

Safety of Cyclooxygenase 2 Inhibitors and Increased Leukotriene Synthesis in Chronic Idiopathic Urticaria With Sensitivity to Nonsteroidal Anti-inflammatory Drugs

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Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) exacerbate various forms of urticaria by a nonallergic mechanism involving inhibition of cyclooxygenases.

Objectives: To assess safety of cyclooxygenase inhibitors in patients with chronic idiopathic urticaria (CIU) and NSAID sensitivity and to evaluate a role of cysteinyl leukotriene metabolism and mast cell activation in sensitivity to NSAIDs in CIU.

Design: Aspirin challenge test followed by randomized, prospective, double-blind, placebo-controlled cross-over trial with cyclooxygenase 2 inhibitors.

Setting: Tertiary referral center of a university hospital.

Patients: Thirty-six patients with CIU.

Interventions: Aspirin challenge test (up to 500 mg); randomized trial with rofecoxib (up to 37.5 mg) and celecoxib (up to 300 mg) in aspirin-sensitive patients. After completion of the trial, 7 patients received naproxen sodium (500 mg) as a positive control.

Main Outcome Measures: Standardized skin examination, skin biopsy with mast cell count, urinary levels of leukotriene E₄ (LTE₄), and serum levels of mast cell tryptase.

Results: Aspirin induced skin eruption in 18 patients. Rofecoxib or celecoxib did not elicit skin eruption in any of the aspirin-sensitive patients. Patients with CIU had higher urinary excretion of LTE₄ than healthy control subjects. Basal urinary levels of LTE₄ and serum mast cell tryptase were increased in aspirin-sensitive compared with aspirin-tolerant patients. Severity and duration of aspirin-induced urticaria showed a positive correlation with urinary LTE₄ excretion. Naproxen precipitated urticaria in 5 of 7 aspirin-sensitive patients and caused further increase in urinary LTE₄.

Conclusions: Cyclooxygenase 2 inhibitors do not induce urticaria in patients with CIU sensitive to NSAIDs. Sensitivity to NSAIDs in CIU is associated with overproduction of cysteinyl leukotrienes and mast cell activation and most likely depends on inhibition of cyclooxygenase 1.

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CHRONIC IDIOPATHIC urticaria (CIU) is clinically defined as continually occurring wheals for at least 6 weeks in the absence of physical urticaria and an identifiable cause.^{1,2} Chronic idiopathic urticaria affects up to 0.1% of the population, with variable but often persistent clinical course. In 30% to 50% of patients, CIU is associated with autoantibodies against the α -chain of the high-affinity IgE receptor Fc ϵ RI present on mast cells³⁻⁷ or IgE molecule.⁸ Thus, the emerging evidence suggests that CIU is a mast cell autoimmune disease.

It is well known that aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs) can exacerbate various forms of urticaria.⁹ Aspirin sensitivity can be con-

firmed by drug challenge tests in 20% to 41% of patients with urticaria.^{10,11} In contrast, the rate of aspirin sensitivity in the normal population is about 1%.^{12,13} Clinical studies investigating NSAID-induced urticaria have rarely made a distinction between CIU and other forms of urticaria. Although some NSAID-induced cutaneous eruptions are immunologic, in most cases the mechanism is pharmacologic. It involves inhibition of cyclooxygenase (COX), a rate-limiting enzyme in the biosynthesis of prostaglandins.¹⁴⁻¹⁷ Susceptible individuals have cross-sensitivity to the entire class of drugs regardless of their chemical structure. The most common clinical presentation is urticaria and angioedema.

