

Safety of a specific COX-2 inhibitor in aspirin-induced asthma

A. SZCZEKLIK, E. NIZANKOWSKA, G. BOCHENEK, K. NAGRABA, F. MEJZA and M. SWIERCZYNSKA

Department of Medicine, Jagellonian University School of Medicine, Cracow, Poland

Summary

Background In a subset of patients with asthma, aspirin and several other non-steroidal anti-inflammatory drugs (NSAID) that inhibit simultaneously cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) precipitate dangerous asthmatic attacks.

Objective We tested the hypothesis that in patients with aspirin-induced asthma the attacks are triggered by inhibition of COX-1 and not COX-2.

Methods and results In twelve asthmatic patients (seven men, five women, average age 39 years) oral aspirin challenge precipitated symptoms of bronchial obstruction with fall in $FEV_1 > 20\%$, and a rise in urinary leukotriene E_4 (LTE_4) excretion; also in five patients the stable metabolite of PGD_2 , $9\alpha,11\beta PGF_2$, increased in urine. The patients then entered a double-blind, placebo-controlled, cross-over study in which they received either placebo or rofecoxib in increasing doses 1.5–25.0 mg for 5 consecutive days, separated by a 1-week wash-out period. No patient on rofecoxib developed dyspnoea or fall in $FEV_1 > 20\%$; mean urinary LTE_4 and $9\alpha,11\beta PGF_2$ urinary levels, measured on each study day for 6 h post-dosing, remained unchanged. Two patients on placebo experienced moderate dyspnoea without alterations in urinary metabolites excretion. At least 2 weeks after completion of the study, all patients received on an open basis 25 mg rofecoxib without any adverse effects.

Conclusions NSAID that inhibit COX-1, but not COX-2, trigger asthmatic attacks in patients with asthma and aspirin intolerance. Rofecoxib can be administered to patients with aspirin-induced asthma.

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Introduction

Most people tolerate aspirin well. Asthmatics, however, are an exception. There is a subset of patients with asthma in whom aspirin precipitates asthmatic attacks. This is a distinct clinical syndrome, called aspirin-induced asthma (AIA) [1,2]. It is not that seldom encountered, as in fact it affects about 10% of adult asthmatics and is under-diagnosed in the asthmatic population [3]. In a recent large European survey [4], 15% of asthmatic patients were utterly unaware of being aspirin-intolerant and realized it

only after provocation tests had been carried out on them. According to Sampson [3], the reason for under-reporting aspirin sensitivity may include the deliberate avoidance of aspirin and other NSAID by asthmatics aware of the risk of adverse reactions, or a lack of recognition by patients of the mild reactions due to the delayed onset of symptoms following aspirin ingestion. In patients with AIA, asthmatic attacks, usually accompanied by naso-ocular symptoms, can be triggered not only by aspirin, but by several other non-steroid anti-inflammatory drugs (NSAID), a fact which makes immunological cross-reactivity most unlikely. The propensity of an NSAID to precipitate bronchoconstriction in such patients is related to its pharmacological efficacy in inhibiting cyclooxygenase (COX) [5].

Correspondence: A. Szczeklik, Department of Medicine, Jagellonian University School of Medicine, 8 Skawinska Street, 31-066 Cracow, Poland. E-mail: mmszczek@cyf-kr.edu.pl

The enzyme, which appears to be central to the mechanism of aspirin intolerance exists in at least two isoforms, COX-1 and COX-2, encoded by distinct genes. Both isoforms are present in normal human respiratory epithelium [6,7], and their expression is similar in bronchial biopsies of aspirin-tolerant and aspirin-intolerant asthmatic patients [8]. Aspirin, indomethacin, naproxen, ibuprofen and ketoprofen, which at low doses precipitate asthmatic attacks in sensitive patients, are more potent inhibitors of COX-1 than of COX-2 [9]. Nimesulide and meloxicam, drugs known to inhibit COX-2 preferentially, are usually well tolerated at moderate doses but cause bronchial obstruction at higher doses [10,11].

The choice of safe NSAID is very restricted in AIA [12]. The adverse reactions can be life-threatening and are feared by both patients and doctors. We wondered whether rofecoxib, a highly specific COX-2 inhibitor [13,14], would be a safe alternative. We therefore studied its tolerability in a group of patients with AIA. We coupled the clinical observation with assessment of the release of cysteinyl-leukotrienes and prostaglandin D₂ —the key mediators of bronchial obstruction triggered off by aspirin-like drugs.

