





LETICIA DE LAS VECILLAS¹ , MARTA SANCHEZ-JAREÑO², MAGDALENA LLUCH-BERNAL¹ ,
SANTIAGO QUIRCE^{1,3} , JAVIER DOMÍNGUEZ-ORTEGA^{1,3} , VALENTÍN LÓPEZ-CARRASCO¹,
PILAR BARRANCO^{1,3}

Nasal challenge with ketorolac: utility and safety in clinical practice

¹Department of Allergy, La Paz University Hospital, IdiPAZ, Madrid, Spain

²Medical Affairs, MSD Spain, Madrid, Spain

³CIBER de Enfermedades Respiratorias (CIBERES), Madrid, Spain

KEY WORDS

Aspirin exacerbated respiratory disease; nasal ketorolac challenge; asthma; nasal polyps.

Corresponding author

Leticia de las Vecillas
Department of Allergy
La Paz University Hospital. IdiPAZ
P^o de la Castellana 261
28046 Madrid, Spain
ORCID: 0000-0003-4969-5678
E-mail: leticia.delasveci@gmail.com

Doi

10.23822/EurAnnACI.1764-1489.321

To the Editor,

aspirin and non-steroidal anti-inflammatory drugs (NSAIDs)-exacerbated respiratory disease (AERD-NERD) is characterized by an underlying Th2 airway disease exacerbated by the intake of this type of medication. The nasal challenge test with NSAIDs, specifically with lysine acetylsalicylic acid (NLC) or ketorolac (NKC), is indicated for its diagnosis as an alternative to oral/bronchial challenges when FEV₁ < 70% or with uncontrolled asthma (1-3). NKC is also used as a first step in aspirin desensitization protocols for AERD-NERD patients (4, 5).

NKC has lower sensitivity, specificity, positive predictive value, and negative predictive value compared to OAC (gold standard) (6). This makes it necessary to perform an OAC to confirm AERD-NERD diagnosis when NKC is negative (1-3). Although NKC is considered a safe technique, some authors have reported extra-nasal symptoms during its performance (6, 7).

To evaluate the diagnostic utility and safety outcomes, we analyzed 19 NKC (intranasal increasing doses of ketorolac every 30 minutes up to 16.38 mg) performed at our institution in AERD-NERD patients. Negative tests were followed by a 500mg OAC. This work was approved by the Ethics Committee of our institution (PI-2860) and all patients gave their written informed consent. Six NKC were negative (32%) (**table I**). Of the patients who reacted, 1 (7.7%) presented isolated bronchial symptoms (chest tightness and FEV₁ decrease ≥ 15%), 5 (38.5%) developed rhinitis (nasal discharge, nasal congestion, sneezing) and 4 (30.7%) presented bronchial symptoms and rhinitis (chest tightness, cough, nasal discharge, nasal congestion, sneezing). Furthermore, there were three patients (23.1%) who developed an anaphylactic reaction (generalized urticaria, palpebral angioedema, ear pruritus, chest tightness, cough, nasal discharge, nasal congestion, sneezing and conjunctivitis): two with a cumulative dose of 16.38 mg and one with 8.82 mg of ketorolac. No significant differences

Table I - Demographics, clinical characteristics and NKC outcomes.

n total = 19	Positive NKC (n = 13)	Negative NKC (n = 6)	P-value
Gender			0.630
Male	7	3	
Female	6	3	
Age (mean ± SD) (range)	45.62 ± 14.13 (25-64)	45.40 ± 17.85 (29-74)	0.979
Smoking habit (n,%)			0.837
Non-smoker	7 (54%)	3 (50%)	
Smoker	1 (8%)	1 (17%)	
Ex-smoker	5 (38%)	2 (33%)	
Baseline eosinophilia (median, IQR)	430 (230-830)	435 (110- 1130)	0.868
Total IgE (median, IQR)	204 (105- 1472)	508 (211-881)	0.374
Previous diagnosis (n,%)			
Rhinosinusitis	1 (8%)	1 (17%)	
Asthma and Rhinosinusitis	2 (15%)	0	
Asthma and polyps	1 (8%)	0	
Rhinosinusitis and polyps	9 (69%)	5 (83%)	
n sinus surgeries (mean ± SD)	1.67 ± 2.06 (non anaphylaxis) 3.43 ± 2 (anaphylaxis)	1.67 ± 2.25	
Actual treatment			0.689
None	0	1	
Corticosteroids + Montelukast	13	5	
Baseline PNIF (mean ± SD) (range) L/min	130 ± 40.4 (60-200)	108.33 ± 41.2 (90-200)	0.568
Baseline FEV ₁ (mean ± SD) (range) mL	3,259.23 ± 1,035.75 (1,870-5,270)	3,526.67 ± 1,022.89 (2,050-4,860)	0.606
NKC outcomes			
Asthma	1	-	
Rhinitis	5	-	
Asthma and Rhinitis	4	-	
Anaphylaxis	3	-	

NKT: Nasal ketorolaco challenge; FEV₁: forced expiratory volume in 1 second; PNIF: peak nasal inspiratory flow.

were found between the 3 patients who suffered an anaphylactic reaction compared to the other 10 patients with a positive NKC. The 6 patients with negative NKC underwent an OCA and two of them presented a positive challenge with bronchial symptoms and urticaria, respectively.

There were 15 patients in our cohort with a confirmed diagnosis of AERD-NERD: 13 with a positive NKC (86%) and 2 with a negative NKC followed by a positive OCA. Extranasal symptoms appeared in 61.5% of patients (38% asthma, 23% anaphylaxis).

