Hypersensitivity to aspirin: Common eicosanoid alterations in urticaria and asthma

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Background: Aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) can precipitate adverse reactions in two apparently different clinical conditions: bronchial asthma and chronic idiopathic urticaria (CIU). Recent evidence indicates that the reactions are triggered by the drugs that inhibit cyclooxygenase-1 but not cyclooxygenase-2.
Objective: To assess whether patients with CIU and aspirin sensitivity share common eicosanoid alterations with patients who have aspirin-sensitive asthma.
Methods: Seventy-four patients with CIU and a history of sensitivity to aspirin and NSAIDs underwent placebo-controlled oral aspirin challenge tests. Concentrations of urinary leukotriene E4 (uLTE4) were measured by ELISA and plasma stable prostaglandin D2 metabolite, 9α,11β prostaglandin F_2 by GC/MS. All measurements were carried out at baseline and after aspirin dosing. Patients were genotyped for the leukotriene C4 synthase (LTC4S) promoter single nucleotide polymorphism.
Results: In 30 of 74 patients, the aspirin challenge was positive, resulting in urticaria/angioedema. In these 30 patients, baseline uLTE4 levels were higher than in nonresponders and the healthy control subjects and increased further (significantly) after the onset of clinical reaction. No such increase occurred in subjects with negative aspirin challenge. Baseline uLTE4 levels correlated with severity of skin reactions. Plasma 9α,11β prostaglandin F_2 levels rose significantly in both aspirin responders and nonresponders, although in the latter group the increase occurred later than in the former. In patients who reacted to aspirin, frequency of $_{-444}$C allele of LTC4S was significantly higher than in patients who did not react.
Conclusions: CIU with aspirin sensitivity is characterized by the eicosanoid alterations, which are similar to those present in aspirin-induced asthma. (J Allergy Clin Immunol 2004;113:771-5.)

Key words: *Urticaria, eicosanoids, aspirin, NSAIDs, asthma*

Shortly after its introduction into therapy, aspirin was implicated as the cause of an anaphylactic reaction. The first case report of acute angioedema/urticaria was published in 1902.[1] Soon it was realized that aspirin might also precipitate violent acute bronchospasm. Over the years, it became evident that aspirin-induced asthma (AIA), as it started to be called, is a distinct clinical syndrome affecting 5% to 10 % of adults with asthma.[2,3] It develops according to a characteristic sequence of symptoms and follows a clinical course that is similar all over Europe[4] and in the United States.[5] Asthmatic attacks triggered by aspirin are associated with inhibition of cyclooxygenase,[6] specifically COX-1 but not COX-2, and are characterized by overproduction of cysteinyl leukotrienes.[3] The interest in AIA has been recently enhanced by introduction into therapy of leukotriene receptor antagonists[7] and by discovery of new cyclooxygenases.[8]

In contrast to AIA, progress in understanding urticaria/angioedema sensitive to aspirin has been slow. Clinicians have been well aware that up to 40% of patients with chronic urticaria have an increase in wheals and swelling after aspirin. It was reported that in some of them not only aspirin but several other NSAIDs that inhibit COX precipitated skin eruptions.[9] However, no studies on eicosanoid metabolism have been carried out.

We and others[10-15] have observed recently that coxibs, selective COX-2 inhibitors, do not precipitate wheals and swelling in patients with chronic urticaria who are sensitive to aspirin. Furthermore, we also noticed that NSAID sensitivity in urticaria is associated with overproduction of cys-LTs, as reflected by increased basal excretion of LTE_4.[10,11] These data were reminiscent of aspirin-induced asthma.[3] We therefore decided to study in a group of patients with chronic idiopathic urticaria (CIU) effects of aspirin on two major mediators: cys-LTs and prostaglandin (PG) D_2.

METHODS

Subjects

The study population consisted of 74 patients with CIU in apparent remission, that is, without any skin symptoms for at least 4 weeks preceding the study (Table I). Diagnosis of CIU required presence of urticaria and/or angioedema every day or almost every day for more than 6 weeks over the last 0.5 to 6 years. All patients gave the history of skin reactions after the ingestion of aspirin or other NSAIDs but had no history of asthma, nasal polyps, or anaphylaxis. Two weeks before beginning of the study, any local steroids or antihistamines and leukotriene receptor antagonists were stopped. Patients were asked to avoid over-the-counter medications and food with artificial flavoring or preservatives. A group of healthy control subjects for comparison of basal urinary LTE_4 and plasma 9α,11βPGF_2 levels consisted of 52 healthy subjects (Table I). They were healthy and had no history of CIU, asthma, or atopic diseases. The patients gave informed consent, and the study was approved by the University Ethics Committee.