Current ideas regarding detailed mechanisms of NSAID sensitivity in CIU are

Table 1. Design of the Study

Time	Day 1	Day 2 Aspirin Dose/ Cumulative Dose, mg	Day 7	Day 8 or Day 15 (Crossover) Rofecoxib Dose/Cumulative Dose, mg	Day 8 or Day 15 (Crossover) Celecoxib Dose/Cumulative Dose, mg
8:30 AM	Placebo	71/71	Placebo	12.5/12.5	100/100
9:30 AM	Placebo	117/188	Placebo	25/37.5	200/300
10:30 AM	Placebo	312/500			

largely inferred from studies of an analogous, well-defined clinical syndrome of aspirin-induced asthma, which affects about 10% of adult asthmatic patients.¹⁸ Both syndromes affect middle-aged individuals, with a female preponderance. Sensitivity to NSAIDs is present in only a subset of patients with asthma and CIU. It is well established that in aspirin-induced asthma the mechanism of sensitivity involves inhibition of COX.^{16,19,20} At the biochemical level, aspirin-induced asthma is characterized by overproduction of cysteinyl leukotrienes and increased urinary excretion of leukotriene E₄ (LTE₄).²¹ Nasal biopsy specimens from aspirin-sensitive patients with asthma contain elevated numbers of leukocytes expressing the cysteinyl leukotriene 1 receptor, expression of which is down-regulated after desensitization to aspirin.^{22,23} Consistently, leukotriene receptor antagonists improve asthma in aspirin-intolerant patients.^{24,25} Analogously, NSAID sensitivity in chronic urticaria is ameliorated by cysteinyl leukotriene receptor inhibitors,^{26,27} but leukotriene metabolism in aspirin-sensitive CIU has not been studied.

Recent reports demonstrated that selective inhibitors of COX-2 (coxibs)²⁸ can be safely used in patients with aspirin-sensitive asthma,²⁹⁻³² implicating inhibition of COX-1 as the principal mechanism triggering asthma attacks by NSAIDs. Several studies, performed without strict subtyping of a rash or confirmation of NSAID sensitivity by a drug challenge test, suggested better tolerability of selective COX-2 inhibitors in patients with a history of cutaneous eruptions induced by aspirin.³³⁻³⁵

The goal of this study was to assess the safety of COX-2 inhibitors in patients with NSAID-exacerbated CIU and to correlate NSAID sensitivity with changes in leukotriene metabolism and mast cell activation. We conducted a double-blind, placebo-controlled, oral drug challenge study investigating the effects of the COX-2 inhibitors rofecoxib and celecoxib in patients with NSAID-sensitive CIU confirmed by aspirin challenge test.

METHODS

STUDY PARTICIPANTS

The study population consisted of 36 patients with CIU in apparent remission and clinical history suggestive of NSAID sensitivity. There were 10 males and 26 females aged 17 to 65 years (mean, 39 years). The average duration of CIU symptoms was 4 years (range, 8 weeks to 16 years). Diagnosis of CIU required presence of angioedema or urticaria every day, or almost every day, for more than 6 weeks.^{1,2} Patients had no evidence or history of asthma, nasal polyps, anaphylaxis, dermatographism, or physical, cholinergic, solar, cold, or delayed pressure urticaria. Two weeks before the beginning of the

study, 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 LTE₄ and mast cell tryptase levels consisted of 23 women and 25 men with a mean $\pm$ SD age of 35 $\pm$ 10 years.

The study was approved by and conducted according to the guidelines of the Ethical Committee of the Jagellonian University School of Medicine in Krakow, Poland. All participants gave informed written consent.

SKIN TESTING WITH LYSINE-ASPIRIN

To exclude an IgE-mediated reaction, 10 aspirin-sensitive patients were tested by skin prick test and intradermal injection of lysine-aspirin (Aspisol; Bayer AG, Leverkusen, Germany; 0.0001%, 0.001%, and 0.01%). None of the patients developed a cutaneous reaction.

DESIGN OF THE STUDY

The experimental protocol is summarized in **Table 1**. All patients received placebo on day 1 of the study. On day 2 they were challenged with increasing doses of aspirin up to the cumulative dose of 500 mg.

Patients with positive aspirin challenge test results entered a randomized, double-blind, placebo-controlled, crossover trial with rofecoxib and celecoxib. This design was chosen to assess potential differences between the drugs. The challenge with these drugs was performed on days 8 and 15. As a positive control, after completion of the trial, 7 aspirin-sensitive patients agreed to receive naproxen sodium (500 mg), a structurally dissimilar non-selective NSAID. All drugs and placebo had identical appearance. Patients, physicians, and ancillary staff participating in the study were blinded as to the protocol.

