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Evidence for the roles of histamine and prostaglandins as mediators in exercise-induced asthma: the inhibitory effect of terfenadine and flurbiprofen alone and in combination

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ABSTRACT: We investigated the effects of terfenadine, a histamine H_1-receptor antagonist, and flurbiprofen, a cyclooxygenase inhibitor, on exercise-induced bronchoconstriction to assess the contribution of the mast cell products histamine and prostaglandins. Eight asthmatics were studied on 4 occasions with treadmill exercise tests. Terfenadine or placebo was administered 3 h prior to exercise, and flurbiprofen or placebo was administered 2 h prior to exercise, in a double-blind randomized trial. Airway calibre was determined by measurement of the forced expiratory volume in one second (FEV_1) immediately prior to exercise challenge, and over 30 min post-exercise. Following placebo, the mean maximum percentage fall in FEV_1 was 39%. This fell to 25% after terfenadine ($p<0.05$), 27% after flurbiprofen ($p<0.05$), and 30% after the active combination (NS). Analysis of the areas under curves of percentage falls in FEV_1 over 30 min showed significant inhibition on all 3 active drug days ($p<0.05$). We conclude that histamine release and prostaglandin generation contribute to exercise-induced bronchoconstriction, although the interaction between these mediators appears complex.

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Exercise-induced asthma (EIA) describes the phenomenon of bronchoconstriction that follows or accompanies exercise in a large number of asthmatics. One proposed mechanism is that drying and hypertonicity of airway lining fluid occurs during exercise-induced hyperventilation, prompting activation of secretion from airway mast cells [1–3]. However, the published literature concerning the detection of mast cell-dependent mediators in EIA is confusing. A number of studies have shown increases in venous plasma concentrations of histamine following EIA [4, 5] but this has not been shown when asthma has been induced by isocapnic hyperventilation [5, 6]. High molecular weight neutrophil chemotactic factor (HMW-NCF) is another mediator that has been used as a marker for mast cell activation in EIA, but the specificity of this mediator in heat-inactivated serum is questionable [7]. Exercise is a potent stimulus for producing a transient leucocytosis which includes basophils, a rich source of histamine. Thus, the measured rise in plasma histamine with EIA has been attributed to the basophil leucocytosis [5].

An alternative approach to assaying putative mediators of EIA in venous blood is to employ specific pharmacological antagonists or inhibitors. To investigate the potential contribution of histamine to EIA, we used the selective histamine H_1-receptor antagonist, terfenadine, which in an oral dose of 180 mg affords an approximately 35 fold protection of asthmatic airways against the bronchoconstrictor effect of inhaled histamine [8], and reduces the immediate allergen response by approximately 50% [9]. We also employed the cyclooxygenase inhibitor, flurbiprofen, which has previously been used to demonstrate the contribution of prostanoids to allergen-provoked bronchoconstriction [9].

In the present study our aim was to dissect the mediator components of EIA by observing the effects of terfenadine and flurbiprofen alone and in combination on the airway response to exercise in a group of 8 subjects with a history of EIA. The volume respired during exercise, and calculated respiratory heat exchange (RHE) and water loss were determined to ensure the repeatability of exercise challenge.

Methods

Subjects

Eight asthmatic subjects (5 male, 3 female; mean age 28 yrs, range 21–40 yrs) participated in the study. All were atopic, in having at least one positive wheal

(>3 mm in diameter) on skin prick testing to *Dermatophagoides pteronyssinus*, mixed grass pollens and cat dander (Bencard, Brentford, Middlesex, UK). All were nonsmokers and had mild asthma, receiving no regular drug therapy other than inhaled β_2-agonists as needed (table 1). Their mean forced expiratory volume in the first second of a forced expiratory manoeuvre from full inspiration (FEV_1) was 91% of predicted (range 65–120%). All were hyperresponsive to histamine with a geometric mean provocation concentration causing a 20% fall in FEV_1 ($PC_{20}FEV_1$) value of 1.74 $mg \cdot ml^{-1}$ (range 0.13–7.69 $mg \cdot ml^{-1}$). None of the subjects had a history of dyspepsia, gastrointestinal disease, or analgesia-induced asthma. On each study day, bronchodilator therapy was withheld for six hours prior to exercise challenge, and the subjects were asked to abstain from caffeine-containing drinks. Written informed consent was obtained from each subject and the study was approved by the Southampton University and Hospitals Ethical Subcommittee.

