

Prevention of severe premenstrual asthma attacks by leukotriene receptor antagonist

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Background: The etiology and treatment of premenstrual exacerbations of asthma (PMA) remain uncertain.

Objective: We investigated the role of cellular mediators released from inflammatory cells in the airflow limitation during PMA.

Methods: Serum levels of leukotriene (LT) B₄, LTC₄, platelet-activating factor, histamine, IL-1 β , IL-4, IL-5, IL-6, and GM-CSF were measured at different time points, first just before or during menstruation when the peak expiratory flow rate (PEFR) began to decrease precipitously and second during the menstrual midcycle week (days 10-16) when the PEFR returned to baseline values in patients with PMA and in age-matched asthma patients without PMA at the same intervals. **Results:** Serum levels of LTC₄ were significantly higher during exacerbations of asthma than after recovery (69.0 ± 16.0 pg/mL vs 24.0 ± 9.5 pg/mL, $P < .05$), whereas those of IL-1 β , IL-4, IL-5, IL-6, GM-CSF, histamine, LTB₄, and platelet-activating factor did not differ between 2 periods in 5 patients with PMA. In contrast, in 5 asthmatic patients without PMA serum levels of cellular mediators did not differ between corresponding periods. Oral administration of pranlukast, an LT receptor antagonist (225 mg twice daily), significantly reduced decreases in PEFR from the baseline values (110 ± 21 L/min with pranlukast vs 233 ± 20 L/min without pranlukast, $P < .01$) in association with an improvement of asthma symptom scores (6.5 ± 1.1 with pranlukast vs 9.8 ± 0.7 without pranlukast, $P < 0.05$) in 5 patients with PMA.

Conclusion: LTs are partly involved in the pathogenesis of PMA, and LT receptor antagonists may be useful for preventing airflow obstruction in patients with PMA. (J Allergy Clin Immunol 1999;104:585-8.)

Key words: Menstruation, asthma, leukotrienes, glucocorticoids, female sex steroids, inflammatory cells

Existing literature suggests that 30% to 40% of asthmatic women have an increase in asthma symptoms just before and during menstruation.¹⁻⁶ However, the mechanisms of worsening of asthma in relation to menstruation are uncertain, although psychologic, immune, and sex hormone-related mechanisms have been proposed.⁷⁻¹⁰

Abbreviations used

LT: Leukotriene
PAF: Platelet-activating factor
PEFR: Peak expiratory flow rate
PMA: Premenstrual exacerbations of asthma

Recently, extensive mast cell activation-degranulation has been shown to be a common feature in the functional layer of the endometrium just before and during menstruation in 107 healthy women.¹¹ Moreover, degranulation of peritoneal mast cells has been reported to be elicited by altering the levels of female steroid hormones in rodents.¹² These findings imply that systemic activation of mast cells may occur throughout the menstrual cycle and may be involved in the pathophysiologic mechanisms of premenstrual exacerbations of asthma (PMA). Because mast cells and T lymphocytes contain a variety of inflammatory mediators such as histamine, leukotrienes (LTs), and cytokines,¹³ we investigated the contribution of cellular mediators predominantly derived from activated mast cells and T lymphocytes to the pathogenesis of PMA.

METHODS

Subjects

Forty-five consecutive women aged 16 to 43 years attending an outpatient clinic for asthma were asked about the variation of their asthma during the menstrual cycle. The questionnaire included questions about the timing of any exacerbation in relation to menstruation, the frequency with which this occurred, the term of incidence, the frequency of admission, and the use of antiasthma drugs. Patients were also asked to record their peak expiratory flow rates (PEFRs) twice daily with use of a Mini-Wright peak-flow meter (Clement Clarke International, Harlow, UK) before bronchodilator treatment throughout a menstrual cycle. Five of 45 asthmatic patients showed decreases in morning PEFR of more than 40% from the baseline values just before or during menstruation. We enrolled these 5 patients with PMA and 5 age-matched patients without PMA (control) in the following studies. The demographic characteristics of 10 patients with or without PMA are shown in Table I. All patients had allergic diathesis (allergic rhinitis or allergic conjunctivitis) and increased levels of total serum IgE (462 ± 54 IU/mL in PMA and 514 ± 72 IU/mL in control). However, none of the patients had worsening of asthma associated with use of non-steroidal anti-inflammatory drugs, exercise, or cold air. Likewise, they did not receive birth control medications such as oral contraceptives. All patients had been hospitalized more than twice

