

Lack of effect of the 5-lipoxygenase inhibitor zileuton in blocking oral aspirin challenges in aspirin-sensitive asthmatics

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Background: Leukotrienes (LTs) have been implicated as major mediators of aspirin-(ASA)-induced respiratory reactions. It was therefore logical to assume that an inhibitor of 5-lipoxygenase (5-LO), such as zileuton, given before and during oral challenges with ASA, might prevent ASA-induced respiratory reactions. Indeed, in prior studies, pretreatment of ASA-sensitive respiratory disease patients with leukotriene modifiers eliminated or attenuated respiratory reactions upon re-challenge with the previously established provoking dose of ASA. However, doses higher than the provoking doses were not administered during these reported studies.

Objective: We wished to determine whether zileuton pretreatment could prevent ASA-induced respiratory reactions in our six volunteers with aspirin-sensitive respiratory disease when ASA challenge doses were started below the usual provoking dose of 60 mg and then increased until a respiratory reaction occurred.

Method: Aspirin sensitivity was established previously in all six patients during a prior ASA oral challenge. In this study, pretreatment with zileuton 600 mg qid was initiated 7 days prior to, and continued during oral ASA challenges. Patients underwent single-blind oral ASA challenges with escalating doses of ASA, every 3 hours, according to our standard protocol.

Results: All six patients reacted to doses of ASA between 45 and 325 mg. Four patients experienced bronchospasm (FEV₁ declined 19% to 53%) while receiving zileuton. All six had naso-ocular reactions. Concentrations of urine LTE₄ also increased significantly (mean 334 pg/mg Cr at baseline, increasing to 1024 pg/mg Cr at respiratory reactions).

Conclusions: During ASA challenges, zileuton, in standard doses of 600 mg qid was associated with increased synthesis of LTs in five of six patients and naso-ocular reactions in all six patients, as well as bronchospasm in four patients.

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INTRODUCTION

Aspirin-sensitive respiratory disease (ASRD) usually begins in adult life

and often requires topical and/or systemic corticosteroids to maintain partial control of aggressive respiratory mucosal inflammation and bronchospasm.¹ In these patients, ingestion of ASA induces a spectrum of respiratory reactions, ranging from pure upper airway reactions to lower airway bronchospasm or any combination of reactions.² Oral ASA challenges are the only available method in the USA for accurately identifying which patients have ASRD. Such challenges have been developed and standardized.^{1,3,4} Eighty-five percent of respiratory reactions, induced during oral ASA challenges, involve both upper and lower

airways and usually last 2 to 6 hours.² All ASRD patients can be desensitized to ASA, with advancing doses of ASA after the original respiratory reaction.¹ This process usually involves one to three additional reactions of diminishing size.

Leukotrienes are a family of lipid mediators derived from arachidonic acid that are potent pro-inflammatory mediators. They play an important pathophysiologic role in asthma, including stimulation of airway smooth muscle contraction, increased microvascular permeability, increased mucus formation, and recruitment of eosinophils into the airways.^{5,6} It is not surprising, therefore, that a number of leukotriene modifiers have been developed by the pharmaceutical industry. These compounds consist of receptor antagonists or inhibitors of leukotriene synthesis at the 5-lipoxygenase enzyme. Encouraging results from the use of leukotriene modifying drugs in the treatment of asthma in general and ASA-sensitive asthmatics in particular have been reported.^{7–13}

Leukotrienes appear to be crucial mediators of ASA-induced respiratory reactions.^{1,14,15} It was therefore logical to propose that an inhibitor of 5-LO might prevent ASA-induced respiratory reactions if given before ingestion of ASA. The role of anti-leukotriene drugs in preventing ASA-induced asthma has been investigated, using threshold doses of ASA or dipyrone given after protection with leukotriene modifiers.^{16–18}

Studies that answer the fundamental question of whether pretreatment with a leukotriene modifier can prevent ASA-induced respiratory reactions,

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when escalating doses of ASA are used in standard oral challenges, have not been reported. This study was therefore performed and contained two goals. First, we wished to determine whether higher doses of ASA, beyond the prior threshold doses or usual provoking doses (60 mg of ASA), would induce respiratory reactions in ASA-sensitive asthmatics. Second, using the standard ASA desensitization protocol,¹ we wished to determine whether or not patients could remain asymptomatic during ASA desensitization if we gave zileuton as pretreatment. Such a "silent desensitization" would allow physicians to conduct this procedure safely in their out patient offices.

