

Effect of misoprostol on patients with aspirin-exacerbated respiratory disease undergoing aspirin challenge and desensitization



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ABSTRACT

Background: Prostaglandin E₂ (PGE₂) is an anti-inflammatory compound that inhibits 5-lipoxygenase activity. Diminished PGE₂ regulation in aspirin-exacerbated respiratory disease (AERD) leads to respiratory reactions on cyclooxygenase 1 inhibition. In vitro studies have found that exogenous PGE₂ stabilizes inflammatory mediator release.

Objective: To examine whether misoprostol (oral prostaglandin E₁ analogue) use during aspirin challenge and desensitization might decrease the severity of aspirin-induced symptoms and make desensitization safer for patients with AERD.

Methods: Forty-five patients undergoing aspirin challenge and/or desensitization were randomized to misoprostol (n = 30) or placebo (n = 15) and compared with a group of historical controls (n = 31). Misoprostol (200 μg) was administered at 30 minutes, 90 minutes, and 4 hours after the first dose of nasal ketorolac. Measured end points included change in forced expiratory volume in 1 second (FEV₁), peak nasal inspiratory flow rate (PNIF), number of treatments received for induced reactions, and adverse gastrointestinal effects.

Results: A difference in FEV₁ and PNIF reduction was detected between misoprostol and placebo (P = .03) and misoprostol and historical controls (P = .01), respectively, during nasal ketorolac challenge. No difference was detected among aspirin reactors. Among all reactors, no difference in magnitude was found for FEV₁ (P = .13) or PNIF (P = .07) reduction across all 3 groups. Total treatment requirement was similar (P = .14). Patients receiving misoprostol were more likely to report adverse gastrointestinal effects (P = .02).

Conclusion: The addition of misoprostol to current aspirin challenge and/or desensitization protocols reveals no protective effect in reducing the intensity of nonsteroidal anti-inflammatory drug–induced symptoms and is not recommended based on the findings in this study.

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Introduction

Aspirin-exacerbated respiratory disease (AERD) is a chronic disease defined by the presence of chronic rhinosinusitis, eosinophilic nasal polyposis, asthma, and intolerance to cyclooxygenase (COX) 1–inhibiting drugs, including aspirin and other nonsteroidal anti-inflammatory drugs (NSAIDs).¹ After ingestion of these drugs, patients with this syndrome will usually produce an array of adverse upper and/or lower airway symptoms, such as ocular tearing, periorbital swelling, rhinorrhea, nasal congestion,

laryngospasm, and/or bronchoconstriction. Extrarespiratory reactions, such as urticaria, angioedema, gastrointestinal (GI) symptoms (nausea, vomiting, abdominal pain), and even hypotension, have also been reported.² It is estimated that 5% to 7% of all individuals with asthma are affected by this condition, but prevalence rates may be significantly higher, nearing 20% to 40%, in individuals with asthma and concomitant chronic rhinosinusitis with nasal polyposis.³

To date, no in vitro testing exists for this disease, and a provocative oral challenge with aspirin or another NSAID remains the gold standard of diagnosis.^{1,4} Once the diagnosis of AERD is confirmed, desensitization to aspirin and continuous daily aspirin therapy improves the clinical course for many of these patients.⁵

Despite ongoing research in the field, the pathophysiology of AERD remains only partly understood. It is considered an acquired and nonimmunologic (pseudoallergic) condition that results from

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an abnormal biochemical response to inhibition of the COX-1 enzyme by aspirin or another COX-1-inhibiting NSAID. At baseline, patients with AERD have an underlying alteration in their arachidonic acid metabolism pathway, which results in an overproduction of proinflammatory cysteinyl leukotrienes (cysLTs) and an underproduction of protective anti-inflammatory prostanoids, particularly prostaglandin E₂ (PGE₂) and its receptor E prostanoid 2 (EP2).^{6–9} The latter is known to be an important regulator of the 5-lipoxygenase pathway. On ingestion of a COX-1-inhibiting drug, this pathway is further dysregulated, and the acute depletion in PGE₂ results in removal of the brake on 5-lipoxygenase activity. This effect subsequently directs arachidonic acid toward the synthesis of cysLTs. In addition to enhanced leukotriene production, decreased PGE₂ levels can also lead to direct activation of mast cells with release of tryptase, histamine, and other inflammatory mediators.¹⁰

