Treatment of Aspirin-intolerant Asthma with Antileukotrienes

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Intolerance to aspirin and related nonsteroidal antiinflammatory drugs (NSAIDs) is a significant clinical problem among subjects with asthma (reviewed in References 1 and 2). Aspirin-intolerant asthmatics often suffer from a particularly severe form of asthma (2). Characteristically, in adult life the subjects develop chronic rhinosinusitis and recurrent polyposis, asthma, and intolerance to aspirin-like drugs. Ingestion of NSAIDs precipitates acute bronchoconstriction, which is often severe and persistent. Extrapulmonary symptoms such as nasal congestion, ocular injection, flush, heat rash, perspiration, and occasionally gastrointestinal symptoms may accompany the airway obstruction, in isolation or in combination. In severe cases the reaction can progress into shock and respiratory arrest.

While there are no *in vitro* tests available for routine clinical diagnosis, the lysine-aspirin bronchoprovocation introduced by Bianco and coworkers (3), has proven useful in identifying aspirin-intolerant patients with asthma. In a prospective comparative study the lysine-aspirin bronchoprovocation was found to be as sensitive as the oral provocation with respect to detection of airway obstruction (4). In that study, 22 consecutive patients with a history and/or clinical findings (asthma, rhinorrhea, nasal polyposis) suggestive of aspirin intolerance were challenged by both routes at least 2 wk apart. Ten of the subjects developed significant bronchoconstriction ($\geq$ 20% drop in forced expiratory volume in 1 s [FEV_1]) during either challenge, with the same absolute sensitivity for both tests (9 of 10). The bronchial provocations evoked reactions that developed more promptly, were limited to the airways, caused a lesser degree of airway obstruction, and were more easily reversed. The differences in challenge methods are summarized in Table 1. In 19 aspirin-tolerant control subjects with the same baseline pulmonary function, inhalation of lysine-aspirin caused no significant changes in FEV_1, supporting the specificity of the test. Although the oral administration is necessary for detection and investigation of extrapulmonary reactions, the bronchial challenge has characteristics supporting it as the first choice both in routine clinical practice and in mechanistic investigations. For the latter purpose, safety aspects and high repeatability (5) provide a considerable advantage over the oral challenge, particularly because a significant proportion of aspirin-intolerant individuals with asthma suffer from severe asthma. The time course of an inhalation challenge with lysine-aspirin is exemplified in Figure 1.

It is well established that cyclooxygenase inhibition is central in the chain of events leading to aspirin-elicited reactions (1). Plasma concentrations of acetylsalicylic acid (ASA), measured at the time of reaction following oral provocations, are of the magnitude (3–30 μM) (6) that has been established to inhibit cyclooxygenases in various test systems (7). Salicylic acid (SA), the main metabolite of ASA, is found at much higher concentrations (20–250 μM) (6). However, SA is not responsible for the intolerance reactions, because provocations with sodium salicylate with commonly used doses (0.5–1.0 g) yield much higher plasma concentrations of SA that are tolerated by NSAID-sensitive individuals (6). Interestingly, *in vitro* studies of intact cells suggest that SA is about 150 times less potent than ASA as an inhibitor of cyclooxygenase type 1 (COX-1), but only 3 times less potent as an inhibitor of COX-2 (8). The difference mainly relates to aspirin being almost 100-fold less potent as an inhibitor of COX-2, with a median inhibitory concentration (IC_{50}) of 278 μM as compared with 1.67 for COX-1 (8). Therefore, the sensitivity of aspirin-intolerant subjects to ASA but not SA may suggest that inhibition of COX-1 rather than COX-2 is involved in the intolerance reaction.

It remains mysterious why only certain individuals with asthma are affected and the precise mechanism behind the reactions is unknown. When the leukotrienes were discovered, it became an attractive hypothesis that arachidonic acid was shunted from the cyclooxygenase to the 5-lipoxygenase pathway when the cyclooxygenase enzyme was inhibited, but more recent research has demonstrated that independent sources of arachidonic acid are used in either eicosanoid pathway (9). Although there is no support for the shunting hypothesis, strong evidence has accumulated to suggest that leukotrienes (LTs) have a central role in aspirin-intolerant asthma.