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TABLE I. Physical characteristics and pulmonary function test results during remission in 5 patients with PMA (No. 1-5) and 5 asthmatic patients without PMA (No. 6-10)

No. of patients	Age (y)	Onset of PMA (y)	Admission times*	FVC (% predicted)	FEV ₁ (% predicted)
1	18	16	3	105	98
2	20	17	4	110	86
3	36	34	3	119	91
4	42	38	5	96	98
5	35	32	2	91	83
6	19	—	2	102	96
7	20	—	3	100	95
8	35	—	3	105	98
9	42	—	2	104	88
10	34	—	2	98	96

FVC, Forced vital capacity.

*Admission times indicate number of hospitalizations for asthma in her life.

because of asthma exacerbations and all patients with PMA had worsening of asthma during every menstrual period. All patients received oral theophylline (300 mg twice daily), inhaled beclomethasone dipropionate (1200 µg daily), and a 200 µg per dose of fenoterol given by a flow-driven inhaler as needed.

Protocol

Patients were asked to record their morning PEFs daily for 3 consecutive menstrual cycles while they took the same regimens described above, except that they received inhaled fenoterol on a regular basis (1 inhalation 4 times daily).

Blood samples for analysis of chemical mediators were drawn twice from each patient, first just before or during menstruation when PEF began to decrease precipitously and second during the midcycle week (days 10-16) when PEF returned to baseline values. Blood samples were drawn from 5 asthmatic women without PMA at the same intervals. Hematocrits were measured on each sample to detect gross changes in blood volume that might account for possible small changes in serum levels of bioactive substances.

Serum concentrations of IL-1β, IL-4, IL-5, IL-6, and GM-CSF were measured by specific ELISAs as reported previously.¹⁴⁻¹⁸ Likewise, serum concentrations of histamine were determined fluorometrically by HPLC.¹⁹ Sera were also processed for LTC₄, LTB₄, and platelet-activating factor (PAF) with use of HPLC and RIA.²⁰⁻²² The range of the RIA standard curve was 10 to 1000 pg/mL.

After completion of control measurements, patients received oral pranlukast (225 mg twice daily), an LT receptor antagonist,²³ in addition to the same regimens as in controls, and recorded their morning PEF during 3 consecutive menstrual cycles.

Patients were also asked to record the following asthma symptoms: nocturnal wheeze, nocturnal cough, morning chest tightness, and daytime wheeze during a menstrual period (day 1-day 7) throughout 3 consecutive menstrual cycles. The symptoms were scored on a scale of 0 to 3 (0 = absent, 1 = mild, 2 = moderate, 3 = severe) and recorded on diary cards. The asthma symptoms were recorded during 3 consecutive menstrual cycles (day 1-day 7) and asthma symptom scores were calculated as described by Wilson et al.²⁴

This study was approved by the Tohoku University Ethical Committee, and informed consent was obtained from each patient.

Statistical analysis

Results are expressed as the mean ± SEM. Statistical analysis was made with the Wilcoxon rank test. Significance was accepted at $P < .05$.

RESULTS

In 5 patients with PMA, serum levels of LTC₄ were significantly higher during PMA compared with those in the midcycle week (69.0 ± 16.0 pg/mL vs 24.0 ± 9.5 pg/mL, $P < .05$). In contrast, histamine (0.1 ± 0.1 ng/mL vs 0.1 ± 0.1 ng/mL, $P > .50$), IL-1β (0.3 ± 0.1 pg/mL vs 0.4 ± 0.4 pg/mL, $P > .50$), IL-4 (not detectable), IL-5 (not detectable), IL-6 (0.8 ± 0.4 pg/mL vs 0.4 ± 0.2 pg/mL, $P > .20$), GM-CSF (not detectable), LTB₄ (151 ± 44 pg/mL vs 263 ± 166 pg/mL, $P > .10$) or PAF (not detectable) did not differ significantly between 2 sample periods. Hematocrit values did not differ between the first and second samples in 5 patients with PMA ($43.9\% \pm 0.1\%$ vs $43.8\% \pm 0.2\%$, $P > .50$).