Study design

After a 2-week run-in period, the patients underwent aspirin testing. The single-blind, placebo-controlled oral challenge test with aspirin was carried out on 2 consecutive days. On day 1, 3 capsules of

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Abbreviations used
CIU: Chronic idiopathic urticaria
COX: Cyclooxygenase
cys-LTs: Cysteinyl leukotrienes
GC-MS: Gas chromatography—negative ion chemical ionization—mass spectrometry
LRA: Leukotriene receptor antagonist
LT: Leukotriene
LTC4S: Leukotriene C4 synthase
NSAIDs: Nonsteroidal anti-inflammatory drugs
PASI: Psoriasis Area and Severity Index
PG: Prostaglandin
uLTE4: Urinary leukotriene E4
$9\alpha,11\beta PGF_2$: Plasma stable prostaglandin D2 metabolite

placebo were administered every hour. On day 2, the patients were challenged with increasing doses of 71, 117, and 312 mg of aspirin at 1-hour intervals. Aspirin and placebo had identical appearance. The challenge procedure with aspirin was interrupted if a cutaneous reaction was observed or when extracutaneous symptoms (bronchospasm, rhinorrhoea, nasal congestion) appeared or if the maximum cumulative dose of aspirin was reached.

FEV_1 and skin reactions were recorded at baseline, before the challenge tests, and then every 15 minutes until 6 hours after the last dose of aspirin or placebo. In patients with positive aspirin challenge, urine samples were collected for LTE_4 estimations at baseline, at the time of appearance of the first skin symptoms (time 0), and then 2 and 4 hours later. In nonresponders, the urine samples were collected at baseline, 1 hour after the last aspirin dosing, that is, when the cumulative dose of 500 mg was reached (time 0), and then 2 and 4 hours later.

Blood for determination of the PGD_2 stable metabolite $9\alpha,11\beta PGF_2$ was collected at baseline, at the time of appearance of the first skin symptoms after aspirin challenge (time 0), and 60, 120, and 240 minutes after the appearance of skin reaction. In nonresponders, blood was drawn at baseline, 1 hour after reaching the dose 500 mg aspirin (time 0), and then 60, 120, and 240 minutes later.

Genomic DNA samples were obtained from peripheral blood of 71 patients (29 reacting to aspirin challenge and 42 nonreacting to aspirin).

Assessment of severity of skin eruption

To standardize the assessment of severity of the skin eruptions, a modified PASI (Psoriasis Area and Severity Index) score was used.[16] For the assessment of urticaria, itching replaced desquamation in the index. Thus, we determined the degree of itching, erythema, and infiltration, expressed as a percentage of involvement of the four main body areas: head, trunk, upper extremity, and lower extremity. Each variable was assessed on a scale of 0 to 4, with 0 indicating no skin involvement and 4 indicating the severe involvement. Calculated PASI score could range from 0 to 72, with 0 indicating no reaction at all and 72 a very serious reaction affecting most of the body. We considered PASI $\geq$10 as severe reaction. PASI score determinations were carried out by an experienced dermatologist at the time of the first appearance of skin lesions and 2, 4, and 6 hours later.

Lung function

Pulmonary function tests were performed on a flow-integrating computerized pneumotachograph (Pneumocsreen, E. Jaeger, Germany).

Biochemical assays

Urinary LTE_4 was measured in unpurified urine samples by direct enzyme immunoassay (Cayman Chemical, Ann Arbor, Mich).[17] Measurements were made at the same time, in duplicates, using the same kit, and expressed in nanograms per milligram of creatinine.

$9\alpha,11\beta PGF_2$ was measured in plasma by gas chromatography—negative ion chemical ionization—mass spectrometry (GC-MS, Hewlett Packard, Palo Alto, Calif) after the extraction stage, through use of a C18 Sep-Pak cartridge, derivatization to pentafluorobenzyl ester, thin-layer chromatography purification, and derivatization to trimethylsilyl ether. [$^2H_4$] $9\alpha,11\beta PGF_2\alpha$ was used as an internal standard in a manner identical to gas chromatography—electron impact mass spectrometry, as reported by Obata et al.[18] Results are expressed in picograms per milliliter.

The LTC_4 synthase single nucleotide polymorphism at a site 444 nucleotides upstream of the translation start was genotyped as described previously.[19]

Statistical analysis

Statistical evaluation was carried out with the use of a personal computer and STATISTICA software (Statsoft Inc). Summary statistics were expressed as median and 25% and 75% percentiles. A multiway ANOVA model, including time as a repeated-measure factor, other factors, and all possible interactions, was used for multiple-group comparisons. The logarithmic transformation was used, when needed, as a variance stabilizing transformation. The post hoc Tukey procedure was used for multiple comparisons. Fisher exact test was used for dichotomous data for two independent random samples. A P value $\leq$.05 was considered statistically significant.