ASSESSMENT OF SEVERITY OF SKIN ERUPTION

To standardize the assessment of severity of the skin eruption, a modified Psoriasis Area and Severity Index (PASI) was used.³⁶ 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 4 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 involvement and 4, severe involvement. Calculated PASI scores range from 0 to 72. We considered a PASI greater than 10 as indicating a severe reaction. The PASI was determined by an experienced dermatologist at the time of appearance of skin lesions and 2, 4, and 6 hours after the drug challenge.

SKIN BIOPSY

One 4-mm punch biopsy was performed from the clinically most prominent lesion in 16 patients. Multiple formalin-fixed, paraffin-embedded sections were stained with hematoxylin-eosin and examined by one of us, an American Board of Pathology–

certified dermatopathologist (A.Z.). The number of mast cells per square millimeter of tissue section was counted after immunohistochemical staining with mast cell tryptase monoclonal antibodies (DAKO, Carpinteria, Calif) by means of a peroxidase-labeled streptavidin-biotin-based detection kit (DAKO). At least forty 0.11-mm² microscopic fields at ×400 magnification were counted in each biopsy specimen. The average ± SD number of mast cells in the field was 11 ± 8 (range, 0-37; total, 722 fields counted).

MEASUREMENTS OF URINARY LTE₄ AND SERUM TRYPTASE

In patients with positive challenge test results, urine samples were collected at baseline, at the time of appearance of the first skin symptoms (time 0), and then 2, 4, and 6 hours later. In nonresponders, the urine samples were collected at baseline, at the end of aspirin dosing (ie, when a cumulative dose of 500 mg was reached [time 0]), and then 2, 4, and 6 hours later. Urine samples were stored in 50-mL aliquots at -70°C. The LTE₄ was measured in unpurified samples by direct enzyme immunoassay (enzyme-linked immunosorbent assay; Cayman Chemical, Ann Arbor, Mich). Measurements were made at the same time in duplicates with the use of the same kit. The results were expressed in picograms per milligram of creatinine.³⁷ Serum tryptase was measured by fluoroenzyme immunoassay (UniCAP 100 Tryptase system; Pharmacia Diagnostics, Uppsala, Sweden) and expressed in micrograms per liter.

AUXILIARY LABORATORY TESTS

Blood was drawn at baseline and then at 2, 4, and 6 hours to measure the number of peripheral eosinophils. Vital signs and forced expiratory volume in 1 second were recorded every 15 minutes until 6 hours after the last dose of a drug.

STATISTICAL ANALYSIS

Statistical evaluation was carried out with STATISTICA software (StatSoft, Inc, Tulsa, Okla). Summary statistics were expressed as mean ± SD for symmetric distributed data and median and 25th and 75th percentiles for nonsymmetric (skewed) distributed data. A multiway analysis of variance model was used for comparing the groups by means and post hoc Tukey procedure for multiple comparisons. Logarithmic transformation was used when needed as variance stabilizing transformation. The relationship between variables was studied by Pearson and Spearman correlation analysis. *P* ≤ .05 was considered statistically significant.

RESULTS

ASPIRIN CHALLENGE

None of the 36 patients developed symptoms after administration of placebo. Eighteen patients challenged with aspirin developed a cutaneous rash. There was no statistical difference in demographic data between the patients with positive results of aspirin challenge test and the nonresponders. Skin reactions developed after 71 mg, 188 mg, and 500 mg of cumulative dose of aspirin in 1, 6, and 11 patients, respectively.