Protective PGE₂ is synthesized in most cells of the body, including epithelial and endothelial cells of the respiratory tract, by the constitutively expressed COX-1 enzyme. PGE₂ primarily exerts its anti-inflammatory effects by targeting the EP2 receptor on T cells and suppressing STAT6 phosphorylation and T_H2-mediated cytokine production.¹¹ Thus, the marked reduction in PGE₂ levels after COX-1 inhibition most certainly plays a large role in the pathogenesis of respiratory symptoms during aspirin or NSAID challenge in patients with AERD.¹²

In support of the role of PGE₂ in the suppression of allergic sensitization and lung inflammation, several small studies have found a bronchoprotective effect with exogenous administration of PGE₂.^{13–15} In 1996, Sestini et al.¹⁴ found that inhaled PGE₂ could attenuate the response to bronchial challenge with lysine-aspirin in aspirin-intolerant individuals with asthma. This observation was associated with a decrease in urinary excretion of leukotriene E₄, a known marker of cysLT overproduction. Consequently, this study posited that the beneficial actions of inhaled PGE₂ are facilitated through suppression of cysLT synthesis in aspirin-sensitive individuals with asthma. In a separate study, IgE-mediated cysLT production was also found to be particularly sensitive to suppression by PGE₂ and was demonstrated to be unique to mast cells of patients with AERD compared with healthy and aspirin-tolerant individuals with asthma.¹⁵

Misoprostol, a synthetic oral prostaglandin E₁ (PGE₁) analogue, also has promise in AERD. Comparable to endogenous PGE₂, misoprostol has high affinity to the EP2 receptor and has been speculated to exhibit a similar mechanism of action on immune function regulation.¹⁶ In murine models, interaction of misoprostol with the EP2 receptor inhibits various immunologic events during sensitization and attenuates the development of allergic inflammation after provocative airway challenge. In wild-type mice, administration of misoprostol during sensitization reduces levels of eosinophils and T_H2 cytokines (interleukins 5 and 13) in bronchoalveolar lavage fluid and total serum IgE levels. These effects were not seen in EP2-deficient mice.¹¹

In human studies, Kowalski et al.¹⁷ revealed that misoprostol administration was capable of inhibiting production of the arachidonic acid metabolite 15-hydroxyeicosatetraenoic acid in vivo by leukocytes in patients with AERD, whereas this effect was not seen in aspirin-tolerant individuals.¹⁷ In another study by Szmidt and Wasiak,¹⁸ misoprostol demonstrated a protective effect on aspirin-induced bronchoconstriction when given at an initial dose of 400 µg followed by a second 200-µg dose 2 hours after aspirin challenge.¹⁸ Misoprostol is also beneficial in non-AERD conditions. One study revealed that high doses of oral misoprostol (600 µg 4 times daily) was favorable in preventing mast cell release in mast cell activation syndromes.¹⁹

Thus, in vitro studies confirm a unique effect of exogenous PGE in stabilization of inflammatory mediator release, and small human

studies suggest decreased reaction severity of aspirin-induced symptoms in AERD. We subsequently turned our interest to the use of misoprostol in further enhancing the safety of aspirin desensitization. The authors hypothesized that the use of misoprostol during aspirin challenge may decrease the severity of aspirin-induced symptoms after NSAID ingestion and may make aspirin desensitization safer for patients with AERD.

Methods

Patient Population

A total of 106 patients underwent aspirin challenge and desensitization at Scripps Clinic between February 2011 and November 2013. Of those, 76 patients were enrolled in the study after obtaining written consent. The study protocol was approved by the Human Subjects Committee of Scripps Clinic. All patients had a history of nasal polyposis, chronic rhinosinusitis, and physician-diagnosed asthma with a forced expiratory volume in 1 second (FEV₁) greater than or equal to 1.5 L or 60% of the predicted value. In addition, all patients reported a history of at least one adverse upper and/or lower airway reaction to aspirin or another NSAID.