LEUKOTRIENES AS MEDIATORS OF ASPIRIN-INDUCED BRONCHOCONSTRICTION

Using the bronchial challenge method, we observed that lysine-aspirin-induced bronchoconstriction was associated with increased urinary excretion of LTE_4 (10). In contrast, the urinary levels of LTE_4 remained unchanged during the course of bronchoprovocation in five individuals with asthma who did not develop an airway obstruction in response to inhaled lysine-aspirin. This observation was in line with concurrent reports that oral aspirin challenge increased urinary LTE_4 (11, 12), and strengthened our interest to evaluate the influence of a leukotriene antagonist on the airway response to aspirin.

The first pharmacologic study, intended to test whether leukotrienes mediated aspirin-induced bronchoconstriction, involved oral challenge and pretreatment with the inhaled leukotriene antagonist SKF-104,353 (13). The study produced some support for leukotriene involvement, but the inhibition was incomplete and not observed among all the subjects. Using bronchial challenge with lysine-aspirin, we were able to find further supporting evidence for a major leukotriene component in aspirin-induced bronchoconstriction (5). In addition to the differences in challenge procedures, we used a more potent antagonist (MK-0679), which was given orally before the provocations. A single dose of MK-0679 or placebo was given

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TABLE 1

CHALLENGE WITH ASPIRIN BY DIFFERENT ROUTES IN ASPIRIN-SENSITIVE SUBJECTS WITH ASTHMA

	Provocation Method	
Summary of Findings	Oral	Bronchial
Bronchoconstriction ($\geq$ 20% fall in FEV_1)	9/10	9/10
Maximal fall in FEV_1 (mean $\pm$ SD)	$-38 \pm 16\%$	$-29 \pm 6\%$
Drugs required for reversal	Bronchodilators and steroids systemically	Inhaled β-agonists
Duration of test session	> 8 h	< 4 h
Extrapulmonary reactions	6/10	0/10

Source: Dahlén and Zetterström (4).

1 h before the start of lysine-aspirin bronchoprovocation. Pretreatment with MK-0679 caused a rightward shift in the dose–response relations for all eight subjects (median shift in aspirin PD_{20} [provocative dose causing a 20% fall in FEV_1] being 4.4-fold) when compared with placebo (exemplified in Figure 2). Thus, higher cumulated doses of aspirin were required in order to elicit the stipulated 20% fall in FEV_1. In the presence of MK-0679, three of the subjects even failed to produce a 20% decrease in FEV_1 after inhalation of the highest available dose of lysine-aspirin. Their PD_{20} values were set as equal to the highest cumulated dose of aspirin given, and despite this underestimate of the influence of the drug, the increase in the geometric mean aspirin PD_{20} was highly significant ($p < 0.001$). In addition, after treatment with MK-0679, the maximal fall in FEV_1 (within 90 min after the last dose of aspirin) was significantly less than after placebo (29 ± 6 versus $42 \pm 5\%$). MK-0679 did not, however, affect the prechallenge FEV_1 values in the hour that passed between drug intake and the start of the provocation. Bronchodilation was therefore not a likely reason for the inhibition of response in this group of subjects with asthma (mean prestudy FEV_1 %pred, 84%; range, 60–99%). Thus, the investigation documented that leukotriene receptor blockade, by a specific competitive antagonist, could blunt the response to lysine-aspirin. In addition, the study supported the excellent repeatability of the bronchial challenge with lysine-aspirin, the 95% confidence interval (CI) for the PD_{20} value being 0.6–1.8 times the observed value (Figure 2).

Israel and coworkers were able to show that pretreatment with the 5-lipoxygenase inhibitor zileuton inhibited the bronchoconstriction induced by oral aspirin challenge (14). Interestingly, they also reported that several of the extrapulmonary symptoms were blocked by zileuton (14). Nasser and coworkers confirmed that another 5-lipoxygenase inhibitor, ZD-2138, was able to inhibit the bronchoconstriction induced by oral aspirin provocation (15). Finally, using another leukotriene-antagonist (ONO-1078) and another NSAID (dipyrone), Yamamoto and coworkers have also provided evidence that the response to bronchial challenge has a major leukotriene component (16). The published studies thus document that the leukotrienes fulfill two of the criteria required to prove a mediator function: (1) They are released in response to aspirin-elicited airway obstruction; (2) the airway reaction to aspirin can be blocked by a specific and potent leukotriene antagonist. Together with demonstrations that inhalation of leukotrienes induces airway obstruction in aspirin-sensitive subjects with asthma (17, 18), it is possible to conclude that the cysteinyl-leukotrienes indeed fulfill all three criteria of being true mediators of aspirin-induced airway obstruction.

