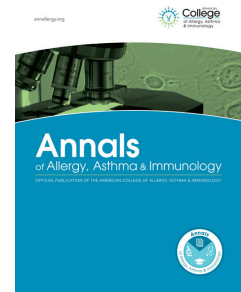


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Intranasal Ketorolac, Diagnosis and Desensitization for Aspirin Exacerbated Respiratory Disease

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Abbreviations: AERD, aspirin exacerbated respiratory disease; ASA, aspirin; ICS, inhaled corticosteroids; LABA, long-acting bronchodilator; LTMD, leukotriene modifying drug; SABA, short-acting bronchodilator;

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Background : Intranasal ketorolac has been proposed as a diagnostic test for AERD as well as a faster, safer and reliable addition to facilitate ASA desensitization. **Objective :** We conducted the first prospective study to dissect the impact of intranasal ketorolac incorporation during ASA desensitization versus standard oral protocols in concert with evaluating its diagnostic utility for AERD.

Methods : AERD subjects were enrolled in a prospective open-label observational study between 11/2006 and 8/2013. Participants selected one of the following desensitization protocols: Intranasal ketorolac one day prior to oral ASA (Group 1, combined) or ketorolac challenge with greater than two weeks elapsing until oral ASA (Group 2, washout). All patients were on a leukotriene modifying drug (Montelukast) for at least 1 week prior to challenge.

Results : Twenty subjects were enrolled: 13 in Group 1; 7 in Group 2. No significant differences were seen for baseline symptom scores or FEV1. Group 1 demonstrated significant increases for the threshold dose of ASA ($p=0.009$), likelihood of having a 'silent ASA desensitization' ($p=0.0147$) and decreased reaction severity to oral ASA ($p=0.036$). There were no significant differences in reaction FEV1, incidence of extrapulmonary symptoms, limited naso-ocular reactions, rescue treatment requirements or time to symptom resolution. There was 100% concordance between reactions to intranasal ketorolac and oral ASA for Group 2, supporting its utility as a diagnostic test for AERD.

Conclusion : Intranasal ketorolac is a useful diagnostic test and adjunct within the combined ketorolac/ASA protocol to achieve effective, efficient and perhaps safer desensitization to ASA for AERD patients.

1 INTRODUCTION

2 Aspirin exacerbated respiratory disease (AERD) is classically characterized by a constellation
3 of nasal polyps, eosinophilic sinusitis, asthma and adverse reactions to aspirin and other COX-1
4 inhibitors. While AERD is disproportionately represented within populations of severe
5 asthmatics, comprising an estimated 14.9% of subjects, a subset have restricted upper airway
6 involvement with polypoid rhinosinusitis ¹. The true prevalence of AERD may be under
7 documented both due to a lack of physician awareness as well as the absence of indirect testing
8 to confirm the diagnosis. In an algorithm-based analysis of electronic health records, 12.4% of
9 patients meeting clinical criteria were not identified as having AERD ². Consistent with the lack
10 of broad recognition, a previously unsuspected AERD diagnosis was able to be established
11 within a patient cohort referred for aggressive eosinophilic rhinosinusitis who were tolerating
12 regular low dose aspirin (ASA) ³.

13 Treatment outcomes for AERD patients are typically disappointing despite efforts to optimize
14 surgical care and pharmacotherapy. Airway inflammation, visually manifest by nasal polyps,
15 tends to relentlessly progress. The clinical course is predictably punctuated by frequent severe
16 respiratory relapse often necessitating systemic corticosteroids and repetitive sinus surgery.

17 ASA desensitization and maintenance has been established as a cost-effective long-term
18 intervention to decelerate the trajectory of AERD ⁴. ASA therapy has been confirmed to slow
19 the regrowth of polyps, delay the return of anosmia, reduce systemic corticosteroid requirement
20 and decrease the overall burden of disease ⁵. Although controlled studies are lacking, biologic
21 agents including dupilumab, mepolizumab and omalizumab also appear promising for the
22 management of AERD subjects ⁶⁻¹¹.

