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Effects of a cyclo-oxygenase inhibitor, flurbiprofen, and an H_1 histamine receptor antagonist, terfenadine, alone and in combination on allergen induced immediate bronchoconstriction in man

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ABSTRACT The effect of flurbiprofen, a potent cyclo-oxygenase inhibitor, on histamine and methacholine reactivity was assessed in seven atopic subjects with asthma. Flurbiprofen 150 mg daily for three days displaced the histamine-FEV_1 concentration-response curve to the right by 1·5 doubling doses, whereas no effect was observed on the response to methacholine. Subsequently the effects of flurbiprofen and terfenadine, a specific H_1 histamine receptor antagonist, on allergen induced bronchoconstriction were studied in seven atopic but non-asthmatic subjects. The subjects inhaled the concentration of grass pollen allergen that had previously been shown to produce a 20% fall in FEV_1 on separate occasions after prior treatment with placebo, flurbiprofen 150 mg daily for three days, terfenadine 180 mg three hours before challenge, and the combination of flurbiprofen and terfenadine. After placebo, allergen challenge caused a mean (SEM) maximum fall in FEV_1 of 37·6% (2·6%) after 20 (3·7) minutes, followed by a gradual recovery to within 15% of baseline at 60 minutes. Terfenadine reduced the maximum allergen provoked fall in FEV_1 to 21·5% (2·2%) and reduced the area under the time-response curve (AUC) by 50% (6%). Flurbiprofen alone reduced the mean maximum fall in FEV_1 to 29·6% (3·2%) and reduced the AUC by 26%. The effect of the combination of flurbiprofen and terfenadine did not differ significantly from that of terfenadine alone. We conclude that histamine and prostaglandins contribute to immediate allergen induced bronchoconstriction and that a complex interaction occurs between the two classes of mediators.

Introduction

In individuals with atopic asthma the magnitude of the airway response to inhaled allergen is a function of mediator release and non-specific bronchial responsiveness.[1] In subjects with mild asthma allergen provocation sufficient to cause bronchoconstriction is accompanied by release into the circulation of the mast cell associated mediators, histamine and high molecular weight neutrophil chemotactic factor,[2] and the secondary mediators, 13,14-dihydro-15-keto-prostaglandin $F_{2\alpha}$,[3] thromboxane B_2,[4] and platelet factor 4.[5] Sodium cromoglycate inhibits allergen provoked bronchoconstriction[6] and attenuates the increase in circulating concentrations of histamine and neutrophil chemotactic factor,[2] implying a role for the mast cell in mediating the response.

Immunoglobulin E dependent activation of mast cells dispersed from human lung tissue[7] or obtained by bronchoalveolar lavage[8] releases both granule derived mediators and newly formed products from the cyclo-oxygenation and 5-lipoxygenation of arachidonic acid. Prostaglandin D_2, the major cyclo-oxygenase product released from human mast cells,[9] is a potent bronchoconstrictor in asthma.[10] The contribution of individual mediators to allergen induced bronchoconstriction can be investigated by using specific pharmacological agents that inhibit synthesis of the mediator or specifically antagonise its effects on target tissues. In this study we have investigated the effect of

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terfenadine, a potent and highly selective H_1 histamine receptor antagonist, and flurbiprofen, a cyclo-oxygenase inhibitor at least 5000 times more potent than aspirin,[11] on histamine and allergen induced bronchoconstriction and skin weal and flare responses in atopic subjects. Flurbiprofen and terfenadine were observed alone and in combination to examine the relative contributions of histamine and prostaglandins to the allergen response in the skin and airways.

