Aspirin induced adverse skin reactions: new pathophysiological aspects

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Clinically, aspirin induced adverse skin reactions resemble true immunologically mediated allergic reactions. However, it is well accepted that aspirin intolerance is not mediated by specific IgE antibodies. The exact mechanisms involved are far from clear[1 2] and therefore no reliable diagnostic in vitro tests exist, and risky and time consuming provocation tests are regarded as the diagnostic gold standard. Most studies of pathophysiological mechanisms deal with nasal polyps or asthma. However, compared with asthma and nasal polyps, aspirin intolerance is very common in chronic urticaria.[3–7] The reason for the preferred organ manifestation is unknown.

Several lines of evidence point to a potent disturbance in the eicosanoid balance (cyclooxygenase theory) resulting in a shift towards increased production of leukotrienes.[8–12]

Our previous studies have shown that aspirin induced adverse skin reactions proved by positive oral provocation tests are common in chronic urticaria[13] and can be characterised by enhanced sulfidoleukotriene production in IL-3 primed leucocyte suspensions after stimulation with C5a.[14 15] This study was undertaken to define the rate of positive oral challenge tests in patients with chronic urticaria and a history of adverse skin reactions to aspirin. We also wanted to investigate the sensitivity and specificity of enhanced sulfidoleukotriene production induced by different basophil agonists for the diagnosis of aspirin intolerance.

Methods

PATIENTS

EDTA anticoagulated blood from 84 patients with chronic urticaria and suspected worsening of urticarial eruptions after intake of aspirin was analysed before oral provocation tests. To define an atopic diathesis total IgE (CAP IgE FEIA, Pharmacia-Biotech, Freiburg, Germany) and Sx1 Phadiatop (RAST atopy screening test for seven common allergens; CAP IgE-FEIA, Pharmacia-Biotech, Freiburg, Germany) were assessed.

ORAL PROVOCATION TEST

Asymptomatic patients were given increasing doses of aspirin in gelatine capsules as inpatients under single blind, placebo controlled conditions. The following increasing doses of aspirin were used: 50 mg, 100 mg, 250 mg, 500 mg, 1000 mg (cumulative dose 1900 mg). Provocation tests were considered positive when objective symptoms such as urticarial eruptions, bronchial asthma, angio-oedema, or anaphylactoid reactions were observed.

RELEASE OF SULFIDOLEUKOTRIENES FROM LEUCOCYTE SUSPENSIONS

Leucocyte suspensions were isolated by dextran sedimentation and analysed for de novo production of LTC_4, LTD_4, and LTE_4 with a commercially available ELISA (cellular antigen stimulation test (CAST); DPC Biermann, Bad Nauheim, Germany). Leucocyte suspensions were pre-incubated with interleukin (IL)-3 (10 ng/ml) for 15 minutes at 37°C. The cells were then stimulated with C5a (10^{-7} M), platelet activating factor (PAF; 10^{-5} M), and f-Met-Leu-Phe (fMLP; 10^{-6} M) for 30 minutes at 37°C. Previous experiments have shown that these concentrations of mediators gave optimal results. Our previous results also showed that stimulation with aspirin could be omitted.[14] In accordance with the instructions of the manufacturer of the SLT-ELISA, anti-FcεRI-mAb (22E7) was used as a positive control and the IL-3 containing stimulation buffer served as a negative control. The sulfidoleukotriene values obtained with the stimulation buffer were subtracted regularly.

STATISTICAL METHODS

The sensitivity and specificity of the in vitro assay were compared with the results obtained from oral provocation tests using a 2×2 contingency table. The following pairs are possible: +/+ = a, –/– = d, +/– = c, and –/+ = b. Sensitivity was $100 \times a/(a + c)$, specificity was $100 \times d/(b + d)$. The following cut off points (after subtraction of IL-3 containing stimulation buffer control) were used: 300 pg/ml for C5a, 150 pg/ml for both PAF and fMLP. Statistical significance of the data was assessed by the Mann-Whitney rank sum test or χ test with $\alpha = 0.05$ using a statistical software package (SigmaStat for Windows, Jantel Scientific, Erkrath, Germany).