RESULTS

Clinical reactions

None of the patients had symptoms after administration of placebo. Thirty patients challenged with aspirin had cutaneous rash. There was no statistical difference in clinical characteristics between the patients with positive aspirin challenge test and the nonresponders (Table I). Skin reactions developed after 71 mg in 1 subject, after 188 mg in 9 subjects, and after 500 mg of cumulative dose of acetylsalicylic acid in 20. The clinical appearance of the rash was consistent with urticaria and angioedema. In 11 patients, PASI score was $\geq$10, and these patients were therefore considered to have severe reactions, whereas in the remaining 19 patients, PASI score was $<$10.

In 27 of 30 patients who reacted to aspirin, the challenge produced no dyspnea, and spirometic values remained stable throughout the observation period. One patient, after ingestion of aspirin at a dose 188 mg, and 2 others after a dose of 500 mg, had rhinorrhea, conjunctivitis, and shortness of breath, with FEV_1 drop exceeding 20%; all these symptoms preceded development of urticaria. The urinary baseline LTE_4 in these 3 subjects who had dual respiratory/urticarial response were as follows: 592, 538, and 1095 ng/mg creatinine; the peak values after aspirin were 4375, 676, and 1819 ng/mg creatinine, respectively. Baseline $9\alpha,11\beta$PGF2 values were 5.1, 4.9, and 4.2pg/mL; the peak values reached after aspirin were 15.5, 5.9, and 5.7 pg/mL, respectively.

Urinary LTE_4

Baseline urinary LTE_4 excretion (Table I) was higher in patients with a positive aspirin test than in patients with a negative aspirin test (P = .005). The latter group, in turn, differed from healthy subjects (P = .0001). Urinary LTE_4 levels did not increase at 2 hours (P = .07) and increased

TABLE I. Characteristics of the subjects studied

	Patients		
	Aspirin challenge positive (n = 30)	Aspirin challenge negative (n = 44)	Healthy control subjects (n = 48)
Sex W/M	23/7	32/12	35/13
Age, y	48 (34-52)	42 (28-49)	43 (30-48)
Total IgE, IU/mL	132.5 (64.6-233)	93.0 (31.4-324.5)	—
Duration of urticaria, y	2 (1-5)	2 (0.5-6)	—
Urinary LTE_4 ng/mg creatinine	535.5 (270.0-1026)	285.5 (178.0-390.0)	110.0 (58.0-152.0)
Plasma 9α,11βPGF_2 pg/mL	4.85 (3.80-6.10)	4.25 (3.05-6.04)	4.55 (2.9-6.0)
Genotype of LTC_4S			
AA	9	26	
AC	16	13	
CC	4	3	

Median (25% to 75% percentiles; lower and upper quartile).

at 4 hours ($P = .03$) after aspirin challenge tests, as compared with baseline values, only in the group of patients with the positive aspirin challenge (Fig 1).

At baseline and after aspirin challenge, urinary LTE_4 levels were the highest in patients with severe skin reactions (PASI score ≥10). They differed significantly from patients with PASI score < 10 ($P = .002$) and from the group of aspirin nonresponders ($P < .001$). There was a moderate correlation between the baseline urinary levels of LTE_4 and the maximal intensity of skin eruption expressed as PASI score (Pearson r = 0.42; $P = .02$).

Plasma 9α,11βPGF_2

At baseline (Table I), plasma levels of 9α,11βPGF_2 did not differ between the three groups. After aspirin challenge, plasma concentrations of 9α,11βPGF_2 rose significantly in the group of patients who had clinical reaction ($P = .03$). They reached the peak 60 minutes after the onset of clinical reaction and returned to baseline values 1 hour later. An increase in the PGD_2 metabolite was recorded also in the group of patients who did not have a clinical reaction to aspirin. The rise appeared to proceed at slower pace; it reached the peak 120 minutes after the cumulative dose of aspirin and approached the baseline levels only 2 hours later (Fig 2). The dose of aspirin had no effect on magnitude of the response of 9α,11βPGF_2 and its duration. There was a tendency for higher baseline plasma concentrations of 9α,11βPGF_2 in patients with severe skin reactions (difference between the groups with PASI score ≥10 and < 10 was $P = .07$).