LEUKOTRIENES AS MEDIATORS OF PERSISTENT AIRWAY OBSTRUCTION IN ASPIRIN-INTOLERANT SUBJECTS WITH ASTHMA

When we measured urinary LTE_4 in aspirin-intolerant subjects with asthma, it was observed that the baseline production of LTE_4 was significantly higher than in aspirin-tolerant subjects with asthma (10). Several investigations performed at this particular time (11, 12, 19) and subsequent studies have confirmed that aspirin-intolerant subjects with asthma have increased urinary excretion of cysteinyl-leukotrienes (20, 21). On the basis of the well-established association between eosinophils and aspirin-intolerant asthma (22–24), and the indications that circulating eosinophils have an enhanced capacity to generate leukotrienes (25), the findings would seem to fit with the hypothesis that the eosinophils are one major source of the baseline production of leukotrienes.

In support of the indications that even when not exposed to NSAIDs, airflow obstruction in aspirin-intolerant subjects has a leukotriene component, it was observed that a single dose of treatment with the leukotriene antagonist MK-0679 induced a prompt improvement in pulmonary function (26). The effect occurred within 30 min and was significantly different from placebo at all time points thereafter up to 5 h, the mean increase varying between 11 and 15% (Figure 3). The mean maximal improvement in FEV_1 was 18% calculated from the peak

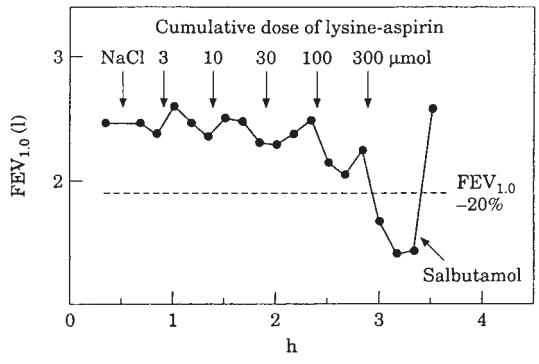

Figure 1. Recordings of pulmonary function (FEV_1) during lysine-aspirin bronchoprovocation in an NSAID-intolerant 43-yr-old woman with asthma, with the protocol used by the author.

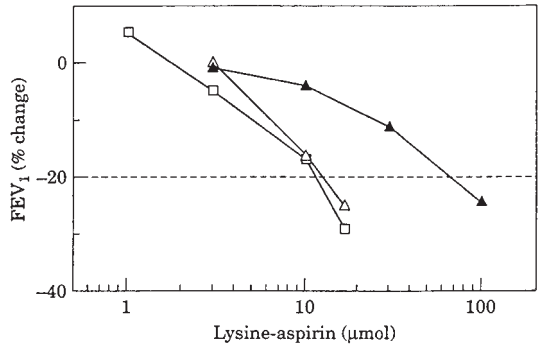

Figure 2. Dose–response relations for lysine-aspirin in an NSAID-intolerant male with asthma (no. 63) who underwent aspirin bronchoprovocations on three occasions: without pretreatment (*open squares*), and after double-blind pretreatment with placebo (*open triangles*) and with the leukotriene antagonist MK-0679 (*filled triangles*).

effect in each individual. For comparison, inhalation of a nebulized solution of salbutamol (2,500 μg) produced a 22.8% increase in FEV_1 in the same patients, which means that the response to this single dose of the leukotriene antagonist was about 80% of maximal reserve for bronchodilation. For the entire 12-h observation period there was a significant increase in mean AUC (area under the FEV_1-versus-time curve) after MK-0679 administration compared with placebo (18.2 ± 6 and -0.49 ± 7 units, $p < 0.05$). The change in AUC after active drug administration ($AUC_{MK\text{-}0679} - AUC_{placebo}$) was found to correlate strongly with the severity of asthma expressed as the sum of each subject's rank order score for FEV_1 %pred and asthma medication. There was also a good correlation between the bronchodilator response to the drug and the sensitivity of each individual to aspirin, expressed as prestudy PD_{20} for ASA.

