

Products of arachidonic acid metabolism and the effects of cyclooxygenase inhibition on ongoing cutaneous allergic reactions in human beings

Paul C. Atkins, MD,^a Burton Zweiman, MD,^a Bruce Littman, MD,^b
Charles Presti, MD,^a Carolyn von Allmen,^a Anne Moskovitz,^a
and J. D. Eskra^b Philadelphia, Pa., and Groton, Conn.

Background: There have been conflicting reports about the effects of inhibition of arachidonic acid metabolism on early- and late-phase cutaneous reactions. We re-examined this question with a unique nonsteroidal antiinflammatory drug, tenidap sodium. Tenidap sodium has been demonstrated in *in vitro* studies to inhibit cyclooxygenase, lipoxygenase, and cytokine production (interleukin-1, interleukin-6, tumor necrosis factor- α).

Methods: In a double-blind, randomized, crossover study, seven pollen-sensitive subjects ingested tenidap (120 mg, by mouth, daily) and placebo for 9 days with a 3-week washout period between treatments. On the eighth day they underwent allergen skin testing, measurable for up to 12 hours, and on the ninth day they underwent 5-hour skin chamber exposures to allergen and buffer. Chamber fluids were analyzed for cellular content, neutrophil granule protein release, cyclooxygenase and lipoxygenase arachidonic acid metabolites, histamine, and tryptase.

Results: Tenidap did significantly inhibit cyclooxygenase metabolites at both antigen and buffer sites but had no effect on histamine, tryptase, lipoxygenase metabolites, or granulocyte infiltration. Neutrophil granule release of lactoferrin was lower at the antigen site during tenidap administration, but there was no reduction of elastase release. Prostaglandin E₂ and leukotriene E₄ increased significantly at antigen sites compared with buffer sites during placebo administration and were the most prominent arachidonic acid metabolites detected.

Conclusion: Tenidap, despite inhibiting cyclooxygenase release at antigen sites, had no effect on skin test responses to antigen or on antigen-induced mediator release or granulocyte infiltration. We conclude that cyclooxygenase metabolites are not important in the development of an allergic cutaneous inflammatory response. (*J ALLERGY CLIN IMMUNOL* 1995;95:742-7.)

Key words: Arachidonic acid metabolism, cyclooxygenase inhibition, cutaneous allergic reactions, tenidap

The cutaneous response to injected allergen has been used as a diagnostic tool to identify clinically allergic subjects and to standardize the biologic

From ^aDepartment of Medicine, Division of Allergy and Immunology, University of Pennsylvania School of Medicine, Philadelphia; and ^bPfizer Central Research, Groton.

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Reprint requests: Paul C. Atkins, MD, 510 Johnson Pavilion, University of Pennsylvania School of Medicine, Philadelphia, PA 19104-6057.

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Abbreviations used

AA: Arachidonic acid
LT: Leukotriene
PG: Prostaglandin
PNU: Protein nitrogen units

activity of allergenic extracts. In the past 2 decades, it has been appreciated that this cutaneous response consists of both an early phase (wheal and flare, peaking from 15 to 30 minutes after injection of allergen) and a late phase (erythema and induration, peaking between 6 and 8 hours after injection).

tion), which can persist in the skin for up to 24 to 48 hours.¹ It is believed that this prolonged "late-phase response" may be more indicative of the chronic inflammatory responses seen in the nose and lungs after challenge with allergen and during natural exposure in the pollen season.²

We and others have reported that products of arachidonic acid (AA) metabolism are formed and persist during ongoing cutaneous allergic responses in human beings.³⁻⁶ We had previously shown that prostaglandin (PG)D₂ was not involved in late-phase cutaneous responses in our model, because corticosteroids ablated the prolonged histamine release and the late-phase response but did not ablate the release of PGD₂.⁷ There have been conflicting reports about the presence and importance of other cyclooxygenase metabolites and the effects of cyclooxygenase inhibition on these responses.⁸⁻¹¹ However, there are no studies that compare the *in vivo* appearance of AA metabolites in the skin before and during the administration of a cyclooxygenase inhibitor versus placebo.

