Effect of inhaled prostaglandin D$_2$ in normal and atopic subjects, and of pretreatment with leukotriene D$_4$

Sally E Sampson, Anthony P Sampson, John F Costello

Abstract
Background - Prostaglandin (PG) D$_2$ is a potent bronchoconstrictor mediator and is found, together with leukotriene (LT) D$_4$, in bronchoalveolar lavage fluid during the early response to allergen challenge in asthmatic subjects. The potency of PGD$_2$ has not been established in normal and atopic non-asthmatic subjects, nor has the contribution of cholinergic mechanisms to PGD$_2$ induced bronchoconstriction in normal subjects. Mediators released simultaneously may interact, so the effect of pre-inhalation of LTD$_4$ on PGD$_2$ responsiveness was investigated.

Methods - Six normal and six atopic non-asthmatic subjects performed histamine and PGD$_2$ challenges on separate occasions. Eight normal subjects performed PGD$_2$ challenges immediately before and 45 minutes after inhalation of 200 μg oxitropium bromide or placebo. Bronchial responsiveness to PGD$_2$ was established in six normal subjects immediately after pretreatment with saline or non-bronchoconstricting doses of methacholine or LTD$_4$ (challenge 1), and again at six hours (challenge 2). All studies were performed in a double blind, randomised, crossover fashion.

Results - PGD$_2$ was 25-fold and 18-fold more potent as a bronchoconstrictor than histamine in atopic non-asthmatic and normal subjects, respectively. Responsiveness (PC$_{35}$sGaw) to histamine and PGD$_2$ correlated significantly ($r=0.917$, n = 12, p<0.001). Oxitropium bromide in a dose of 200 μg inhibited PGD$_2$ induced bronchoconstriction by 37.5%, although in two of these subjects no inhibition was seen. Pre-inhalation of LTD$_4$ and methacholine shifted the dose-response curve of PGD$_2$ to the left by 4.6-fold and 2.4-fold, respectively.

Conclusions - PGD$_2$ is a potent bronchoconstrictor in normal subjects, which is partly mediated by cholinergic mechanisms in some subjects. No significant interaction was found between LTD$_4$ and PGD$_2$ in six normal subjects.

Key words: prostaglandin D$_2$, leukotriene D$_4$, asthma.

Asthma is characterised by reversible airways obstruction, chronic bronchial mucosal inflammation, and bronchial hyperresponsiveness. The airways obstruction is due to smooth muscle contraction, and to airway oedema and mucus hypersecretion caused by inflammation. Inflammatory mediators including prostaglandin D$_2$ (PGD$_2$) have been implicated in these processes.

Prostaglandin D$_2$ is synthesised by alveolar macrophages, platelets and mast cells, and is the most potent bronchoconstricting prostanoid known. The immediate bronchoconstriction induced by allergen is largely due to the release of inflammatory mediators from mast cells, and PGD$_2$ is the principal cyclooxygenase product of human lung mast cells following immunological or ionophore stimulation. Increased levels of PGD$_2$ are found in bronchoalveolar lavage fluid during the early response to allergen challenge and in the bronchoalveolar lavage fluid of mild asthmatics. Other actions of PGD$_2$ relevant to asthma, although relatively weak, include augmented capillary permeability, increased mucus secretion, and induction of neutrophil infiltration into skin.

Hardy et al. have shown that PGD$_2$ is 30 times more potent than histamine as a bronchoconstricting agent in asthmatic subjects, with a longer duration of action. Although several groups have subsequently confirmed the potency of PGD$_2$ in asthmatic subjects, none has given a concentration of inhaled PGD$_2$ to normal subjects sufficiently high to measure the concentration provoking a 35% fall in specific airways conductance and therefore to assess potency. Pretreatment with ipratropium bromide inhibits PGD$_2$ induced bronchoconstriction by up to 79% in asthmatic subjects, suggesting that bronchoconstriction is due to a combination of direct and cholinergically mediated mechanisms. However, the effect of cholinergic antagonists on PGD$_2$ induced bronchoconstriction has not been established in normal subjects.