Concerning the mechanism behind the bronchodilation produced by MK-0679, it is known that this drug, as well as other new leukotriene receptor antagonists, are specific in their mode of action and devoid of general smooth muscle relaxant properties (27–29). Initial studies with these leukotriene antagonists in healthy volunteers (30) or in subjects with mild asthma (31), failed to show evidence of bronchodilation. The finding of bronchodilation in a group of aspirin-sensitive subjects with asthma, differing with respect to asthma severity (e.g., range of FEV_1 %pred was 58–99%) and with best effect in the most severely compromised subjects, adds support to the hypothesis that ongoing leukotriene formation in the airways is a prerequisite for a bronchodilator response to drugs that block the action or release of leukotrienes. Likewise, bronchodilator effects of antileukotrienes have been observed in studies of aspirin-tolerant subjects with compromised baseline pulmonary function (32–34).

Interestingly, the best effect of MK-0679 was seen in those patients who were kept on relatively high doses of inhaled corticosteroids. It is commonly believed that corticosteroids abrogate formation of all arachidonic acid metabolites. However, *in vitro* studies of isolated human neutrophils have shown that

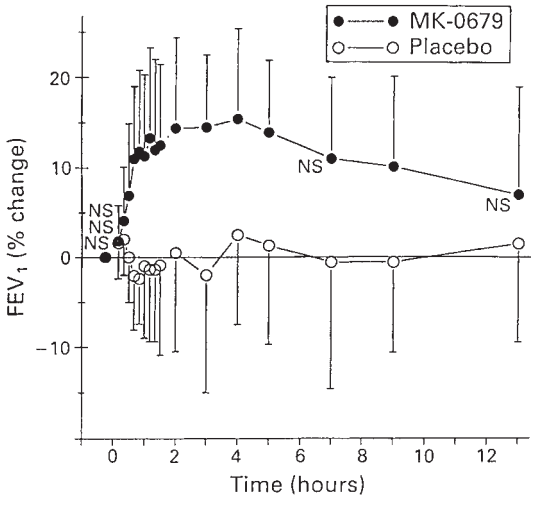

Figure 3. Basal pulmonary function (FEV_1) monitored in eight NSAID-intolerant patients with asthma for 12 h after ingestion of the leukotriene antagonist MK-0679 or placebo. Data are expressed as mean (SD) percent change in baseline FEV_1 (mean of two efforts) during each study day. Treatment difference is significant ($p \leq 0.05$) at all time points except when indicated (NS, nonsignificant, $p > 0.05$).

corticosteroids generally do not inhibit leukotriene production (35). In support of this observation, treatment with systemic or inhaled corticosteroids fails to alter urinary excretion of LTE_4 either at baseline (35, 36) or after allergen bronchoprovocation in patients with asthma (37). Therefore, one hypothesis that is currently evolving is that leukotriene antagonists may add to the existing treatment strategies in asthma by blunting components of the airway inflammation that are unaffected by glucocorticosteroids.

Finally, a concluded treatment trial with the 5-lipoxygenase inhibitor zileuton supports the notion that leukotrienes indeed mediate persistent airway obstruction and other symptoms in aspirin-intolerant subjects with asthma (38). The study was conducted in collaboration between the group at our institute and E. Nizankowska and A. Szczeklik in Kraków, Poland. From each center, 20 subjects with asthma, aspirin intolerance, and characteristic chronic nasal symptoms were recruited. The diagnosis of aspirin intolerance was documented by previous provocations with oral and/or inhaled aspirin on several occasions, but for three cases by an unequivocal history including emergency room visits after NSAID ingestion. The majority of subjects had suffered from asthma for more than 5 yr, and all subjects had demonstrated reversibility of bronchoconstriction after inhalation of a β-stimulant. Zileuton (600 mg four times daily, orally) or placebo was administered for 6 wk in a cross-over double-blind design with a 4-wk washout period in between. This was an add-on study and all subjects were receiving concomitant treatment with high doses of inhaled (38 subjects, mean dose of 1,030 μg of budesonide or beclomethasone daily) and/or oral (14 subjects, 4–25 mg of prednisolone daily) glucocorticosteroids. Long-acting β-agonists, long-acting antihistamines, or theophylline were not used throughout the study. At inclusion, patient medications had remained unchanged for at least 4 wk.