Despite the progress achieved, barriers remain with respect to the appropriate diagnosis and treatment of AERD. Foremost among these is the risk of provoking severe, possibly life-threatening reactions encompassing bronchospasm, gastrointestinal, cutaneous involvement and laryngospasm with exposure to ASA and NSAIDs. The necessity to provide the appropriate infrastructure to address these potential serious adverse events as well as the time-consuming nature of ASA challenge and desensitization present daunting obstacles for many practitioners^{12, 13}.

Intranasal ketorolac has been proposed as a faster, safer and reliable alternative to oral ASA challenge for the diagnosis of AERD¹⁴. In the wake of the initial publication, Lee et al investigated a modified protocol where intranasal ketorolac was incorporated prior to oral ASA in an effort to enhance safety and abbreviate the time course for desensitization. The authors reported that 90% of patients were desensitized following ketorolac exposure accompanied by an overall reduction in reaction severity in comparison with historic controls. The majority of patients recorded only limited naso-ocular symptoms¹³. This approach has now been adopted at Scripps Clinic as well as other institutions⁵. While a logical extrapolation from the European experience with lysine-aspirin (which is not available in the United States)^{15 16}, a direct comparison of the impact of combined ketorolac vs standard oral ASA desensitization has not been previously undertaken.

We conducted the first prospective study to dissect the influence of intranasal ketorolac administration prior to oral ASA versus standard ASA desensitization. AERD subjects were enrolled in either Group 1: intranasal ketorolac one day prior to oral ASA (combined) or Group 2: ketorolac challenge with greater than two weeks elapsing until oral ASA (washout). To determine the impact of ketorolac incorporation outcomes were analyzed for the threshold dose

46 of ASA, symptom severity, graded treatment and time required for reaction resolution. The
47 study further allowed for an examination of intranasal ketorolac for the diagnosis of AERD.
48 Heretofore the diagnostic utility and relative safety had been extrapolated from a combined
49 ketorolac/ASA challenge protocol. The outcome of our investigation forms the basis for this
50 report.

51

52 **METHODS:**

53 The investigation was designed as a prospective open label observational study. Following IRB
54 approval by the Southern California Permanente Medical Group (SCPMG) enrollment was
55 completed between 11/2006 and 8/2013. Informed consent was obtained by one of the authors
56 (SCC). Each subject signed the written consent approved by the SCPMG IRB.

57 *Subjects*

58 Individuals 18 years or older meeting diagnostic criteria for AERD⁵ referred for ASA
59 desensitization were eligible to participate. After informed consent, subjects were requested to
60 select one of two protocols for ASA desensitization. Their decision reflected their personal
61 preference as to what was most convenient for scheduling. Subjects were not compensated for
62 the study and their participation was completely voluntary. Individuals referred with AERD
63 who chose not to participate were offered standard oral ASA desensitization and not included in
64 the analysis.

65 The two protocols were distinguished by the timing of administration for intranasal ketorolac:
66 Group 1: Intranasal ketorolac challenge on the day prior to oral ASA desensitization (combined
67 group) and Group 2: Intranasal ketorolac and oral ASA separated by an at least a 2-week
68 interval (wash-out group). Patients continued to use their usual controller medications including
69 long acting bronchodilators, leukotriene modifying drugs (LTMD), and intranasal, inhaled, or
70 systemic corticosteroids. Patients who had not been receiving a LTMD prior to the study were
71 started on montelukast at least 1 week prior to their challenge date. Baseline FEV₁ was
72 required be >70% of predicted for study inclusion.

73 Patients with bleeding disorders, peptic GI disease, recent MI or other underlying medical
74 conditions that would interfere with asthma or anaphylaxis treatment and those taking warfarin
75 or beta blockers were excluded from this study.