(PK Morgan Ltd) and also input to the microcomputer. Assuming 100% humidity of expired air, respiratory heat exchange during the exercise test was calculated breath by breath by the microcomputer, using the formula for respiratory heat exchange described by DEAL *et al*, [10]:

$$RHE = V\{HC(Ti-Te) + HV(WCi-WCe)\}$$

where RHE is the respiratory heat exchange in kilojoules; V is total ventilation during exercise in litres, BTPS; HC is heat capacity of air (= 0.001216 $kJ \cdot l^{-1} \cdot °C^{-1}$); Ti is inspired air temperature in °C; Te is expired air temperature in °C; HV is heat of vaporization of water (= 0.00232 $kJ \cdot mg^{-1}$); WCi is water content of inspired air ($mg \cdot l^{-1}$); and WCe is water content of expired air ($mg \cdot l^{-1}$). Measurements of FEV_1 were performed using a dry wedge spirometer (Vitalograph, Buckingham, UK), with the highest of 3 initial readings being taken as the baseline value.

Table 1. – Subjects' characteristics

Subject	Age yrs	Sex	% predicted FEV_1	Treatment	PC_{20} histamine $mg \cdot ml^{-1}$
1	24	F	120	S	1.47
2	21	M	68	S	1.74
3	24	M	88	S	1.34
4	21	M	95	S	7.69
5	27	F	106	S	1.09
6	28	F	104	S	0.13
7	36	M	82	S	0.54
8	40	M	65	S	0.88

S: salbutamol by metered dose inhaler as required; FEV_1: forced expiratory volume in one second; PC_{20}: provocation dose of histamine causing a 20% decrease in FEV_1.

Exercise challenge and physiological measurements

Subjects exercised on an electrically driven treadmill (PK Morgan Ltd, Chatham, Kent, UK), while inspiring dry air at room temperature and atmospheric pressure from a 200 *l* Douglas bag *via* a mouthpiece connected to a two-way valve, and expired into the ambient air. The temperature of ambient laboratory air ranged from 16.5–23.0°C and the relative humidity varied between 47–84%. Type K thermocouples (Tempcon Instrumentation Ltd, Holmdale Industrial Estate, Chichester, UK) with time constants of 0.6 s in air were placed in the expiratory and inspiratory ports of the valve and used to record inspiratory and expiratory air temperatures breath by breath. The thermocouples were connected to voltage conversion circuitry, and the output connected to an analogue to digital converter on a BBC microcomputer, which was programmed to use the mean inspiratory and the peak expiratory temperature recordings in subsequent calculations. The volume of inspired air was measured using a Parkinson Cowan gas meter

Each subject initially undertook a minimum of three trial 6 min exercise tests on the treadmill on separate days, using the noseclip and mouthpiece, until they were comfortable with the procedure. During each of the exercise tests they respired dry air from a reservoir in a 200 *l* Douglas bag, which was supplemented from an air cylinder as necessary. On completion of the exercise task single measurements of FEV_1 were made at 1, 3, 5, 10, 15 and 30 min. The gradient and speed of the treadmill were constant during the course of each trial test, but were adjusted at the beginning of subsequent tests so that a maximum fall in FEV_1 from the pre-exercise level during these trial tests of at least 25% was achieved. During each test, the rate of RHE plotted against time was displayed continuously on the computer monitor, to ensure that this occurred at a uniform rate. Once an adequate exercise task had been determined which was well tolerated, the treadmill gradient and speed were kept constant in all subsequent tests in that subject.

