Clinical course and urinary eicosanoids in patients with aspirin-induced urticaria followed up for 4 years

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Background: Little is known about the course of aspirin-induced urticaria. A special regulatory role of cysteinyl leukotrienes and prostaglandin D_2 (PGD_2) has been postulated.
Objective: We performed a long-term observation on clinical course, aspirin sensitivity, and urinary eicosanoids in patients with aspirin-induced urticaria.
Methods: For 4 years, we followed up 22 patients with chronic idiopathic urticaria and aspirin hypersensitivity who restrained from the use of aspirin and other COX-1 inhibitors. Aspirin challenges were performed in 2002 (all results were positive) and repeated in 2006. Levels of urinary leukotriene E_4 (LTE_4) and the main PGD_2 metabolite, $9\alpha11\beta PGF_2$, were measured at the same time points.
Results: During the follow-up period, the severity of urticaria has decreased. In 14 of 22 patients, the results of aspirin challenge remained positive. In 2002, these 14 patients responded to aspirin with a significant increase in urinary LTE_4 and $9\alpha11\beta PGF_2$ levels. When studied 4 years later, they showed a similar response of $9\alpha11\beta PGF_2$ ($P = .047$) and a tendency toward an increase in LTE_4 level ($P = .057$). There was a correlation between the urinary LTE_4 concentration after aspirin challenge and the intensity of skin eruptions. The dose of aspirin had no effect on the magnitude of response of both LTE_4 and the PGD_2 metabolite. In the remaining 8 patients, negative aspirin challenge results were not associated with changes in the urinary eicosanoids studied.
Conclusions: Aspirin hypersensitivity manifesting as urticaria/angioedema remains present after 4 years in about two thirds of patients. Aspirin-precipitated skin reactions associate with increased excretion of LTE_4 and PGD_2. (J Allergy Clin Immunol 2009;123:174-8.)

Key words: *Urticaria, aspirin-induced urticaria, aspirin sensitivity, eicosanoids, leukotriene E_4, prostaglandin D_2*

Abbreviations used
AIU: Aspirin-induced urticaria
LTE_4: Leukotriene E_4
PASI: Psoriasis Area and Severity Index
PGD_2: Prostaglandin D_2
$9\alpha11\beta PGF_2$: Prostaglandin D_2 metabolite

Some patients with chronic idiopathic urticaria have wheals and even angioedema after aspirin administration. In others aspirin causes an obvious increase in the underlying urticaria. The reaction can occur in just 15 minutes or up to 24 hours after aspirin ingestion, but on average, it develops within 1 to 4 hours. Most cases resolve within a few hours, but in severe reactions bouts of multiform skin eruptions can continue for 10 days after aspirin intake.[1-7]

The histologic spectrum of cutaneous reactions to aspirin[8] is dominated by a classic pattern of urticarial tissue. Occasionally, an interstitial fibrohistiocytic reaction pattern can develop. In sporadic patients, a perivascular dermal lymphocyte infiltrate or paucicellular mucinosis was observed.

Recent evidence indicates that the mechanism of aspirin-induced urticaria (AIU) is related to inhibition of COX-1.[9] This explains the cross-reactivity of various COX-1 inhibitors with different chemical structure. In contrast, COX-2 inhibitors are generally well tolerated by patients with AIU.[10-13] Eicosanoid alterations, similar to those observed in patients with aspirin-induced asthma, were reported in patients with AIU.[9] Specifically, in both clinical syndromes, aspirin challenges were accompanied by an increase in cysteinyl leukotriene and prostaglandin D_2 (PGD_2) levels. AIU aggregates in families inheriting the leukotriene C_4 variant.[14] This segregation does not follow a clear Mendelian pattern. The human leukocyte antigen DRD1*1302-DQB1*0609-DPB1*0201 haplotype was found to be a strong genetic marker in the Korean population.[15]

AIU can be a long-lasting ailment. However, little is known about the duration and perseverance of the sensitivity, as well as the eicosanoid alterations that accompany it. This prompted the study here reported, in which we followed up a well-characterized group of patients over a period of 4 years.