Patients and methods

Patients

Twelve patients with diagnosis of AIA, confirmed by aspirin provocation tests completed the study. Their clinical characteristics are shown in Table 1. Eleven of the patients studied suffered also from chronic rhinosinusitis, 10 had had nasal polyps diagnosed in the past. Aminophylline and long-acting β_2 -mimetics were withheld for 48 h before the study. Short-term β_2 -mimetics were not allowed 8 h before the study procedure. The doses of both oral (two patients on

4 mg methylprednisolone/day) and inhaled corticosteroids remained unchanged throughout the period of the study.

Within the 3 months preceding the proper study, independently from the protocol for this study, the subjects underwent placebo-controlled, oral aspirin challenge tests with urinary LTE₄ and 9 α ,11 β PGF₂ measurements. The patients then entered a double-blind, placebo controlled, cross-over study, consisting of two 5-day challenge periods. Every morning a single dose of the active drug or placebo was administered. On the first of the challenge days placebo was given to all patients. Rofecoxib was administered on days 2–5 in progressively increasing doses: 1.25, 5, 12.5 and 25 mg. Following a 1-week wash-out period the patients who received the rofecoxib were switched over to placebo and vice versa. All patients were hospitalized twice for 5 consecutive days for each of the periods. Clinical observation, spirometry and nasal flows were carried out every 30 min for 8 h post-dose, then every 2 hours for the next 4 h, and finally after 24 h, prior to the next day dosing. Two-hour urine samples were collected at baseline and at 2, 4, 6 and 8 h for the determination of cysteinyl leukotrienes and 9 α ,11 β PGF₂ during consecutive days of the study. It was decided that the presence of the following reactions should terminate any further challenge: asthma attack, > 20% drop in FEV₁, or definite naso-ocular or laryngospastic reactions. At least 2 weeks after completing the double-blind study, all the patients were hospitalized, and received on an open basis 25 mg rofecoxib followed by 24 h clinical observation and pulmonary function testing.

Challenge tests

Pulmonary function tests with measurement of FEV₁, FVC, ME_F₅₀ were carried out with the aid of a spirometer

Table 1. Patients' characteristics

Characteristics	Values
Number of subjects	12
Sex, F/M	5/7
Age (yr), mean, range	38.9 (20–60)
Duration of asthma (yr), mean, range	8.75 (2–24)
FEV ₁ – initial value (%predicted), mean, range	86.8 (62.2–112.6)
Peripheral blood eosinophilia (% in blood smear), mean, range	7 (1–16)
Dose of inhaled steroids (μ g/24 h), mean, range	900 (0–1600)
Basal urinary LTE ₄ excretion (pg/mg creatinine), geometric mean (95%CI)	1164.8 (692.1–2523.7)
Basal urinary 9 α ,11 β PGF ₂ excretion (ng/mg creatinine), mean $\pm$ SEM	1.12 $\pm$ 0.1

Pneumo 2000 (abc MED, Cracow, Poland), and peak expiratory flow (PEF) was measured using a peak flow meter (Clement Clarke International Ltd, Edinburgh, UK).

Oral challenge test with aspirin [15] was carried out on 2 consecutive days. On the first day, two capsules of placebo, separated by 2.5 h, were administered; FEV₁ values were allowed to vary by <15% from baseline. If greater variations in FEV₁ occurred, the patient was considered not to be in a stable condition and was excluded from further testing. On the second day, the patient received incremental doses of acetylsalicylic acid up to a total dose of 500 mg. Clinical observations and pulmonary function tests were recorded every 30 min. The challenge procedure was interrupted if a decrease of at least 20% in FEV₁ was observed or when severe extrabronchial symptoms appeared. The provocative dose causing a 20% fall in FEV₁ was calculated and recorded as PD₂₀.

Urine collection and analysis

In aspirin provocation tests the urine samples were collected at baseline, and then 2, 4 and 6 h after FEV₁ fall >20% or after administration of the second capsule of placebo.

LTE₄ excretion was analysed by an enzyme-linked immunosorbent assay (ELISA, Cayman Chemicals, Ann Arbor, MI, USA) as reported by Kumlin et al. [16].

Excretion of 9 α ,11 β PGF₂ was analysed by gas chromatography/mass spectrometry using the electron impact method according to Nagakura et al. [17].