In this study we report the effects of the administration sodium, an investigative antirheumatic drug, on the release of AA metabolites and skin responses during ongoing cutaneous allergic responses. *In vitro* studies with human cells (polymorphonuclear neutrophils and mononuclear cells) have shown that tenidap inhibits both the cyclooxygenase and lipoxygenase metabolism of AA and inhibits cytokine production (interleukin-1, interleukin-6, tumor necrosis factor- α).^{12, 13} One investigation, published in abstract form, demonstrated a reduction in synovial fluid lipoxygenase and cyclooxygenase metabolites in patients treated with tenidap.¹⁴ This study attempts to determine whether inhibition of *in vivo* production of products of AA in cutaneous antigen-induced reactions affects antigen skin test reactivity or mediator release.

METHODS

Subjects

Seven male subjects with skin reactivity to 10 protein nitrogen units (PNU)/ml or less of ragweed or grass pollen extract, who exhibited at least 5 mm of induration 6 hours after intradermal injection of 10 PNU/ml of ragweed or grass pollen extract, agreed to participate in this study after informed consent was obtained. Six of the subjects reacted to both grass pollen and ragweed, and one subject reacted to ragweed only. This study was approved by the Human Subjects Committee of the University of Pennsylvania School Medicine.

Clinical protocol

All subjects participated in a randomized, double-blind, crossover study for 9 days in which placebo or tenidap sodium (CP-66, 248-2, a 3-substituted 2-oxindole derivative) (120 mg, by mouth, daily) was given, separated by 21 days. On the eighth day of placebo and tenidap administration, intradermal injection of serial 10-fold dilutions of grass pollen and/or ragweed extracts (10 to 0.001 PNU/ml) was performed. Skin wheal was measured at 20 minutes, and induration was measured at hourly intervals for 12 hours. On the ninth day of placebo and tenidap administration, four blisters were induced by heat and suction; the epidermis was removed, and after a 5-minute wash with buffered saline solution, skin chambers were placed over the sites.¹⁵ Two sites were filled with buffer and two with antigen (ragweed or grass pollen) solution (100 PNU/ml) for 1 hour. The fluid was removed, and sites were rinsed vigorously and replaced with like solution for a further 4-hour incubation as previously described.¹⁵ Fluids removed at 1 hour and after the fifth hour were centrifuged; the cells were collected and counted, and supernatant was stored at -70°C for analysis of mediators.

Chamber fluid assays

AA metabolites. Leukotriene (LT)C₄, LTE₄, LTB₄, and PGE₂ in chamber fluids were diluted 1:11 in elution buffer and assayed with specific enzyme immunoassays (Cayman Chemical Co., Ann Arbor, Mich.). The cross-reactivities of the specific assays were: (1) LTC₄, 46% with LTD₄ and 2% with LTE₄; (2) LTE₄, 10% with LTC₄ and 9% with LTD₄; (3) LTB₄, <0.02% with LTC₄, LTD₄, and LTE₄; (4) PGE₂, <0.2% with other prostaglandins.

Tenidap concentrations. Tenidap concentrations were measured by UV high-performance liquid chromatography after samples were extracted in the solid phase.

Histamine. Histamine was measured with a radioenzymatic assay.¹⁶

Tryptase. Tryptase was measured by Lawrence Schwartz, MD, Medical College of Virginia, with an ELISA.¹⁷

Elastase and lactoferrin. Elastase and lactoferrin were measured with a separate ELISA, as previously reported.¹⁶

Statistical evaluations

Results were analyzed with a paired *t* test after a two-way repeated-measures analysis of variance was performed for each of the parameters. The slope of the regression line was calculated from a linear regression of the plot of the antigen dose (horizontal axis) and the skin wheal diameter (vertical axis) for early- (20 minutes) and late-phase (6 hours) skin responses. The slopes of the regression lines during tenidap administration and placebo administration were compared to determine whether tenidap altered the skin response to antigen. Paired *t* tests were used to determine significance.

TABLE I. Mean changes in regression line slopes for skin test studies

Treatment	n	Mean change in slope*	Tenidap vs placebo	95% CI	t Statistic	p Value
Challenge: grass						
Early						
Tenidap	7	0.0041	0.506	-0.0517, 0.1529	1.21	0.27
Placebo	7	-0.0465				
Late						
Tenidap	7	0.0387				
Placebo	7	-0.0648	0.1035	-0.0586, 0.2656	1.56	0.17
Challenge: ragweed						
Early						
Tenidap	7	0.0023				
Placebo	7	-0.0081	0.0104	-0.0413, 0.0622	0.52	0.63
Late						
Tenidap	7	0.0160				
Placebo	7	0.0593	0.0433	-0.2278, 0.1411	0.60	0.57

CI, Confidence interval.