76 ***Challenge/Desensitization Protocols***

77 Subjects were continuously observed in the outpatient clinic with one on one nursing, IV
78 access, oximetry and vital signs. Oxygen and cardiopulmonary resuscitation kits including an
79 automated external defibrillator were immediately accessible.

80 Symptom scores and spirometry (FEV₁) were recorded at baseline and every half hour.

81 Medications available for administration during reactions included oral antihistamines,
82 cimetidine, oxymetazone nasal spray, olopatadine ophthalmic solution, albuterol and
83 ipratropium for nebulization, solumedrol, prednisone, and epinephrine.

84 ***Ketorolac challenge:***

85 Subjects were administered intranasal doses at 30 minute intervals: nasal saline (1 spray each
86 nostril), 2.08 mg ketorolac (1.04 mg per nostril), 4.16 mg, 8.32 mg, and 12.48 mg (adopted
87 from White et al)¹⁴. Challenges were considered positive if patients identified a change from
88 baseline symptoms based on their numerical score (outlined below). Treatment was
89 administered at the onset of reaction and once symptoms resolved, the desensitization was
90 progressed per protocol. FEV₁ was measured at baseline and at the time of symptoms, and the
91 ratio of the lowest FEV₁ during the challenge relative to the baseline FEV₁ assessed.

92 ***Aspirin challenge***

93 Oral ASA administration followed previously published desensitization guidelines at 3 hour
94 intervals with doses of 40.5mg, 81mg, 162mg, 325mg, 650mg¹⁷. FEV₁ was measured at
95 baseline and before each dose of ASA as well as at symptom onset, and the ratio of the lowest
96 FEV₁ during the ASA challenge relative to the baseline FEV₁ assessed.

97 *Symptom scores*

98 Symptom scores were assessed at baseline, pre-dosing, and post-reaction using eight
99 components (nasal congestion, runny nose, sneezing, itchy nose, itchy/watery eyes, tight throat,
100 wheezing and chest tightness) which the patients self-rated on a scale of 0-3 as previously
101 reported¹⁸. The scales were based on symptom severity as follows: 0= no symptom; 1= mild,
102 barely noticeable symptoms; 2= moderate, somewhat troublesome symptoms; 3= symptoms are
103 much worse than you generally experience or are making you very uncomfortable.

104 Loss of smell, abdominal pain, shortness of breath and cough were also recorded at baseline
105 and during the challenges. Rash, pruritus, and headache were also queried during the
106 evaluations. Symptom scores were recorded at baseline and at each ASA dose. The change in
107 symptom score from baseline to threshold ASA dose as well as the cumulative symptom score
108 for all doses during the entire oral ASA challenge were also analyzed.

109 *Treatment Score*

110 Treatment required for symptom resolution was graded by the following scale: 0 points=no
111 treatment; 1= topical medication (eye drops, nasal decongestant spray); 2=antihistamines; 3=
112 nebulizer treatment with albuterol and/or ipratroprium; 4= steroids or epinephrine. The scale
113 was based on consensus opinion of the authors.

114 ***Time to symptom resolution***

115 Time from symptom onset to resolution following a provoking dose of either ketorolac or ASA
116 was recorded as an additional surrogate for reaction severity.

117 ***Analysis of the impact of ketorolac incorporation on ASA desensitization***

118 The primary outcome compared the threshold dose of ASA during desensitization (defined as
119 the first dose of ASA eliciting a reaction reflected by any upper and/or lower respiratory tract
120 signs or symptoms consistent with conjunctivitis, rhinitis, laryngospasm, and bronchospasm or
121 decrease in FEV₁ compared to baseline) for subjects enrolled in Group 1 and Group 2¹⁸. The
122 secondary outcome compared the severity of the ASA threshold provoked reactions including:
123 the change in symptom score from baseline to threshold; cumulative symptom score; treatment
124 score; and time to symptom resolution.