Genotyping and data analysis

Genotyping for LTC₄ synthase polymorphism was performed as described previously [18].

In the statistical evaluation the differences between variables were analysed using Student's *t*-test and variance analysis. The assumption of normality was verified using the Shapiro–Wilk test. Correlation between variables was estimated using the Pearson correlation coefficient. Calculations were made with *Statistica* software by StatSoft (Tulsa, OK, USA).

Results

Aspirin provocation tests

In all patients oral aspirin challenge triggered dyspnea and a fall in FEV₁ >20% (Fig. 1). Nasal discharge and/or nasal blockade developed in nine subjects, itching of the eyes in five, headache in five, gastro-intestinal discomfort in four, and facial rash in two. Mean aspirin PD₂₀ was 98.3 mg (range 52–175 mg). The symptoms were relieved

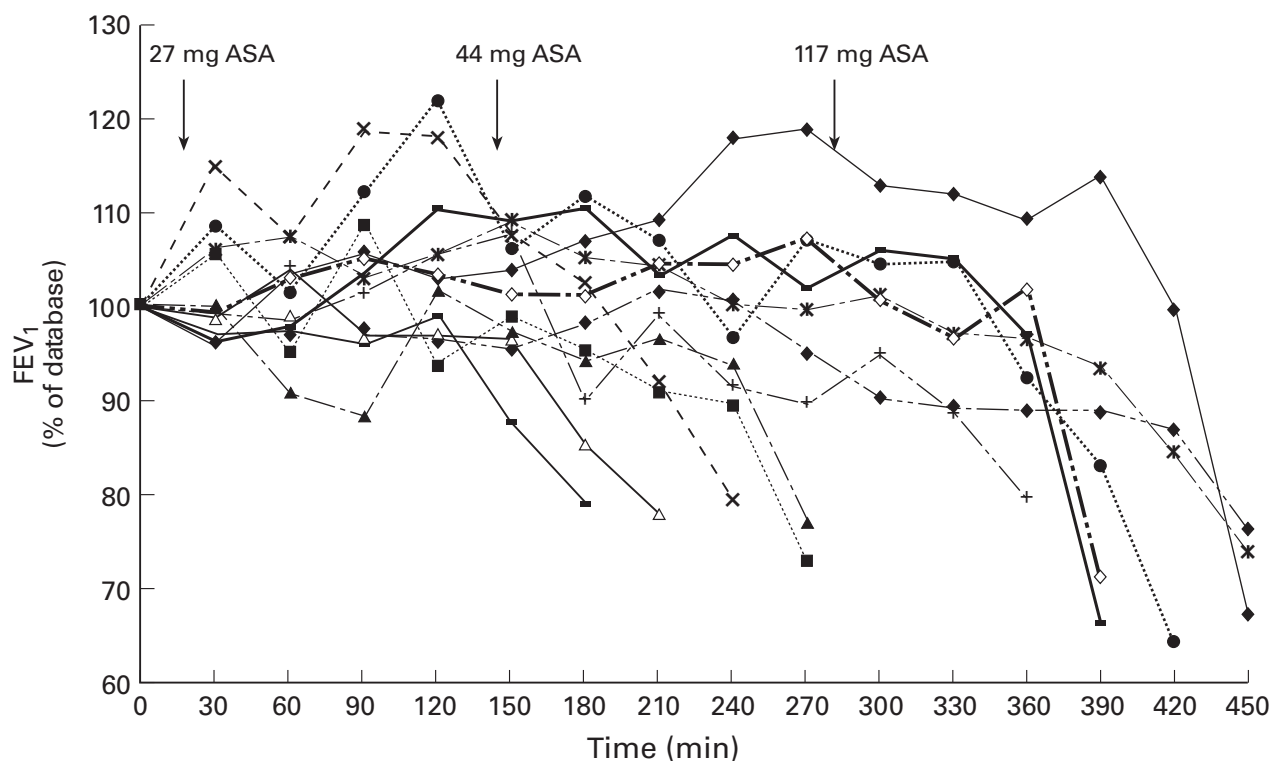


Fig. 1. Oral aspirin challenge in 12 individual AIA patients.