METHODS

Patients

The study group consisted of 22 patients with chronic idiopathic urticaria and aspirin sensitivity. They were recruited from a population of 30 patients with urticaria who in the year 2002 had positive aspirin challenge results and measurement of eicosanoid urinary metabolites. The remaining 8 patients from the original population were either lost or did not agree to participate.

The 22 patients were asked to use diet without artificial flavoring and preservatives and avoid aspirin and other COX-1 inhibitors. They were followed

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TABLE I. Patients' characteristic and parameters studied in all subjects (n = 22) and in subgroups with positive (n = 14) and negative (n = 8) aspirin challenge results separately

	AIU (n = 22)	AIU++ (n = 14)	AIU+− (n = 8)
Age (y)	49.0 ± 12.5, 53 (40-56)	47.6 ± 11.3, 52.5 (40.0-55.0)	51.5 ± 14.8, 54.5 (44.5-61.0)
Female/male sex	16/6	11/3	5/3
Duration of urticaria (y)	12.2 ± 9.5, 7.0 (5-19)	11.4 ± 7.1, 7.5 (5.0-19.0)	13.5 ± 13.0, 6.0 (4.8-24.0)
Urinary LTE_4 levels at baseline (pg/mg creatinine)	463.8 ± 332.3, 419.0 (313.0-495.5)	485.0 ± 411.8, 406.8 (295.5-550.0)	426.8 ± 117.3, 422.5 (326.3-479.8)
Urinary $9\alpha11\beta PGF_2$ at baseline (ng/mg creatinine)	0.380 ± 0.145, 0.367 (0.275-0.500)	0.395 ± 0.146.0, 0.363 (0.280-0.515)	0.353 ± 0.150, 0.367 (0.210-0.485)
Total IgE (IU/mL)	184.3 ± 257.4, 116.5 (39.1-218)	118 ± 77.0, 116 (39.1-193.0)	299.4 ± 404.8, 157.0 (32.5-390.5)
Blood eosinophil count	225.8 ± 224.5, 181 (90-293)	239.7 ± 247.1, 212 (90.0-303.0)	201.4 ± 191.8, 167 (72.0-257.5)

AIU, Patients with aspirin-induced urticaria with a positive aspirin test result in the year 2002; *AIU++*, patients with a positive aspirin test result twice in the 2002 and 2006; *AIU+−*, patients with a positive aspirin test result in 2002 and a negative result in 2006.
Values are expressed as the mean ± SD and median (25th and 75th percentiles). Baseline values of eicosanoids in patients in the AIU, AIU++, and AIU+− groups are shown (values represent means of 2 estimations performed on placebo and aspirin days). There was no statistical difference between the subgroups in the parameters presented in the table.

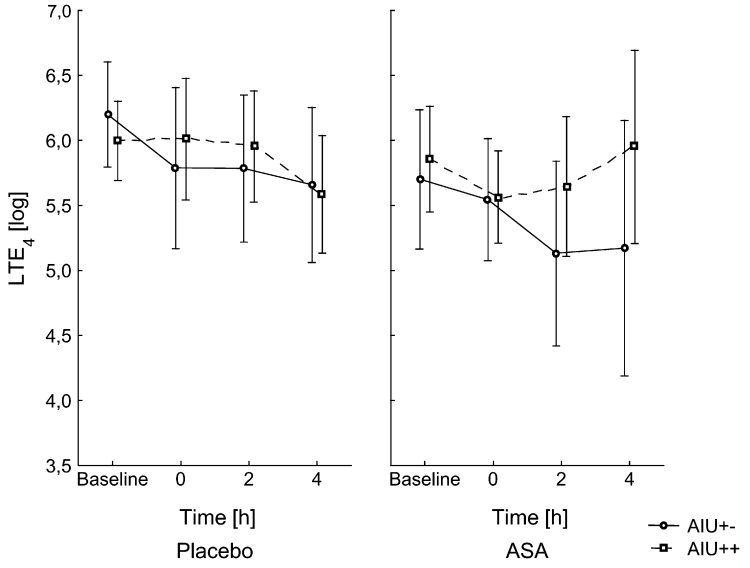

FIG 1. LTE_4 urinary values (mean ± SD) after challenge with placebo or aspirin in the 2 groups studied (AIU++ and AIU+−). For explanation, see the text.

up at the outpatient clinic at least twice a year by the same physician, and history, symptoms, and treatment were recorded. Four years later, all patients underwent aspirin challenge and had levels of urinary eicosanoids measured.