Misoprostol

Misoprostol is a medication approved by the US Food and Drug Administration for the clinical use of preventing NSAID-induced gastric ulceration. It is also used for a variety of indications in the practice of obstetrics and gynecology, including medical abortion, labor induction and treatment of postpartum hemorrhage.²⁰ Common adverse effects include nausea, stomach upset, diarrhea, and headache. Given the risk of abortion, preterm birth, uterine perforation, and/or fetal death as complications if used during pregnancy, all women of childbearing age (18–55 years) were excluded from the study unless they had a documented history of bilateral tubal ligation, hysterectomy, or bilateral oophorectomy.

Randomization and Protocol

This was a single-blinded study in which patients were randomized 2:1 to receive misoprostol (n = 30) or placebo (n = 15). To enhance the power of the study and to lessen the likelihood that any result was determined by chance, the patients in the misoprostol and placebo groups were compared with a group of historical controls (n = 31). This group included a set of individuals who did not receive the study drug or placebo but met the same inclusion criteria and were undergoing aspirin challenge during the same time as the study. Given the considerable variation in patient responses to aspirin challenge, it was hypothesized that this subset of patients would assist in confirming any true difference seen between the misoprostol and placebo groups.

All 76 patients had the diagnosis of AERD confirmed during oral aspirin challenges and were desensitized according to our published protocol at Scripps Clinic (Fig 1). Patients who did not experience a positive reaction during oral aspirin challenge were not included in this study. The Scripps Clinic protocol includes the use of leukotriene-modifying drugs (LTMDs) for a minimum of 7 days before the procedure and the use of intranasal ketorolac during challenge. Both improve the safety of aspirin challenges.^{21,22} All patients continued to take their usual controller medications, including inhaled, intranasal and/or oral systemic corticosteroids, and long-acting bronchodilators.

Figure 1 shows our standard protocol, which was modified for the study to include the administration of 200 µg of oral misoprostol or placebo 30 minutes before the start of the challenge. Misoprostol has a short biologic half-life of 20 to 40 minutes, and the peak effect can be reached in approximately 30 minutes.²³

Time	Intranasal Ketorolac/Oral Aspirin Dose
DAY 1	
8:00 am	1 spray (one nostril) (1.26 mg) ← 200 µg misoprostol
8:30 am	1 spray/nostril (2.53 mg)
9:00 am	2 sprays/nostril (5.05 mg)
9:30 am	3 sprays/nostril (7.58 mg) ← 200 µg misoprostol
10:30 am	60 mg aspirin
12:00 pm	60 mg aspirin ← 200 µg misoprostol
DAY 2	
8:00 am	150 mg aspirin
11:00 am	325 mg aspirin

Figure 1. Modified nasal ketorolac and oral aspirin desensitization protocol. Ketorolac (60 mg/2 mL) was mixed with preservative-free normal saline (2.75 mL). Each spray delivers 1.26 mg of ketorolac solution. Spirometry and objective clinical evaluation were performed before each dose.

Therefore, administration of the drug at this time would allow it to reach adequate plasma levels before patients begin to react to the nasal ketorolac challenge.

On the basis of a large database of more than 1,500 patients who have undergone aspirin challenge and desensitization at Scripps Clinic, most patients react to the 5.05-mg dose of nasal ketorolac (administered at 60 minutes), with onset of symptoms typically between 60 and 90 minutes. Subsequently, the patients received a second 200-µg oral dose of misoprostol (or placebo) at 90 minutes and a final 200-µg oral dose (or placebo) 4 hours after the first dose (1.26 mg) of nasal ketorolac. Misoprostol has a duration of action of 3 hours.²⁴ Therefore, administration of the drug at these time points should provide adequate drug coverage for each step of the intranasal ketorolac challenge and first dose of oral aspirin.

