Nasal challenge with ketorolac: utility and safety in clinical practice

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To de 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 extranasal 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.

Six NKC were negative (32%) (Table). Of the patients who reacted, 1 (7.7%) presented isolated bronchial symptoms (chest tightness and FEV_1 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 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).
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 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 (anaphylaxis) 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.

Contribution statement

All authors confirm contributions to the paper including study conception and design, data collection, analysis and interpretation of results, draft manuscript preparation and editing and revision. All authors reviewed the results and approved the final version of the manuscript.

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Conflicts of Interest

The authors declare that they have no conflicts of interest related to this work.

Ethics approval and consent to participate

This work was approved by the Ethics Committee of our institution (PI-2860) and all patients gave their written informed consent.

Statistical analysis

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

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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 & Rhinosinusitis	2 (15%)	0	
Asthma & polyps	1 (8%)	0	
Rhinosinusitis & polyps	9 (69%)	5 (83%)	
Nº 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) L	3259.23 ± 1035.75 (1870- 5270)	3526.67 ± 1022.89 (2050- 4860)	0.606
NKC outcomes			
Asthma	1	-	
Rhinitis	5	-	
Asthma & Rhinitis	4	-	
Anaphylaxis	3	-	

NKT: Nasal ketorolaco challenge; FEV_1: forced expiratory volume in 1 second; PNIF: peak nasal inspiratory flow