
Intranasal ketorolac challenge for the diagnosis of aspirin-exacerbated respiratory disease

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Background: Intranasal administration of aspirin-lysine has been used in Europe for the diagnosis of aspirin-exacerbated respiratory disease. It has a low adverse effect profile and is believed to be safer for asthmatic patients, particularly those with a low baseline forced expiratory volume in 1 second, in whom oral aspirin challenge would be contraindicated. Ketorolac, a nonsteroidal anti-inflammatory drug useful for severe pain, is available in the United States in parenteral form.

Objective: To determine whether ketorolac nasal challenge has acceptable specificity and sensitivity for diagnosing aspirin-exacerbated respiratory disease.

Methods: Twenty-nine patients with suspected aspirin-exacerbated respiratory disease were challenged with nasal ketorolac before oral challenge and desensitization with aspirin. Symptoms, objective changes in nasal examination findings, and peak nasal inspiratory flow values were recorded. Nasal lavage fluid for cysteinyl leukotriene analysis was collected. Ketorolac doses of 2.1, 5.2, or 7.8 mg were administered and compared with the results of oral aspirin challenge.

Results: Eighteen patients had a positive challenge reaction to oral aspirin. Ketorolac nasal inhalation had a sensitivity of 78% and a specificity of 64%. Patients in the reactor group had significantly higher levels of cysteinyl leukotrienes after ketorolac challenge than in the nonreactor group. Mild bronchospasm occurred in 3 patients, and 2 of these occurred at higher starting doses of ketorolac.

Conclusions: Nasal ketorolac administration is a reasonably accurate and safe method for diagnosing aspirin-exacerbated respiratory disease.

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INTRODUCTION

Aspirin-exacerbated respiratory disease (AERD) affects up to 21% of asthmatic patients.¹ Patients classically exhibit chronic sinusitis, nasal polyposis, and asthma as manifestations of aggressive underlying airway inflammation. The distinguishing characteristic of this disease occurs when individuals ingest a drug that inhibits the enzyme cyclooxygenase-1 (COX-1). Therapeutic doses of aspirin or other nonsteroidal anti-inflammatory drugs (NSAIDs) can lead to life-threatening bronchospasm and the nasal symptoms of obstruction, rhinorrhea, sneezing, and pruritus. Conclusive evidence exists that leukotrienes are the primary mediators of the aspirin-induced reaction in AERD.

Currently, the only tests available for identifying patients with AERD are challenge tests with any drug that blocks COX-1. Preferably, this testing is conducted in a blinded, dose-escalating manner to maximize accuracy. The ability to correctly diagnose AERD is important because a history of NSAID-induced reactions is sometimes inaccurate. With accurate diagnosis, aspirin desensitization and continued daily aspirin therapy have been shown to have a positive effect on long-term outcomes in patients with AERD.² Thus, accurate challenges are important to identify patients who may benefit

from aspirin desensitization and those who do not have AERD and have needlessly been avoiding all medicines that inhibit COX-1.

Throughout the world, 4 different methods of provocative challenge in AERD have been reported: bronchial, nasal, oral, and intravenous.^{3–7} Oral challenge is the only method available in the United States owing to the unavailability of an aqueous formulation of aspirin, such as aspirin-lysine, which is routinely used in Europe. Nasal challenge with aspirin-lysine has been shown to have satisfactory sensitivity and specificity and an acceptable safety profile.^{6,8}

Ketorolac tromethamine is an NSAID approved in the United States for moderate-to-severe pain in oral and intramuscular or intravenous formulations. Also, 0.4% and 0.5% ketorolac are approved for ophthalmologic use as topical anti-inflammatory agents. Ketorolac is a potent inhibitor of COX-1 and COX-2 in vitro, with potency equivalent to that of indomethacin and diclofenac sodium.⁹ Ketorolac, given intramuscularly or orally in therapeutic doses of 40 to 60 mg, has been reported in several cases to cause serious bronchospasm in patients with AERD.^{10–13} In fact, an exacerbation of asthma was observed in 1 patient with AERD after 0.5% ketorolac tromethamine was inadvertently applied to her eyes.¹⁴

There is limited information regarding the use of ketorolac for nasal application. Ketorolac administered intranasally was found to have an absolute bioavailability of 91%.¹⁵ Ketorolac administered intranasally would be expected to block local COX-1 activity and when given in small doses might cause a

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reaction in patients with AERD that is limited to the nasal mucosa. This, along with the European experience with intranasal aspirin-lysine, led us to speculate whether ketorolac could be used as a safe half-day outpatient test to diagnose AERD in the United States. This pilot study was designed to determine optimal intranasal dosing of ketorolac and the sensitivity and specificity afforded by such a test.