The remainder of the aspirin challenge and desensitization procedure remained unchanged. Serial measurements, including symptom scores, FEV₁, and peak nasal inspiratory flow (PNIF) rate, were collected throughout the procedure per protocol.

Reactions

Positive aspirin reactions were recorded and classified based on the characteristics of the reaction: naso-ocular reaction alone (pure rhinitis, ocular reactions, or both; maximal FEV₁ decrease <15%), bronchial reaction alone (decrease in FEV₁ >15% without naso-ocular reaction), naso-ocular reaction with mild bronchial reaction (FEV₁ decrease of 15%–20%), or classic reaction (naso-ocular reaction with FEV₁ decrease >20%). All reactors were treated with appropriate rescue therapy as according to standard protocols.

End Points

The primary end point was the maximum percentage change in the FEV₁ measurement and/or percentage change in the PNIF rate. Secondary end points included the total number of treatments required to treat aspirin-induced symptoms. The latter was further subcategorized into respiratory and nonrespiratory treatments. The frequency of GI symptoms was also evaluated. In addition, categorical outcomes indicating an observed decrease (yes or no) in PNIF and FEV₁ during ketorolac- and/or aspirin-induced reactions were constructed and similarly compared across groups given the adverse effect profile of misoprostol.

Statistical Analysis

Decreases in PNIF and FEV₁ measurements, the number of total treatments received (respiratory and nonrespiratory), and the presence or absence of GI symptoms were compared between the

misoprostol, placebo, and historical control arms. For quantitative outcomes, Kruskal-Wallis tests were performed to examine group differences, whereas Mann-Whitney tests were used to examine pairwise differences. For categorical outcomes, Freeman-Halton and Fisher exact tests were used, respectively. Statistics are presented without correction for multiple testing. $P < .05$ was used for determining statistically significant associations. All analyses were performed in R statistical software, version 3.2.3 (R Development Core Team).

Results

Baseline Patient Characteristics

All 76 patients who were enrolled in the study were successfully desensitized according to the protocol. All 3 groups were similar with respect to age, sex, atopy, baseline symptom scores, and prior sinus operations. The mean patient age was 50.8 years. One hundred percent of patients were taking a LTMD at the time of oral aspirin challenge, of which 97% were taking montelukast. The mean number of total sinus operations across all 3 groups was 2.9.

FEV₁

Figure 2 shows the percentage change in FEV₁ decrease for all study patients throughout the entire challenge and desensitization procedure (combined nasal ketorolac and oral aspirin reactors). The ranges in FEV₁ reduction for individuals in the misoprostol, placebo, and historical control groups were 0% to 36%, 0% to 30%, and 0% to 68%, respectively. There was a single outlier in FEV₁ reduction in the historical control group, with a decrease of 68% after reaction to 5.05 mg of nasal ketorolac.

When comparing all reactors, no binary difference (change or no change) in FEV₁ reduction was detected across all 3 study groups ($P = .66$) (Table 1). When evaluating the overall magnitude of FEV₁ reduction between these groups, patients in the misoprostol group experienced a larger percentage in FEV₁ reduction compared with placebo patients ($P = .03$); however, this finding was not seen when comparing misoprostol and historical controls ($P = .64$) or placebo and historical controls ($P = .29$). This finding is thought to be insignificant because the overall magnitude in FEV₁ reduction for all reactors did not statistically differ ($P = .13$).

We then compared FEV₁ reduction between nasal ketorolac and oral aspirin reactors. There was a statistical difference found among