METHODS

Patients

Approval from the Human Subjects Committee and the General Clinical Research Center was obtained and all subjects gave their informed consent. Six otherwise healthy asthmatic volunteers with documented ASA-sensitive asthma were selected as the study population. All demonstrated the typical quadrad of chronic asthma, nasal polyposis, chronic sinusitis, and ASA sensitivity. Patients who entered this study had to have undergone a positive oral ASA challenge in the past in our General Clinic Research Center (GCRC) in order to document their ASA sensitivity. These baseline challenges occurred between 2 weeks and 6 years earlier (1992–1998) and are detailed in Table 2.

The six patients enrolled in this study were 44 to 72 years of age and included two males (GE and BM) and four females. All had experienced 1 to 5 episodes of ASA-induced asthma attacks after ingesting 650 mg of ASA outside the hospital and prior to their

first evaluation in our institution. Four of the six had also experienced cross-reacting asthmatic attacks after ingesting ibuprofen. All six had undergone at least one oral challenge in our GCRC without protection with zileuton (see baseline challenges in Table 2). The years of those prior challenges were 1992 for NF, GE, and DB, 1997 for SW, and BM and 2 weeks prior to our current study in 1998 for patient PV. Five patients were taking nasal and bronchial corticosteroids during both challenges and patient PV was taking prednisone 30 mg qod during both oral ASA challenges, which were 2 weeks apart. The following patients were also taking systemic corticosteroids: NF was receiving methylprednisolone 6 mg qod during both challenges, DB and BM prednisone 10 mg qod during both challenges and GE and SW received 1 to 6 bursts of prednisone per year but none during either oral ASA challenges. Patient GE was taking theophylline 200 mg qd during both oral ASA challenges.

Study Design

The current study of zileuton pretreatment was performed during 1997 and 1998 (Table 2). For each sequential challenge/desensitization study, pretreatment with zileuton (Zyflo, Abbott Laboratories, Chicago, IL) 600-mg film tablets qid was started 7 days prior to ASA challenge. To maximize compliance, all patients were counseled about the importance of taking all zileuton tablets and for 48 hours before ASA challenges RNs dispensed zileuton in the GCRC. Zileuton was continued before and through the ASA challenge studies at a dose of 600 mg every 6 hours.

For this current study, patients were admitted to the GCRC on the day before the first placebo challenge day. FEV₁ (best of three expiratory efforts) was measured every hour during the challenge periods. On the days of placebo and ASA oral challenges, zileuton was dispensed at the following times: 06:00, 12:00, 18:00, and 24:00 hours. Oral placebo, on one day, and ASA challenge on the next day, were started at 07:00 hours. On day 1, placebo challenges were conducted at 3-hour intervals to establish stability of airways. All patients had stable baseline FEV₁ values (change from AM baseline varied between 0% to 10%) during the 9-hour placebo challenge days. On challenge day 2, oral ASA challenges were started at 7:00 AM using our standard protocol (Table 1). Aspirin respiratory sensitivity was defined as a decline of 20% or more in FEV₁ and/or naso-ocular reactions within 3 hours after incremental oral ASA challenges. If naso-ocular reactions occurred with a 15% to 20% decline in FEV₁, this was classified as a mixed upper and lower respiratory reaction. After ASA induced respiratory reactions were treated and had cleared (2 to 24 hours), the same dose of ASA was repeated. Doses were then escalated over several days until desensitization was completed (650 mg ASA without reactions).¹⁹ The number of respiratory reactions to ASA during standard (unprotected) ASA desensitization was available from prior challenge studies in each of the six study subjects and was compared with the number of reactions to completion of desensitization with zileuton protection.

Signs and symptoms of reactions in the upper airways were simultaneously recorded using a standard symptom scoring system. A positive response consisted of rhinorrhea plus any of the following: ocular chemosis, injection and periorbital swelling, nasal congestion, and paranasal sinus pain. The scores were recorded as 0 = absence of any reactions, 1 = nasal congestion alone, 2 = partial nasal obstruction with ocular injection, 3 = complete nasal obstruction with ocular injection

Table 1. Single Blind Three-Day Oral ASA Challenge Protocol*

Time	Day 1	Day 2	Day 3
7:00 AM	Placebo	aspirin, 30 mg	aspirin, 150 mg
10:00 AM	Placebo	aspirin, 45–60 mg	aspirin, 325 mg
1:00 PM	Placebo	aspirin, 60–100 mg	aspirin, 650 mg

* May be altered by MD, depending upon patient profile, lung function, degree of prior reaction, etc.

and paranasal headache, and 4 = severe reactions with periorbital edema and severe manifestations of all naso-ocular signs and symptoms.