Table 2. – Baseline FEV_1 values immediately prior to exercise challenge pre-study and following each drug treatment

		Treatments			
Subjects	Pre-study	Placebo	Terfenadine	Flurbiprofen	Combination
1	3.60	3.80	4.15	3.95	4.15
2	3.25	2.95	3.40	3.45	3.90
3	3.95	3.80	4.80	3.15	4.70
4	4.10	4.85	4.35	5.00	5.00
5	3.40	3.60	3.60	3.40	3.60
6	2.80	2.20	3.00	2.60	2.80
7	3.40	4.00	4.55	3.90	4.50
8	2.90	2.25	3.25	2.80	3.30
Mean	3.43	3.43	3.89	3.53	3.99
SEM	0.16	0.34	0.25	0.29	0.28

FEV_1: forced expiratory volume in one second.

Table 3. – Volume of dry air respired and respiratory heat exchange (RHE) during each exercise test following each drug treatment

	Placebo		Terfenadine		Flurbiprofen		Combination	
Subjects	Volume *l*	RHE kJ	Volume *l*	RHE kJ	Volume *l*	RHE kJ	Volume *l*	RHE kJ
1	240.7	15.1	282.4	20.5	238.8	15.0	253.7	18.7
2	296.0	23.7	272.0	22.9	252.3	22.4	273.7	23.2
3	274.1	29.5	277.8	29.0	272.4	34.4	276.7	26.8
4	287.2	20.7	243.0	25.4	237.2	14.8	282.7	18.8
5	231.4	21.4	208.9	14.5	224.5	17.9	214.6	17.4
6	197.3	14.2	192.8	14.5	241.9	17.5	224.0	18.5
7	266.1	20.6	299.9	22.4	297.6	18.4	292.3	21.5
8	255.6	21.0	255.4	18.8	235.1	17.6	271.0	23.7
Mean	256.1	20.8	254.0	21.0	250.0	19.8	261.1	21.1
SEM	11.4	1.7	13.2	1.8	8.5	2.3	9.9	1.2

Study protocol

The study was conducted in a double-blind, placebo-controlled and randomized fashion. Each subject performed 4 exercise tests, each undertaken at the same time of day, with intervals of between 5–7 days between each visit. Three hours prior to each test they received either terfenadine 180 mg orally or matched placebo, and two hours prior to each test flurbiprofen 150 mg orally or matched placebo. Thus, on the 4 visits they received either: i) placebos alone; ii) terfenadine 180 mg; iii) flurbiprofen 150 mg; or iv) the active combination of terfenadine 180 mg and flurbiprofen 150 mg. The greatest of three FEV_1 estimations made immediately prior to exercise testing was taken as the baseline FEV_1, and subjects then undertook the 6 min exercise task at the predetermined treadmill slope and speed.

Data analysis

Baseline FEV_1 values on the 4 study days were compared using two-way analysis of variance (2-way ANOVA). The airways response following exercise was expressed as the percentage change in FEV_1 from the pre-exercise baseline estimation, and plotted against time. From the resulting plots, both the maximum percentage fall in FEV_1 post-exercise, and the area under the curve (AUC) determined by trapezoidal integration of the percentage fall in FEV_1 against time over 30 min were calculated. The effects of drug treatment on the airways response to exercise were compared with respect to the maximum percentage falls in FEV_1 using 2-way ANOVA, followed by the Tukey Honestly Significant Difference test for multiple comparisons [11]. AUC estimations were not assumed to be parametric, therefore comparison of the AUC was made between drug treatments using Friedman's test for multiple matched samples, followed by the Wilcoxon signed rank test for paired samples.

Repeatability of the maximum percentage fall in FEV_1 following exercise challenge was assessed by comparison of the data from the placebo study days with the data from the final exercise tests prior to study entry, using the method described by BLAND and ALTMAN [12].

The inhibitory effect of the active treatments on the exercise-induced decrease in FEV_1 was also examined