METHODS

Participants

Twenty-nine individuals were recruited from a potential population of 32 patients referred to Scripps Clinic (La Jolla, CA) to undergo aspirin challenge and desensitization. The protocol was approved by the human subjects committee and the General Clinical Research Center (GCRC) advisory committee, both at Scripps Clinic. All referred patients had clinical features consistent with AERD, including at least 1 historical asthma attack coinciding with the ingestion of therapeutic doses of aspirin or another NSAID. Nearly all the patients had underlying persistent asthma, and all had chronic sinusitis and nasal polyposis. In the referral population, an approximately 15% rate of negative oral aspirin challenge results was previously recorded.^{16,17} To participate in oral aspirin challenges, patients were required to have a baseline forced expiratory volume in 1 second (FEV₁) greater than 60% of predicted and less than 10% variability during oral placebo challenges.

In the present study, 3 patients were excluded: 1 declined participation, 1 could not generate flow through the peak nasal inspiratory flow (PNIF) meter, and 1 had unstable asthma, rendering the patient ineligible to undergo oral aspirin challenge. All the patients continued their baseline controller therapies, which included montelukast in 20 individuals, zafirlukast in 1, inhaled corticosteroids in 24, long-acting β -agonists in 21, nasal corticosteroids in 21, and systemic corticosteroids in 10.

Oral Aspirin Challenge

Oral aspirin challenges were performed using a standard protocol,¹⁸ beginning with 30 mg of aspirin and advancing the dose (to 45 or 60 mg, 60 or 100 mg, 100 or 150 mg, 150 or 325 mg, and 650 mg) every 3 hours during 9-hour days over the following days of their hospital admission. Patients were evaluated hourly or earlier as symptoms prompted. Aspirin challenges induce a spectrum of reactions, including classic reactions, with a decline in the FEV₁ of at least 15% combined with a naso-ocular reaction (nasal congestion, rhinorrhea, sneezing, conjunctival itching or hyperemia, periorbital edema, or paranasal headache); pure lower respiratory reactions (wheezing and chest tightness combined with a $\geq 20\%$ decline in FEV₁); naso-ocular reactions only; and negative responses. If an aspirin-induced reaction occurred, the patient was treated symptomatically. Typical respiratory reactions lasted 2 to 4 hours, although reactions occasionally lasted as long as 12 hours. Aspirin doses were then advanced until 650 mg of aspirin was given without adverse effects.

Doses of Ketorolac for Nasal Challenge

Ketorolac tromethamine (American Pharmaceutical Partners Inc, Schaumburg, IL) for injection (60 mg/2 mL) was prepared in various dilutions after mixture with 13 mL of preservative-free isotonic sodium chloride (total volume, 15 mL). The dilution of ketorolac was placed in an empty Nasacort AQ spray bottle (Sanofi-Aventis, Bridgewater, NJ) that deployed 0.13 mL of fluid in each spray. Because this was the first study of ketorolac for nasal challenge in AERD, 2 different concentrations of ketorolac solution were used to find a concentration that yielded acceptable sensitivity with low reaction severity.

