The role of thromboxane in allergen-induced asthmatic responses

P.J. Manning, W.H. Stevens, D.W. Cockcroft, P.M. O'Byrne

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ABSTRACT: In this study we evaluated the role of thromboxane in causing allergen-induced early and late asthmatic responses and airway hyperresponsiveness in asthmatic subjects. Twelve atopic subjects with stable asthma and documented early and late asthmatic responses to an inhaled allergen were treated with placebo or CGS 13080, a specific thromboxane synthetase inhibitor, given orally (200 mg four times daily) for two days before, the day of, and the day after allergen inhalation. Treatments were administered in a double-blind, placebo-controlled, crossover fashion. The effect of pretreatment with CGS 13080 was examined on serum TxB_2 levels and the magnitude of the asthmatic responses after inhaled allergen. Serum TxB_2 levels increased significantly from 96 $ng \cdot ml^{-1}$ (sem 29) 3 h after diluent to 151 $ng \cdot ml^{-1}$ (sem 27) 3 h after allergen (p=0.008). CGS 13080 pretreatment markedly inhibited the levels of TxB_2 at all time points before and after inhaled allergen (p=0.0001) and had a small but significant effect on the magnitude of the early asthmatic responses after allergen (p=0.0009). CGS 13080 did not alter either late asthmatic responses, baseline airway responsiveness, or the increase in histamine airway responsiveness after allergen. These results suggest that allergen-induced early asthmatic responses, but not late responses or allergen-induced airway hyperresponsiveness, are partly caused by thromboxane release.
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Inhaled allergen is an important cause of asthma in clinical practice. In the laboratory, allergen inhalation tests are a useful tool for investigating allergen-induced asthmatic responses. Allergen inhalation causes airway narrowing, usually within 15 min, in sensitized subjects. This early asthmatic response resolves within 2–3 h. In 50% of adult subjects exposed to allergen, a late bronchoconstrictor response, which begins 3–4 h after allergen inhalation, also occurs [1]. The late asthmatic response is more prolonged than the early response and is associated with airway hyperresponsiveness to bronchoconstrictor stimuli such as histamine or methacholine [2], which can last for days or weeks following allergen exposure [3].

The precise mechanisms for the development of the airway responses following inhaled allergen are unclear. The early asthmatic response is believed to occur because of the release of bronchoconstrictor mediators such as histamine [4], the sulphidopeptide leukotrienes [5, 6] and thromboxane [7, 8]. The late response and subsequent airway hyperresponsiveness is associated with an acute inflammatory response, as

measured by the influx of inflammatory cells, such as eosinophils [9], into the airways.

Thromboxane may also be involved in the pathogenesis of airway hyperresponsiveness after allergen inhalation. Studies in dogs have demonstrated that pretreatment with a thromboxane synthetase inhibitor, OKY 046, prevents the development of airway hyperresponsiveness after allergen inhalation [10]. OKY 046 also prevents the development of airway hyperresponsiveness following inhaled leukotriene B_4 [11] and ozone exposure [12] in dogs. In addition, indomethacin, an inhibitor of cyclooxygenase and therefore of thromboxane and prostaglandin synthesis, inhibits the development of airway hyperresponsiveness following allergen in allergic sheep [13] and in human subjects [14].

The purpose of this study was to evaluate the possible role of thromboxane in causing allergen-induced asthmatic responses. This was done by examining the effects of a specific thromboxane synthetase inhibitor, CGS 13080 (imidazo [1, 5–2] pyridine-5-hexanoic acid) [15], on levels of serum thromboxane B_2 (TxB_2), which

is the spontaneous hydrolytic product of thromboxane A_2, and on the development of asthmatic responses after inhaled allergen.

Methods

Subjects

Twelve subjects were studied in the clinical research laboratories of McMaster University Medical Center, Hamilton and Section of Respiratory Medicine, University Hospital, Saskatoon, Canada (table 1). All the subjects had a history of current or previous asthma, and all had previously documented early and late asthmatic responses and increased airway responsiveness following exposure to inhaled allergen. The baseline forced expired volume in 1 s (FEV_1) was >75% predicted normal [16] in all subjects on all study days (table 1). All the subjects were atopic, as determined by 1 or more positive responses to skin prick tests with 16 common allergens. The subjects with current or seasonal asthma were studied when their asthma was mild and controlled by inhaled β_2–agonists alone, with no exacerbations of asthma for at least four weeks. There was no current exposure to allergens to which subjects were sensitized, except for house dust mite. The study was approved by each hospital's Ethics Committee and subjects gave written informed consent before beginning the study.