Time of sampling	After aspirin		After placebo		<i>P</i>
	Mean	CI	Mean	CI	
0	1152.5	814.9–2441.4	1164.7	692.1–2523.7	0.65
0–2	1967.4	1484.1–4717.1	782.4	501.4–1681.5	0.022
2–4	3885.9	2231.0–12640.2	543.1	235.0–1451.9	0.018
4–6	5061.4	3344.5–20286.3	578.7	213.5–1889.0	0.018

Table 2. The geometric means and 95% CI of LTE₄, following aspirin vs. placebo, expressed as pg/mg creatinine

by β 2-mimetics and sporadically by corticosteroids. Placebo challenge was negative in all.

In all patients, except one, the reactions were accompanied by a marked rise in LTE₄ excretion (Table 2). Total amount of LTE₄ released over 6 h after aspirin was significantly higher ($P = 0.004$) than after placebo. No correlation was found between peak LTE₄ values and either aspirin PD₂₀ dose or LTC₄ synthase genotype. It is of interest that the only patient who showed no urinary LTE₄ response to aspirin, was also the only one without history of rhinitis. She had basal urinary LTE₄ approaching the range of normal subjects and responded to aspirin challenge with a 2.8-fold rise in urinary PGD₂ metabolite.

Excretion of 9 α ,11 β PGF₂ remained unchanged following aspirin challenge in seven of 12 patients, but showed a

1.8–2.8-fold increase in five patients. One subject had marked fluctuations in release of the PGD₂ metabolite both on placebo and aspirin.

Placebo challenge resulted in no significant changes of urinary excretion of either LTE₄ or 9 α ,11 β PGF₂.

Rofecoxib vs. placebo

All patients completed the 5-day-long rofecoxib testing. No patient developed dyspnea or a fall in FEV₁ > 20% (Fig. 2). One subject reported traces of blood in nasal discharge on days 3–5 of rofecoxib administration, another had transient urticaria lasting 30 min, after receiving 5 mg of rofecoxib, but not after the higher doses of the drug.