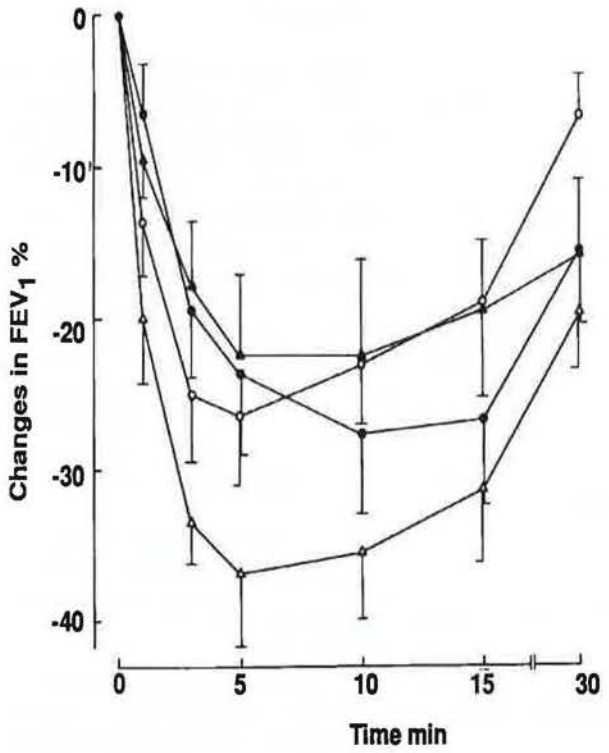

Fig. 1. – Percentage falls in FEV_1 over 30 min from pre-exercise baseline values following exercise challenge for each of the drug treatments: placebo (open triangles); terfenadine (closed triangles); flurbiprofen (open circles); and flurbiprofen plus terfenadine (closed circles). Each point represents the mean±SEM for 8 asthmatic subjects. FEV_1 forced expiratory volume in one second.

Results

When compared to oral placebo, the mean baseline FEV_1 values increased by 13.4% and 16.3% after terfenadine alone and the combination of active drugs respectively, while after flurbiprofen alone the mean increase was only 2.9% (table 2). Analysed as 4 groups by 2-way ANOVA, these changes were statistically insignificant.

The volume of room air inhaled and the calculated respiratory heat exchange during the exercise tests were not significantly different on any of the study days (table 3). The mean calculated water loss ±SEM during exercise was 7.0±0.5 mls following placebo, 7.2±0.6 mls following terfenadine, 6.4±0.7 mls following flurbiprofen, and 6.9±0.3 mls following the combination (NS).

With each of the 3 drug treatments and placebo, the exercise task produced falls in FEV_1 reaching a mean maximum fall 5 min post-exercise on the placebo and flurbiprofen days, and a mean maximum fall 10 min post-exercise when terfenadine or the drug combination had been given (fig. 1). After oral placebo, the fall in FEV_1 remained depressed below baseline at 30 min, with a mean percentage fall of 20±4% at that time (fig. 1).

Terfenadine alone reduced the post-exercise fall in FEV_1 expressed as a percentage of pre-exercise baseline (table 4). The inhibitory effect of terfenadine was most apparent in the first 5 min post-exercise and was negligible by 30 min. For the group as a whole, terfenadine reduced the mean maximum percentage fall in FEV_1 by 34±11% (range -6%–85%) ($p<0.05$). When

Table 4. – Maximum percentage falls in FEV_1 after exercise pre-study and following each drug treatment

		Treatments			
Subjects	Pre-study	Placebo	Terfenadine	Flurbiprofen	Combination
1	54	49	48	25	36
2	46	49	28	36	37
3	44	50	10	25	4
4	33	12	11	5	8
5	34	29	10	16	26
6	32	32	17	35	39
7	43	44	46	39	51
8	43	44	29	36	38
Mean	41	39	25	27	30
SEM	3	5	6	4	6

FEV_1: forced expiratory volume in one second.

by subtracting the absolute response after the active drug from that after placebo, and expressing the percentage inhibition as a function of time. Least squares linear regression was used to examine the relationship between baseline spirometry and bronchoconstrictor response expressed as the AUC.

analysed for the whole response between 0–30 min and compared to placebo, the mean AUC was reduced by 32% after terfenadine ($p<0.0$ (table 5).

Flurbiprofen alone also inhibited the post-exercise fall in FEV_1. For the group as a whole, flurbiprofen reduced the maximum percentage fall in FEV_1 by a mean of

31±8% (range -9%–60%) ($p<0.05$). The mean inhibitory effect of flurbiprofen was evident throughout the 30 min post-exercise documented, but was greatest at 30 min (fig.1). The mean AUC of percentage fall in FEV_1 plotted against time was reduced by 42% after flurbiprofen ($p<0.01$) (table 5). There was no significant correlation between the protection offered by terfenadine and that offered by flurbiprofen, whether assessed as AUC or as the maximum percentage fall in FEV_1.