An aspirin oral challenge test was performed twice, in 2002 and 2006, by using the same protocol[9] in the same laboratory. The test was carried out on 2 consecutive days: on day 1, placebo was administered, and on day 2, aspirin was administered. Before the test, the medications were withheld according to international guidelines.[16] In patients who had positive aspirin challenge results in 2002 and 2006 (AIU++), urine samples were collected for measurement of leukotriene E_4 (LTE_4) and $9\alpha11\beta PGF_2$ (a PGD_2 metabolite) levels at baseline, at the time of appearance of the skin symptoms (time 0), and then 2 and 4 hours later. In patients with a positive result on aspirin challenge in 2002 and a negative result in 2006 (AIU+−), urine samples, in case of absent clinical reaction, were collected at baseline, 1 hour after the last aspirin dose (ie, when the cumulative dose of 500 mg of aspirin was reached [time 0]), and then 2 and 4 hours later.

Urinary eicosanoid determinations

Urinary LTE_4 was measured in unpurified urine samples by means of direct enzyme immunoassay (Cayman Chemical, Ann Arbor, Mich), following the same procedure as in the year 2002.[9] Levels of LTE_4 were expressed in picograms per milligram of creatinine.

The urinary concentration of $9\alpha11\beta PGF_2$ was measured by means of gas chromatography–negative ion chemical ionization–mass spectrometry (Hewlett-Packard, Palo Alto, Calif) by using the same procedure used in 2002.[9] Results were expressed in nanograms per milligram of creatinine.

Assessment of the severity of skin eruption

A modified Psoriasis Area and Severity Index (PASI) score was used to standardize the assessment of the severity of skin eruptions during aspirin challenge tests. For the assessment of urticaria, itching replaced desquamation in the index.[9] The 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 (Pneumoscreen; E. Jaeger, Würzburg, Germany).

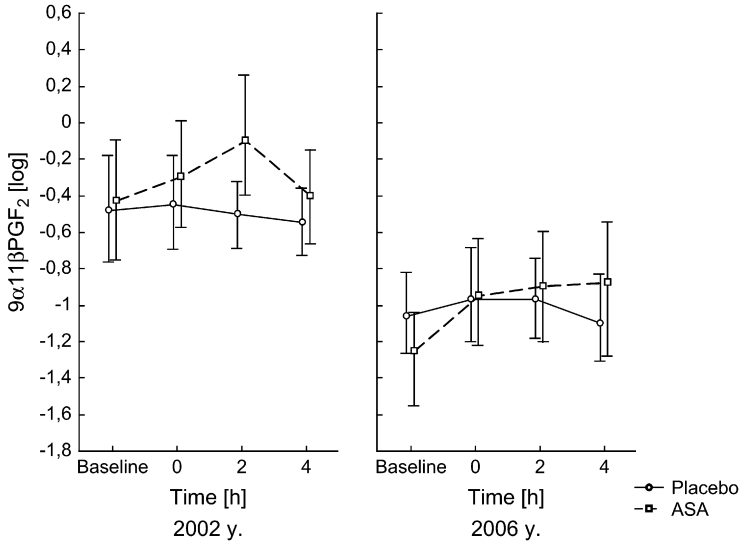

FIG 2. Response of urinary $9\alpha11\beta PGF_2$ to placebo or aspirin *(ASA)* challenge in the whole group of 22 patients in 2002 and 2006.

Statistical analysis

Summary statistics were expressed as the mean and SD for symmetrically distributed data or the geometric mean and 25% and 75% percentiles for nonsymmetrically (skewed) distributed data. The multiway ANOVA model was used for multiple-group comparisons. Logarithmic transformation was used when needed as a variance-stabilizing transformation. The Fisher exact test was used for dichotomous data for 2 independent random samples. A P value of .05 or less was considered statistically significant.