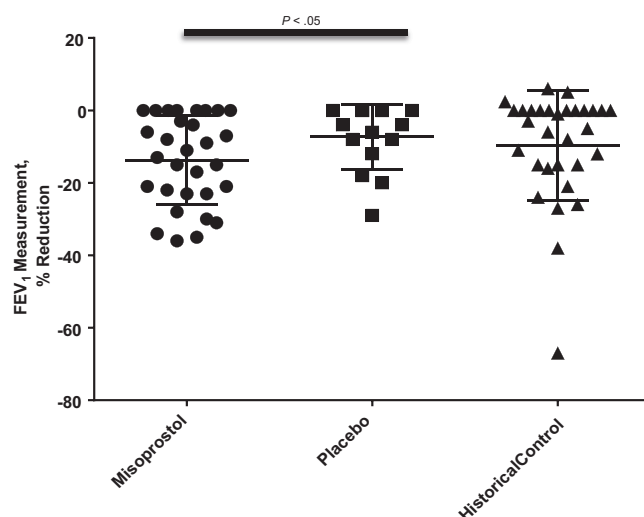


Figure 2. Percent reduction from baseline forced expiratory volume in 1 second (FEV₁) during aspirin challenge and desensitization (all reactors). Data are presented as means (SDs).

Table 1
Frequency of Upper and Lower Airway Reactions Among Nasal Ketorolac and Oral Aspirin Reactors

Variable	Positive Δ, no. (%)	Negative Δ, no. (%)	No change, no. (%)	Total reactors (ketorolac and aspirin), no.
PNIF				
Misoprostol	1 (2)	26 (43)	33 (55)	60
Placebo	0 (0)	10 (33)	20 (67)	30
Control	3 (5)	16 (26)	43 (69)	62
Total reactions	4 (3)	52 (34)	96 (63)	152
FEV₁				
Misoprostol	0 (0)	27 (45)	33 (55)	60
Placebo	0 (0)	10 (33)	20 (67)	30
Control	4 (6.5)	22 (35.5)	36 (58)	62
Total reactions	4 (3)	59 (39)	89 (58)	152

Abbreviations: Δ, change; FEV₁, forced expiratory volume in 1 second; PNIF, peak nasal inspiratory flow.

all ketorolac reactors ($P = .01$), with more patients in the misoprostol group having a larger magnitude of FEV₁ reduction after nasal ketorolac challenge compared with placebo ($P = .002$). However, no difference in FEV₁ reduction from nasal ketorolac was seen between misoprostol and historical controls ($P = .18$) or placebo vs historical controls ($P = .06$). No binary or magnitude difference was found between any of the study group patients who reacted to oral aspirin ($P = .11$).

PNIF

The percentage of reduction in PNIF rate for all reactors is shown in Figure 3. Ranges in PNIF reduction among those in the misoprostol, placebo, and historical control groups were 0% to 100%, 0% to 100%, and 0% to 85%, respectively.

When comparing all reactors, a binary (change or no change) difference in PNIF reduction was detected among the 3 study groups ($P = .02$), with a difference seen in patients in the misoprostol group compared with historical controls ($P = .01$) (Table 1). No difference was detected when comparing the misoprostol group and the placebo group ($P = .13$) or the placebo group and the historical controls ($P = .53$). Overall, no difference was seen in regard to the magnitude of PNIF reduction across all 3 study groups ($P = .07$).

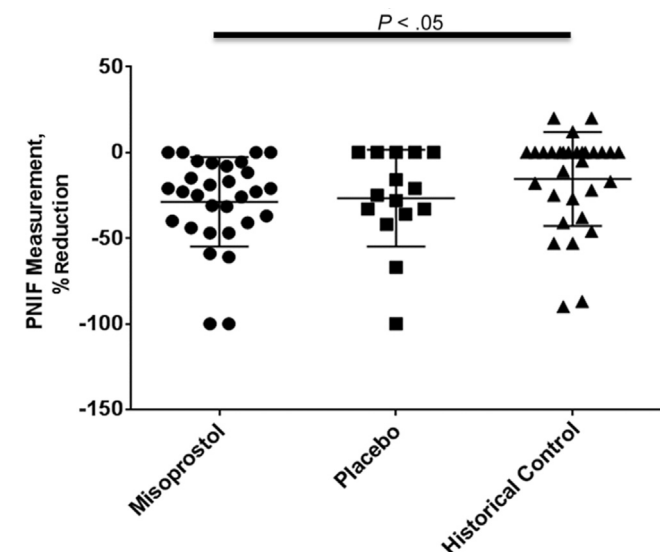


Figure 3. Percent reduction from baseline peak nasal inspiratory flow rate (PNIF) during aspirin challenge and desensitization (all reactors). Data are presented as means (SDs).