On the contrary, during the placebo period two subjects

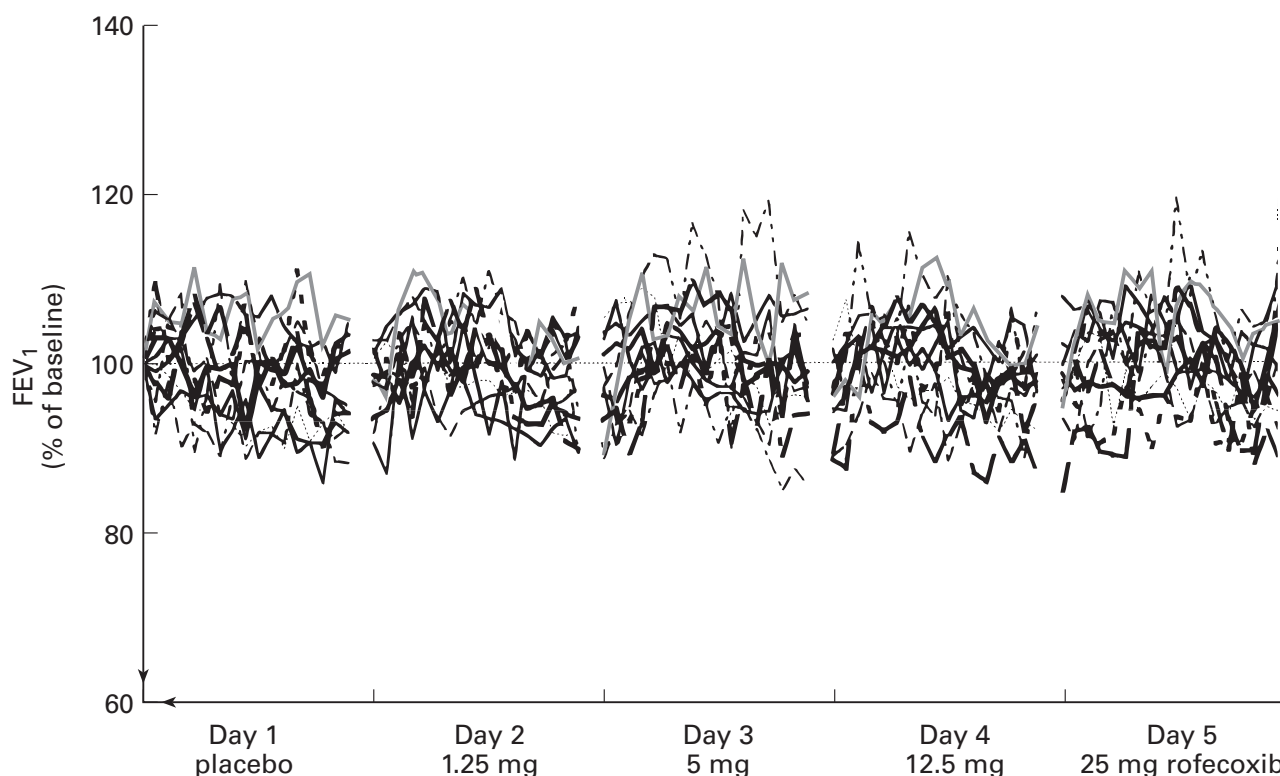


Fig. 2. Individual FEV₁ courses following oral rofecoxib challenge in 12 AIA patients.

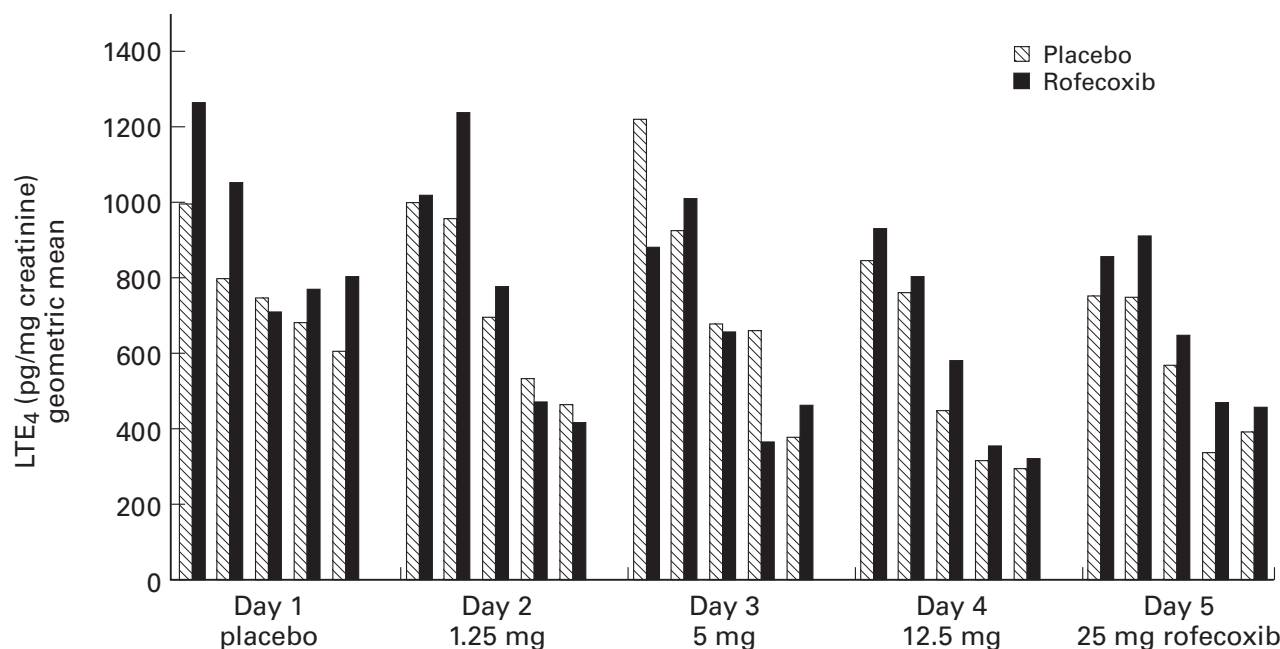


Fig. 3. Urinary LTE₄ excretion following rofecoxib challenge vs. placebo. On each study day urine was sample every 2 h for 8 h.

suffered from asthma attacks. In a 20-yr-old woman, on the second day of testing, 4 h after placebo, sudden shortness of breath and a 35% fall in FEV₁ occurred; symptoms resolved after salbutamol and 40 mg methylprednisolone. Next day she had a regular menstrual period; she was known to have premenstrual asthma exacerbations in the past. In a 37-yr-old man bronchoconstriction gradually developed into an asthma attack on the third day of placebo administration. This was accompanied by a 70% rise in urinary PGD₂ metabolite, but not a rise in LTE₄. Despite treatment with β 2-mimetics and corticosteroids, the attacks occurred again on 2 consecutive nights. Before the placebo administration this patient's FEV₁ was the lowest of the whole group (61% predicted), and for the 3 days preceding the attack he had the highest basal urinary LTE₄ levels (4.500–5.500 pg/mg creatinine), exceeding five times the basal values he had at the time of aspirin challenge. Two other patients receiving placebo experienced short lasting single episodes of epistaxis, headache or itching of eyelids.

