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). A 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 bronchconstriction (> 20% drop in forced expiratory volume in 1 s \(\text{FEV}_1\)) 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 \(\text{FEV}_1\), 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 \(\mu M\)) (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 \(\mu M\)) (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 \(\mu M\) 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 L\(\text{TE}_4\) (10). In contrast, the urinary levels of L\(\text{TE}_4\) 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 L\(\text{TE}_4\) (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 (M K-0679), which was given orally before the provocations. A single dose of M K-0679 or placebo was given
Bronchoconstriction was therefore not a likely reason for the inhibition of response in this group of subjects with asthma. In addition, the study supported the excellent repeatability of the bronchial challenge with lysine-aspirin, the 95% confidence interval (CI) for the 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 ± 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. Bronchodilatation 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 M K-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 M K-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 underestimation 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 ± 5%). M K-0679 did not, however, affect the prechallenge FEV$_1$ values in the hour that passed between drug intake and the start of the provocation. Bronchodilatation 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). Inter-
effect in each individual. For comparison, inhalation of a nebulized solution of salbutamol (2,500 μg) produced a 22.8% increase in FEV₁ 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 FEV₁-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-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 FEV₁ %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 PD₂₀ for A SA.

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 FEV₁ %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 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 LTE₄ 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 FEV₁ 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, FEV₁ 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).

Figure 3. Basal pulmonary function (FEV₁) 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 FEV₁ (mean of two efforts) during each study day. Treatment difference is significant (p < 0.05) at all time points except when indicated (NS, non-significant, p > 0.05).
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 < 0.001) and for rhinorrhea (p < 0.01) L/min differences from placebo (open circle), respectively.

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 anti-leukotrienes 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 anti-leukotrienes 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.

References


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.
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