125 ***Utility of Intranasal Ketorolac for the diagnosis of AERD***

126 Subjects in Group 1 and 2 were collectively examined for the relationship between ketorolac
127 reactions and the clinical diagnosis of AERD. For Group 2 subjects, the concordance between
128 intranasal ketorolac and oral ASA reactions was compared.

129 ***Statistics***

130 All statistical analyses were performed using nonparametric tests. Data was analyzed using the
131 Wilcoxon ranked sum test, the Fisher's exact test, or Kendall's Tau test. P-values less than 0.05
132 were considered significant. Analyses were done using JMP Pro software (SAS Institute, Cary,
133 North Carolina). Results are shown as median with 25%-75% interquartile range.

134 RESULTS

135 *Subjects*

136 A total of 20 patients meeting clinical criteria for the diagnosis of AERD were enrolled in the
137 study. Baseline demographic information is included in Table 1, and results of the challenges
138 are shown in Table 2. All subjects were on montelukast during the study. There were a total of
139 13 patients included in Group 1, the combined group and 7 patients in Group 2 with >2 week
140 spacing between ketorolac and ASA administration, the wash-out group.

141 Although the subjects were self-assigned for the two protocols, Group 1 and Group 2 appeared
142 to be of comparable severity at the time of the study. There was no significant difference
143 between groups for baseline symptom severity scores ($p=0.78$) or baseline FEV₁ ($p=.54$) (Table
144 3).

145 *Analysis of the impact of ketorolac challenge on ASA desensitization*

146 The primary study outcome compared the threshold dose of ASA during desensitization for
147 subjects enrolled in Group 1 and Group 2. For the eight AERD subjects in Group 1 who
148 experienced no symptoms during oral ASA administration (silently desensitized), a value of
149 650 mg for the threshold dose was assigned for the analysis. The difference for the primary
150 endpoint, threshold dose of ASA, was highly significant with a p value of 0.009 (Table 3,
151 Figure 1). This remained highly significant when the two subjects who had the negative
152 reactions to ketorolac in Group 1 were excluded.

153 When analyzed for the likelihood of having a silent desensitization to the oral ASA there was a
154 significant difference between Group 1 and Group 2. Eight of the subjects in the combined

group had no reaction to ASA oral administration whereas all subjects reacted in the washout group ($p < 0.015$; Fisher's exact test). When the two subjects who met the clinical criteria for AERD (discussed in the following section) but did not react to either ketorolac or ASA were removed from the analysis the results remained significant ($p < 0.04$, Fisher's exact test).

The secondary outcome compared the severity of the ASA provoked reactions in the two cohorts. A significant attenuation of the change in symptom score from baseline to threshold ($p = 0.036$) and the ratio of the lowest FEV₁ to baseline FEV₁ ($p = 0.029$) were seen in Group 1; however neither change remained significant when silent desensitization subjects were excluded (Table 3). There were no significant differences between the groups in the other severity parameters (Table 3). No significant differences were found in the proportion of subjects with limited naso-ocular ($p = 0.558$) or extrapulmonary ($p = 0.222$) reactions (data not shown).

Utility of Ketorolac challenge for the diagnosis of AERD

Eighteen of the 20 AERD patients had a positive intranasal ketorolac challenge. The two subjects with negative ketorolac challenges also had negative challenges to oral ASA – both were in Group 1. Each subject met clinical criteria for AERD (eosinophilic polypoid rhinosinusitis, asthma, historic reactions to ASA and NSAIDs, multiple endoscopic sinus surgeries with polyp regrowth). Neither subject had previously been on a LTMD. As per protocol, each had been started on montelukast >1 week prior to the combined ketorolac/ASA desensitization. The subjects were interpreted as having a 'silent' desensitization related to the LTMD and continued on the ASA with improvement during clinical follow up (data not shown).

177 Every subject with a positive ASA challenge also had a positive ketorolac challenge. In
178 contrast, 6 subjects in Group 1 were silently desensitized when the ASA challenge immediately
179 followed. These 6 subjects could not be distinguished clinically from those who weren't
180 silently desensitized. No instances of silent desensitization were observed in Group 2 subjects
181 where the ASA challenge followed 2-weeks or more after the ketorolac challenge.