There is increasing evidence that inhalation of one mediator can potentiate the bronchoconstriction or cause increased responsiveness to another, and such interactions within a complex network of mediators may be important in asthma. Prostaglandin F$_{2α}$ increases histamine responsiveness in normal subjects, and in asthmatic subjects histamine responsiveness is augmented by prior inhalation of PGD$_2$. In normal subjects leukotriene (LT) D$_4$ potentiates PGF$_{2α}$ responsiveness by approximately sevenfold, and a broncho-
constricting dose of LTD₄ increases methacholine responsiveness for up to two weeks. Inhaled LTE₄ increases histamine responsiveness in asthmatics for up to one week, and LTC₄ enhances the immediate bronchoconstriction induced by PGD₂ and histamine in asthmatics, although the effects seen are small. The mechanisms of these interactions have not been fully elucidated.

In this study we wished to investigate the potency of PGD₂ as a bronchoconstrictor in normal subjects and to examine the contribution of cholinergic mechanisms to this. We also aimed to discover whether atopic non-asthmatic subjects showed any differences in response from non-atopic subjects, and to examine the effect of pretreatment with LTD₄ on airway responsiveness to PGD₂. We therefore investigated the bronchoconstrictor potency of PGD₂ in six atopic non-asthmatic and six non-atopic normal subjects, the effect of an anti-cholinergic agent, oxitropium bromide, on PGD₂ induced bronchoconstriction in eight subjects, and the interaction of LTD₄ with PGD₂ responsiveness in six normal subjects.

Methods

Subjects
All subjects were non-smokers with no history of respiratory disease and were not studied within six weeks of a respiratory tract infection. Atopic non-asthmatic subjects had a positive skin prick test (>3 mm) to two or more of a battery of nine common allergens. Caffeine- or theophylline-containing food and drinks were withheld for 12 hours before each study day. Informed consent was obtained from all subjects, and the studies were approved by King's College Hospital ethics committee.

Effects of inhaled PGD₂ in non-atopic normal and atopic non-asthmatic subjects
Six normal subjects (two men) of mean (SE) age 25.7 (2.4) years and six atopic non-asthmatic subjects (three men) of mean (SE) age 23.8 (1.7) years took part in the study. Bronchial responsiveness to histamine and to PGD₂ was measured on two occasions at least two weeks apart in a double blind, randomised, crossover fashion. The potency ratio for PGD₂ relative to histamine was calculated as the geometric mean of individually determined ratios of PC₁₅sGaw histamine to PC₁₅sGaw PGD₂. The duration of PGD₂ induced bronchoconstriction was defined as the time taken for specific airways conductance (sGaw) to return to within 10% of control values. The repeatability of histamine and PGD₂ challenges was assessed on two occasions at least two weeks apart in two groups of five subjects.

Cholinergic mediation of PGD₂ induced bronchoconstriction
Eight non-atopic normal subjects (two men) of mean (SE) age 25.3 (2.1) years participated in the study. Subjects attended the laboratory on two occasions separated by at least two weeks. Bronchial responsiveness to PGD₂ was determined 45 minutes after inhalation of either placebo or 200 µg oxitropium bromide (Boehringer Ingelheim Ltd, Bracknell, UK) as two puffs from a metered dose inhaler in a randomised, double blind, crossover fashion. The percentage inhibition of PGD₂ induced bronchoconstriction by oxitropium bromide was calculated at the highest concentration of PGD₂ given on the placebo day, as the difference between the maximum falls in sGaw after oxitropium and placebo (measured as % change from baseline), divided by the maximum fall after placebo (%).

Interaction of inhaled LTD₄ on PGD₂ responsiveness
Six normal subjects (four men) of mean (SE) age 25.2 (1.7) years were recruited. Subjects initially attended the laboratory on two occasions for bronchial responsiveness to methacholine and LTD₄. They returned for three further visits, separated by at least two weeks, when bronchial responsiveness to PGD₂ was measured after pretreatment with either 0.9% saline or non-bronchoconstricting concentrations of methacholine or LTD₄ and again six hours after pretreatment. Pretreatments were given in a randomised, double blind, crossover fashion. Repeat non-bronchoconstricting doses of LTD₄ methacholine, or saline alone were given to three separate subjects to assess cumulative effects.

