenoceptor density was not apparent, while children on theophylline alone even showed increased receptor density (16). Even though these data do not arise from blinded intervention studies, they may suggest an interaction between theophylline and β2-adrenoceptor agonists regarding the cellular expression of β2-adrenoceptors. It is not unlikely that such interaction could occur at the level of cyclic 3′5′-adenosine monophosphate (cAMP) and the cAMP response element binding protein (CREB) (32–34). It could be hypothesized that theophylline, by its inhibition of phosphodiesterases (e.g., PDE III and IV), increases CREB and thereby the transcription of the β2-adrenoceptor gene (32, 34). Our study was not designed to examine such a possibility, but apparently, β2-adrenoceptor function in vivo remained unaltered by theophylline in asthmatics. The alternative possibility is that the potential beneficial effect of theophylline on β2-adrenoceptor density is abolished during long-term treatment, because prolonged theophylline-induced elevation of cAMP may lead to further β2-adrenoceptor uncoupling and thereby to reduced CREB activity and β2-adrenoceptor gene transcription (32). Obviously, these interactive mechanisms require further exploration.

What are the clinical implications of our findings? Our failure to prevent the development of tolerance to the bronchoprotective effect of β2-adrenoceptor agonist by theophylline extends similar observations with inhaled corticosteroids (14, 15, 27). Apparently, theophylline as a widely used anti-asthma drug (35) is also not able to prevent such tolerance. Even though the clinical significance of tolerance to the bronchoprotective effects by regular β2-adrenoceptor agonists remains to be established, its persistence with any concurrent medication so far should be taken into consideration by clinicians treating patients with asthma. Potential hazards of the observed tolerance cannot be excluded in those patients at the severe end of the clinical spectrum (10, 11, 36), who indeed may have periods of combined treatment with long-acting β2-
adrenoceptor agonists and theophylline (1). Therefore, other drugs such as oral steroids (37) need also to be examined regarding their potential to restore the bronchoprotective effects of β2-adrenoceptor agonists in asthma.

References