The provoking dose was defined as the dose of ASA responsible for the first respiratory reaction. The elapse time was defined as the time from ingestion of ASA to onset of the respiratory reaction.

Urinary Excretion of LTE_4

Urine samples were obtained at time of (1) prechallenge on challenge day 2 between 6 and 7 AM, (2) first naso-ocular/asthmatic reaction, and (3) 3 hours after ASA desensitization to 650 mg of ASA. The concentration of LTE_4 was determined by enzyme immunoassay using triplicate determinations.²⁰

Statistical Analysis

Statistical analysis was accomplished by using two computer programs. The first program determined the differences in means for challenge data at baseline compared with zileuton-protected challenges. Paired Student's *t* test using Stat View 4.01 for Mac (Abacus Concepts Inc, Berkeley, CA). The second program analyzed statistically changes in urinary LTE_4 values between baseline and reaction using

the Student's *t* test (Instat, San Diego, CA).

RESULTS

Oral ASA Challenge/Desensitization Results

Six volunteer patients underwent initial ASA challenges from 2 weeks to 7 years prior to the repeat ASA challenges with zileuton pretreatment (Table 2). For the initial or baseline challenges, the mean provoking dose of ASA was 57 mg, although individual responses varied between 30 and 100 mg. By contrast, the mean provoking dose of ASA with zileuton pretreatment was 122 mg (range 45 to 325 mg) without a statistically significant difference between baseline and zileuton-protected provoking doses ($P = .24$). Despite zileuton protection, all patients experienced at least naso-ocular reactions during ASA challenges. The four ASRD patients who experienced asthmatic reactions to ASA at baseline, again experienced bronchospastic reactions to ASA during zileuton protection, ranging from 19% to 53% declines in FEV_1 values (NF, GE, PV, and DB). There was a tendency for higher provoking doses of ASA to initiate respiratory reactions while receiving zileuton in three patients (NF, PV,

and DB) but the differences did not reach statistical significance with this small sample size. The mean elapsed time to respiratory reactions during baseline ASA challenges, following provoking doses of ASA, was 2.2 hours. Similarly, the mean elapse time to respiratory responses with zileuton pretreatment was 2.0 hours ($P = .75$). Naso-ocular scores during ASA challenges were mean 2.7 (baseline) and after zileuton protection 2.0 [$(P = .36)$]. After ASA challenges with zileuton pretreatment, mean decline in % FEV_1 values were 23%, as compared with a mean baseline FEV_1 value of 18% ($P = .23$). None of these changes were statistically significant. Patient GE experienced a moderate decline of FEV_1 values during baseline challenge (28% following 100 mg of ASA). Interestingly, he experienced a dramatic respiratory reaction while receiving zileuton protection (FEV_1 decreased 53% after 45 mg of ASA). GE was the only study patient to experience multiple respiratory reactions to escalating doses of ASA before ASA desensitization was completed. The other five were desensitized during one ASA-induced respiratory reaction (naso-ocular reaction only in BM and SW).

Table 2. Oral ASA Challenge Results

Patient	Baseline (without Zileuton pretreatment)				Zileuton Pretreatment			
	Provoking Dose ASA (mg)	Elapsed Time (hours)	Naso-ocular Score (0-4)	ΔFEV_1 (%)	Provoking Dose ASA (mg)	Elapsed Time (hours)	Naso-ocular Score (0-4)	ΔFEV_1 (%)
N.F.	60	2.0	3	22	100	2.8	3	19
G.E.	100	1.0	2	28	45	1.0	2	53
P.V.	30	3.0	3	27	60	2.9	3	34
D.B.	60	2.0	3	26	100	2.5	2	31
S.W.	60	3.0	2	2	100	1.0	2	2
B.M.	30	2.0	3	0	325	2.0	3	0
Mean	57	2.2	2.7	18	122	2.0	2.5	23
Std. Dev.	26	0.75	0.52	13	102	0.86	0.22	20
SEM	11	0.3	0.21	5.3	42	0.35	0.3	8.3

Paired Student's *t* test comparing baseline to zileuton-protected ASA challenge events:

Provoking doses of ASA: $P = .24$.

Elapse times: $P = .75$.

Naso-ocular reactions: $P = .36$.

Change in FEV_1 values: $P = .23$.