Lung function measurement
Baseline lung function assessment was performed in all subjects. The forced expiratory volume in one second (FEV₁) was measured (mean of three values) using a dry wedge bellows spirometer (Vitalograph Ltd, Bucks, UK). Specific airways conductance (sGaw) (mean of 16 values) was measured in an automatic pressure-flow plethysmograph (Gould 2800 Autobox, Sensormedics, Salford, UK). Flow at 30% of vital capacity above residual volume (Vmax₉₀) (mean of five values) was obtained from partial expiratory flow volume manoeuvres using a rolling seal spirometer (P K Morgan Ltd, Gillingham, UK) attached to a differentiator (P K Morgan) and analysed by computer (Amstrad PC2086) using software developed by Mr K Allen (Medical Physics Department, King's College Hospital).

Bronchial challenge testing
Bronchial responsiveness was measured using a modification of a standard protocol. Responsibility was defined as the provocation concentration (PC) of histamine, PGD₂, methacholine, or LTD₄ causing a fall of 35% in sGaw (PC₁₅sGaw) and a 30% fall in Vmax₉₀ (PC₁₅Vmax₉₀) from control values. Half log dilutions of histamine acid phosphate from 1 to 100 mM were prepared by King's College Hospital Pharmacy using 0.9% saline as diluent, with 0.5% chlorbutol BP, and stored at
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Table 1  Geometric mean provocation concentration (PC) and related potencies of inhaled histamine and PGD₂ for airways conductance (sGaw) and flow at 30% of vital capacity above residual volume (Vmax₃₀)

<table>
<thead>
<tr>
<th></th>
<th>PGD₂</th>
<th>Histamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PC₃₀sGaw (mM)</td>
<td>Potency†</td>
</tr>
<tr>
<td>Non-atopic</td>
<td>40.3</td>
<td>1</td>
</tr>
<tr>
<td>Atopic</td>
<td>13.4</td>
<td>16.5</td>
</tr>
<tr>
<td>PGD₂</td>
<td>Non-atopic</td>
<td>2.26*</td>
</tr>
<tr>
<td>Atopic</td>
<td>0.53*</td>
<td>25.4</td>
</tr>
</tbody>
</table>

* p<0.05 compared with histamine.
** p<0.005 compared with PC₃₀sGaw.
† Potency with respect to histamine.

Wilcoxon signed rank tests. Correlations were assessed by linear regression analysis. All other data were analysed by appropriate non-parametric tests. All analyses were performed using the Minitab statistical software package.

Results

INHALED PGD₂ IN NORMAL AND ATOPIC NON-ASTHOMATIC SUBJECTS

Baseline lung function tests were not significantly different (p>0.05) between study days in either the normal or atopic non-asthmatic subjects. PGD₂ was tolerated well, although initial concentrations caused a significant cough in all subjects. Inhaled PGD₂ caused bronchoconstriction in both normal and atopic non-asthmatic subjects. In normal subjects bronchoconstriction was more clearly apparent as falls in sGaw than in Vmax₃₀ which remained above 70% of control values in all subjects, and thus PC₃₀sGaw could not be calculated. Compared with normal subjects, atopic non-asthmatic subjects were, on average, 4.29-fold (95% CI 0.78 to 11.59) more responsive to PGD₂ (p=0.031); however, the 3.01-fold (95% CI 1.11 to 16.56) greater histamine responsiveness seen in the atopic non-asthmatic group was not significantly different from that in the normal subjects (p=0.174). Both normal and atopic non-asthmatic subjects were more responsive to PGD₂ than to histamine (table 1), with PGD₂ being 17.8 (95% CI 9.62 to 38.9) and 25.4 (95% CI 15.5 to 41.8) times, respectively, more potent (geometric mean) than histamine when PC₃₀sGaw was measured. There was no significant difference in potency compared with histamine between the two groups (p=0.295).

The correlation between airway responsiveness to inhaled histamine with that to PGD₂ in normal and atopic non-asthmatic subjects is shown in fig 1. The combined correlation coefficient for PC₃₀sGaw histamine with PC₃₀sGaw PGD₂ in normal and atopic non-asthmatic subjects was highly significant (r=0.917, p<0.001, n=12). Atopic non-asthmatic subjects (n=5) took significantly longer to recover from PGD₂ induced bronchoconstriction.