Table 1. – Subjects characteristics

Subject	Age	Sex	Allergen	Medications
1	46	F	D. Farinae	S not daily
2	36	M	D. Farinae	S not daily
3	34	F	D. Farinae	S not daily
4	23	F	D. Farinae	S not daily
5	37	F	D. Farinae	nil
6	23	M	D. Farinae	nil
7	25	F	Ragweed	S not daily
8	23	M	Ragweed	nil
9	25	F	Cat dander	S not daily
10	30	M	Cat dander	S not daily
11	42	M	Grass pollen	S not daily
12	21	M	Tree pollen	nil

S: Salbutamol

Study Design

Subjects attended the laboratory on 9 study days divided into three periods. In the first period, subject characteristics were documented and a diluent inhalation test with saline was performed. The second and third study periods were similar to the saline day except that allergen replaced saline as the inhalation test. In addition, two histamine inhalation tests were carried out, the initial one on the day prior to and the second one on the day after the allergen test in order to document the change in airway responsiveness following allergen exposure.

During the second and third study periods, subjects were pretreated with either the thromboxane synthetase inhibitor CGS 13080 200 mg or placebo administered orally four times daily for two days before, the day of, and the day after allergen inhalation. The allergen inhalation tests were carried out 1 h following a dose of medication. The study was double-blinded, randomized, with a crossover design.

The response to inhaled allergen is determined, in part, by the level of airway responsiveness, therefore each study period was started only when airway responsiveness to histamine had returned to within a single doubling concentration of the initial baseline value. Inhaled β_2-agonists were withheld for at least 8 h before either the histamine or the allergen inhalation tests.

Histamine inhalation tests

This test was carried out by the method of COCKCROFT et al. [17] using a Wright nebulizer with an output of 0.13 ml·min^{-1}. After nebulization of saline, increasing doubling concentrations of histamine phosphate were inhaled until a 20% fall in FEV_1 was obtained. Dose-response curves were drawn on a semilogarithmic non-cumulative scale. The concentration causing a 20% fall in FEV_1 (PC_{20}) was interpolated from the individual dose response curves.

Allergen Inhalation Tests

Allergen inhalation tests were performed as previously described [1] using a Wright nebulizer with an output of 0.13 ml·min^{-1}. The nose was clipped and aerosols were inhaled through a mouth piece during tidal breathing. The starting concentration of inhaled allergen extract was determined from prick tests with the same extract and the histamine PC_{20} in the entry period, using the formula described by COCKCROFT et al. [18]. This starting concentration was two doubling concentrations below that predicted to cause a 20% fall in FEV_1. Doubling concentrations of allergen were inhaled for 2 min and the FEV_1 was measured 10 min after each inhalation. If the FEV_1 had fallen by 15% or more, the FEV_1 was repeated at 10 minute intervals until no further fall in FEV_1 was observed. The FEV_1 was then measured at 20, 30, 45, 60, 90 and 120 min and then at hourly intervals until 7 h after the inhalation.

The house dust mite, tree and grass pollen allergen extracts were obtained from Miles/Hollister-Stier, Mississagua, Ontario and the ragweed and cat dander extracts were obtained from Dr. Jerry Dolovich, Hamilton, Ontario. Extracts were stored at -70°C and diluted for skin tests and allergen inhalation on the day of use.

Diluent Inhalation Tests

Diluent inhalation tests were performed in a similar manner to the allergen and the same Wright nebulizer was used. Subjects inhaled diluent (phosphate buffered

saline with 1.5% benzyl alcohol) for 2 min on 3 occasions 10 min apart. Each inhalation was followed by measurements of FEV_1 using the same schedule followed during the allergen inhalation tests.

Serum Thromboxane B_2 measurements

Five ml of blood was collected in a glass tube containing no anticoagulant. Four samples were obtained on each study day, just prior to and 3, 7 and 24 h following the saline or allergen inhalation tests. The blood samples were incubated in a water bath for 1 h at 37°C. The samples were then centrifuged at 2000 g for 15 min to separate serum from the clot. The serum was then aspirated into a polypropylene tube and frozen at -70°C until analysis using the radioimmunoassay method as previously described [15]. The radioimmunoassays were performed blinded by Ciba-Geigy, New Jersey.