LTE_4 and 9α,11βPGF_2 levels were not measured in healthy subjects because they were previously documented not to change after aspirin challenge.[20,21]

LTC_4 synthase genotyping

There were 35 (49.3%) individuals homozygous for the wild-type allele (AA), 29 (40.8%) heterozygous, and 7 (9.9%) homozygous for $_{-444}$C allele (CC). Genotype distribution of LTC_4S polymorphism in patients with positive aspirin challenge was 31% (AA), 55.2% (AC), and 13.8% (CC), whereas among patients with negative challenge, there were 61.9% (AA), 31% (AC), and 7.1% (CC). In both groups of patients, genotype frequencies followed genetic equilibrium, though in aspirin responders $_{-444}$C-positive genotypes (AC or CC) were significantly more common ($P < .01$, Fisher exact test). Accordingly, frequency of $_{-444}$C allele in patients who reacted to aspirin was significantly higher than in patients who did not react ($q = 0.414$ vs $q = 0.226$; $P = .016$, Fisher exact test). The genotype and allele frequencies of the negative challenge group did not differ from population data on healthy subjects.[37]

DISCUSSION

All the patients studied by us had CIU and gave a history suggestive of aspirin sensitivity. When challenged with aspirin, only 40% had positive skin response. This clearly shows that aspirin hypersensitivity needs to be confirmed by provocation testing and also that it may show temporary fluctuations. The number of 40% aspirin responders corresponds to the upper level reported by the other authors[22,23] in an unselected population of CIU. Perhaps higher doses of aspirin exceeding 500 mg might have provoked a reaction in some negative patients.

The group of aspirin-sensitive patients had at baseline markedly elevated urinary LTE_4 levels, which distinguished them from both aspirin-tolerant CIU patients and the control group. Urinary LTE_4 values were the highest in the patients with most severe skin reactions. These results confirm our recent preliminary observations.[10,11] A novel finding is that aspirin precipitated a further statistically significant rise in urinary LTE_4 as compared with baseline values only in the group of patients who had clinical reactions after the response to challenge. When Di Lorenzo et al[24] compared urinary LTE_4 levels in 5 CIU patients sensitive to aspirin with 10 CIU tolerating aspirin well, they found no difference at baseline but an increase in LTE_4 after aspirin only in the former group. In vitro, release of cys-LTs by peripheral blood leukocytes from aspirin-sensitive asthmatic patients is dependent on PGE_2 biosynthesis, which becomes impaired by nonsteroidal anti-inflammatory drugs.[25] Our results might also explain good clinical response to therapy with leukotriene receptor antagonists (LRAs), reported[26,27] in most patients with chronic urticaria and aspirin sensitivity.

Cys-LTs, of which LTE_4 is the final urinary metabolite, can be produced by eosinophils and basophils. Both these

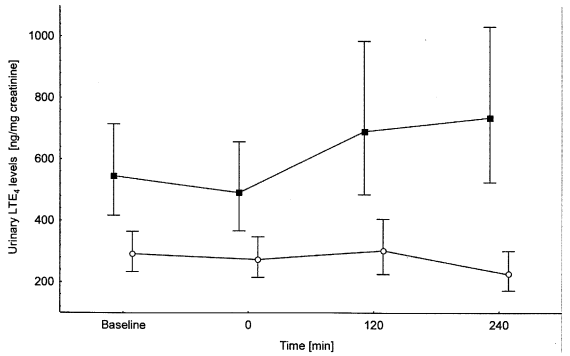

FIG 1. Urinary LTE_4 levels (means and 95% CI) after aspirin challenge in 30 patients with CIU who responded with clinical reaction (*squares*) and in 44 patients with CIU who showed no clinical response (*open circles*). In responders, urine was collected at baseline, at the time of appearance of the first symptoms (time 0), and then 2 and 4 hours later. In nonresponders, urine was collected at baseline, 1 hour after reaching 500 mg aspirin (time 0), and then 2 and 4 hours later. Baseline urinary LTE4 was significantly higher in aspirin-positive patients and increased significantly after aspirin only in this group. Mean values of urinary LTE_4 levels are expressed as ng/mg creatinine.