After separating nasal ketorolac and oral aspirin reactors, a higher reduction in PNIF measurement was found in patients in the misoprostol group who reacted to nasal ketorolac compared with historical controls ($P = .01$). However, no difference was seen between the misoprostol and placebo groups ($P = .55$) or the placebo group and historical controls ($P = .20$) who reacted to nasal ketorolac. Similar to FEV₁ reduction, no binary or magnitude difference was seen between any study group patients who reacted to oral aspirin ($P = .94$).

Reaction Times

The frequency of reaction rates at each step of the modified oral aspirin challenge and desensitization procedure was determined. In our experience, historical data indicate that most patients react to the 5.05-mg dose of nasal ketorolac. For those who have a positive challenge result to oral aspirin, most patients react to the first 60-mg dose.

There was no statistical difference in ketorolac reaction rates between the misoprostol and placebo groups ($P = .92$), but there was a difference seen between the misoprostol group and the historical controls ($P = .003$). No difference was detected at the most common ketorolac dose (5.05 mg) compared with placebo ($P = .33$) or controls ($P = .19$).

No difference in aspirin reaction rates was observed between the misoprostol and placebo groups ($P = .13$) or between the misoprostol group and the historic controls ($P = .52$). This includes no difference seen at the first 60-mg dose of aspirin compared with placebo ($P = .20$) and control ($P = .77$).

Treatment Use

When analyzing the total number of treatments required throughout oral challenge and desensitization, no significant difference was found in the misoprostol, placebo, and historical control groups, with each group requiring a mean of 2.5 to 4 total medications throughout the entire procedure ($P = .14$) (Fig 4).

The total treatments required were then subcategorized into respiratory (albuterol, levalbuterol) vs nonrespiratory (diphenhydramine, cetirizine, azelastine, odansetron, oxymetolazine) treatments. Again, no significant difference was found among each of the 3 study populations ($P = .28$). On average, each group required more nonrespiratory than respiratory medications throughout the oral aspirin challenge and desensitization procedure (Fig 5).

GI Symptoms

A true difference was found in the number of reported GI adverse effects among all 3 groups ($P = .02$), with the highest incidence of symptoms occurring in the misoprostol group relative to the historical controls ($P = .01$). No difference was detected between the misoprostol and placebo groups ($P = .72$). As shown in Figure 6, a total of 8 (26%) of 30 patients who received misoprostol reported adverse effects, including nausea, abdominal pain, bloating, and/or diarrhea, during or after the completion of the protocol.

Discussion

Despite previously published data supporting the efficacy of exogenous PGE in stabilization of inflammatory mediator release and reduction in aspirin-induced symptoms, we were unable to confirm a clinical benefit during aspirin desensitization. Our study reveals that treatment of patients with AERD with misoprostol has no effect in reducing the intensity of lower or upper airway symptoms that occur after aspirin or NSAID ingestion and may lead to the development of unwanted GI adverse effects. Therefore, the addition of misoprostol to current aspirin challenge and desensitization protocols is not recommended.

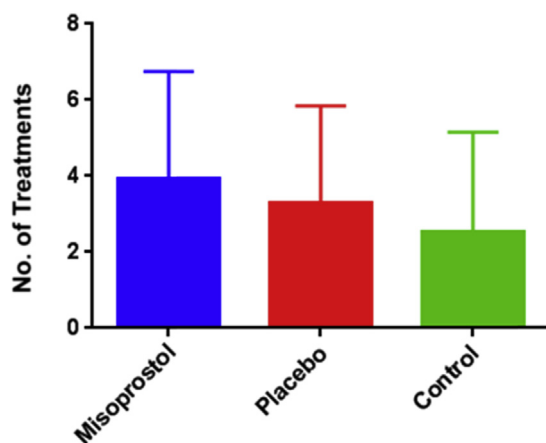


Figure 4. Total number of treatments received during aspirin challenge and desensitization. Each solid bar represents the mean number of treatments, with total treatment range shown.