The clinical appearance of the rash was consistent with urticaria and/or angioedema. The maximal PASI averaged 12.3 ± 9.8. In 4 patients, skin lesions were more

Table 2. Urinary LTE₄ and Serum Mast Cell Tryptase in Healthy Control Subjects and Patients With Aspirin-Tolerant and Aspirin-Sensitive Chronic Idiopathic Urticaria*

Group	LTE ₄ , pg/mg of Creatinine	Tryptase, µg/L
Healthy controls (n = 48)	110.5 (58-152)	4.47 (3.51-5.65)
CIU		
Aspirin tolerant (n = 18)	269 (179-385)	4.98 (1.97-7.65)
Aspirin sensitive (n = 18)	569 (285-693)	7.8 (6.13-10.9)
All patients (n = 36)	349 (260.5-622.0)	7.19 (4.57-8.89)

Abbreviations: CIU, chronic idiopathic urticaria; LTE₄, leukotriene E₄.

*For comparison, values from the entire CIU cohort are also shown. Values represent median and 25th to 75th percentiles. In the case of LTE₄, there was a statistical difference between all the groups. In the case of mast cell tryptase, CIU (aspirin positive) differed significantly from both CIU (aspirin negative) and healthy subjects (multiway analysis of variance with post hoc Tukey test).

polymorphous with additional annular gyrate and figurate erythematous macules and plaques.

In 16 of 18 patients, aspirin challenge produced no complications. One patient developed transient conjunctivitis, rhinorrhea, and shortness of breath, with a 25% fall in forced expiratory volume in 1 second after ingestion of 312 mg of aspirin, which preceded development of urticaria by an hour. The symptoms subsided spontaneously. The patient then admitted having had chronic rhinitis for the past year, with recent bouts of cough and phlegm production, but no nasal polyps. One patient had a transient mild shortness of breath with a 22% fall in forced expiratory volume in 1 second but without any other symptoms. This patient had no history of chronic sinusitis or nasal polyps.

URINARY LTE₄ AND SERUM TRYPTASE

Table 2 shows the baseline urinary levels of LTE₄ and serum mast cell tryptase before the first placebo challenge. The LTE₄ levels were significantly higher in patients with CIU than in healthy controls. The LTE₄ and serum mast cell tryptase levels were significantly higher in the patients with positive results of aspirin challenge test than in nonresponders. The increased LTE₄ levels were recorded in all 5 samplings of urine collected before drug challenge tests or administration of placebo. For patients with CIU, the results of the other 4 LTE₄ estimations were as follows: 403 (234-771), 608 (221-1058), 348 (245-564), and 451 (202-882) pg/mg of creatinine.

There was a statistically significant correlation between the baseline urinary levels of LTE₄ and the maximal intensity of skin eruption expressed as PASI (**Figure 1**) and duration of the rash (Pearson *r* = 0.64; *P* = .04; not shown).

There was no correlation between a dose of aspirin and the number of eosinophils in the peripheral blood or the intensity or duration of the skin reaction.

Figure 2 shows the time course of urinary levels of LTE₄ during aspirin challenge in patients with CIU. There was a trend to further increase in LTE₄ levels after aspirin challenge in aspirin-sensitive patients. How-

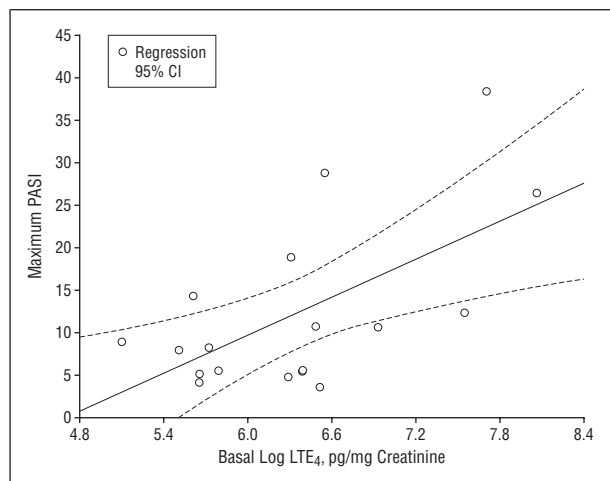


Figure 1. Correlation between basal levels of leukotriene E₄ (LTE₄) and maximal intensity of urticaria induced by aspirin challenge, expressed as Psoriasis Area and Severity Index (PASI) (Pearson $r=0.64$, $P<.007$, $n=18$). CI indicates confidence interval.