When compared to placebo, the combination of terfenadine and flurbiprofen inhibited the maximum percentage fall in post-exercise FEV_1 by a mean of 20±13% (range -25%–91%), which failed to reach statistical significance ($p>0.05$). The reduction in the mean AUC by the drug combination was 22% which was statistically significant ($p<0.05$). There were no significant differences between any of the 3 active treatments in protecting against EIA, whether expressed as maximum percentage fall in FEV_1 or AUC.

The repeatability of the maximum percentage falls in FEV_1 following exercise was assessed by comparison of the final pre-study exercise tests with those on the placebo study days [12] (table 4). The mean bias was 2.5±2.9% (NS) with the coefficient of repeatability being ±19.3% (for example, and disregarding bias, for an observed maximum fall of 30%, a repeated test would give a fall with a 95% likelihood of being in the range 10.7–49.3%). A more reliable estimate of repeatability was obtained by combining the data from this study with those from another study with 12 subjects using exactly the same technique and performed by the same investigators (paper in preparation). This gave a coefficient of repeatability of 22.1% (CI 13.9–30.3%).

For none of the drug treatments was a significant relationship found between the pre-exercise baseline FEV_1 and the degree of protection afforded against the subsequent falls in FEV_1 provoked by exercise.

Table 5. – Areas under curves of percentage fall in FEV_1 against time over 30 min following each drug treatment

	Treatments			
Subjects	Placebo	Terfenadine	Flurbiprofen	Combination
1	1214	1235	476	829
2	1128	663	473	859
3	657	250	248	56
4	261	169	76	165
5	624	219	301	441
6	741	334	819	823
7	1157	1135	826	1264
8	961	595	720	827
Mean	843	575	492	658
SEM	117	147	98	143

FEV_1: forced expiratory volume in one second.

Discussion

This study was designed to use a selective histamine H_1-receptor antagonist and a cyclooxygenase inhibitor to assess the contributions made by histamine and prostanoids to exercise-induced asthma. Terfenadine, whether administered alone or in combination with flurbiprofen had a major inhibitory action in 5 of 8 subjects. Flurbiprofen alone also inhibited the response in the majority of subjects, but had a lesser effect on the maximum post-exercise fall in FEV_1 than that achieved with terfenadine alone. The drug combination proved to have an inhibitory effect that was less marked than that found with either drug used alone. These results provide strong evidence for the contributory role of both histamine and prostanoids in EIA, but between subjects the contribution made by each class of mediator is variable.

On the basis that cromolyn sodium could inhibit EIA when administered prior to exercise challenge, a role for mast cell mediator release in the response was suggested. The contradictory evidence provided by a number of investigations on circulating mediators in EIA has not provided the clear-cut evidence required to implicate unequivocally mast cell activation in the response. Since histamine is the only known preformed bronchoconstrictor mediator of human airway mast cells, then it should play a contributory role in EIA if mast cell activation is involved. To investigate this we chose to use a high dose of terfenadine (180 mg) since at this dose it produces approximately 35 fold protection of the airways against the constrictor effect of inhaled histamine without having any significant effect on the response to methacholine [8, 13].

Previous studies using histamine H_1-receptor antagonists administered either by inhalation [14] or orally [15] have reported a protective effect against subsequent exercise-induced bronchoconstriction. PATEL [16] showed that oral terfenadine given to asthmatic subjects in a dose of 180 mg 4 h prior to exercise challenge reduced the mean maximum post-exercise fall in FEV_1 from baseline by about one third. Our study has shown that terfenadine administered in the same dose 3 h prior to exercise gives about the same degree of protection, in reducing the mean fall in FEV_1 by 35% (table 3). The protective effect showed no correlation with the absolute baseline values of FEV_1, indicating that the action of terfenadine did not depend on an effect on baseline airway calibre. When investigating the protective effect of this drug against the bronchoconstrictor action of inhaled histamine, up to 50 fold differences in efficacy were observed [8] and it is possible that the variability in inhibition of EIA observed in our study is partly a function of the pharmacodynamics of terfenadine rather than entirely due to a variable contribution of histamine to the response. On the basis of the specificity of terfenadine for the histamine H_1-receptor [13], our results point to an important role for histamine in EIA.