182 There was no significant difference between Group 1 and Group 2 with respect to the threshold
183 dose for reaction to intranasal ketorolac ($p=0.736$) (Table 4, Figure 1). The 2 subjects who had
184 a silent ketorolac challenge were assigned a threshold dose of 24.96 mg--results remained non
185 statistically significant if these two subjects were excluded from the analysis. No significant
186 differences between the groups were seen in the other severity measures during the intranasal
187 ketorolac challenge (Table 4). The proportion of subjects with limited naso-ocular and
188 extrapulmonary reactions also did not reach statistical significance between groups ($p=1.0$)
189 which would be consistent with the comparability of the group's severity at baseline. Finally,
190 the intensity of the symptoms during the ketorolac challenge did not correlate with the severity
191 of the symptoms during the subsequent ASA challenge ($p=0.146$ for Group 1 and $p=0.652$ for
192 Group 2; Kendall's tau test).

193 **DISCUSSION**

194 AERD was initially recognized in the early 1900s not long after the initial synthesis of ASA ¹⁹
195 ²⁰. While the nomenclature has varied over the years, Samter's description in 1968 of the
196 clinical features ²¹ continues to form the basis for current disease-defining criteria. Our
197 understanding of AERD pathophysiology has evolved to encompass an appreciation of multiple
198 factors, including: mast cell activation (with generation of mediators such as PGD₂);
199 arachidonic acid cascade imbalance (including the diminution of PGE₂'s down regulatory
200 influence); augmented levels and sensitivity to cysteinyl leukotrienes such as LTE₄; and
201 potential role of platelets and T cell prostanoid receptors²². Additionally, the contribution of
202 both cellular (innate lymphoid cell) and cytokine (IL-33, and TSLP) components of the innate
203 immune system has been increasingly recognized to play a role in AERD based on both murine
204 and human studies²². While a genetic transmission has yet to be established environmental
205 exposures such as tobacco smoke and viral illness have been invoked as possibly influencing
206 disease expression²². Despite the substantial scientific progress that has been made, the
207 fundamental basis for the development of AERD has remained elusive ²².

208 AERD has a significant deleterious impact on the quality of life of affected individuals. Amid
209 the multiple related morbidities, anosmia has been cited as among the most significant ²³.
210 Beyond loss of the ability to enjoy the pleasure and protection that the ability to smell confers
211 there may be additional consequences that have yet to be fully explored. Nasal airflow and the
212 ability to smell are intimately linked to memory formation and retrieval raising the prospect that
213 there may be cognitive sequelae from sustained anosmia ²⁴. 19 subjects in our study (13/13
214 Group 1 and 6/7 Group 2) reported anosmia (Table 1) which in light of these concerns would
215 appear worthy of treatment.

216 The use of desensitization and long-term ASA maintenance as an effective strategy for
217 controlling AERD was first reported in 1980 by Donald Stevenson ¹⁷. When initially proposed,
218 this approach was greeted with a high degree of skepticism. ASA desensitization and
219 maintenance was subsequently validated and accepted in the wake of open, randomized and
220 double-blind trials confirming its efficacy ^{25 26}. ASA therapy has now been adopted at multiple
221 centers treating AERD patients.

222 Diagnosis is the first step towards the appropriate treatment for any disorder. White et al
223 proposed intranasal ketorolac challenge as a relatively rapid and safer alternative to oral ASA
224 for the confirmation of AERD ¹⁴. Ketorolac nasal inhalation was estimated to have 78%
225 sensitivity and 64% specificity in their report ¹⁴. In their study all subjects had ketorolac
226 combined with oral ASA initiated within four hours of the intranasal challenge. The limitation
227 of this design was acknowledged by the authors who expressed that it would have enhanced the
228 ability to analyze the sensitivity and specificity of ketorolac as a diagnostic test to have a week
229 interval separating the challenges. There was also an absence of homogeneity in their cohort
230 with regard to use of LTMD. We did not collect data regarding race/ethnicity of our subjects so
231 cannot comment on whether there would be differences.