Initially, a total dose of 7.8 mg of ketorolac (3.9 mg in each nostril) was chosen (using 6 mg/mL of ketorolac). Two healthy individuals experienced no irritant nasal reactions after intranasal sprays using this dose of ketorolac. After administration, patients were observed for 120 minutes. After 1 patient had severe nasal symptoms and another developed bronchospasm after challenge with 7.8 mg of ketorolac, we decreased the maximum concentration of ketorolac to 4 mg/mL. A graded-dose challenge protocol was also initiated, with the first dose of 1.05 mg (2 sprays) to each nostril followed by observation for 120 minutes. If there was no reaction at this time, a subsequent dose of 2.6 mg (5 sprays) per nostril (total dose, 5.2 mg) was administered, followed by observation for another 120 minutes. Patients were instructed not to swallow any ketorolac that may drip into their posterior pharynx. The total time to perform the nasal challenge was 240 minutes, or approximately a half day.

Ketorolac nasal challenge was performed during the first 4 hours of the 2- to 3-day aspirin desensitization for all consenting patients. Ideally, patients would undergo ketorolac nasal challenge and then return after a 1-week washout for aspirin challenge. However, our patient population was referred from out of town, so this was not feasible; thus, all the patients underwent oral aspirin desensitization within hours of ketorolac nasal challenge. The effects of ketorolac nasal challenge on the outcome of aspirin challenge were considered but could not be avoided in this study population.

Nasal Lavage

After informed consent was obtained, enrolled patients agreed to undergo nasal challenge as outlined previously herein. Before nasal challenge, baseline nasal lavage was performed. Using 10 mL of isotonic sodium chloride, 5 mL was instilled into each nostril by means of a 10-mL syringe while the head was extended. Patients expelled lavage fluid into a plastic collecting cup after 10 seconds. Samples were centrifuged at 3,500g at 4°C for 20 minutes, and aliquots of the supernatant were stored at -70°C .

Measurement of PNIF has previously been shown to be a valid alternative to acoustic rhinometry in the evaluation of nasal obstruction after nasal challenge with aspirin-lysine.¹⁹ A PNIF meter (In Check Nasal; Clement Clarke International, Essex, England) with a cushioned facemask was used to measure nasal inspiratory flow. Patients were instructed to

press the facemask firmly against their face and to inspire as forcefully as possible through the nose while their mouth was closed. The best of 3 efforts was used to determine PNIF. Peak nasal inspiratory flow was measured at baseline and then every 30 minutes until the study was completed or the patient had a positive reaction. A significant decline in PNIF was defined as a decrease greater than 20% from baseline values.

Criteria for a Positive Ketorolac Challenge Reaction

Because this diagnostic test has not been previously conducted, we decided to measure as many changes in nasal response as possible. The clinical response to ketorolac was used to determine whether a challenge response was positive or negative. Patients were required to have nasal symptoms such as profuse rhinorrhea; repeated sneezing; nasal, palate, or ocular pruritus; epiphora; or ocular hyperemia. Reactions were scored on a 5-point scale from 0 to 4 (0 = the absence of any reactions; 1 = nasal congestion and rhinorrhea alone; 2 = rhinorrhea and nasal congestion plus ocular pruritus, hyperemia, or chemosis; 3 = complete nasal obstruction, ocular pruritus, hyperemia, or chemosis and paranasal headache; and 4 = severe reactions with periorbital edema and severe manifestations of all other naso-ocular signs and symptoms). A decrease in PNIF of more than 20% from baseline was recorded but was not considered diagnostic of a positive ketorolac challenge response unless accompanied by nasal or ocular signs and symptoms.

Measurement of Eicosanoids

Levels of cysteinyl leukotrienes (LTs) and 11β -prostaglandin $F_{2\alpha}$ (11β -PGF $_{2\alpha}$) were measured using enzyme immunoassay kits (520501.1 and 516521; Cayman Chemical Co, Ann Arbor, MI). The cysteinyl LT enzyme immunoassay kit had 100% specificity for LTC $_4$ and LTD $_4$ and 67% specificity for LTE $_4$. There was less than 0.01% specificity for LTA $_4$, LTB $_4$, PGD $_2$, PGE $_2$, PGF $_{2\alpha}$, and thromboxane B $_2$. The lower limit of detection was 13 pg/mL. The 11β -PGF $_{2\alpha}$ kit had 100% specificity for 11β -PGF $_{2\alpha}$, 10% specificity for 2,3-dinor- 11β -PGF $_{2\alpha}$, and less than 0.01% specificity for LTB $_4$, PGD $_2$, PGE $_2$, PGF $_{2\alpha}$, PGF $_{2\beta}$, and thromboxane B $_2$. The lower limit of detection for this assay was 5.5 pg/mL. Samples were run undiluted and at a 1:5 dilution with sterile water.