RESULTS

Over the period of 4 years, hives, occasionally accompanied by swelling of the face and hands unrelated to nonsteroidal anti-inflammatory drugs, occurred in all patients. The number of patients experiencing episodes of urticaria decreased; in the first year, 22 patients had bouts of urticaria, and in the fourth year, only 12 had urticaria. The intensity of spontaneous urticaria, as well as its frequency, decreased. The number of patients who required long-term medical treatment also decreased. Thus the second-generation antihistamines were used during the first year in 9 patients, but during the fourth year, they were used only in 2 patients; a tricyclic antidepressant (doxepin) was initially used in 2 patients but in none in the fourth year. Five patients were treated with systemic steroids during the first year, but none were so treated at the end of the study.

Oral aspirin provocation test

None of the patients had symptoms after administration of placebo. In 14 (63.6%) of 22 patients, the results of aspirin challenge tests were positive. Those patients had skin rash, angioedema, or both, but dyspnea was absent, and spirometric values remained stable throughout the observation period. There were no statistical differences in clinical characteristics between the patients who had positive aspirin challenge results (n = 14, AIU++) and those who tolerated aspirin well (n = 8, AIU+−; Table I).

In 2006, none of the patients had skin reactions after a 71-mg cumulative dose of aspirin. After 188 mg, urticaria/angioedema developed in 6 subjects, and after 500 mg, it developed in 8 subjects. Patients with a lower cumulative dose of aspirin (≤188mg) in 2002 had more frequently positive aspirin challenge results in the year 2006 ($P = .046$). The severity of their skin eruptions after aspirin challenge (PASImax score) was lower than 4 years before ($P = .02$, ANOVA).

Urinary eicosanoids

Baseline levels. Comparison of baseline urinary LTE_4 levels in 2006 and 2002 showed no difference in either the whole group (n = 22) or in the subgroups studied ($P > .05$, data not shown). However, the baseline $9\alpha11\beta PGF_2$ levels in 2002 were significantly higher than in 2006 in the total group of 22 patients (0.796 ± 0.471 vs 0.366 ± 0.171 ng/mg creatinine, $P < 0.001$), as well as in the subgroup of AIU++ patients (0.876 ± 0.485 vs 0.347 ± 0.164 ng/mg creatinine; $P < .003$).

Aspirin challenge. Baseline urinary LTE_4 excretion (Table I) did not differ between patients with positive (n = 14, AIU++) and negative (n = 8, AIU+−) aspirin challenge results ($P = .92$). After placebo, urinary LTE_4 levels gradually decreased in both study groups ($P = .002$, ANOVA), a phenomenon observed also 4 years earlier. Urinary LTE_4 levels have a tendency to increase after aspirin challenge tests compared with baseline values ($P = .057$) only in the group of patients (AIU++) with positive aspirin challenge results (Fig 1). After challenge, urinary LTE_4 levels were the highest in patients with severe skin reactions. There was a correlation between the urinary levels of LTE_4 4 hours after aspirin challenge and the maximal intensity of skin eruption expressed as the PASI score (Spearman $r = 0.64$, $P = .01$). The dose of aspirin had no effect on the magnitude of the response of LTE_4.

In 2006, the response of $9\alpha11\beta PGF_2$ to aspirin challenge was similar to that recorded in 2002, although the baseline values were distinctly lower and the response less accentuated (Fig 2). Analysis of the subgroups based on the presence or absence of clinical symptoms revealed that placebo administration produced no significant differences in the urinary PGD_2 metabolite levels in either group ($P = .25$, ANOVA). After aspirin challenge, urinary concentrations of $9\alpha11\beta PGF_2$ increased significantly only in the

group of patients who had a clinical reaction. They reached their peak at the moment of clinical reaction (increase from 0.347 ± 0.164 to 0.516 ± 0.352 ng/mg creatinine, $P = .047$) and returned to baseline values 4 hours later. The dose of aspirin had no effect on the magnitude of the response of $9\alpha 11\beta PGF_2$. In the AIU+− subgroup PGD_2 metabolites after aspirin showed a tendency to increase, which did not reach statistical significance ($P = .086$, ANOVA).