Fig 1 shows consistent decreases in PEF just before or during the menstrual period in the 5 patients with PMA before they received pranlukast. However, pranlukast inhibited maximal decreases in PEF in the 5 patients and significantly reduced a mean decrease in PEF from baseline values (110 ± 21 L/min with pranlukast vs 233 ± 20 L/min without pranlukast, $P < .01$) (Fig 1). Likewise, pranlukast significantly improved asthma symptom scores (6.5 ± 1.1 with pranlukast vs 9.8 ± 0.7 without pranlukast, $P < .05$) in the 5 patients with PMA (Fig 2).

In contrast, in 5 asthmatic patients without PMA neither PEF (423 ± 16 L/min [perimenstrual] vs 418 ± 22 L/min [midcycle]) nor serum levels of cellular mediators differed between corresponding periods. Patients without PMA did not receive additive treatment with pranlukast because PEF did not decrease just before or during menstruation.

DISCUSSION

The current study shows that serum levels of LTC₄ were increased during PMA and that PMA was attenuated by the LT receptor antagonist pranlukast. Although the origin of cysteinyl LTs in the sera is uncertain, there are several candidates, including T lymphocytes, basophils, and mast cells, that orchestrate airway inflammation in asthma.

Several studies have shown the influence of female sex steroids on inflammatory cells such as mast cells and basophils. Vliagoftis et al¹² reported that estrogen receptors were found on rat peritoneal mast cells and that estradiol augmented nonspecific mast cell degranulation in vivo. Likewise, greater responses were observed during menses in 70 of 246 skin-test reactions with allergens in patients with allergic rhinitis and asthma.²⁵ Furthermore, IgE-mediated histamine release from basophils is shown to be suppressed by progesterone in patients with cyclic urticaria.^{26,27} Because serum levels of progesterone decrease precipitously just before menstruation, decreases in progesterone might facilitate degranulation of basophils and mast cells. Mast cells are abundantly distributed along the bronchial tree, and activation of mast cells could elicit release of mediators that cause air-