Methods

The study was undertaken in two stages. Firstly, the influence of flurbiprofen on the airway response to histamine and methacholine was assessed in seven atopic patients with mild asthma. The subjects were aged 21–44 years and had a mean FEV_1 of 91·7% (SEM 7·2%) predicted, and their asthma was controlled with inhaled β_2-adrenoreceptor agonists alone. Since flurbiprofen was shown to reduce airway responsiveness to histamine in these subjects, a second study was carried out on seven atopic but non-asthmatic subjects (aged 21–25 years), none of whom had a 20% fall in FEV_1 after inhaling histamine at a concentration of 32 mg/ml. None of the subjects in either study was taking oral or inhaled corticosteroids, sodium cromoglycate, theophylline, or antihistamines, and none had a history of analgesia induced asthma, upper gastrointestinal ulceration, or dyspepsia. Both studies were approved by the Southampton Hospitals and University Ethical Committee, and informed consent was obtained from each subject.

STUDY 1: EFFECT OF FLURBIPROFEN ON HISTAMINE AND METHACHOLINE RESPONSIVENESS IN ATOPIC ASTHMATIC SUBJECTS

Each subject was given a test dose of 50 mg flurbiprofen under supervision and the forced expiratory volume in one second (FEV_1) was recorded every 15 minutes for 90 minutes to detect any adverse response to flurbiprofen. Each patient then underwent an inhaled histamine or methacholine concentration-response challenge on four separate days at least 10 days apart after prior treatment with flurbiprofen 50 mg three times daily for three days or matched placebo. Aerosols of histamine and methacholine were generated with an Inspiron Mini-neb nebuliser with the specifications described below. Increasing doubling concentrations of agonist were inhaled at five minute intervals, FEV_1 being measured three minutes after each inhalation. The study was stopped when the FEV_1 had fallen by 20% from the postsaline baseline value.

STUDY 2: EFFECT OF TERFENADINE AND FLURBIPROFEN ON THE AIRWAY RESPONSE TO ALLERGEN IN ATOPIC NON-ASTHMATIC SUBJECTS

Each subject initially underwent an inhalation challenge test to determine the concentration of allergen required to provoke a 30% fall in FEV_1 nine minutes after challenge. Allergen solutions were prepared from a 6% stock solution of mixed grass pollen extract (group B2, Bencard, Brentford, Middlesex) to produce a range of concentrations from 10^{-6} to $10^{-1} \times 6$ mg/ml. All solutions were nebulised from a starting volume of 2 ml in an Inspiron nebuliser (CR Bard International, Pennywell Industrial Estate, Sunderland) driven by compressed air at 8 l/min^{-1}. Allergen challenge was performed using a method modified from that described by Chai *et al.*[12] Subjects were instructed to inhale five breaths of each solution from end tidal volume to total lung capacity. After baseline FEV_1 had been recorded five breaths of nebulised saline were inhaled and FEV_1 recorded after two minutes. If the FEV_1 did not fall by more than 10% from the starting baseline, allergen challenge was undertaken with 10-fold increasing concentrations of grass pollen or house dust mite allergen and FEV_1 measurements recorded two and nine minutes after each inhalation. If less than a 15% fall from the control FEV_1 occurred nine minutes after the first allergen solution the next dilution was given. If the FEV_1 fell by more than 15% but less than 30%, double the concentration of allergen was administered in the subsequent challenge. The procedure was discontinued when the FEV_1 had fallen by 30% from the postsaline baseline and this concentration of allergen (PC_{30} FEV_1) was used in subsequent single dose allergen time course studies.

On four subsequent occasions, separated by at least 10 days, single dose inhalation challenges carried out with the PC_{30} FEV_1 concentrations of allergen after prior treatment with flurbiprofen 50 mg three times daily for three days, terfenadine 180 mg three hours before challenge, or matched placebos. Subjects received, single blind and in random order. (*a*) flurbiprofen and placebo; (*b*) terfenadine and placebo; (*c*) flurbiprofen and terfenadine; (*d*) double placebo. FEV_1 was recorded before and two minutes after inhalation of nebulised 0·9% saline. If the FEV_1 after saline had not fallen by 10% from baseline, the PC_{30} concentration of allergen was administered and the FEV_1 recorded at regular intervals for one hour after challenge.

Histamine and allergen dose-response curves were also constructed for the skin at each visit, by means of intradermal injections of histamine acid phosphate (4–128 mg/ml) and six concentrations of grass pollen allergen ($1–10^{-6} \times 6$ mg/ml). A standardised skinprick

procedure was used and the area of each weal was measured after 10 minutes by planimetry.