232 Our study removed the ambiguity cited by White et al by imposing greater than 2 weeks
233 between exposures for Group 2. Group 2 subjects demonstrated a complete concordance
234 between ketorolac and ASA challenges for symptom provocation, supporting the utility of
235 ketorolac challenge as a diagnostic test for AERD. Collectively, 18 subjects referred for AERD
236 had a positive intranasal ketorolac challenge. Two subjects, each meeting clinical criteria for
237 AERD in Group 1 had negative ketorolac and ASA challenges. Both were interpreted as
238 related to use of LTMD (montelukast) and continued on the ASA with improvement during

follow up. This is consistent with prior literature that LTMD and specifically montelukast can abrogate reactivity to ASA (and by extrapolation of the prior literature, NSAIDs) in a minority of subjects with AERD²⁷.

Given the acknowledged limitations of White's study design¹⁴ our report would expand confidence in the sensitivity (100%) of ketorolac as a diagnostic test for AERD. Overall specificity in contrast was unable to be accurately determined due to the 'silent desensitization(s)' in the combined group to ASA. It is noted however that if the analysis was limited to the washout group the finding would be 100% for both sensitivity and specificity.

The threshold dose for reaction to intranasal ketorolac was similar between Group 1 and Group 2 ($p=0.736$) as expected based on their comparable severity at baseline. The 2 subjects who had negative challenges were assigned a threshold dose of 24.96 mg for the analysis--results were still not significant if these two subjects were excluded. Additionally, there were no significant differences between the groups in any of the parameters reflecting severity of the ketorolac reaction including the treatment required.

Several patients who reacted to intranasal ketorolac in White's initial report did not have reactions to the oral ASA exposure which followed¹⁴. Lee et al expanded this observation by examining whether intranasal ketorolac challenge prior to oral ASA would provide an improved, safer and abbreviated method for ASA desensitization¹³. In their study they reported fewer asthma symptoms, extra-pulmonary reactions and a greater percentage of naso-ocular limited reactions using this approach¹³. Based on the outcome of their investigation this modified protocol has now been adopted by the Scripps Clinic investigators. The ability of intranasal ketorolac challenge to induce either partial or complete ASA desensitization is

261 consistent with earlier reports using intranasal lysine-aspirin (which is not available in the
262 USA)^{15 16}.

263 Questions regarding the safety and utility of combined intranasal ketorolac/oral ASA challenge
264 remained despite Lee's report. First, the subjects in the Lee paper only underwent combined
265 intranasal ketorolac/oral ASA challenge and were compared to a historical control group
266 challenged only with oral ASA from 3 to 6 years before the study group¹³. While the control
267 group was said to be have had similar clinical characteristics to the combined challenge group,
268 the threshold dose even for an individual patient is difficult to predict despite the weighting of
269 certain factors and may vary over time²⁸. Second, the percent of subjects using a LTMD was
270 different between the active group and the historical controls (93% vs 77%, $p = 0.001$). The
271 absence of LTMDs has been previously reported as a risk factor for more severe ASA reactions
272²⁸ and to have a variable impact on reaction severity during ASA provoked challenge²⁷. Taken
273 together the statistical analysis utilizing the modified protocol and historic "similar" controls is
274 problematic.