*Difference between the mean posttreatment and mean pretreatment values of the slopes of regression line relating the mean wheal induration diameter to antigen challenge concentration.

TABLE II. Tenidap versus placebo (0 to 1 hour chamber fluid results)

	Placebo			Tenidap		
	Buffer	Antigen	Net*	Buffer	Antigen	Net
Histamine	1 ± 0.30	71 ± 10	70 ± 10	1 ± 0.5	84 ± 11†	83 ± 12
Tryptase	4 ± 1.7	231 ± 46†	227 ± 46	5 ± 1.8	287 ± 62†	281 ± 61
PGE ₂	0.72 ± 0.30‡	0.71 ± 0.20‡	0	0.07 ± 0.05	0.04 ± 0.02	0
LTC ₄	0 ± 0	0.14 ± 0.05	0.14 ± 0.05	0.05 ± 0.04	0.13 ± 0.04	0.08 ± 0.03
LTC ₄	0.01 ± 0.01	1.22 ± 0.50†	1.21 ± 0.47	0.44 ± 0.40	1.20 ± 0.30†	0.76 ± 0.32

Values are expressed as means ± SEM in nanograms per milliliter, unless otherwise indicated.

*Net mediator release (antigen-buffer).

†p < 0.02 versus buffer site.

‡p < 0.012 versus tenidap values.

RESULTS

Skin test responses

There were no differences in immediate or late-phase skin responses during tenidap administration versus placebo administration as determined by: (1) the smallest dose resulting in a 10 mm wheal, (2) the wheal response to 10 PNU/ml of antigen, and (3) the maximal late-phase induration at 6 to 12 hours after intradermal injection of 1 or 10 PNU/ml of antigen. Statistical assessment of these early- and late-phase responses, with the slope of the antigen dose regression line as shown in Table I, confirmed the lack of effect of tenidap on these responses.

Chamber fluid mediators

The results of analyses of mediators in the chamber fluids from 0 to 1 hour are shown in Table

II. The most striking findings during this period are the significantly increased levels of histamine, tryptase, and LTE₄ at sites of antigen exposure (compared with buffer sites), which were not affected during tenidap administration. In addition, PGE₂ was present in chamber fluid at both antigen and buffer sites during placebo administration but was almost totally absent during tenidap administration.

Table III shows the results in the 1- to 5-hour chamber fluids. When placebo was given, there was a significantly greater exudation of granulocytes and increased levels of the neutrophil granule components, lactoferrin and elastase, at antigen sites (vs buffer sites), similar to results reported previously by Zweiman et al.¹⁸ In addition, the levels of histamine, PGE₂, LTC₄, and LTE₄ were significantly greater in chamber fluids at the anti-

TABLE III. Tenidap versus placebo 1 to 5 hour chamber fluid results

	Placebo			Tenidap		
	Buffer	Antigen	Net*	Buffer	Antigen	Net
Histamine	6 ± 1.8	39 ± 7.8†	33 ± 7.2	2.6 ± 0.3	24 ± 4†	22 ± 4
PGE ₂	1.51 ± 0.8†	2.37 ± 1.1†‡	0.85 ± 0.33§	0.09 ± 0.04	0.37 ± 0.25†	0.27 ± 0.25
LTC ₄	0.08 ± 0.03	0.68 ± 0.16†	0.60 ± 0.16	0.44 ± 0.08†	0.44 ± 0.08†	0.43 ± 0.09
LTE ₄	0.30 ± 0.24	7.69 ± 1.4†	7.4 ± 1.38	0.04 ± 0.01	4.77 ± 1.1†	4.73 ± 1.12
LTB ₄	0.39 ± 0.14	0.91 ± 0.27	0.52 ± 0.15	0.34 ± 0.15	2.01 ± 1.5	1.67 ± 1.35
Granulocytes (10 ³)	1241 ± 552	4651 ± 1353†	3581 ± 1452	1853 ± 620	3640 ± 978†	1787 ± 600
Elastase	108 ± 35	195 ± 45†	114 ± 51	88 ± 27	277 ± 47†	116 ± 45
Lactoferrin	11 ± 5	25 ± 10†	14 ± 5	13 ± 6	16 ± 4	3 ± 5

Values are expressed as means ± SEM in nanograms per milliliter, unless otherwise indicated.