DATA ANALYSIS

Baseline FEV_1 values obtained before histamine or methacholine challenge after flurbiprofen or placebo pretreatment were analysed with Student's t test for paired data. The percentage change in FEV_1 from the postsaline FEV_1 was plotted against each concentration of histamine or methacholine. The provocation concentration of each agonist causing a 20% fall in FEV_1 (PC_{20}) was derived from the concentration-response curve by linear interpolation. The logarithmic Pc_{20} values for histamine and methacholine were compared after flurbiprofen and placebo by means of Student's t test for paired data, and after each treatment the geometric mean PC_{20} values for histamine and methacholine were calculated.

For study 2 the FEV_1 response to allergen challenge on the four treatment days, expressed as a percentage of the postsaline baseline value, was plotted against time. The area under the curve (AUC)—that is, the time-response curve for FEV_1 and baseline FEV_1—was calculated by trapezoid integration and expressed as a percentage of the area obtained after placebo. Linear regression analysis was used to assess the rate of fall in FEV_1 in the first nine minutes after allergen challenge and the rate of recovery during the last 30 minutes of the study. Analyses of variance and the Newman-Keuls procedure were used to analyse differences in baseline FEV_1 values, the maximum fall in FEV_1 after allergen challenge, the slope of the fall in FEV_1, the slope of the subsequent rise in FEV_1, the AUC, and changes in skin weal area after the various treatment combinations.

Results

STUDY 1: EFFECT OF FLURBIPROFEN ON HISTAMINE AND METHACHOLINE RESPONSIVENESS IN ATOPIC ASTHMATIC SUBJECTS

There was no significant difference between baseline levels of FEV_1 after placebo and after flurbiprofen (table). After both placebo and flurbiprofen methecholine and histamine caused concentration related falls in FEV_1 in all subjects. After placebo the geometric mean PC_{20} for methacholine, 0·69 (range 0·23–1·76) mg/ml, did not differ significantly from that after flurbiprofen, 0·89 (0·12–2·8) mg/ml. Flurbiprofen, however, caused an increase in the geometric mean PC_{20} histamine from 0·56 (0·33–1·07) to 1·82 (0·42–8·19) mg/ml by comparison with placebo ($p < 0·01$).

STUDY 2: EFFECT OF FLURBIPROFEN AND TERFENADINE ON ALLERGEN INDUCED BRONCHOCONSTRICTION IN ATOPIC NON-ASTHMATIC SUBJECTS

There was no difference in baseline FEV_1 values between the four treatment days (table). After placebo allergen inhalation produced a mean maximum fall in FEV_1 of 37·6% (SEM 2·6%) in the first 15–20 minutes, followed by a gradual recovery to within 15% of baseline at 60 minutes (figure). After terfenadine (180 mg) the initial decline in FEV_1 with inhaled allergen was slower than that after placebo ($p < 0·01$) and the maximum fall of 21·5% (2·2%) was significantly less than that achieved after placebo ($p < 0·01$). Terfenadine had a maximum inhibitory effect during the first 15 minutes of challenge, with diminishing effect thereafter. Recovery of FEV_1 occurred in parallel to that of placebo.