When the outcome of the treatment periods was evaluated, it was evident that zileuton caused both acute and chronic improvement in pulmonary function. At 4 h after the first dose of treatment the increase in FEV_1 was seen only on zileuton treatment days; the treatment difference was 7.5% (95% CI, 3–12%; $p < 0.01$) corresponding to 0.18 L. The improvement in pulmonary function was maintained over the 6 wk period as shown both by spirometry recordings at the clinic visits, and by daily peak flow recordings at home (Figure 4). Thus, at the end of the 6 wk, FEV_1 was increased by 0.14 L during the zileuton period and the mean difference compared with placebo was 0.19 L (95% CI, 0.06–0.31 L; $p < 0.01$). In contrast, there was no improvement during the placebo period, suggesting that the subjects were relatively well controlled by their concomitant treatment. Moreover, the improvement occurred despite lower use of β-agonist during zileuton (2.7 ± 0.4 versus 3.3 ± 0.5 daily doses during placebo, $p < 0.05$). There were also fewer asthma exacerbations when the subjects were receiving zileuton (one versus five patients taking placebo). It has been documented in a trial including 401 aspirin-tolerant subjects with asthma that zileuton reduced the number of asthma exacerbations highly significantly (39, 40).

Furthermore, bronchial responsiveness to histamine was reduced during treatment with zileuton. The mean shift in histamine PD_{20} after the 6-wk treatment corresponded to a 1.5 doubling dose ($p < 0.5$), whereas there was no change in histamine responsiveness during the placebo treatment. Zileuton also attenuated aspirin-induced bronchoconstriction when tested in half of the subjects after 4 wk of treatment. This confirms previous indications (5, 13–16) that leukotrienes mediate a significant component of the airway obstruction evoked by aspirin in aspirin-intolerant subjects with asthma. Whether

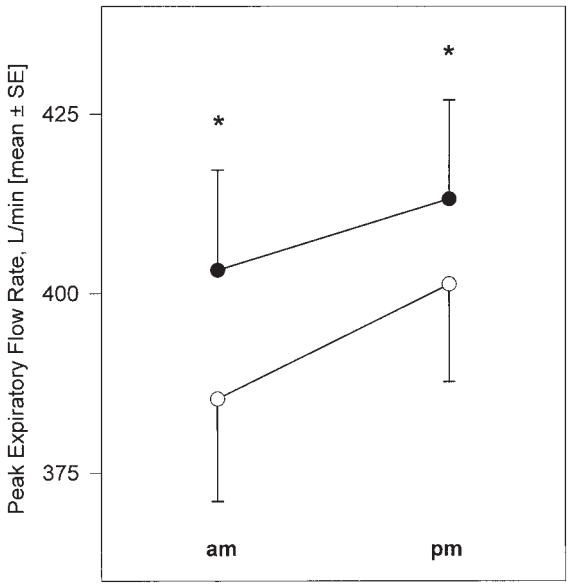

Figure 4. Comparison between treatments of peak expiratory flow rate (PEFR) data; the average for each subject over the respective 6-wk period is used for calculations of treatment means. Morning and evening PEFR values were higher during zileuton treatment (*closed circle*), corresponding to 18 ($p < 0.001$) and 12 ($p < 0.01$) L/min differences from placebo (*open circle*), respectively.