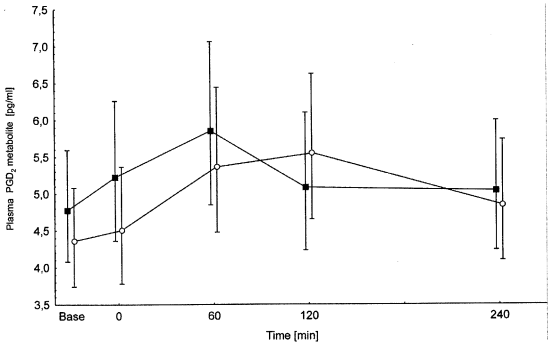

FIG 2. Plasma $9\alpha,11\beta PGF_2$ levels (means and 95% CI) after aspirin challenge in 30 patients with CIU who had clinical response (*squares*) and in 44 nonresponders (*open circles*). In the responders, blood was drawn before the challenge (baseline), at the time of appearance of symptoms (time 0), and 60, 120, and 240 minutes later. In nonresponders, blood was drawn at baseline, 1 hour after reaching the dose 500 mg aspirin (time 0), and 60, 120, and 240 minutes later. In both groups, the PGD_2 metabolite studied increased significantly after aspirin challenge, though the course of increase was not the same. Mean values of plasma levels of $9\alpha,11\beta PGF_2$ are expressed as pg/mL.

cells are a rich source of eicosanoids and both are believed to play important role in CIU. We therefore studied release of another eicosanoid, that is, PGD_2. This is the predominant cyclooxygenase metabolite of arachidonic acid in mast cells but not in basophils.[28] Because of rapid metabolism and artifactual generation of prostaglandins during sampling and isolation of plasma, it is recognized that measuring metabolites rather than the parent compound is the most efficacious method of assessing the prostaglandin's endogeneous production. $9\alpha,11\beta PGF_2$ is a major stable metabolite of PGD_2, which in fact boast biological activity. The mass spectrometry measurement of $9\alpha,11\beta PGF_2$ in blood is highly accurate and sensitive.

Using this method, we have recently demonstrated[21] that in patients with AIA, as opposed to healthy subjects, aspirin challenge precipitated the clinical reaction, accompanied by a rise in plasma levels of the PGD_2 metabolite. A similar rise was observed in the patients with CIU. This phenomenon occurred both in patients who had urticaria/angioedema after aspirin challenge and in those who did not. Although PGD_2 release appeared to occur earlier in clinical responders than in nonresponders, the peak values reached were similar. Thus, target cells, most likely mastocytes, had an enhanced propensity to release PGD_2, perhaps being sensitized by autoantibodies,[29-34] but this remains to be proved. It is interesting to note that clinical signs and laboratory markers of autoimmunity were reported in some patients with aspirin-induced asthma.[35]

Demonstration of histamine release from healthy donor basophil or mast cells remains the gold standard for establishing an autoimmune basis of CIU.[32] There are good reasons to consider histamine a leading mediator in urticaria. Our results indicate that cys-LTs and PGD_2 should also be taken into consideration. This notion gets support from a study on local effects of eicosanoids in human skin. Cys-LTs in nanomolar amounts were able to induce cutaneous vasodilation with edema formation and a neutrofil infiltrate, and these responses were enhanced by PGD_2.[36]

Inheritance of the allelic variant $_{-444}C$ of LTC_4 synthase, which we attributed to moderately enhanced expression of the enzyme,[37] appears to associate with aspirin-triggered CIU in a manner similar to aspirin-induced asthma. Though not confirmed by replication studies,[38,39] this variant correlated with capacity for cysteinyl leukotrienes biosynthesis[40] or with clinical response to cysteinyl leukotreine antagonist.[41] Detection of the genetic association between LTC_4 synthase polymorphism and aspirin-triggered CIU, second to severe AIA,[3] corroborates the hypothesis on common mechanisms underlying these two clinical syndromes.

Finally, our data point to emerging basic similarities between the two distinct clinical syndromes with sensitivity to aspirin, that is, CIU and rhinitis/asthma. These syndromes, cared for by different specialists, may occur simultaneously in the same patient, without him being even aware of this, as was the case in 3 of 30 subjects studied by us. The similarities that we are referring to can be summarized as follows: (1) Clinical reactions (either cutaneous or bronchial) are precipitated by the drugs that inhibit COX-1 but not COX-2. (2) Baseline urinary LTE_4 levels, believed to reflect global cys-LTs biosynthesis, are markedly increased. (3) Ingestion of aspirin leads to further massive release of cys-LTs. (4) Aspirin releases PGD_2 in both aspirin-sensitive asthmatic patients and in patients with CIU and a history of NSAID intolerance.

Perhaps aspirin, by depleting protective PGE_2,[42,43] promotes unrestrained synthesis of cys-LTs and release of mediators such as PGD_2 from mast cells. Our results might help explain both the pathophysiology of CIU (cys-LTs cause vascular permeability, which becomes enhanced by PGD_2), as well as good clinical response to LRA in several patients with CIU. We still do not know the reasons for

profound alterations in basal eicosanoid biosynthesis in the two syndromes discussed. Latent viral infection and autoimmunity remain fascinating possible mechanisms for future studies.

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