Results

ORAL PROVOCATION TESTS WITH ASPIRIN

Of 84 patients with a clear history of aspirin induced adverse skin reactions (urticaria and/or angio-oedema) only 21% had positive clinical reactions to oral provocation with aspirin. No cross reactivity to acetaminophen (paracetamol) was found; 78% of the pseudoallergic patients were women and 39% were atopic compared with 53% and 49%, respectively, among the aspirin tolerant patients.

DE NOVO PRODUCTION OF SULFIDOLEUKOTRIENES IN LEUCOCYTE SUSPENSIONS

Patients with positive oral provocation tests to aspirin had significantly higher levels of de novo sulfidoleukotriene production than subjects with negative oral provocation tests after

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Table 1 De novo production of sulfidoleukotrienes (SLT) in patients with positive and negative oral provocation test (OPT) to aspirin

	SLT (pg/ml)	
	*OPT positive**	*OPT negative**
C5a (10^{-7} M)	n = 18	n = 66
Mean	692	117
Median	583	79
Min–max	45–2010	0–549
	p<0.0001	
PAF (10^{-5} M)	n = 8	n = 32
Mean	371	56
Median	300	45
Min–max	141–647	0–198
	p<0.0001	
fMLP (10^{-6} M)	n = 8	n = 32
Mean	444	123
Median	582	84
Min–max	11–848	0–647
	p<0.01	

PAF = platelet activating factor; fMLP = f-Met-Leu-Phe.
*Randomly selected patients with a history of adverse skin reaction to aspirin.

stimulation with C5a, PAF, and fMLP (table 1). There was no correlation between sulfidoleukotriene production and total serum IgE and/or the detection of specific IgE antibodies. Total serum IgE levels of aspirin tolerant and intolerant subjects did not show any significant difference. Moreover, C5a, PAF, or fMLP induced sulfidoleukotriene release did not correlate with results obtained with anti-FcεRI as stimulating agent.

SENSITIVITY AND SPECIFICITY OF DE NOVO SULFIDOLEUKOTRIENE PRODUCTION FOR ASPIRIN INTOLERANCE

Sensitivity and specificity of stimulated sulfidoleukotriene production in IL-3 primed leucocyte suspensions were 83% and 94% for C5a (cut off 300 pg/ml), 88% and 94% for PAF (cut off 150 pg/ml), and 63% and 81% for fMLP (cut off 150 pg/ml), respectively. Using identical cut off values, the sensitivity and specificity increased to 88% and 91% when two stimuli were positive. In the case of increased sulfidoleukotriene production to all three basophil agonists (C5a, PAF, and fMLP), sensitivity decreased to 50% while specificity reached 100%.

Discussion

Our data clearly show that it is not possible to diagnose aspirin induced adverse skin reactions reliably on history alone since only 21% of patients with a clear cut history of provoked skin eruptions had positive oral provocation tests. This result agrees with published data on aspirin induced asthma.[3 16] Women were particularly affected by aspirin induced adverse skin reactions, and atopy or total serum IgE levels were not associated.

It was shown that the incomplete basophil agonists C5a, PAF, and fMLP resulted in a significantly higher production of sulfidoleukotrienes in subjects with aspirin intolerance than in aspirin tolerant subjects. Furthermore, we found that C5a, PAF, and fMLP induced sulfidoleukotriene release represents a sensitive and specific diagnostic tool for pseudoallergy to aspirin. These data therefore support the hypothesis that a shift in the eicosanoid balance towards higher leukotriene production may play a major pathophysiological role, not only in aspirin induced asthma, but also in aspirin induced adverse skin reactions.

Taken together, our data indicate that pseudoallergic reactions to aspirin are characterised by an enhanced susceptibility of basophils to incomplete agonists such as C5a, PAF, and fMLP, resulting in a significant production of sulfidoleukotrienes which may be responsible for mediating the inflammatory skin response in a group of aspirin sensitive patients.

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