Analysis

The effect of CGS 13080 was compared with placebo on the levels of serum TxB_2, baseline airway calibre as measured by FEV_1, histamine airway responsiveness, allergen-induced early and late asthmatic responses and allergen-induced increases in histamine airway responsiveness.

All analysis of the histamine PC_{20}s were performed on log transformed data and therefore summary statistics are expressed as geometric mean and percent standard error of the mean (%SEM). All other summary statistics are expressed as mean and standard error of the mean. The bronchoconstrictor responses during the early (0–1 h) and late (3–7 h) asthmatic responses, and the serum thromboxane B_2 levels on the saline, placebo and CGS 13080 study days were compared using two way ANOVA.

The comparison of the log difference (the arithmetic ratio) of histamine PC_{20} before and 24 h after allergen in both study periods is the appropriate assessment of placebo and CGS 13080 pretreatment on changes in airway responsiveness after allergen. A log difference of 0 signifies no change in airway responsiveness. The effect of CGS 13080 and placebo on baseline histamine responsiveness and on the increases in histamine responsiveness after allergen were compared using two-tailed Student t-tests for paired observations. Statistical significance was accepted at the 95% level.

Results

Treatment with the thromboxane synthetase inhibitor, CGS 13080 had a small but statistically significant effect on the magnitude of the early asthmatic responses after inhaled allergen (fig. 1). There was significantly less bronchoconstriction at all time points up to 1 h after allergen during CGS 13080 treatment when compared to the bronchoconstriction after allergen

during placebo treatment (p=0.0009). The mean maximal early fall in FEV_1 during the first hour after allergen during placebo treatment was 27% (SEM 3.9%) compared to 21% (SEM 3.3%) after allergen during CGS 13080 treatment.
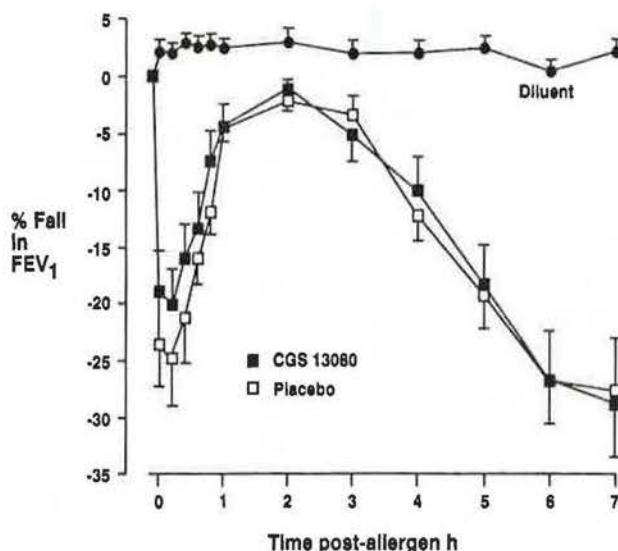

Fig. 1. – The mean fall in forced expiratory volume in one second (FEV_1) after inhaled diluent (solid circles) and during the early and late asthmatic response after inhaled allergen after placebo (open squares) and CGS 13080 (closed squares) pretreatment. CGS 13080 had a small but statistically significant effect on the magnitude of the early but not the late asthmatic responses.

CGS treatment did not alter the late asthmatic response, baseline FEV_1, baseline histamine airway responsiveness, or the increase in histamine airway responsiveness after inhaled allergen. There was no significant difference in the bronchoconstriction at all time points between 3–7 h following allergen after CGS 13080 treatment when compared to the bronchoconstriction following allergen after placebo (p=0.95) (fig. 1). The mean maximal late fall in FEV_1 between 3–7 h after placebo was 28% (SEM 4.7%) and after CGS 13080 was 29% (SEM 4.6%). The mean baseline FEV_1 values before and after 2 days of CGS 13080 were 3.26 l (SEM 0.23) and 3.32 l (SEM 0.23) (p=0.73). The mean histamine PC_{20} during the placebo period was 3.22 mg·ml^{-1} (%SEM 1.36) and during the CGS 13080 period was 2.64 mg·ml^{-1} (%SEM 1.31) (p=0.33). Following allergen inhalation during the placebo period the mean histamine PC_{20} decreased to 1.25 mg·ml^{-1} (%SEM 1.37) (p<0.0001) and during the CGS 13080 period decreased to 1.11 mg·ml^{-1}(%SEM 1.32) (p=0.003) (fig. 2). The mean log difference of the histamine PC_{20} pre-post allergen was 0.41 (SEM 0.06) during the placebo period and 0.38 (SEM 0.10) during CGS 13080 treatment (P=0.73).