4°C until required. Half log dilutions of methacholine (0.02–6.32 mM) were prepared and stored in an identical manner. Prostaglandin D₂ was supplied dissolved in ethanol (Cascade Biochem Ltd, Reading, UK), and stored at -80°C. Immediately before a challenge the ethanol was evaporated to dryness under nitrogen and the PGD₂ was resuspended in methanol:saline (1:25) to produce a concentration of 10 mM. Serial log dilutions to 1 μM were made using 0.9% sodium chloride. Leukotriene D₄ (Cascade Biochem Ltd) was supplied dissolved in ethanol. Immediately before each challenge, LTD₄ was diluted with 0.9% sodium chloride to give serial half log dilutions from 0.2 M to 200 μM. Methanol concentration in the inhaled solutions did not exceed 4% in any study. Subjects initially inhaled diluent by tidal breathing from a Wright nebuliser, driven by air at 8 l/min for two minutes. The calibre of the airways was monitored by measurements of sGaw (mean of eight values) at one and six minutes and Vmax₃₀ (mean of two values) at three and eight minutes after inhalation to provide control measurements. Increasing concentrations of agonist were inhaled in the same manner as diluent and the response expressed as a percentage of the mean control values for sGaw and Vmax₃₀. Log₁₀ dose-response curves were constructed and PC₃₀sGaw and Vmax₃₀ obtained by linear interpolation. If Vmax₃₀ fell by less than 30%, PC₃₀sGaw was obtained by extrapolation provided that PC₃₀sGaw was reached within the next doubling dilution, and PC₃₀sGaw was taken as the maximum concentration of PGD₂ if sGaw had not fallen by 35% at this point.

PRETREATMENT WITH SALINE, METHACHOLINE OR LTD₄

From initial dose-response curves to methacholine and LTD₄ the highest concentration of each agonist causing a fall in sGaw of less than 10% from control was established. On subsequent study days the initial PGD₂ challenge was performed, with each concentration of PGD₂ being immediately preceded by a two minute inhalation of either saline or the previously determined non-bronchoconstricting concentration of methacholine or LTD₄.

DATA ANALYSIS

Provocation concentrations were log transformed before analysis by Mann-Whitney or
Table 2 Concentration of PGD<sub>2</sub> provoking a fall in airways conductance of 35% (PC<sub>35sGaw</sub>) measured 45 minutes after inhalation of placebo or oxitropium bromide and the percentage inhibition of PGD<sub>2</sub> induced bronchoconstriction by oxitropium bromide

<table>
<thead>
<tr>
<th>Subject no.</th>
<th>PC&lt;sub&gt;35sGaw&lt;/sub&gt; PGD&lt;sub&gt;2&lt;/sub&gt; (mM)</th>
<th>% Inhibition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Oxitropium bromide</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>1.5</td>
<td>42.5</td>
</tr>
<tr>
<td>2</td>
<td>6.32</td>
<td>45.5</td>
</tr>
<tr>
<td>3</td>
<td>3.0</td>
<td>20.9</td>
</tr>
<tr>
<td>4</td>
<td>1.2</td>
<td>38.1</td>
</tr>
<tr>
<td>5</td>
<td>1.4</td>
<td>97.9</td>
</tr>
<tr>
<td>6</td>
<td>6.32</td>
<td>−15.2</td>
</tr>
<tr>
<td>7</td>
<td>5.7</td>
<td>75.0</td>
</tr>
<tr>
<td>8</td>
<td>5.2</td>
<td>−5.1</td>
</tr>
<tr>
<td>Geometric mean</td>
<td>3.88</td>
<td>5.92</td>
</tr>
</tbody>
</table>