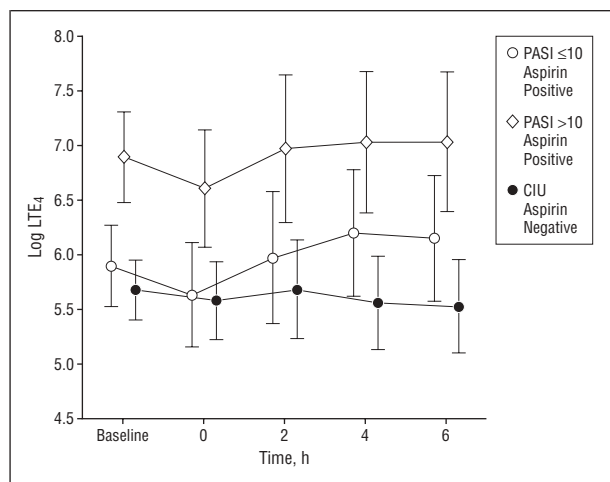


Figure 2. Time course of urinary levels of leukotriene E₄ (LTE₄) after aspirin challenge in patients with no, mild (Psoriasis Area and Severity Index [PASI], ≤ 10), and intense (PASI score, >10) cutaneous reaction to aspirin. Values are expressed as means and 95% confidence intervals; $n=18$. CIU indicates chronic idiopathic urticaria.

ever, the differences did not reach statistical significance in the entire cohort or in subgroups with mild (PASI ≤ 10) or severe (PASI >10) skin reaction.

DOUBLE-BLIND, RANDOMIZED, CROSSOVER TRIAL WITH ROFECOXIB AND CELECOXIB

None of the 18 patients with positive aspirin challenge test results developed a skin reaction during challenge with placebo, rofecoxib (up to 37.5 mg), or celecoxib (up to 300 mg). There were no significant changes in LTE₄ levels during challenge test with rofecoxib or celecoxib.

CHALLENGE WITH NAPROXEN

To exclude desensitization to NSAIDs, 7 aspirin-sensitive patients received naproxen sodium (500 mg) after completion of the trial with coxibs. Three patients with strong reactions to aspirin (PASI, 24.3 ± 14.7) de-

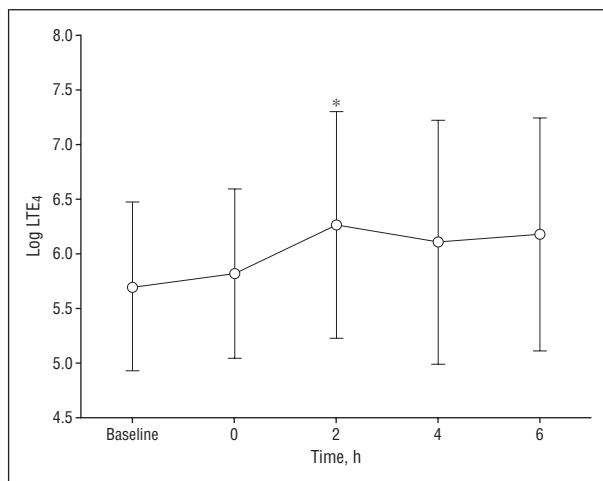


Figure 3. Time course of urinary levels of leukotriene E₄ (LTE₄) after naproxen sodium (500 mg) in 7 patients with previous positive aspirin challenge test. Values are expressed as means and 95% confidence intervals. Asterisk indicates $P=.03$, multiway analysis of variance with post hoc Tukey test.

veloped strong reactions to naproxen (PASI, 17.5 ± 4.0). Two patients with weaker responses to aspirin (PASI, 11.8 ± 7.3) developed mild urticaria (PASI, 4 and 8). No skin eruption was observed in the remaining 2 patients. Naproxen induced a significant increase in urinary LTE₄ levels 2 hours after appearance of the urticaria (**Figure 3**).