To analyze possible associations SAS 9.3 software (SAS, Institute, Cary, NC, USA) was used.

The study by White *et al.* (6) found that 17% of patients with positive NKC had a decrease in FEV₁ > 15% and the study by Quiralte-Castillo *et al.* (7) 4/21 patients presented with asthma symptoms although just 1 showed a decrease in FEV₁ > 15%. When combined with OCA to desensitize AERD-NERD patients, NKC breakthrough reactions were associated with bronchospasm in 24% (5) to 39% (4) of cases and with extrapulmonary symptoms (ana-

phylaxis) in 7% (5) to 28% (4). If clinical signs appeared during the nasal or oral challenge, they were not specified.

Miller *et al.* (8) reported that 21/100 of positive NLC had bronchial and nasal symptoms but only 2 had decreased FEV1 > 15%. Seven patients also had urticaria. In positive NLC, Alonso-Llamazares *et al.* (9) and Casdevall *et al.* (10) reported exclusively nasal symptoms.

Inflammatory mediators migrate from the nasal mucosa to the lower airways after nasal challenge, causing bronchial inflammation (3). NKC has been proposed as a safer diagnosis challenge for patients contraindicated to bronchial or oral challenges. Despite not being statistically significant probably because of sample size, our findings suggest the technique may not be as safe in daily clinical practice as previously reported due to significant bronchial and systemic breakthrough reactions.

Differences in populations, drug-delivery techniques, and/or monitoring techniques may explain the disparity in results. A nasal nebulizer spray cannot provide us with information about where ketorolac tromethamine is being applied or how much can reach the lower airways (4). Contrary to this, administering L-ASA by means of a dosimeter allows accurate measurement of the dose and monitoring of the effective inspiratory volume at each step of the bronchial challenge (1). For all these reasons, we question the NKC indication in patients with FEV1 < 70% or with uncontrolled asthma.

In conclusion, in our cohort, NKC with 16.38 mg is a useful method for AERD-NERD diagnosis combined with an oral challenge. However, safety concerns have to be considered.

Fundings

None.

Contributions

All authors: conceptualization, data curation formal analysis, writing – original draft, writing – review & editing.

Conflict of interests

The authors declare that they have no conflict of interests.

References

- Izquierdo-Domínguez A, Bobolea I, Doña I, Campo P, Segura C, Ortega N, et al. Statement of the Spanish Society of Allergology and Clinical Immunology on Provocation Tests With Aspirin/Nonsteroidal Anti-inflammatory Drugs. *J Investig Allergol Clin Immunol.* 2020;30(1):1-13. doi: 10.18176/jiaci.0449.
- Kowalski ML, Asero R, Bavbek S, Blanca M, Blanca-Lopez N, Bochenek G, et al. Classification and practical approach to the diagnosis and management of hypersensitivity to nonsteroidal anti-inflammatory drugs. *Allergy.* 2013;68(10):1219-32. doi: 10.1111/all.12260.
- Bentabol-Ramos G, Saenz de Santa Maria-Garcia R, Vidal-Diaz M, Eguiluz-Gracia I, Testera-Montes A. The Utility of Nasal Challenges to Phenotype Asthma Patients. *Int J Mol Sci.* 2022;23(9):4838. doi: 10.3390/ijms23094838.
- Lee RU, White AA, Ding D, Dursun AB, Woessner KM, Simon RA, et al. Use of intranasal ketorolac and modified oral aspirin challenge for desensitization of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol.* 2010;105(2):130-5. doi: 10.1016/j.anai.2010.05.020.
- Cook KA, Modena BD, Wineinger NE, Woessner KM, Simon RA, White AA. Use of a composite symptom score during challenge in patients with suspected aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol.* 2017;118(5):597-602. doi: 10.1016/j.anai.2017.02.016.
- White A, Bigby T, Stevenson D. Intranasal ketorolac challenge for the diagnosis of aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol.* 2006;97(2):190-5. doi: 10.1016/S1081-1206(10)60012-9.
- Quiralte-Castillo J, Ávila-Castellano MR, Cimbollek S, Benaixa P, Leguisamo S, Baynova K, et al. Nasal Ketorolac Challenge Using Acoustic Rhinometry in Patients With Aspirin-Exacerbated Respiratory Disease. *J Investig Allergol Clin Immunol.* 2017;27(3):169-74. doi: 10.18176/jiaci.0118.
- Miller B, Mirakian R, Gane S, Larco J, Sannah AA, Darby Y, et al. Nasal lysine aspirin challenge in the diagnosis of aspirin - exacerbated respiratory disease: asthma and rhinitis. *Clin Exp Allergy.* 2013;43(8):874-80. doi: 10.1111/cea.12110.
- Alonso-Llamazares A, Martínez-Cóccera C, Domínguez-Ortega J, Robledo-Echarren T, Cimarra-Alvarez M, Mesa del Castillo M. Nasal provocation test (NPT) with aspirin: a sensitive and safe method to diagnose aspirin-induced asthma (AIA). *Allergy.* 2002;57(7):632-5. doi: 10.1034/j.1398-9995.2002.t01-1-13447.x.
- Casdevall J, Ventura PJ, Mullaol J, Picado C. Intranasal challenge with aspirin in the diagnosis of aspirin intolerant asthma: evaluation of nasal response by acoustic rhinometry. *Thorax.* 2000;55(11):921-4. doi: 10.1136/thorax.55.11.921.