The results of our study may be influenced by the concomitant use of LTMDs, such as montelukast, given that this class of drugs has already been found to prevent or reduce the severity of lower respiratory tract reactions during aspirin challenge.²¹ Therefore, the protective benefit of misoprostol may have been masked by the standardized use of LTMDs during our challenge and desensitization protocol. Nonetheless, our data indicate that the use of misoprostol in conjunction with LTMDs likely does not provide any added benefit in reducing severity of upper and/or lower airways reactions (based on FEV₁ and PNIF measurements) during aspirin challenge.

Alternatively, when Sestini et al¹⁴ found that PGE₂ prevented aspirin-induced bronchoconstriction via reduced production of inflammatory cystLTs, this finding was observed at an inhaled dose of 100 µg per patient. Given that misoprostol and its metabolites are extensively metabolized by the liver, the oral doses that were administered in our study may not have been able to reach sufficient concentration in the lower airways to have a substantial effect. This has been considered by other studies, which also failed to demonstrate any protective effect of misoprostol in aspirin-sensitive patients with asthma.²⁵

Another prior study demonstrated a protective effect with oral misoprostol; however, this benefit was only observed to a *single* predetermined aspirin dose.¹⁸ This finding argues that the protective effect of oral PGE₁ analogues may follow a particular dose-response curve. In the case of our study in which patients underwent complete desensitization with exposure to multiple increases

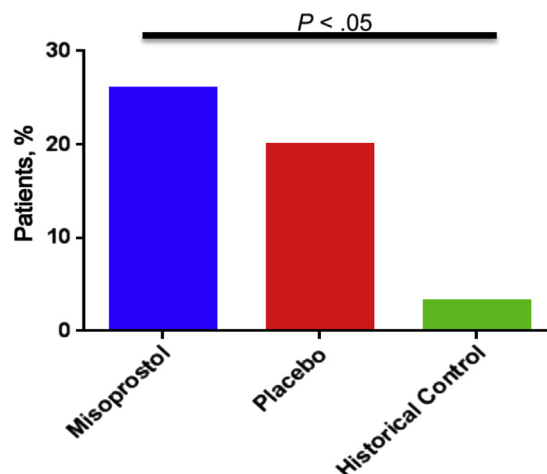


Figure 6. Percentage of patients reporting gastrointestinal symptoms during aspirin challenge and desensitization.

in aspirin doses, the oral dose of misoprostol might need to be higher or more frequently dosed to reproduce this protective effect during aspirin desensitization. In support of this consideration, it has been suggested that misoprostol-induced cyclic adenosine monophosphate (cAMP) elevation might occur in a dose-dependent manner, although inverted dose-response curves have also been demonstrated with this drug.^{26,27} Therefore, it appears that a fine line exists between the dose of misoprostol that provides maximal therapeutic benefit and the dose that results in loss of favorable action and increase in adverse effects.

A trend toward an increase in FEV₁ and PNIF reduction during nasal ketorolac challenge was seen in the misoprostol group; however, these results were not consistent with placebo and historical controls. Therefore, it is difficult to interpret the true significance of this information. We suspect that the difference in FEV₁ reduction between the misoprostol and placebo groups and the difference in PNIF reduction between misoprostol and historical controls is secondary to the variability of reactions during aspirin challenges. Otherwise, any true change should be seen when comparing patients taking misoprostol and placebo as well as patients taking misoprostol to historical controls.

Given our administration schedule and the half-life time of misoprostol (20–40 minutes), it is possible that patients may have been unprotected during certain stages of the aspirin challenge and desensitization protocol, particularly at 60 and 150 minutes. This finding corresponds to administration of the 5.05-mg dose of nasal ketorolac and the first 60-mg dose of oral aspirin, respectively. These reaction doses have historically been the most common during our challenges. If the negative results of our study could be explained by an erroneous dosing schedule, we should expect a higher rate of positive challenges to either dose in the misoprostol group. However, no difference in reaction rates was seen at either of these common provoking doses among all 3 groups.