SKIN BIOPSY RESULTS

Urticaria was diagnosed histologically in 12 of 16 skin biopsy specimens. Biopsy specimens from 2 patients with annular lesions showed a more complex pattern with a component of interstitial granulomatous reaction previously described in association with drugs.³⁸ In 1 patient, a mild perivascular mononuclear infiltrate was present. Surprisingly, but without obvious explanation, the biopsy specimen in 1 patient demonstrated pauc inflammatory interstitial mucinosis.

Tissue sections contained 99 ± 22 mast cell tryptase-positive cells per 1 mm². The number of mast cells did not correlate with intensity of skin eruption (PASI) or serum mast cell tryptase levels (Spearman $r=0.38$, $P>.14$).

COMMENT

Our study confirms high prevalence of NSAID sensitivity in CIU. Patients with CIU are often denied this class of medications because of fear of untoward reactions to NSAIDs. Our findings demonstrated lack of cross-reactivity between aspirin and 2 COX-2 inhibitors, rofecoxib and celecoxib. These findings are in line with recent reports that showed good tolerability of coxibs in patients with clinical history of NSAID-induced skin eruptions^{33,34} and NSAID-induced asthma,²⁹⁻³² with the exception of one study³⁵ that found 3% and 33.3% cross-reactivity with rofecoxib and celecoxib, respectively, in patients with NSAID-sensitive skin eruptions. The reasons for discrepancy in estimated cross-reactivity rates to coxibs in this study and our results are not easy to understand, but they may be due to different study popu-

lations or challenge protocols. In comparison, our study had a very uniform patient population, restricted to individuals with strictly defined CIU and positive results of aspirin challenge test.

In addition to clinical implications, our findings shed a new light on the mechanisms involved in NSAID sensitivity in CIU. Lack of reaction to local injections of lysine-aspirin is consistent with a nonimmunologic mechanism of aspirin-induced rashes. Aspirin and older NSAIDs are nonselective inhibitors of COXs. The lack of cross-reactivity with coxibs strongly suggests inhibition of COX-1 as the principal mechanism involved in aspirin-induced exacerbation of CIU. However, possible involvement of a recently discovered third isoform of COXs, COX-3, or other yet undiscovered COXs cannot be excluded.³⁹ Differential selectivity toward inhibition of COX-1 may also explain the results with naproxen, which induced urticaria in 5 of 7 patients with positive results of aspirin challenge test. Naproxen is a nonselective COX inhibitor, but with lower potency toward COX-1 than aspirin.⁴⁰

Increased urinary LTE₄ levels indicate increased global cysteinyl leukotriene production in CIU. Urinary LTE₄ levels were invariably elevated when measured on 5 occasions during the period of 2 weeks as compared with levels in healthy controls. The LTE₄ levels correlated with the intensity and duration of the reaction to aspirin. In addition, urinary LTE₄ levels showed a trend to further rise after aspirin administration. In a group of 7 patients challenged with naproxen, further increase in LTE₄ level above the baseline reached statistical significance. These results point to cysteinyl leukotrienes as major effector molecules in CIU and mediators of NSAID sensitivity. This suggestion is corroborated by recent reports showing that leukotriene receptor inhibitors block aspirin-induced urticaria²⁶ and improve CIU.^{27,41}

Mast cells are the most likely source of increased leukotriene production in CIU. They are the target of pathogenic anti-FcεRI antibodies. They are also the key cells in urticaria⁴² and a known source of leukotrienes. A role of mast cell activation in NSAID sensitivity in CIU is supported by our findings of elevated serum levels of mast cell tryptase, a specific mast cell-derived protein marker, in patients with aspirin sensitivity. There was no correlation between the number of mast cells in skin biopsy specimens and the intensity of skin eruption or serum mast cell tryptase levels. These results support the notion that increased activation of mast cells rather than their increased number is responsible for elevated levels of mast cell tryptase. However, we could not compare the number of mast cells in patients with positive aspirin challenge test with those in nonresponders or healthy subjects, as skin biopsies were not performed in the latter 2 groups.