On placebo treatment, a small, but not statistically significant, increase in serum TxB_2 levels occurred 3 h after allergen inhalation when compared to the pre-allergen baseline levels (p=0.07); however, when

compared to the levels at 3 h after the diluent inhalation, the increase was significant. The mean levels were 151 $ng \cdot ml^{-1}$ (SEM 27.4) 3 h after allergen compared to 96 $ng \cdot ml^{-1}$ (SEM 28.4) 3 h after diluent (p=0.008) (fig. 3).
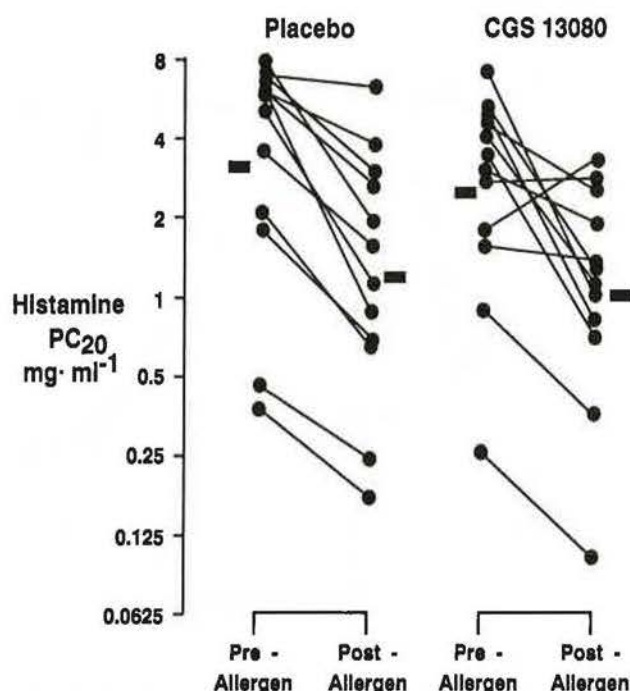

Fig. 2. – Airway responsiveness to inhaled histamine, expressed as the histamine concentration causing a 20% fall in forced expiratory volume in one second (PC_{20}), measured the day before and the day after allergen inhalation during placebo and CGS 13080 pretreatment. Allergen inhalation increased histamine airway responsiveness, which was not inhibited by CGS 13080 pretreatment.
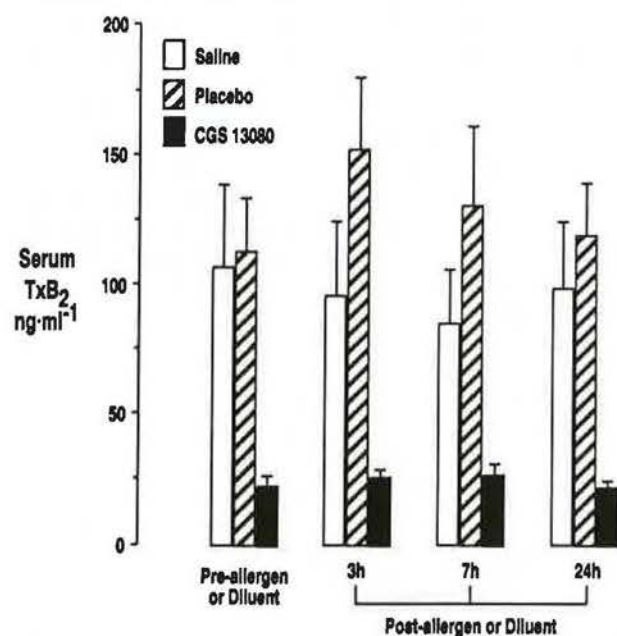

Fig. 3. – Serum thromboxane B_2 (TxB_2) levels measured before, and at 3 h, 7 h and 24 h after inhalation of diluent (open bars) and after inhalation of allergen after placebo (hatched bars) CGS 13080 (closed bars) pretreatment. Serum TxB_2 levels increased at 3 h after allergen compared to diluent. CGS 13080 pretreatment inhibited the serum TxB_2 levels.

At 7 h, the TxB_2 levels were again slightly, but not significantly, increased after allergen at 130 $ng \cdot ml^{-1}$ (SEM 30.5) compared to 85 $ng \cdot ml^{-1}$ (SEM 21.0) after diluent at the same time point (p=0.10). No other significant differences in serum TxB_2 levels were demonstrated either at baseline or at the other time points following allergen exposure during the placebo period (fig. 3).