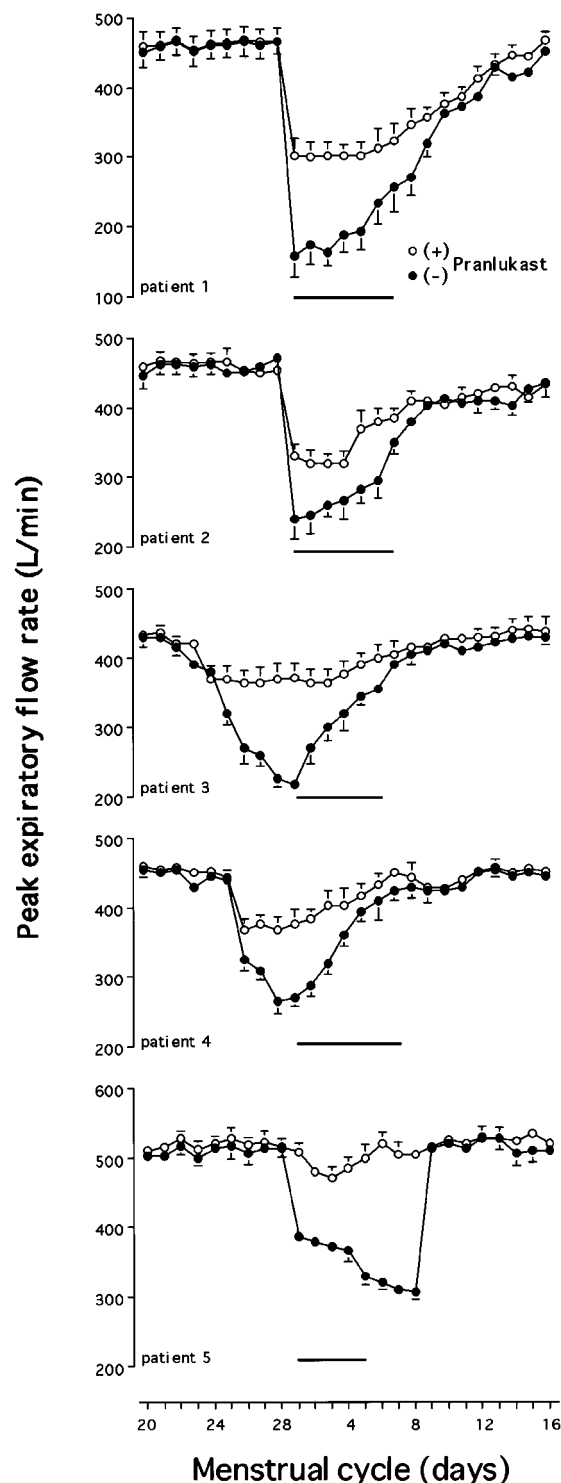


FIG 1. PEFRs before and after treatment with pranlukast in each patient with PMA. Data are mean $\pm$ SEM from 3 consecutive menstrual cycles. Horizontal bars, Menstruation.

way inflammation. However, the current study failed to show increases in serum levels of histamine in patients with PMA. This may be explained by the rapid degradation of histamine in the body.²⁸

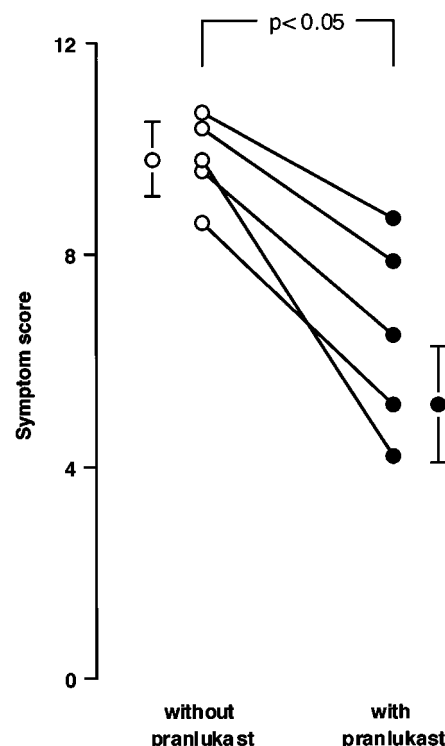


FIG 2. Effects of treatment with pranlukast, an LT receptor antagonist, on symptom scores during premenstrual asthma attack in 5 patients with PMA. Mean values ($\pm$ SE) are indicated by open and closed circles with error bars.

The patients enrolled in the current study who were resistant to conventional treatment had striking decreases in PEFR during PMA, as described previously.⁸ Beynon et al⁸ reported 3 patients with life-threatening PMA resistant to conventional treatment, including high-dose corticosteroids, but who responded to intramuscular progesterone. We also reported a case of severe menstrual exacerbations of asthma accompanied by luteal insufficiency that was successfully treated with cyclic hormone therapy.⁹ Derimanov and Oppenheimer²⁹ reported a case of worsening of asthma after oral contraceptives were taken. These observations suggest that female steroid hormones might be involved in the pathogenesis of PMA.

The 5-lipoxygenase products of arachidonic acid metabolism are important mediators of airway obstruction in asthma.³⁰⁻³⁴ LTs can impair mucociliary clearance, enhance mucus secretion, chemotactically attract leukocytes to the airways, and facilitate pulmonary vascular permeability to cause edema.³⁰ Thus antagonists of the cysteinyl-LT receptor, as well as drugs that interfere with LT formation, have been shown to blunt the magnitude of the obstructive response induced by cold dry air, hyperventilation, exercise, allergen, and aspirin.³²⁻³⁴ In the current study we also show the ability of LT antagonists to attenuate PMA.

The current study suggests that LTs may be partly

involved in the pathogenesis of PMA. A further study with a large number of patients is needed to translate the current findings to PMA in general.

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