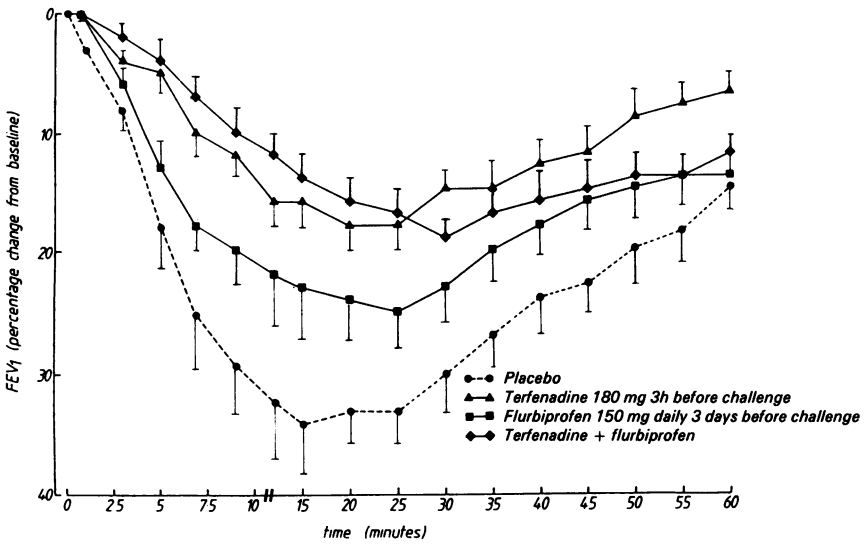
After flurbiprofen the initial rate of fall of FEV_1 following allergen was significantly slower than after placebo ($p < 0·01$) or terfenadine ($p < 0·05$), reaching a mean maximum fall of 29·6% (3·2%) from the postsaline baseline value, which was significantly different from that after placebo ($p < 0·05$). This was followed by recovery to within 13·7% (3·4%) of baseline at 60 minutes.

When terfenadine was combined with flurbiprofen the allergen induced maximum fall in FEV_1 was slightly less (21% (2·9%)) than with terfenadine alone, although the difference did not reach statistical significance and the fall was significant ($p < 0·01$) only in the comparison with placebo. The rate of recovery was significantly ($p < 0·05$) slower with the drug combination than after placebo but not after terfenadine or flurbiprofen alone.

All three active treatments significantly inhibited the overall fall in FEV_1 (AUC) after allergen over 60 minutes. Compared with placebo, terfenadine inhibited the response by 50% (SEM 6%) ($p < 0·01$),

Baseline mean (SEM) FEV_1 on the various study days

	Placebo	*Flurbiprofen*	*Terfenadine*	*Flurbiprofen + terfenadine*
Atopic asthmatic subjects				
Histamine challenge	3·38 (0·95)	3·71 (1·12)	—	—
Methacholine challenge	3·58 (1·06)	3·57 (0·97)	—	—
Atopic non-asthmatic subjects				
Allergen challenge	4·6 (0·63)	4·42 (0·63)	4·61 (0·67)	4·52 (0·63)



Effect of placebo, flurbiprofen, terfenadine and the combination of flurbiprofen and terfenadine on allergen induced bronchoconstriction in atopic normal subjects.

flurbiprofen by 26% (9%) ($p < 0.05$), and the combination of terfenadine and flurbiprofen by 45% (8%). The protection resulting from the combination did not differ from that achieved with terfenadine alone.

Skinprick tests with increasing concentrations of both histamine and allergen produced dose related skin weal responses, with a mean total weal area after allergen and after histamine of 2·58 (SEM 0·28) and 2·68 (0·27) cm^2 respectively. Treatment with flurbiprofen increased the mean total weal area to histamine by 28% (NS) and to allergen by 36% ($p < 0.01$). Terfenadine, alone or in combination with flurbiprofen, substantially inhibited the weal response to both histamine and allergen. The mean total weal area to histamine was inhibited 94% (3%) ($p < 0.01$) by terfenadine alone and by 97% (2%) ($p < 0.01$) by the combination of terfenadine and flurbiprofen, the two values not differing significantly. Terfenadine alone reduced the mean total weal area for allergen by 62% (4%) ($p < 0.01$), which was not significantly different from that produced by the treatment combination (59% (4%)).

Discussion

This study has shown that in atopic non-asthmatic subjects inhaled allergen causes rapid bronchoconstriction, reaching a maximum at 15 minutes and improving over the following 45 minutes, a finding similar to the airway response observed in atopic asthmatic patients.[13] We have confirmed our previous observation that in atopic subjects oral terfenadine, a potent and selective H_1 histamine receptor antagonist, inhibits allergen induced bronchoconstriction by about 50%.[13] After terfenadine the initial rate of fall in FEV_1 with inhaled allergen was slower than that observed after placebo, reflecting the rapid release of histamine from activated mast cells in the bronchial mucosa.