Eleven of the 29 participants were challenged in the GCRC. The GCRC had access to the laboratory facilities required to collect, process, and store nasal lavage samples. The other 18 participants were challenged in the Allergy, Asthma, and Immunology Clinic at Scripps Green Hospital, where research laboratory services were unavailable. Therefore, nasal lavage fluid was not collected or processed for these 18 individuals.

Statistical Analysis

The Wilcoxon matched pairs signed rank test was used to compare cysteinyl LT levels before and after ketorolac challenge in ketorolac reactors and nonreactors. $P < .05$ was considered statistically significant.

RESULTS

The specific responses to ketorolac challenge and to subsequent oral aspirin challenge are seen in Table 1. The patients were assigned a number in the order in which they were challenged. Three patients had FEV $_1$ declines after ketorolac challenge but no bronchospasm to oral aspirin challenge (patients 2, 7, and 24). Four patients developed bronchospasm to oral aspirin challenge after having a positive ketorolac challenge reaction but with no associated decline in FEV $_1$ (patients 16, 18, 19, and 23).

This test had an unexpected result after a positive ketorolac challenge reaction in some individuals. Four of the 18 patients who reacted to ketorolac had no further reaction to oral aspirin challenge (patients 10, 11, 15, and 24). Seven patients had negative ketorolac challenge responses and negative oral aspirin challenge responses. Four patients had negative ketorolac challenge reactions and positive oral aspirin challenge reactions. Thus, this test is 78% sensitive and 64% specific, with a positive predictive value of 78% and a negative predictive value of 64%. Three positive ketorolac reactors developed significant declines in spirometric measures (FEV $_1$) during nasal challenge alone. All 3 episodes of bronchospasm occurred at higher doses of ketorolac (7.8 and 5.2 mg).

The results of PNIF measurement are given in Table 1. Twelve of the 18 patients with positive ketorolac challenge reactions had a greater than 20% decrease in PNIF. Five of the 11 patients with no symptoms during ketorolac challenge had greater than 20% declines in PNIF. Two of these patients had greater than 40% declines in PNIF and, despite having no symptoms during ketorolac challenge, went on to have a positive oral aspirin challenge reaction. Individual changes in cysteinyl LT levels are shown in Figure 1. A significant difference in cysteinyl LT levels was seen in the ketorolac reactor group after ketorolac challenge ($P = .047$).

DISCUSSION

This study shows the usefulness of ketorolac nasal inhalation challenge in the diagnosis of AERD. These results compare favorably with those of previous studies^{6,8} using aspirin-lysine for nasal challenge. These European studies showed sensitivity of 86.7% and 80% and specificity of 95.7% and 92.5% with aspirin-lysine intranasal challenge in the diagnosis of AERD. We show that in most patients with AERD, nasal administration of ketorolac can induce typical nasal reactions.

One surprising finding from this study is that 4 participants possibly became desensitized to aspirin during nasal ketorolac administration. Owing to scheduling requirements, all the patients received oral aspirin less than 24 hours after ketorolac nasal challenge and usually within 4 hours. During ketorolac challenge, 3 of these 4 patients (patients 10, 15, and 24) had objective findings associated with their nasal symptoms, including declines in PNIF and FEV $_1$. Although these may represent false-positive challenges, another explanation is that the desensitization process was initiated during ketorolac administration so that further doses of oral aspirin were