Mean 37.5

Geometric mean 3.88 5.92

Mean 37.5

Cholinergic mediation of PGD<sub>2</sub> induced bronchoconstriction

There was no significant difference (p>0.05) in baseline lung function tests between study days. Inhaled oxitropium bromide (200 μg) produced significant bronchodilation, causing mean (95% CI) increases from baseline in FEV<sub>1</sub> (3.75% (1.09 to 6.41), p = 0.014), sGaw (82.1% (44.7 to 119.5), p = 0.014), and Vmax<sub>30</sub> (34.8% (16.3 to 53.4), p = 0.014) at 45 minutes compared with pretreatment values. Due to the relative insensitivity of Vmax<sub>30</sub> to PGD<sub>2</sub> induced bronchoconstriction in normal subjects, bronchial responsiveness was recorded as PC<sub>35sGaw</sub> only. Mean (95% CI) inhibition of PGD<sub>2</sub> induced bronchoconstriction by oxitropium bromide in eight subjects was 37.5% (95% CI 5.8 to 69.1), although in two cases no inhibition was seen (table 2).

Interaction of inhaled LTD<sub>4</sub> with PGD<sub>2</sub> responsiveness

Three subjects inhaled six non-bronchoconstricting concentrations of LTD<sub>4</sub> methacholine, and saline from a Wright’s nebuliser driven by air at 8 l/min. There was no evidence of a cumulative effect when concentrations were given at 12 minute intervals, which was the minimum time between pre-inhalations during the study. Mean sGaw remained within 10% of the baseline value at all time points.

There was no difference in baseline lung function between the three study days or between first and second challenges (p>0.05), except the FEV<sub>1</sub> at challenge 1 on the methacholine study day was significantly higher than at challenge 1 on the saline study day (p = 0.036). PGD<sub>2</sub> responsiveness was not altered by pretreatment with saline, with no significant difference between challenges 1 and 2 (p = 0.59; fig 3). Pre-inhalation of LTD<sub>4</sub> caused a mean (95% CI) increase in PGD<sub>2</sub> responsiveness of 4.6-fold (0.6 to 36.7) compared with saline, but this was not significant (p = 0.142). After six hours bronchial responsiveness had recovered, being significantly lower at challenge 2 than at challenge 1 (p = 0.036). However, pre-inhalation of methacholine also produced a non-significant 2.4 (0.7 to 8.1)-fold increase in responsiveness at challenge 1 (p = 0.142).

At six hours there was no significant difference in PGD<sub>2</sub> responsiveness between the three treatment groups (p>0.05).
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Discussion

The results show that PGD2 is a potent bronchoconstrictor in atopic non-asthmatic and normal subjects, being 25 times and 18 times more potent than histamine, respectively. There was a positive linear correlation between histamine and PGD2 responsiveness when atopic non-asthmatic and normal subjects were considered together, in agreement with previous studies which have shown that asthmatic subjects who are hyperresponsive to histamine and methacholine are also hyperresponsive to PGD2. Both PGD2 and histamine challenges were reproducible in the five normal subjects tested. PGD2 repeatability is reported as being less than that for histamine or LTD4 in asthmatic subjects, which may reflect the greater lability of bronchial responsiveness in asthmatic subjects. The potency of PGD2 compared with histamine (18 times in normal subjects) is similar on a molar basis to that described for asthmatic subjects (17.8–32.4).10–12

Atopic non-asthmatic subjects were 3.01 times and 4.29 times more responsive to histamine and PGD2, respectively, than normal subjects. Although none of the atopic non-asthmatic subjects had any history of respiratory symptoms, other allergic diseases were not excluded. The increased bronchial responsiveness seen in this group agrees with the increased bronchial responsiveness seen in atopic subjects from a random population and in asthmatics who show bronchial hyperreactivity to various stimuli including histamine,10–14 prostaglandins,10–12 and methacholine.10–12

Atopic subjects without asthma share, to a lesser extent, some of the features of bronchial mucosal inflammation observed in subjects with asthma, including mast cell degranulation, eosinophil activation, and collagen deposition in the basement membrane; these subclinical features may result in a degree of bronchial responsiveness in atopic non-asthmatic subjects. Despite similar baseline lung function tests and a similar degree of bronchoconstriction following inhalation of PGD2, atopic non-asthmatic subjects took significantly longer for sGaw to return to baseline. This may reflect the increased peripheral bronchoconstriction induced in this group as detected by changes in Vmaxso.