Further mechanistic studies are obviously needed to elucidate likely complex regulatory relationships between biochemical pathways involved in NSAID sensitivity in CIU. However, interpretation of our data in the context of current understanding of a role of prostaglandins and leukotrienes in inflammation^{25,43} and pathomechanism of CIU allows us to suggest a plausible scenario (**Figure 4**). Our study links increased production

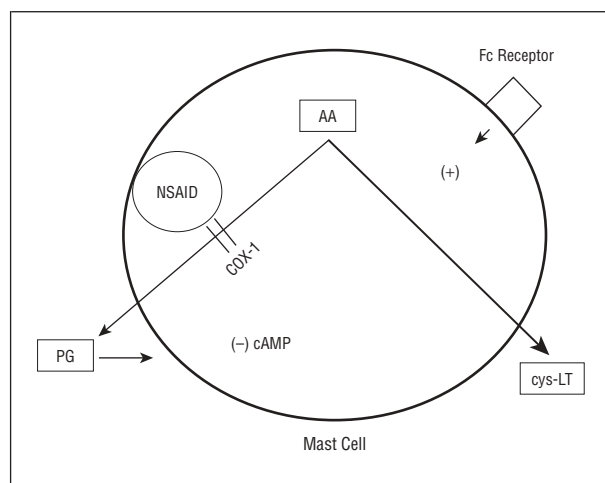


Figure 4. Proposed mechanisms involved in nonsteroidal anti-inflammatory drug (NSAID) sensitivity in chronic idiopathic urticaria. Our study suggests that chronic idiopathic urticaria is associated with in vivo activation of mast cells and increased synthesis of cysteinyl leukotriene (cys-LT). Activating mechanisms may include Fc receptor activation. Mast cell activation is under negative influence of cyclooxygenase (COX) 1-dependent prostaglandins (PG) such as prostaglandins E₂ and D₂, generated from arachidonic acid (AA), which are known to inhibit mast cell activation via cyclic adenosine monophosphate (cAMP)-dependent mechanism. Synthesis of inhibitory prostaglandins is blocked by nonselective NSAIDs but not by COX-2 selective coxibs, implicating involvement of COX-1. Activation of other cell types (eosinophils, neutrophils) participating in urticarial reaction in response to mast cell-derived mediators may also be affected by NSAIDs in a similar manner.

of cysteinyl leukotrienes in CIU with mast cell activation, which is probably induced by anti-FcεRI receptor antibodies⁷ or other triggers of urticaria. However, we can only speculate about the COX inhibition-sensitive mechanisms. It is logical to propose that inhibition of COX-1 by nonselective NSAIDs results in removal of the inhibitory effect of COX-1-derived metabolite or metabolites on mast cells and other inflammatory cells, thus unmasking activating mechanisms that lead to exacerbation of urticarial reaction. Prostaglandins E₂ and D₂, known inhibitors of mast cell, neutrophil, eosinophil, and endothelial cell activation via their cyclic adenosine monophosphate stimulatory effect, are possible molecules involved. Unfortunately, we were not able to assess global production of prostaglandins in our study, as their urinary levels reflect mostly local production by the kidney. In this context, it is interesting that circulating histamine-releasing serum factors, similar to those in patients with CIU, have been detected in most patients with intolerance to multiple NSAIDs but no clinical history of CIU.⁴⁴ These findings suggest that NSAIDs may unmask subclinical CIU in a subset of patients.

Additional studies are needed to assess whether similar mechanisms are involved in NSAID-induced exacerbation of other types of urticaria and whether coxibs can be safely used in mast cell proliferative disorders such as urticaria pigmentosa or systemic mastocytosis, where NSAIDs can induce mast cell degranulation and lethal anaphylactic shock.

In summary, this study demonstrates that COX-2 inhibitors can be safely used in patients with CIU sensitive to NSAIDs. Sensitivity to NSAIDs in CIU is associated with overproduction of cysteinyl leukotrienes and

increased levels of mast cell tryptase consistent with mast cell activation. Eruptions induced by NSAIDs can be triggered by removal of COX-1–dependent prostaglandins, but further studies are needed to assess the potential role of newly discovered COX-3 or perhaps yet undiscovered isoforms of COX.

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Drs Zembowicz and Mastalerz contributed equally to this study.

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