Additional reasons for the negative results of our study may be potentially explained by the difference in chemical structure between PGE₁ and PGE₂ and whether this may alter misoprostol's ability to interact with the EP2 or other EP receptors. Despite prior studies reporting protective effects of these prostaglandin analogues, receptor binding and signaling *in vivo* could also be dependent on a particular threshold dose and might influence an effect on unknown off-target sites.

The pharmacologic action of misoprostol, akin to *in vivo* PGE₁ and PGE₂, is thought to be primarily mediated via the interaction with the EP2 receptor and the resultant increase in intracellular cAMP levels²⁸; however, it has been suggested that misoprostol

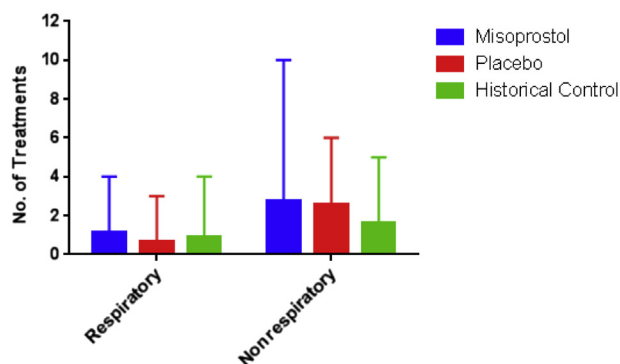


Figure 5. Total number of respiratory vs nonrespiratory treatments received during aspirin challenge and desensitization. Each solid bar represents the mean number of treatments, with total treatment range shown.

may be less proficient than PGE₂ in stimulating adenylate cyclase production.²⁹ This could further explain why misoprostol has not been able to successfully or consistently reproduce the broncho-protective effects seen in previous studies with exogenous PGE₂.^{13–15} Furthermore, misoprostol may actually have higher affinity for EP3 rather than EP2³⁰; interactions through the EP3 receptor are inhibitory on cAMP synthesis and clinically result in bronchoconstriction.^{28,31} It is possible that the simultaneous activation of both receptors neutralize the actions of misoprostol and may account for the negative findings in this study.

In addition to the dysregulation between PGE₂ and cysLT synthesis in AERD, there has been new insight into the potential role of proinflammatory PGD₂ in this disease. A recent study found higher levels of PGD₂ production among patients with AERD who were unable to tolerate aspirin desensitization.³² These patients also had higher rates of airflow obstruction during aspirin reactions and were also more likely to experience extrapulmonary adverse effects, particularly GI reactions. Although further studies are necessary to determine the specific role of PGD₂ (and other PGs), it supports the multifaceted nature of AERD and aspirin reactions. Thus, it is unlikely that misoprostol by itself would be able to mitigate the complex biochemical dysfunction in this disease.

Misoprostol use in AERD has been suggested as a method to potentially reduce GI complications associated with continuous daily aspirin therapy.³³ The effect of misoprostol on prevention of COX-1–induced gastritis is unlikely to be uniquely beneficial in AERD but could be used, as in any patient taking NSAIDs long term, to limit GI disease. However, when used before desensitization, our study found that use of misoprostol may actually result in an increase of GI adverse effects, particularly nausea, abdominal pain, and diarrhea. This may be the result of direct interaction with EP3 receptors on parietal cells or potentially failure of misoprostol to suppress PGD₂ production during aspirin reactions (as discussed above). In our clinical experience, the GI adverse effects of misoprostol appear to wane with regular use.

In conclusion, the use of the oral PGE₁ analog misoprostol combined with the standard modified aspirin challenge and desensitization protocol at Scripps Clinic did not reduce symptom severity as originally hypothesized. On the basis of this study, misoprostol use does not appear to improve the overall safety of aspirin challenges and may result in a higher frequency of adverse GI symptoms. With these findings, we do not recommend the addition of misoprostol to current aspirin challenge and/or desensitization guidelines. Further studies with higher or more frequent misoprostol dosing could be considered but might be limited by GI adverse effects.

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