Immunological activation of human lung mast cells generates substantial amounts of the bronchoconstrictor prostanoid prostaglandin (PG) D_2,[7] which could also contribute to allergen provoked bronchoconstriction in vivo. To determine the contribution of PGD_2 and other bronchoconstrictor prostanoids to the immediate reaction, we investigated the effect of the cyclo-oxygenase inhibitor flurbiprofen. The published reports of the influence of cyclo-oxygenase inhibitors on the airways response to inhaled allergen are confusing.[14-20] Two studies[17,20] have shown that indomethacin partially attenuates the bronchoconstrictor response to allergen in patients with asthma. Fish *et al*,[16] however, were unable to show any effect of indomethacin (50 mg six hourly for 96 hours) on the allergen response in atopic asthma, while in atopic normal subjects the response was potentiated. At first sight these conflicting reports are difficult to explain. One possible reason is that, at the doses used, insufficient concentrations of drug were available at the surface of the airways to inhibit cyclo-oxygenase activity of mediator secreting cells effectively. In support of this, Kleeberger *et al*,[21] studying antigen induced bronchoconstriction in dogs, found that indomethacin in an intravenous dose of 4 mg/kg was necessary to inhibit PGD_2 release into the broncho-

alveolar lumen after challenge. For this reason we chose flurbiprofen, which is more potent than aspirin or indomethacin in inhibiting microsomal cyclo-oxygenase by factors of 5000 and 20 times respectively.[11] To ensure maximum inhibition of cyclo-oxygenase a dose regimen of flurbiprofen 150 mg daily for three days was chosen.

It was our initial intention to observe the effects of flurbiprofen on allergen provoked bronchoconstriction in patients with atopic asthma, but before undertaking this study we examined the effects of the drug on the airway response to histamine and methacholine. Despite having no effect on methacholine responsiveness, flurbiprofen had a significant inhibitory effect on the airways response to histamine, displacing the concentration-response curve to the right by more than one doubling concentration. Walters *et al* reported that inhalation of $PGF_{2\alpha}$ caused an increase in airway sensitivity to histamine[22] and that therapeutic doses of indomethacin reduced airways reponsiveness to histamine[23] in asthmatic subjects, leading them to suggest a contributory role for prostanoids in the constrictor airway response to this mediator. Platshon and Kaliner[24] found that histamine is capable of releasing $PGF_{2\alpha}$ from human lung tissue in vitro, and that a similar response was also mediated by a more specific H_1 agonist, 2-methyl histamine, and inhibited by an H_1 histamine receptor antagonist. Thus part of the bronchoconstrictor effect of histamine in asthma could be mediated by endogenously released $PGF_{2\alpha}$, removal of which by a cyclo-oxygenase inhibitor would be expected to reduce the airways response to histamine. Flurbiprofen is unlikely to have affected non-specific bronchial responsiveness directly since the drug had no effect on the airway response to methacholine, a muscarinic agonist that contracts airway smooth muscle directly. Other possible explanations for flurbiprofen's alteration of histamine responsiveness in asthma include inhibition of the reflex component of bronchoconstriction produced by histamine, down regulation of histamine H_1 receptors, and modulation of postreceptor events coupled to histamine mediated contraction of smooth muscle.

Whatever the mechanism responsible for flurbiprofen's effect on histamine responsiveness in asthma, its action precluded us from using asthmatic patients for dissecting the component of the allergen response attributable to prostanoids since endogenously released histamine causes at least 50% of the bronchoconstrictor response to allergen.[13] Walters *et al*[22] found that indomethacin had no effect on histamine responsiveness in atopic non-asthmatic subjects, unlike the asthmatic subjects; for this reason the major part of the study was conducted on atopic non-asthmatic subjects in whom the airways response to inhaled histamine fell well outside the asthmatic range (> 32 mg/ml). We did not consider it ethical to administer histamine in concentrations of more than 32 mg/ml because of the risk of laryngeal oedema, so we were unable to confirm the observations of Walters *et al.* Pretreatment with flurbiprofen inhibited bronchoconstriction with inhaled allergen by about 30% over the first 60 minutes, covering the immediate response. As can be seen from the figure, flurbiprofen produced its maximum inhibitory effect between 7 and 25 minutes and this correlates well with time course of PGD_2 release from immunologically activated lung mast cells in vitro with maximum release of PGD_2 at 15 minutes.[7]