PGD2 causes bronchoconstriction of human airway smooth muscle both by direct mechanisms, acting via the thromboxane receptor, and by cholinergically mediated mechanisms. Ipratropium bromide is an anti-cholinergic agent which acts as a potent bronchodilator in both normal and asthmatic subjects. We showed a significant increase in all lung function parameters measured, with sGaw, F EV1, and Vmaxso increasing by 82.1%, 3.75%, and 34.8%, respectively, following inhalation of 200 μg ipratropium. Ipratropium caused a mean 37.5% inhibition of PGD2-induced bronchoconstriction, shifting the dose-response curve to the right in six out of eight subjects. It is not clear why in two of the subjects there was no inhibition, but these subjects did bronchodilate after inhalation of ipratropium, suggesting that the drug had reached the airways. In asthmatic subjects a 79% inhibition of PGD2 induced bronchoconstriction by ipratropium bromide has been reported. Thus, in normal subjects cholinergic mediation of PGD2-induced bronchoconstriction may play a relatively smaller part than in asthmatic subjects. It is unlikely that the reduction in bronchoconstriction was due to functional antagonism as it has been shown that bronchodilation produced by cholinergic agents does not affect responsiveness to inhaled bronchoconstrictors; however, the data were standardised as percentage baseline to overcome the effect of bronchodilation.

There are methodological problems when investigating the interaction of inhaled mediators. Different investigators have chosen different techniques, making comparisons between studies difficult. We were unable to demonstrate any significant interaction of inhaled sub-bronchoconstricting doses of LTD4 or methacholine on PGD2 responsiveness in normal subjects. LTD4 produced a 4.6-fold shift in the PGD2 dose-response curve which failed to reach significance (p = 0.142) compared with saline pretreatment, but this is similar in magnitude to the significant sevenfold increase in PGF2α responsiveness seen in asthmatic subjects pretreated with a non-bronchoconstricting dose of LTD4. However, the latter study established dose-response curves to PGF2α over a period of days to avoid the multiphasic dose-response characteristics of this prostaglandin, and there may have been changes in the reactivity to various stimuli including histamine, LTC4 and methacholine do increase the baseline contractile state of isolated human airway, they do not, unlike other mediators, increase methacholine sensitivity of the tissue.

We controlled for possible physiological interactions by measuring the effect of non-bronchoconstricting concentrations of methacholine on PGD2 responsiveness. While responsiveness was increased in comparison with saline pretreatment, the effect was less than that seen following pretreatment with LTD4 which suggests that LTD4 may have only increased PGD2 responsiveness. These changes did not reach significance, possibly because of the relatively few subjects studied, and the possibility of a false negative result cannot be excluded.

The role of prostanoids such as PGD2 in allergic asthma is unclear. Although mast cell derived prostanoids are generated during bronchoconstrictor responses to allergen, non-specific cyclo-oxygenase (COX) inhibitors lack significant therapeutic benefit, and may even exacerbate asthmatic symptoms, probably due to concomitant inhibition of the synthesis
of PGE₁ which may have a protective role. PGE₂ is only a weak bronchodilator but it blocks allergen induced bronchoconstriction in man,³⁴ probably by reducing the synthesis of bronchoconstrictor mediators including PGD₂, PGF₂α, and the cysteinyl leukotrienes in a number of cell types.³⁵ Our results reinforce understanding of the potency of inhaled PGD₂ in normal subjects and of the hyperresponsiveness shown to PGD₂ even in atopic non-asthmatic subjects, and support the development of specific COX-2 inhibitors, which may block the synthesis of bronchoconstrictor prostanoids from inflammatory cells, without eliminating constitutive PGE₂ protection.³⁶

In conclusion, PGD₂ is a potent bronchoconstrictor in normal and atopic non-asthmatic subjects, and challenges are highly repeatable. Responsiveness to PGD₂ in these groups relative to histamine was similar to that described in asthmatics by other workers. Intriguingly, atopic non-asthmatic subjects were significantly more responsive to PGD₂ than normal subjects. Compared with previous studies in asthmatic subjects, a smaller proportion of PGD₂ induced bronchoconstriction in normal subjects is mediated by cholinergic mechanisms. We were unable to demonstrate any interaction between LTD₄ and PGD₂ in six normal subjects.

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