*Net mediator release (antigen-buffer).

†*p* < 0.01 versus buffer site.

‡*p* < 0.05 versus tenidap values.

§*p* < 0.05 versus tenidap values.

gen challenge sites. Although the mean level of LTB₄ was greater during tenidap administration than during placebo administration, there was no significant enhancement of LTB₄ production during tenidap administration. Comparison of LTB₄ levels at antigen sites during tenidap administration and placebo administration revealed a lower level in four of seven subjects and an increase in three of seven subjects. The increase in the mean LTB₄ level during tenidap administration compared with placebo administration is due to a single subject who had levels of 2.3 during placebo administration and 10.9 during tenidap administration. Removing this outlier results in essentially equivalent LTB₄ levels of 0.72 during tenidap administration versus 0.91 during placebo administration. During tenidap administration, there was no significant reduction of granulocyte exudation or elastase levels at either antigen or buffer sites when compared with the periods of placebo administration. However, lactoferrin levels were reduced to the point at which there was no significant difference between levels at antigen sites and those at buffer sites.

PGE₂ levels were reduced considerably at both antigen and buffer challenge sites during tenidap administration (vs placebo administration). However, increases in LTC₄ and LTE₄ levels were not significantly inhibited when tenidap was given.

A new finding in these studies is that PGE₂ and LTE₄ were the most prominent AA metabolites recovered at antigen sites after continuous exposure of the skin to antigen in the 1- to 5-hour period. Because we did not have enough chamber fluid to assay specifically for LTD₄ (which requires chromatographic separation), we relied on the

relative specificities of the enzyme immunoassays. The LTC₄ assay cross-reacts with LTD₄ (46%) but not with LTE₄ (2%), whereas the LTE₄ assay has very little cross-reactivity (10%) with either LTD₄ or LTC₄. Therefore LTE₄ is the major lipoxygenase metabolite recovered in antigen site chamber fluids.

In addition to the absolute amount of mediator recovered at antigen and buffer sites (Tables II and III), we have also analyzed the net (antigen-buffer) increase in mediator release. Analysis of variance of the net increase in PGE₂ from 1 to 5 hours on tenidap and placebo days demonstrated a significant effect for drug administration (*p* = 0.011). Paired *t* tests indicated a significant reduction of net PGE₂ (0.86 vs 0.27, *p* < 0.05) during tenidap administration. There was no other significant difference in net mediator release or cell accumulation between tenidap administration and placebo administration.

Mean tenidap levels during tenidap administration were 22.8 µg/ml in the plasma and 1.4 and 0.8 µg/ml in the 0- to 1-hour period, increasing to 4.4 and 6.6 µg/ml in the 1- to 5-hour antigen- and buffer-challenged chamber fluids, respectively. In vitro studies would suggest that these concentration in the chamber fluids were adequate for inhibition of prostaglandin synthesis.¹²

DISCUSSION

In this study we have determined that the products of AA metabolism released most prominently during ongoing cutaneous allergic responses are PGE₂ and LTE₄. A significant increase of PGE₂ release does not occur at the antigen site until after the first hour, whereas LTE₄ levels are significantly

increased in the first hour at antigen sites and rise even further during the 1- to 5-hour antigen exposure. In addition, we have shown that although tenidap administration significantly lowered PGE levels at both antigen and buffer sites, there was no effect on cutaneous early- or late-phase skin responses. The recovery of LTC₄ and LTE₄ or granulocytes at the sites of antigen exposure were not significantly reduced when tenidap was given. Tenidap did seem to reduce chamber fluid levels of lactoferrin but not elastase. Because elastase is in neutrophil azurophilic granules and lactoferrin is in specific granules, these results may indicate selective inhibition of specific granule secretion by tenidap. This evidence suggests that cyclooxygenase metabolites do not play a major pathogenic role in late cutaneous allergic reactions.