We have previously shown that a combination of histamine and PGD_2, when administered by inhalation to subjects with asthma in equibronchoconstrictor concentrations, had purely additive effects.[25] If these two mediators were released together from activated bronchial mast cells after allergen challenge, the combination of terfenadine and flurbiprofen might be expected to produce additive inhibition of allergen provoked bronchoconstriction. The figure, however, shows that the drug combination produced no greater protection of the airways against allergen than did terfenadine alone.

Allergen provocation of isolated human airways releases various eicosanoids in addition to PGD_2, including sulphidopeptide leukotrienes, PGE_2, and PGI_2.[7,26] There is evidence that cyclo-oxygenase products may act through a negative feedback to inhibit release of other mediators. Peters *et al*[27] have shown that PGE_2 inhibits anaphylactic histamine release from human lung mast cells, and Adams and Lichtenstein[19] have reported that indomethacin enhances allergen induced histamine release from isolated human bronchus. Morone *et al*[28] have also shown with human basophils that indomethacin reverses the inhibition of histamine release by PGE_2 in a dose related manner. Thus cyclo-oxygenase inhibition may lead to enhanced release of other mediators.

An alternative explanation for our findings is that blockade of the cyclo-oxygenase pathway leads to an increase in archidonic acid metabolism along the 5-lipoxygenase pathway to yield a greater release of bronchoconstrictor leukotrienes. Although this is theoretically attractive, recent evidence indicates that the two enzyme systems utilise different pools of arachidonic acid.[29] Peters *et al*[30] found inhibition of anti-IgE and ionophore induced release of PGD_2 from human lung mast cells with indomethacin but this was not associated with any increase in release of other arachidonic acid metabolites such as the leukotrienes.

To gain further insight into the contribution of histamine and prostanoids in allergen induced acute allergic reponses, we studied the effect of terfenadine and flurbiprofen alone and in combination on the

immediate skin weal response to allergen. In a dose that almost completely inhibited the skin weal response to histamine, terfenadine inhibited the response to allergen by only 62%, implying that mediators other than histamine contribute to the allergen induced increase in postcapillary venule permeability. Flurbiprofen, on the other hand, produced a significant 36% potentiation of the weal response. This may be due to the capacity of flurbiprofen to remove an inhibitory prostaglandin, thereby increasing the vascular response to released histamine or enhancing mast cell degranulation. The former possibility is particularly attractive since the skin weal response to histamine was also enhanced, although in the small number of subjects studied this did not reach statistical significance. Another possible explanation is that cyclo-oxygenase blockade leads to an increase in the allergen provoked production of leukotrienes, which have also been shown to be highly potent in increasing vascular permeability.[31]

In conclusion, the use of terfenadine, as a highly selective and specific antagonist of histamine at the H_1 receptor, has shown that in atopic normal subjects about half of the immediate allergen induced bronchoconstrictor response can be accounted for by mast cell derived histamine. On the basis of the known pharmacological specificity of flurbiprofen at therapeutic concentrations on the cyclo-oxygenase enzyme system, we conclude that prostaglandins contribute to the increased airways responsiveness to histamine in subjects with asthma and, at least in atopic non-asthmatic subjects, to allergen provoked immediate bronchoconstriction but not to the skin weal response. The combination of terfenadine and flurbiprofen in the airways and skin produce complex results, which could be interpreted as enhanced release of further agonist mediators or removal of inhibitory prostaglandins. The further definition of the potential role of inhibitor prostanoids in allergen induced bronchoconstriction will have to await the availability of specific prostanoid receptor antagonists.

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