275 By employing a prospective comparative design and controlling for LTMDs, our report is the
276 first study to evaluate the relative impact and safety of ketorolac incorporation vs standard oral
277 ASA desensitization protocols. Our findings revealed a highly significant difference between
278 the combined group and washout cohorts for the primary endpoint – the threshold dose which
279 provoked a reaction to ASA. Intranasal ketorolac was able to desensitize patients to ASA
280 during the combined protocol in 6 of the 11 subjects who reacted to ketorolac. This finding
281 was highly significant as well. The data supports that intranasal ketorolac challenge can
282 desensitize a substantial proportion of AERD subjects and increase the dose of ASA required to
283 provoke a reaction even in those who are not desensitized. We also observed a significant

284 decrease in the change in symptom score from baseline to threshold in Group 1 vs Group 2.
285 Like Lee, we observed a significant decrease in the FEV₁ fall during oral ASA challenge in
286 Group 1; however when the 8 subjects who did not react to oral ASA challenge were excluded,
287 no difference in the fall of FEV₁ was seen. We did not see any significant differences in a
288 variety of other parameters reflecting the severity of the oral ASA challenge symptoms. We
289 note that all of our subjects were receiving a LTMD, and that the oral ASA challenge symptoms
290 were relatively mild in both groups.

291 The outcomes of our prospective study confirmed Lee's report that intranasal ketorolac pre-
292 challenge either completely or partially desensitizes patients to oral ASA. While there is a
293 suggestion based on the change in symptoms at the time of ASA reaction that the response to
294 ASA is milder, we were unable to confirm Lee's assertion that the combined protocol differed
295 in a statistically significant way from standard oral desensitization with respect to other
296 surrogates of severity.

297 Our study validates the diagnostic utility of ketorolac intranasal challenges to identify AERD
298 subjects. We also demonstrated a significant impact of intranasal ketorolac challenge on the
299 day prior to oral ASA desensitization in increasing both the threshold oral ASA dose and the
300 probability of silent ASA desensitization. There was a suggestion of reduced symptoms
301 however the relative severity of reactions and overall safety of the combined ketorolac vs
302 standard oral ASA desensitization will require further studies with larger sample sizes to arrive
303 at meaningful conclusions. This prospective, open label observational study demonstrates that
304 intranasal ketorolac challenge affords an improved method to both diagnose and facilitate ASA
305 treatment for patients with AERD.

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Table 1. Demographics and characteristics of subjects

							Journal Pre-proof		Regular Medications [°]					
Group	Age/ gender	AERD Diagnosis*	Asthma	Allergic Rhinitis	Nasal Polyposis	Anosmia	Number Sinus Operations	Tobacco Use	Montelukast	Omalizumab	ICS/ LABA	Daily Prednisone	SABA Use	Baseline FEV ₁ (liters)
I (Combined)														
1	51/F	5 years	yes	yes	yes	yes	0	none	yes	no	ICS/LABA	0	<2x/month	2.00
2	51/F	2 years	yes	yes	yes	yes	2	yes	yes	no	ICS/LABA	0	1x/year	2.85
3	44/M	11 years	yes	yes	yes	yes	2	yes	yes	no	ICS/LABA	0	2x/week	3.09
4	50/F	4 years	yes	no	yes	yes	3	none	yes	no	none	0	1-2x/month	2.70
5	51/F	6 years	yes	yes	yes	yes	5	yes	yes	no	none	0	1-2x/month	2.63
6	68/M	10 years	yes	no	yes	yes	0	Former Pipe	yes	no	none	0	1x/month	3.81
7	32/M	5 years	yes	yes	yes	yes	2	none	yes	no	ICS	10mg	1x/every 2 months	3.15
8	50/F	5 years	yes	yes	yes	yes	1	none	yes	no	ICS/LABA	0	none	2.23
9	56/F	29 years	yes	yes	yes	yes	1	none	yes	no	ICS/LABA	0	1-2x/week	1.89
10	46/M	5 years	yes	yes	yes	yes	1	none	yes	no	ICS	0	1x/month	3.25
11	53/F	5 years	yes	yes	yes	yes	2	none	yes	no	ICS/LABA	0	>2x/week	1.98
12	30/M	4 years	no	yes	yes	yes	1	none	yes	no	ICS	0	none	4.13
13	62/F	26 years	yes	no	yes	yes	3	yes	yes	no	ICS	0	2x/month	2.10
II (Washout)														
1	23/F	2 years	yes	yes	no	no	0	none	yes	no	ICS/LABA	0	1-2x/month	2.74
2	42/F	10 years	yes	yes	yes	yes	5	yes	yes	no	ICS/LABA	0	1-2x/week	2.37
3	19/M	2 years	yes	yes	yes	yes	Not Recorded	none	yes	no	ICS/LABA	0	2-3/month	4.39
4	34/F	6 years	yes	yes	yes	yes	2	none	yes	yes	ICS/LABA	40mg	multiple x/day	2.84
5	42/M	5 years	yes	yes	yes	yes	3	none	yes	no	ICS/LABA	10/5mg QOD**	<2x/month	4.81
6	54/M	11 years	yes	yes	yes	yes	2	yes	yes	no	ICS/LABA	5mg	none	2.35
7	52/F	3 years	yes	yes	yes	yes	2	none	yes	no	ICS/LABA	0	<2x/month	2.66