Urinary Excretion of LTE_4

Figure 1 contains information regarding concomitant measurement of urinary LTE_4 values in the six patients during repeat ASA challenges with zileuton concomitant treatment. Baseline values were a mean of 334 ± 88 SE in pg/mg Cr and this increased substantially during ASA induced reactions (mean 1024 ± 256 SE, in pg/mg Cr). The four patients who experienced upper and lower respiratory reactions when doses of ASA were escalated (NF, GE, PV, and DB) also had the highest increases in reaction LTE_4 values, which were significantly increased from baseline ($P = .01$). These biochemical studies further supported the clinical observations that zileuton did not prevent LT formation.

DISCUSSION

This is the first study to examine whether a 5-lipoxygenase inhibitor (5-LO) inhibitor, zileuton, could prevent ASA-induced respiratory reactions if given before ASA doses that were advanced above threshold-provoking doses of ASA. We demonstrated that four asthmatic patients experienced about the same degree of bronchospasm with and without zileuton but a larger provoking dose of ASA was required to initiate the reaction in three of these four patients. All six patients reacted to ASA with naso-ocular reactions with and without zileuton protection, indicating that zileuton pretreatment did not prevent upper respiratory reactions in any of our patients.

In addition, LTE_4 urine concentrations increased in five of six patients coincident with ASA-induced lower or upper respiratory reactions, again confirming that 5-LO enzyme was insufficiently inhibited to prevent formation of new LTs. Urine LTE_4 concentrations have been used to estimate total body leukotriene synthesis. Since the work of Christie et al¹⁴ and Kumlin et al,¹⁵ it has been reported that ASA-induced respiratory reactions are closely associated with increasing concentrations of urinary LTE_4 , usually within 2 to 4 hours after onset of respiratory reactions. It has been estab-

lished in prior studies that a rise in urine LTE_4 is expected during ASA-induced reactions.

A study using the selective LTD_4 receptor antagonist SK&F 104353 by inhalation, prevented oral ASA-induced bronchospasm in four of five ASA-sensitive asthmatics when comparing the same provoking dose (ranging from 30 to 120 mg of ASA given orally).²¹ Even in the four subjects, where repeat ASA provoking doses did not induce bronchospasm, the protection ranged from marginal (16% decrease in FEV_1 with the patient requesting albuterol bronchodilation) to complete prevention of reactions to ASA in three patients. Uncertainty about the effectiveness of SK&F-104353 to block formation of leukotrienes, particularly because of the inhaled delivery route, as well as the low challenge doses of oral ASA (30 to 120 mg), did not allow definitive conclusions about the effectiveness of this LTD_4 antagonist in preventing oral ASA-induced asthma. Larger challenge doses of ASA were not used in this study.

Dahlen et al²² compared MK-0679, a potent leukotriene receptor antagonist, given as a single 750-mg oral dose prior to ASA-lysine inhalation challenges, with placebo in a double-blind protocol. In eight ASA-sensitive asthmatic subjects, pretreatment with MK-0679 substantially shifted the dose-response to inhaled ASA-lysine.

Three of the eight with MK-0679 pretreatment were protected from bronchospasm after receiving the highest doses of ASA-lysine (600 and 720 μmol). In the other five patients, after pretreatment with the LTD_4 receptor antagonist, bronchospasm occurred as the doses of ASA-lysine by inhalation were advanced to a high enough concentration.

In a study by Israel et al,¹⁸ eight ASA-sensitive asthmatic patients, previously shown to react to threshold provoking doses of oral ASA (20 to 300 mg range, 90 mg mean), were shown to be protected in both the upper and lower respiratory tracts from the same threshold doses of ASA after pretreatment with zileuton. Furthermore, during zileuton-protected ASA challenges, there was a concomitant blunting of the expected increase in urinary LTE_4 . These studies gave encouragement to the idea that zileuton might prevent ASA-induced respiratory reactions by reducing synthesis of LTs during ASA oral challenges. The ASA-sensitive patients recruited in the Israel study¹⁸ generally had mild-to-moderate ASA respiratory disease. In their study patients, the mean provoking dose of ASA was 90 mg and none required maintenance systemic corticosteroids. The capability of zileuton to block respiratory reactions, following larger doses of ASA, above the threshold challenge doses was not addressed in their study.