Statistical analysis revealed no changes in urinary excretion of LTE₄ (Fig. 3) and 9 α ,11 β PGF₂ (data not shown) over the periods of rofecoxib or placebo administration. In five patients who responded to aspirin with a rise in 9 α ,11 β PGF₂, rofecoxib had no effect on this urinary metabolite.

Single administration of 25 mg rofecoxib

Following administration of rofecoxib in a single 25 mg

dose no adverse symptoms were recorded in any patient over a 24-h observation period; FEV₁ showed no change.

Discussion

Although the number of the patients studied by us was limited, we performed multiple evaluations of the sensitive biochemical markers known to reflect intolerance to aspirin in asthma. Indeed, a distinct urinary LTE₄ rise occurred in 11 of 12 patients following aspirin challenge, but in none following placebo. Intensity of the response was not related either to aspirin dose, as reported by some [19], though not all [16,20], authors, or to LTC₄ synthase genetic polymorphism [21]. Contrary to the results obtained in 24 AIA patients subjected to inhalation challenge with lysine-aspirin [22], we did not observe the effect of the polymorphism on LTE₄ excretion in 12 patients who underwent oral aspirin challenge. Much stronger LTE₄ response to oral than to inhaled aspirin challenge [15], could have overshadowed the possible influence of the polymorphism.

Another marker assessed by us was PGD₂, measured as its stable metabolite in urine. In AIA patients release of PGD₂ in response to aspirin challenge has been less studied [23] than LTE₄ response and found to be less consistent. When lysine-aspirin was instilled in a segmental bronchus of 11 AIA patients [24], two responded with massive release of PGD₂ into BAL, three showed no changes, and six exhibited a fall in PGD₂ values of varying intensity. In another study [25], following inhalation challenge with

lysine-aspirin, the major urinary metabolite of PGD₂ increased in six of nine AIA patients, became moderately depressed in two, and remained unchanged in one. Similarly, out of 12 patients studied by us, only five showed a distinct rise in the urinary PGD₂ metabolite following aspirin challenge. Increase in PGD₂ release following aspirin is believed to reflect mast cell activation in AIA [20,25,26].

In the 12 patients studied, aspirin triggered signs of bronchial obstruction, usually accompanied by facial rash and naso-ocular symptoms, a rise in urinary LTE₄ and occasionally also an increase in urinary PGD₂ stable metabolite. Rofecoxib was free of all these actions. In a controlled, double-blind study it fared even better than placebo, the use of which was associated, most likely accidentally, with asthma attacks in two cases. These results suggest that rofecoxib can be taken by patients with AIA. However, much larger studies are needed to preclude the possibility of rare exacerbations occurring in patients with more severe NSAID-intolerance than those studied here, and in patients taking larger doses of rofecoxib for long periods. The problem is of clinical importance, since aspirin intolerance is a marker of severe asthma, and appears to be under-diagnosed in the asthmatic population. Under-reporting and under-diagnosis of aspirin sensitivity may have serious consequences. In a large French survey [27], 25% of asthmatic patients requiring emergency mechanical ventilation were found to suffer from AIA. Introduction into therapy of a 'better aspirin' [28] might be of substantial benefit to patients with asthma.

There is sufficient evidence to indicate that aspirin precipitates asthmatic attacks in sensitive patients not through an allergic mechanism, but by a pharmacological action, namely by inhibition of cyclooxygenase [1,3,29]. The expression of COX-1 and COX-2 is similar in bronchial biopsy specimens obtained from ASA-tolerant and ASA-intolerant patients [8], while in nasal polyps COX-2 expression and activity appears to be diminished [30,31]. The results presented in this study indicate that in AIA, COX-1 might be the culprit and not COX-2 isoform. Therefore, inhibition of COX-2 was not associated with a rise in LTE₄ output. Interestingly, rofecoxib, contrary to indomethacin [32], had no effect on urinary levels of the stable PGD₂ metabolite. It follows that this prostaglandin is not synthesized via COX-2 in AIA. The reason for the altered response of COX-1 to aspirin in AIA eludes us. A latent virus infection could affect COX-1 function [24]; such an hypothesis remains to be proved.

Acknowledgements

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