* Years since initial reaction to ASA/NSAID

** 10 mg/5 mg alternating doses every other day

° All subjects were using a topical nasal steroid

Table 2. Results of ketorolac and ASA challenges

Group	Ketorolac Challenge Threshold (mg)	ASA Challenge Threshold
I (Combined)		
1	12.48	650
2	8.32	162
3	2.08	325
4	24.96	650
5	12.48	650
6	12.48	650
7	8.32	81
8	2.08	40.5
9	4.16	40.5
10	24.96	650
11	8.32	650
12	4.16	650
13	8.32	650
II (Washout)		
1	12.48	81
2	4.16	40.5
3	8.32	40.5
4	8.32	81
5	4.16	81
6	4.16	81
7	12.48	81

Table 3. ASA challenge results

Parameter	Group 1 [°]	Group 2 [°]	p-value*
Baseline symptom score	0 (0, 1)	0 (0, 2)	0.78
Baseline FEV ₁ (ml)	276 (210, 315)	274 (252, 362)	0.54
ASA threshold dose (mg)	650 (162, 650)	81 (61, 81)	<0.01
Change in symptom score from baseline to threshold	0 (0, 4)	5 (3.5, 7)	<0.04
Change in symptom score from baseline to threshold (silent desensitization excluded)	7 (4, 7)	5 (3.5, 7)	0.81
Total symptom score	6 (2.00, 13.00)	15 (12, 19.5)	0.15
Treatment required	4 (1, 4)	4 (3, 4)	0.79
Time to symptom resolution (min)	35 (30, 80)	105 (52.5, 177.5)	0.11
% of baseline FEV ₁ of the lowest measured FEV ₁	91 (88, 97)	81 (73, 87)	<0.03
% of baseline FEV ₁ of the lowest measured FEV ₁ (silent desensitization excluded)	90 (86, 91)	81 (73, 87)	

[°] Median (interquartile range)

* All tests were analyzed by the Wilcoxon ranked sum test

Table 4. Ketorolac challenge results

Parameter	Group 1[°]	Group 2[°]	p-value*
Ketorolac threshold dose	8.32 (4.16, 12.48)	8.32 (4.16, 10.4)	0.74
Change in symptom score from baseline to threshold	4 (1, 5.65)	4 (2.75, 8.5)	0.31
Treatment required	1 (0.5, 1)	1 (0.5, 3)	0.79
Time to symptom resolution (min)	82.5 (51.25, 117.5)	95 (90, 150)	0.66
% of baseline FEV ₁ at lowest measured FEV ₁	93 (91, 97)	92 (87, 96)	0.89

[°] Median (interquartile range)

* All tests were analyzed by the Wilcoxon ranked sum test

FIGURE LEGEND

Figure 1. Threshold dose of ASA (dark grey) or ketorolac (light grey) in Group 1 versus Group 2. Box graph showing the median (heavy line), 25-75% interquartile range (shaded box), and maximum and minimum values (whiskers).