DISCUSSION

We had an opportunity to follow-up a group of patients with well-documented AIU over a period of 4 years. After 4 years, we could also retest their sensitivity to aspirin using the oral provocation test, as well as again measure urinary eicosanoid metabolites, which showed distinct alterations at entry to the study. The advantage of the study was that the patients were followed up by the same physician, and both provocation tests and biochemical measurements were performed at the same laboratory by using the same methods.

Over the period of 4 years, the intensity of urticaria decreased. This was reflected by a decrease in the severity and frequency of spontaneous urticarial eruptions, a decrease in hospitalizations, and a progressively lower number of antihistamines and corticosteroids prescribed. The reason for this improvement could have been total avoidance of aspirin and other drugs that inhibit COX-1 and perhaps also the elimination diet. Regular clinical care was probably another important factor.

Despite a distinct clinical improvement, about two thirds of the patients remained hypersensitive to aspirin, and the results of the provocation tests were definitely positive in them. It is of interest that one of these patients, who reacted 4 years earlier to 188 mg of aspirin not only with skin eruptions but also with rhinorrhea, conjunctivitis, shortness of breath, and a decrease in FEV_1 of less than 20%, now responded only with a skin reaction after challenge with 500 mg. Elimination of aspirin sensitivity has been reported in aspirin-induced asthma,[16] but it is a rare phenomenon. We cannot exclude the possibility that the higher dose of aspirin, exceeding 500 mg, would have precipitated bronchial or skin reactions in our patients.

In subjects who remained hypersensitive to aspirin, the aspirin provocation test produced eicosanoid responses similar to those 4 years earlier. The magnitude of the response was, however, less accentuated, which could be linked to the gradual improvement in the patients' clinical state. Thus in all patients aspirin challenge resulted in clinical reaction and an increase in urinary LTE_4 levels in contrast to the group of 8 patients who lost their hypersensitivity to aspirin. The urinary LTE_4 value reached the highest levels in subjects with the most severe skin reactions. The dose of aspirin used, however, had no effect on the clinical response, a phenomenon already observed earlier.[9] Finally, urinary levels of a stable PGD_2 metabolite showed significant changes only in the group of patients with positive aspirin challenge results.

Several explanations can be offered for the blunted reactivity to aspirin in our patients after the 4-year follow-up period. Chronic idiopathic urticaria itself has a variable clinical course. Elimination of aspirin and other COX-1 inhibitors might have lessened the predisposition to the reactions. An unknown causative factor responsible for aspirin hyperreactivity could also stop the reactions. Eventually, autoimmune abnormalities present in a substantial fraction of patients with idiopathic urticaria,[1,4,17,18] including those with aspirin sensitivity,[19,20] could subside. From our long-term observation, the mechanism involved in urticarial eruption seems to correlate well with the clinical status of the patient. Systemic overproduction of PGD_2 metabolites and cysteinyl leukotrienes, triggered by aspirin, predicts a phenotype of AIU and seems to be a biologic hallmark of the inflammatory mechanism involved. Thus aspirin and other drugs sharing a similar pharmacologic profile are required to reveal underlying biochemical abnormalities of arachidonic acid cascade. Perhaps aspirin, by depleting protective PGE_2, promotes unrestrained synthesis of cysteinyl leukotrienes and release of such mediators as PGD_2 from mast cells. In aspirin-induced asthma this seems to be a likely mechanism.[21] PGD_2 is the major COX metabolite almost entirely generated by activated mast cells.[22] In bronchial asthma mast cells infiltrate airway smooth muscle, a phenomenon associated with high PGD_2 levels in the sputum.[23] Decreased reactivity of the skin mast cells or a decrease in their number is the plausible, although hypothetical, explanation for both clinical improvement of urticaria and depression of aspirin sensitivity in our patients. Thus, reduction in skin mast cell reactivity is accompanied by a return of biosynthesis of proinflammatory mediators of arachidonic acid to normal levels.

Key messages

- **Aspirin hypersensitivity manifesting as urticaria/angioedema remains present after 4 years in about two thirds of patients.**
- **The aspirin-triggered skin reactions are accompanied by a tendency toward overproduction of cysteinyl leukotrienes and PGD_2.**

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