Table 1. Results of Ketorolac Intranasal Challenge

Patient No.	Ketorolac reactor	Dose, mg	Bronchial response, %	Nasal score	Nasal peak flow change, %	Oral provoking dose, mg	Oral challenge reaction
Positive ketorolac challenge and positive oral aspirin challenge reactions							
2*	Yes	7.8	15 ↓ FEV ₁	2+	55 ↓	100	NO
4	Yes	7.8	None	1+	21 ↓	60	NO
7	Yes	5.2	17 ↓ FEV ₁	1+	43 ↓	100	NO
8*	Yes	5.2	None	4+	45 ↓	100	NO
13	Yes	2.1	None	3+	64 ↓	60	NO
14*	Yes	2.1	None	3+	18 ↓	100	NO
16	Yes	2.1	None	1+	13 ↓	60	NO + 35% ↓ FEV ₁
18	Yes	2.1	None	2+	8 ↓	30	NO + 20% ↓ FEV ₁
19	Yes	2.1	None	1+	38 ↑	60	NO + 16% ↓ FEV ₁
20	Yes	5.2	None	1+	26 ↓	60	NO
23	Yes	2.1	None	2+	39 ↓	60	NO + 20% ↓ FEV ₁
26	Yes	2.1	None	1+	36 ↓	60	NO
28	Yes	2.1	None	3+	59 ↑	100	NO
29	Yes	2.1	None	2+	33 ↓	30	NO
Negative ketorolac challenge and negative oral aspirin challenge reactions							
1	No	NA	NA	0	35 ↓	Negative	Negative
3	No	NA	NA	0	153 ↑	Negative	Negative
9	No	NA	NA	0	17 ↓	Negative	Negative
12	No	NA	NA	0	23 ↓	Negative	Negative
17	No	NA	NA	0	13 ↑	Negative	Negative
22	No	NA	NA	0	27 ↓	Negative	Negative
25	No	NA	NA	0	18 ↑	Negative	Negative
Positive ketorolac challenge and negative oral aspirin challenge reactions							
10	Yes	5.2	None	2+	34 ↓	None	None
11	Yes	5.3	None	1+	30 ↑	None	None
15	Yes	5.2	None	3+	25 ↓	None	None
24	Yes	5.2	20 ↓ FEV ₁	1+	30 ↓	None	None
Negative ketorolac challenge and positive oral aspirin challenge reactions							
5	No	NA	NA	0	0	100	NO
6	No	NA	NA	0	6 ↓	150	NO
21	No	NA	NA	0	46 ↓	60	NO + 18% ↓ FEV ₁
27	No	NA	NA	0	43 ↓	325	20% ↓ FEV ₁ , no NO

Abbreviations: FEV₁, forced expiratory volume in 1 second; NA, not applicable; NO, naso-ocular symptoms.

* The patient had profuse leukotriene release after ketorolac challenge (as seen in Fig 1).

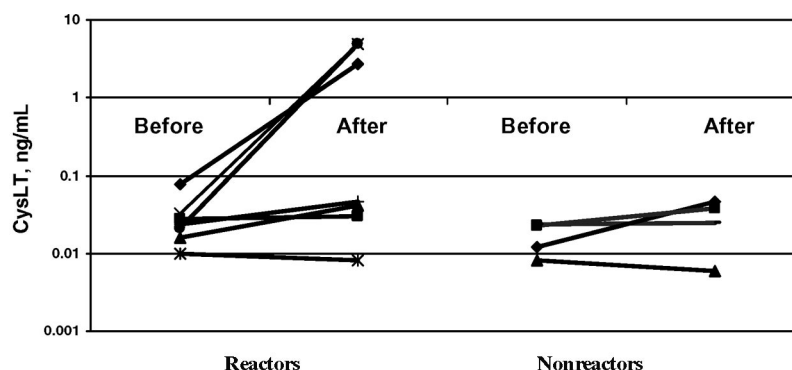


Figure 1. Cysteinyl leukotriene (CysLT) levels before and after ketorolac nasal challenge in ketorolac reactors ($P = .047$) and nonreactors ($P = .38$).

delivered after COX-1 desensitization was completed. All 4 patients gave convincing histories of asthma attacks after

previous exposure to full therapeutic doses of aspirin. However, none of the 4 patients were available for rechallenge

with aspirin after a 7-day washout. We believe that desensitization to oral aspirin from nasal ketorolac administration is scientifically plausible. Given the high suspicion of disease in all 4 patients and corroborating declines in PNIF and FEV₁ in 3 patients, desensitization may have occurred in 1 or more of these patients. If all 4 of these ketorolac reactors were considered for statistical purposes as true positives, the sensitivity of the test would increase from 78% to 82%. The specificity would be much more significantly affected (increasing from 64% to 100%), although the value of this screening test lies in its sensitivity rather than its specificity.