The present study is the first to show an inhibitory effect of a cyclooxygenase inhibitor on EIA itself. Previous evidence for the possible role of eicosanoids in

EIA comes from studies using high airflow as the stimulus. TOGIAS *et al.* [17] found elevated levels of prostaglandin (PG) D_2 in nasal washings following nasal cold air challenge in subjects with rhinorrhoea. FREED *et al.* [18] in anaesthetized normal dogs showed an increase in peripheral airways resistance after high flow dry air challenge, and a clear increase in levels of PGD_2 in lavage fluid. It is likely, therefore, that cooling and drying of the bronchial mucosa of patients with asthma is sufficient to release newly formed mast cell mediators in addition to preformed histamine.

Our findings conflict with previous work in exercise using indomethacin as an inhibitor of lung cyclooxygenase [19, 20]. O'BYRNE and JONES [19] employed a regimen of 3 days' treatment with indomethacin 100 mg daily and failed to show an inhibitory effect on EIA, although a milder degree of bronchoconstriction was induced in their asthmatic subjects compared with ours (a mean fall in FEV_1 of 19% compared with 39% in our study). It is possible that the extent of prostaglandin release is related to the strength of the exercise stimulus. Alternatively, differences in the sensitivity of lung cyclooxygenases to the two drugs and access of the drugs to luminal inflammatory cells may lead to differences in the degree to which the generation of bronchoconstrictor and bronchodilator eicosanoids are inhibited. In support of this, flurbiprofen has been shown to inhibit the immediate bronchoconstrictor response to bronchial allergen challenge, attributed to inhibition of bronchoconstrictor prostanoid generation [9], whereas indomethacin is without consistent effect [21]. In contrast, indomethacin pretreatment inhibits refractoriness to repeated challenge with exercise [19, 20] and bronchial hypotonic challenge [22], ascribed to inhibition of the generation of bronchodilator prostanoids. Indomethacin treatment prior to bronchial allergen challenge reduces the rise in plasma thromboxane levels, while augmenting the increase in plasma levels of 6-keto-$PGF_{1\alpha}$ [23], suggesting that indomethacin does not uniformly abolish pulmonary cyclooxygenase activity *in vivo* at conventional doses. This is supported by work in the isolated dog lung where indomethacin has been shown to have differential effects on parenchymal prostanoid generation, for example markedly reducing levels of 6-keto-$PGF_{1\alpha}$ at a drug concentration without any effect on tissue levels of $PGF_{2\alpha}$ [24]. In addition, UNDEM *et al.* [25] demonstrated that indomethacin incubation of finely minced suspended human lung fragments augmented the release of sulphidopeptide leukotrienes following antigen challenge. Thus, any effect of indomethacin on mast cell derived contractile prostaglandins may be masked by a concomitant increase in the release of contractile leukotrienes.

We chose the propionic acid derivative flurbiprofen because of its specificity and potency as a cyclooxygenase inhibitor. It has been shown to be 2,000 times more potent than aspirin and 10 times more potent than indomethacin as an inhibitor of guinea-pig lung microsomal cyclooxygenase, having an IC_{50} of 10^{-7} M [26, 27]. Other activities which have been studied include a membrane-stabilizing effect at therapeutic levels on erythrocytes similar to that exhibited by indomethacin [28] although the relevance of this observation is debatable, and an absence of an inhibitory effect on the release of β-glucuronidase from mouse peritoneal macrophages, a model in which indomethacin has an inhibitory effect [29]. Flurbiprofen potently inhibits the generation of cyclooxygenase products from suspended human lung tissue (IC_{50} 1.4 nM) while having no significant effect on leukotriene generation [30]. We have previously shown this drug had no effect on non-specific airways reactivity when administered as a single oral dose [31]. Thus, the most likely explanation for the inhibitory action of flurbiprofen in EIA is the suppression of stimulus-related generation of bronchoconstrictor prostanoids.