CGS 13080 significantly inhibited the baseline TxB_2 levels and the levels at all time points after inhaled allergen (fig. 3). The mean TxB_2 levels during CGS 13080 treatment, 3 h after allergen, were 25 $ng \cdot ml^{-1}$ (SEM 10.2), which was significantly different to the values 3 h after allergen during placebo treatment (p=0.0001).

Discussion

This study has demonstrated that serum TxB_2 levels increase following the early asthmatic response to inhaled allergen in subjects with mild asthma. These increases in thromboxane are prevented by treatment with CGS 13080, a thromboxane synthetase inhibitor, which also partially inhibits the early asthmatic response. CGS 13080 did not however influence either the late asthmatic response or the airway hyperresponsiveness following allergen stimulation. These results suggest that thromboxane is in part responsible for the bronchoconstriction which occurs during the early response after inhaled allergen but is not responsible for the late asthmatic response or the airway hyperresponsiveness after inhaled allergen.

TxA_2 has a short half-life of approximately 30 s. In this study, we measured serum TxB_2, which is the spontaneous hydrolytic product of TxA_2, before, during and after the allergic responses mainly to evaluate patient compliance in taking the study drug, which should reduce serum TxB_2 levels [15], and to ensure the inhibition of thromboxane synthesis persisted during all of the physiologic measurements. To this end, the measurements of serum TxB_2 after allergen were made at 3 h, 7 h and at 24 h. The finding of increased serum TxB_2 levels following the early asthmatic response confirms observations of SHEPHARD et al. [19], who demonstrated increased plasma TxB_2 levels after allergen inhalation in asthmatic subjects, with peak levels between 45 min to 2 h after allergen. It is likely, therefore, that we missed the peak increases in serum TxB_2 after allergen inhalation in this study. Despite this, a significant increase was demonstrated after the early response at 3 h, when compared to the levels measured after diluent inhalation. The comparison between the serum TxB_2 levels measured after allergen inhalation and diluent inhalation was made to ensure the levels were measured at the same time of day and after a similar number of forced expiration manoeuvres. These results support other studies which have indicated that serum TxB_2 is increased after allergen inhalation [19]. However, it is likely that these levels reflect the capacity of platelets to release thromboxane ex vivo [20], rather than thromboxane release in the lungs as part of an allergic response. Thus the increased serum TxB_2

levels after allergen inhalation may be a marker of platelet activation, which has been described after allergen inhalation [21].

CGS 13080, the thromboxane synthetase inhibitor used in this study, is highly selective and potent in human subjects [15, 22], with 99% maximal inhibition of thromboxane production with lower doses than were used in the current study [15]. Consistent with this evidence, CGS 13080 treatment effectively inhibited both the pre-allergen basal serum levels of TxB_2 and also the rise in serum TxB_2 after inhaled allergen in this study. The extent of the inhibition (approximately 80%) was less than previously reported with this inhibitor [15]; however, inhibition occurred in all subjects through the active treatment period, indicating compliance with the study medication. CGS 13080 treatment also partially inhibited the magnitude of the early bronchoconstrictor response to allergen (mean 22% inhibition), presumably due to inhibition of thromboxane release. However, there is evidence that during thromboxane synthetase inhibition, endoperoxides are shunted into the production of prostacyclin [15, 22] and prostaglandin E_2 [15]. Therefore, the inhibition of the early asthmatic response could occur through production of these inhibitory prostanoids. However, BEASLEY et al. [7] showed a similar degree of inhibition (mean 23.6%) of the early asthmatic response to inhaled allergen following treatment with a thromboxane receptor antagonist. This thromboxane antagonist would not cause shunting of endoperoxides. The results of these studies support a role for thromboxane playing a small role in the bronchoconstriction which occurs during the first hour after inhaled allergen. Clearly, other bronchoconstrictor mediators, for example the sulphidopeptide leukotrienes [5, 6], are playing a much greater part in causing this response.