These findings can be evaluated further in the light of previous observations in this area of study. There have been a number of other studies of arachidonate metabolites during cutaneous allergic responses. We previously reported an increased release of LTC₄ in a prolonged fashion for up to 5 hours in skin chambers at sites of antigen exposure in the skin of allergic subjects.³ In that study we had measured mediator release hourly after a single hour of exposure to antigen. Others, using a higher dose, after a single hour of exposure to allergen in skin chambers, have demonstrated an early appearance of PGD₂ (within the first 1 to 4 hours) and later appearance of LTC₄ (5 to 7 hours) as the predominant AA metabolites at sites of antigen exposure.^{4,6}

The effects of inhibitors of cyclooxygenase on immediate and late-phase skin responses to antigen have been studied by several investigators. In two studies no change was observed in early- or late-phase cutaneous responses during topical⁸ or systemic⁹ administration of cyclooxygenase inhibitors. However, in two other studies, indomethacin¹⁰ and a combination of aspirin and antihistamine¹¹ resulted in a 35% to 50% reduction of the late cutaneous response to allergen. However, in none of these studies was evidence presented to show whether cyclooxygenase metabolism of AA was actually inhibited at antigen-challenged skin sites during drug administration. Drug levels at the site were also not assessed. Therefore our report is the first demonstration that late-phase allergic skin responses are not affected, even though local cyclooxygenase metabolism is markedly inhibited. Further, measurement of drug levels in the chamber fluid showed that tenidap was delivered to the skin in amounts sufficient to inhibit AA metabolism.

Tenidap is a unique antiinflammatory agent the structure of which is a 3-substituted-2 oxindole derivative. It has been shown to inhibit the release of both LTB₄ and PGE₂ from human peripheral polymorphonuclear cells in vitro.¹¹ Our studies are the first to describe the in vivo effects of tenidap in the skin of human beings. It is of interest that at the doses used, a significant tenidap level was achieved in skin chamber fluid and that tenidap virtually abolished the PGE production in the skin at the sites of both buffer and antigen exposures. Despite the findings in in vitro studies mentioned previously, there was no significant reduction of the predominant lipoxygenase metabolites LTC₄ and LTE₄. This may be explained by the fact that tenidap is more than 99% bound to protein and the potency of tenidap as an inhibitor of 5-lipoxygenase is about 800 times less than its potency as an inhibitor of cyclooxygenase.¹²

Although the source of the PGE₂ cannot be determined from these studies, previous studies have shown that the skin itself produces predominantly PGE₂ under a variety of conditions, including antigen challenge of skin homogenates and UV light stimulation.^{19,20} In vitro studies have suggested that PGE₂ may downregulate functions of both neutrophils and basophils.^{19,20} Although we saw no effect of tenidap on in vivo histamine release in either the 0- to 1-hour or 1- to 5-hour periods, we did see a decrease in neutrophil lactoferrin release, perhaps consistent with in vitro studies of the effects of tenidap on neutrophil degranulation.¹²

It is probable that infiltrating granulocytes also contributed to the PGE₂ at sites of antigen exposure because there was a pronounced increase during the 1 to 5-hour period when granulocytes accumulated. In addition, the granulocytes were activated at sites of antigen exposure, releasing both lactoferrin and elastase.

The source of lipoxygenase metabolites in these allergic inflammatory responses is not yet defined. We suggest that these metabolites are produced by several cell types. The mast cell is a source of LTC₄ (as we have previously demonstrated in the skin).³ Both eosinophils and monocytes, when activated, can secrete LTC₄; these cells, which are not present in the chamber fluids, but which we have shown to be present at the blister base and in skin biopsy specimens from patients with cutaneous allergic responses may therefore also be sources of LTC₄ in the chamber fluids.^{22,23} That infiltrating cells may be participating is suggested by the dramatic increase of LTE₄ during the 1- to 5-hour

period, at a time when inflammatory cells are accumulating in the chamber fluids. The finding of this study that LTE_4 levels were greater than LTC_4 levels may reflect the longer duration of antigen challenge before the chamber fluid was collected, compared with 1-hour collection periods in our previous study.³ This longer period may allow conversion of LTC_4 to LTE_4 by increased exuding granulocytes or resident skin cells.

In summary, we have shown that PGE_2 and LTE_4 are the main arachidonate metabolites released during ongoing cutaneous allergic reactions. Inhibition of PGE_2 production did not affect early- or late-phase skin test reactivity or the amount of histamine released at the sites. Therefore it is unlikely that cyclooxygenase metabolites of AA are playing important roles in the development of these allergic cutaneous inflammatory responses.

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