Patients 2, 7, and 24 developed bronchospasm during ketorolac challenge. In 1 of these patients, the reaction occurred to 7.8 mg of ketorolac. This patient was the second challenged in the GCRC for this protocol. Although her bronchospasm was mild (15% decline in FEV₁), we thought it was prudent to decrease the challenge dose to 5.2 mg of ketorolac in all further challenges. One patient developed an FEV₁ decline of 17% at this dose, so 1 further alteration to the protocol was made so that patients would undergo a graded challenge beginning with 2.1 mg of ketorolac and, if the response was negative, then would increase to 5.2 mg of ketorolac. The final patient developed a 20% decline in FEV₁ from 5.2 mg of ketorolac but did not react to 2.1 mg of ketorolac. One of the theoretical benefits of nasal provocation challenge is localization of the reaction to the nasal mucosa, thus protecting severe or unstable asthmatic patients from bronchospasm. Reports of bronchospasm from nasal aspirin-lysine challenge exist. Pawlowicz et al²⁰ showed a decrease of at least 15% in FEV₁ in all 7 patients with AERD who underwent nasal provocation with aspirin-lysine. This is contrasted with 2 recent studies^{6,8} that did not record bronchospasm in 61 patients undergoing nasal challenge with aspirin-lysine. One notable difference in the study by Pawlowicz et al was the use of a total of 36 mg of aspirin-lysine compared with 16 and 18 mg in the 2 studies that did not observe bronchospasm. This is consistent with our observations regarding dosing of ketorolac in the present nasal challenge study. In the present study, all 3 asthmatic responses to ketorolac challenge occurred at higher doses of ketorolac. Finally, systemic absorption of ketorolac through the nasal mucosa may occur and could account for differences in systemic effects.¹⁵

In 3 of the 4 patients with false-negative ketorolac challenge reactions (patients 5, 6, and 27), the oral provoking dose of aspirin was higher than that typically seen in AERD. The provoking doses of 100 to 325 mg, as seen in 3 patients, suggest that higher doses of ketorolac may increase the sensitivity of this test. For example, in patients who have a negative nasal challenge reaction to 5.2 mg of ketorolac, increasing to 7.8 mg before terminating the challenge might increase sensitivity without significantly affecting adverse effects or safety.

Leukotriene modifier drugs could alter the outcome of ketorolac challenge. In this study, 14 (78%) of 18 patients with positive ketorolac challenge reactions were taking an LT

modifier drug. Of the 11 patients with negative ketorolac challenge reactions, 7 (64%) were taking an LT modifier drug. Nasal corticosteroid use was 72% in the ketorolac reactor group and 73% in the nonreactor group. These findings suggest that the use of neither LT modifiers nor intranasal corticosteroids affected the outcome of ketorolac challenge.

Three inflammatory mediators are synthesized or released and measured during the upper and lower airways response to aspirin in AERD (histamine, LTC₄, and PGD₂).^{21,22} We showed elevations in cysteinyl LTs in nasal lavage that are significantly higher in individuals who reacted to ketorolac than in those who did not. We were also interested in trying to detect an elevation of 11 β -PGF_{2 α} (the metabolite of PGD₂) in nasal lavage fluid, which has thus far been demonstrated only in plasma and urine.²¹ The sensitivity of our assay was not high enough to detect 11 β -PGF_{2 α} in nasal lavage fluid as a marker for PGD₂ synthesis.

In summary, nasal challenge with ketorolac is a simple and reasonably safe alternative to oral aspirin challenge in the diagnosis of patients with suspected AERD. It was well tolerated in all patients, with no noticeable irritant effects. Ketorolac nasal challenge can be completed in a maximum of 240 minutes (a half-day session). Two of the 3 episodes of bronchospasm that occurred were related to higher doses of ketorolac, and all were mild and easy to treat. The ability to desensitize patients to aspirin by using ketorolac nasal challenge is worthy of further study.

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