Thromboxane does not appear to be important in causing the physiologic manifestations of the late asthmatic response or airway hyperresponsiveness after allergen. We could not demonstrate a significant increase in serum thromboxane during the late asthmatic response, which is consistent with the findings of SHEPHARD et al. [8]. Also, CGS 13080 did not influence the magnitude of the late response. An important role for thromboxane in the pathogenesis of allergen-induced airway hyperresponsiveness has been suggested by studies which have demonstrated in dogs that OKY 046, a thromboxane-synthetase inhibitor, prevents allergen-induced airway hyperresponsiveness [10]. In addition, OKY 046 also prevents ozone [12], platelet activating factor [23] and leukotriene B_4-induced airway hyperresponsiveness [11]. Also, the cyclooxygenase-inhibitor, indomethacin, inhibits the development of allergen-induced airway hyperresponsiveness in sheep [13] and humans [14], which has suggested that a cyclooxygenase product of arachidonate metabolism is involved. The current study suggests that thromboxane is not the cyclooxygenase product involved in causing allergen-induced airway hyperresponsiveness.

Indomethacin is a potent inhibitor of cyclooxygenase and therefore inhibits thromboxane production.

However, neither we [14], nor others [8, 24], have been able to demonstrate inhibition of the early asthmatic response in asthmatic subjects by indomethacin pretreatment. These results suggest that either indomethacin is not an effective inhibitor of thromboxane production in the lungs, or that the bronchoconstriction after inhaled allergen is both stimulated and inhibited by different cyclooxygenase products, or that indomethacin allows shunting of arachidonate into the production of the bronchoconstrictor sulphidopeptide leukotrienes. Support for the latter hypothesis comes from studies by FISH et al. [24], who demonstrated that indomethacin enhanced the bronchoconstrictor responses to inhaled allergen in nonasthmatic, atopic subjects, which suggests that indomethacin can promote the production of bronchoconstrictor mediators after allergen. Also, in sheep, treatment with indomethacin enhances the production of leukotrienes [25]; however these same investigators could not find evidence for this effect of cyclooxygenase inhibition after allergen challenge in human subjects [26].

CGS 13080 pretreatment administered orally did not inhibit baseline airway calibre, as measured by the FEV_1, or baseline pre-allergen histamine airway responsiveness. This suggests that thromboxane is not an important mediator in controlling baseline airway function. These results differ from those of FUJIMURA et al. [27], who demonstrated a significant reduction in acetylcholine airway responsiveness following oral treatment with the thromboxane synthetase inhibitor, OKY 046. The reason for these differences is not clear but may be due to differences in the pharmacological profile of the drugs used, in the subjects studied, or in the fact that different bronchoconstrictor agonists were used.

In summary, the results from this study suggest that thromboxane is, in part, responsible for the early but not the late asthmatic responses nor the airway hyperresponsiveness after inhaled allergen in asthmatic subjects.

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Rôle du thromboxane dans les réponses asthmatiques après provocation allergénique. P.J. Manning, W.H. Stevens, D.W. Cockcroft, P.M. O'Byrne.

RÉSUMÉ: Dans cette étude, nous avons évalué rôle du thromboxane dans les réponses asthmatiques précoces et tardives induites par les allergènes, et dans l'hyperréactivité bronchique des sujets asthmatiques. Douze sujets atopiques avec un asthme stable et des réponses précoces et tardives documentées à un allergène inhalé, ont été traités par un placebo ou par le CGS 13080, un inhibiteur spécifique du thromboxane synthetase, administré par voie orale à raison de 200 mg 4 fois par jour au cours des deux journées précédant l'inhalation d'allergène, le jour de cette provocation, et le jour suivant. Les traitements ont été administrés avec permutation croisée au cours d'un essai en double anonymat avec contrôle par placebo. L'effet du pré-traitement au CGS 13080 a été examiné à la fois sur les niveaux de TxB₂, sériques et sur l'amplitude des réactions asthmatiques après inhalation de l'allergène. Les niveaux de TxB₂ ont augmenté significativement de 96 ng·ml⁻¹ (SEM 29) 3 heures après l'inhalation de l'agent diluant, jusqu'à 151 ng·ml⁻¹ (SEM 27) 3 heures après l'inhalation de l'allergène (p=0.008). Un pré-traitement au moyen de CGS 13080 a inhibé considérablement les niveaux de TxB₂ à tous les moments avant et après l'inhalation de l'allergène (p=0.0001) et a eu un effet léger sur l'amplitude des réactions asthmatiques précoces après allergène (p=0.0009). CGS 13080 n'a modifié, ni la réaction asthmatique tardive, ni la réactivité bronchique de base, ni l'augmentation de la réactivité des voies aériennes à l'histamine après provocation allergénique. Ces résultats suggèrent que les réactions asthmatiques précoces induites par les allergènes, mais non les réactions tardives ou l'hyperréactivité d'origine allergénique, sont partiellement causées par la libération de thromboxane.
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