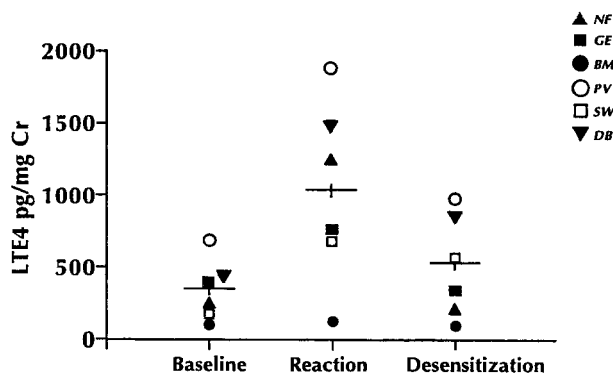


Figure 1. Zileuton failed to block LTE_4 elevation during reaction to ASA. Urine samples were collected at indicated time points and analyzed for LTE_4 by EIA. There was a significant rise in LTE_4 levels during the reaction to ASA ($*P = .01$) in asthmatics with a classic reaction ($n = 4$), but not in asthmatics with only a naso-ocular reaction ($n = 2$).

Our current study contrasts with the Israel study¹⁸ in several ways. The Israel study was a placebo-controlled, double-blind crossover study in which individuals took placebo or zileuton 4 times daily for 6 to 8 days before being re-exposed to only the threshold doses of ASA. Our study was unblinded with respect to zileuton therapy and doses of ASA were escalated to the next level and beyond, until a respiratory reaction occurred. In our study, ASA-induced upper respiratory reactions occurred in all six subjects and bronchospasm in four. In other words, either these respiratory reactions were the result of actions by other mediators (histamine, PAF, prostaglandin D₂, kinins activated by tissue kallikreins, etc) in addition to or in place of LTs, or LTs were not adequately inhibited by zileuton and contributed significantly to the respiratory reactions. The later conclusion seems to be most reasonable in explaining the reactions in five of six patients, because associated biochemical evidence, in the form of increasing LTE₄ concentrations in the urine, appeared during their respiratory reactions. In the sixth patient (BM), LTE₄ concentrations remained the same during his naso-ocular reaction and therefore we can logically assume that zileuton may have blocked LT synthesis and his reaction resulted from other mediators. One might conjecture that histamine release into nasal secretions, as previously reported,²³ may be responsible for part or all of the naso-ocular reactions in some patients, particularly BM, since zileuton would not be expected to prevent histamine from stimulating nasal and ocular receptors. In a study by Hui et al, zileuton pretreatment decreased airway responses to inhaled allergen by only about 50%, again demonstrating, with another bronchial stimulatory mechanism, that zileuton incompletely protected bronchial airways.²⁴ Finally, we do not believe that the differences between our study and the Israel study can be attributed to our study subjects being non-compliant in taking zileuton. All subjects were reliable adults who understood the importance of taking

zileuton 4 times per day. Furthermore, 48 hours before oral ASA challenges, all patients were admitted to GCRC where RNs took over the duties of dispensing zileuton 600 mg every 6 hours.

Our conclusion is that recommended therapeutic doses of zileuton 600 mg qid are insufficient in preventing ASA-induced upper or lower respiratory reactions in all ASA-sensitive asthmatic patients. Since ASA-induced reactions are dose dependent, zileuton pretreatment appeared to shift the dose-response curve upward in the majority of our patients, such that a larger dose of ASA induced the reactions. With a small sample size of only six patients, however, the differences did not meet statistical significance. Our data support the conclusion that zileuton blocked bronchospastic reactions to the prior threshold doses of ASA in three of our four asthmatic responders, as was reported by Israel et al.¹⁸ When the same three patients received higher doses of ASA, bronchospasm occurred. Furthermore, zileuton failed to protect one patient (GE), when he was given a smaller provoking dose of ASA.

The original goal of "silent" ASA desensitization could not be achieved. Such a goal is worth pursuing, since outpatient ASA desensitization could then be performed with complete safety and patients could then begin therapeutic regimens of daily ASA without the expense and inconvenience of hospitalization.

Finally, asthmatic patients who are taking zileuton 600 mg qid for control of asthma are vulnerable to upper and lower respiratory tract reactions after ingestion ASA or other NSAIDs. The therapeutic dose reported by most patients is usually two ASA tablets (650 mg) or its equivalent NSAID dose. As shown with patients GE and PV in our current study, however, a pediatric aspirin tablet of 81 mg would be a sufficient dose to induce a large asthmatic reaction in some patients theoretically protected by zileuton therapy. It would therefore seem prudent to assume that zileuton will not protect our ASA-sen-

sitive asthmatic patients from ASA or NSAIDs and to provide this important information to our patients.

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