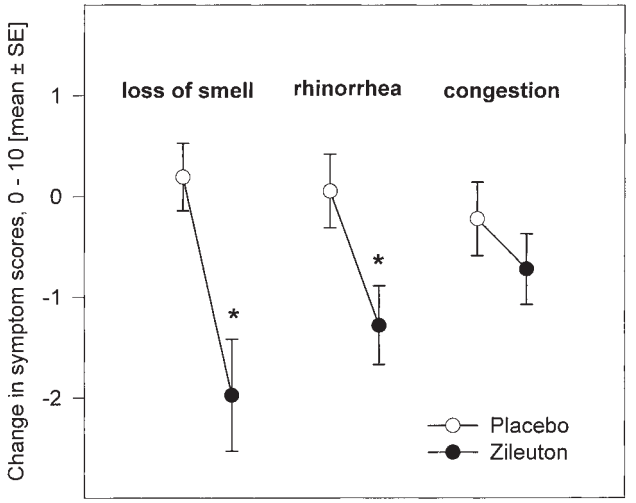

Figure 5. Nasal symptom scores, assessed on a visual analog scale, showed a significant reduction in loss of smell and rhinorrhea after 6 wk of treatment with zileuton.

5-lipoxygenase inhibition in subjects with asthma can change airway sensitivity to leukotrienes had previously not been evaluated. It is theoretically conceivable that this might occur as a response at the receptor level to reduced synthesis of the endogenous agonists. However, we found no change in bronchial responsiveness to LTD_4 during the treatment with zileuton. Together, the results of the aspirin challenge and the LTD_4 challenge support the specific mode of action of zileuton as a 5-lipoxygenase inhibitor (41).

Since nasal application of leukotrienes induces swelling of the nasal mucosa (42, 43), it was hypothesized that leukotrienes may contribute to the chronic nasal problems in this group of individuals with asthma. Observations during a previous study of the acute influence of a leukotriene antagonist on aspirin-intolerant subjects with asthma (26) provided circumstantial support for this hypothesis. Therefore, nasal function was assessed by a visual analog scale (VAS) before and on the last day of each treatment period (Figure 5). There was a marked reduction in the VAS scores for loss of smell ($p < 0.01$) and for rhinorrhea ($p < 0.05$) whereas congestion and daily measurements of peak nasal inspiratory flow showed changes that did not attain significance. It is possible that some of the therapeutic effects of zileuton relate to inhibition of LTB_4 as well, since LTB_4 has been detected in nasal lavage fluid after allergen challenge (43).

Thus, the study supported the hypothesis that inhibition of leukotrienes may provide a new therapeutic alternative in aspirin-intolerant asthma. The improvements observed were particularly encouraging because the 5-lipoxygenase inhibitor zileuton at the employed dose level caused only a partial (36%) inhibition of leukotriene biosynthesis, measured as urinary excretion of leukotriene E_4. Furthermore, the finding that addition of the 5-lipoxygenase inhibitor zileuton caused improvement over and above that provided by treatment with glucocorticoids lends further support to the concept that antileukotrienes and glucocorticoids treat different parts of the airway inflammation. Investigations have established that *in vivo* formation of leukotrienes, as well as that of other eicosanoids, is not altered even by high doses of inhaled or oral glucocorticosteroids (35–37, 44). This is implicated in our study as well, where the subjects were chronically treated with glucocorticosteroids, but nevertheless excreted LTE_4 into the urine. In fact, the levels of urinary LTE_4 were in the high concentration range previously observed in other studies of aspirin-intolerant subjects with asthma (10–12). Studies of aspirin-tolerant subjects with asthma also suggest that addition of antileukotrienes may reduce the need for treatment with high doses of glucocorticosteroids (45), when side effects become an issue.

CONCLUSIONS

The last two decades have provided major advances in the understanding of the syndrome of aspirin-induced asthma. First, the establishment that inhibition of the cyclooxygenase is the common denominator of drugs that cause the intolerance reactions provided focus that has been instrumental both for clinical care and mechanism-based research (1). Second, the discoveries that leukotrienes mediate important components of both spontaneous and aspirin-induced airway obstruction have opened the path for a new treatment that appears likely to be beneficial for several manifestations of this syndrome. However, it remains uncertain exactly how the intolerance reactions may be triggered and how the NSAID intolerance is acquired. Much more research on cellular and molecular mechanisms is needed. One poorly understood phenomenon relates to the desensitization after an adverse reaction, and the finding that intolerance to NSAIDs waxes and wanes over time. Neither are the reasons for the clinical association between NSAID intolerance and the two other manifestations of the aspirin triad, asthma and nasal polyposis, particularly well understood. It is possible that different mechanisms are involved and that the unifying hypothesis will remain elusive.

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