Assuming that histamine and prostaglandin release both contribute to exercise-induced bronchoconstriction, and their effects are independent of one another, one would expect the protective effects of terfenadine and flurbiprofen to be at least additive. Indeed, by interacting equiconstrictor concentrations of PGD_2 and histamine, we have shown an additive constrictor effect on airway calibre [32]. In the present study the overall inhibitory influence of the drug combination, although significant, was less than that exhibited by either drug alone. This lack of an additive effect has been noted previously when these drugs were used to inhibit bronchoconstriction by adenosine 5'-monophosphate [33]. The lack of an additive interaction between terfenadine and flurbiprofen may indicate that prostanoid release comprises a component of bronchoconstriction induced by endogenously released histamine in asthma. A precedent for this has already been set by showing that histamine can release an array of prostanoids from human lung tissue *in vitro* [34]. These include PGE_2 and PGI_2, which are bronchodilator agonists [35, 36], and the bronchoconstrictor $PGF_{2\alpha}$. The combined effects of these prostanoids on airway calibre has not been determined. Moreover, prostaglandins E_1 and $F_{2\alpha}$ inhibit histamine release from human lung tissue in response to IgE- dependent stimuli at high concentrations, while augmenting the response at low concentrations [37], indicating their capacity to modulate mast cell function [38].

From this study we conclude that both histamine and prostanoids contribute as mediators in the pathogenesis of EIA. For histamine, the likely source is mast cells. While this may also be true for contractile prostaglandins such as PGD_2, our data with flurbiprofen suggests a complex interaction between histamine release and endogenous synthesis of prostaglandins. The level at which this interaction occurs cannot be determined until more specific inhibitors of prostaglandin-mediated effects become available.

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Preuve des rôles de l'histamine et de la prostaglandine comme médiateurs dans l'asthme d'effort: l'effet inhibiteur de la terfenadine et du flurbiprofen seuls et en combinaison. J.P. Finnerty, S.T. Holgate.

RÉSUMÉ: L'activation des mastocytes a été impliquée dans la bronchoconstriction induite par l'effort. Nous avons investigué les effets de la terfenadine, un antagoniste des récepteurs histaminiques H_1, et du flurbiprofen, un inhibiteur de la cyclo-oxygénase, sur la bronchoconstriction induite par l'effort, afin d'apprécier la contribution des produits mastocytaires que sont l'histamine et les prostaglandins à cette réponse. Huit sujets asthmatiques, dont l'asthme d'effort avait été documenté antérieurement, ont été étudiés à 4 reprises. La terfenadine ou un placebo ont été administrés 3 heures avant l'effort, et le flurbiprofen ou un placebo administrés 2 heures avant l'effort, dans un essai randomisé en double aveugle. La provocation consistait en un effort sur tapis roulant pendant 6 minutes, avec inspiration d'air sec à la température ambiante. Le calibre des voies aériennes a été déterminé par mesure du VEMS (FEV_1) immédiatement avant la provocation d'effort et pendant 30 minutes après l'effort. La réponse à la provocation d'effort a été examinée, à la fois sous forme du pourcentage maximum du chute du VEMS et de la zone sous la courbe (AUC) du pourcentage de chute du VEMS contre le temps pendant 30 minutes. Après placebo, le pourcentage moyen de chute maximum du VEMs est de 39%; celui-ci s'abaisse à 25% après terfenadine ($p<0.05$) et à 27% après flurbiprofen ($p<0.05$), alors qu'après la combinaison des deux produits actifs, la chute moyenne est réduite à 30%, ce qui n'atteint pas une signification statistique. L'analyse des données de "surface sous la courbe" montre une inhibition significative de la bronchoconstriction induite par l'effort au cours des 3 jours d'administration des produits actifs ($p<0.05$). Nous concluons que, la libération d'histamine comme la production de prostaglandine, peut-être d'origine mastocytaire, contribuent au développement de la bronchoconstriction induite par l'effort, quoique l'interaction entre ces divers médiateurs apparaisse comme complexe.

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