ORIGINAL ARTICLE

Nasal Ketorolac Challenge Using Acoustic Rhinometry in Patients With Aspirin-Exacerbated Respiratory Disease

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Abstract

Background: Safer and less time-consuming alternatives to single-blind placebo-controlled oral challenge (SBPCOC) have been sought for the diagnosis of aspirin-exacerbated respiratory disease (AERD). Nasal challenges with various nonsteroidal anti-inflammatory drugs and assessment methods have been developed.
Objective: Our objective was to evaluate the utility and safety of nasal ketorolac challenge (NKC) using acoustic rhinometry in patients with suspected AERD.
Methods: The study population comprised 36 patients with suspected AERD. NKC was performed with placebo (saline) and 13 mg of ketorolac sprayed as aerosol into both nostrils. A positive challenge result was defined as an increase of ≥30% in nasal symptoms (recorded using a visual analog scale) and a 30% drop in the sum of the volumes of both nasal cavities at 2-8 cm. Patients with a negative NKC result underwent SBPCOC with aspirin (cumulative dose of 750 mg).
Results: A naso-ocular reaction during NKC was detected in 21 patients. Four patients also developed mild asthma exacerbations (although only 1 experienced a decrease in FEV_1 >15%). No other significant adverse events occurred. The remaining 15 patients with a negative NKC result had a negative response during aspirin SBPCOC.
Conclusion: NKC assessed using acoustic rhinometry is a reliable method for the study of patients with AERD. We suggest that NKC assessed with acoustic rhinometry was useful and safe for selection of candidates for safe oral aspirin challenge.

Key words: Ketorolac. Nasal challenge. Aspirin-exacerbated respiratory disease.

Resumen

Introducción: El test de exposición simple ciego controlado con placebo (TEC) con aspirina es el patrón–oro para el diagnóstico de la enfermedad respiratoria exacerbada por aspirina (EREA), aunque presenta un riesgo elevado de reacciones durante su realización. Por este motivo, se han desarrollado diferentes procedimientos de provocación nasal con aspirina, lisina y ketorolaco.
Objetivo: Evaluar la utilidad y la seguridad del test inhalatorio nasal con ketorolaco (TNK) usando un rinómetro acústico en pacientes con sospecha de EREA.
Métodos: Se incluyeron 36 pacientes con sospecha de EREA. El TNK se realizó con placebo (solución salina) y 13 mg de ketorolaco instilado como aerosol en ambas fosas nasales. Un test de exposición positivo se definió como un aumento del 30% o más de los síntomas nasales registrados mediante una escala analógica visual y un descenso mayor del 30% en la suma de ambos volúmenes de las cavidades nasales entre 2 a 8 cm del vestíbulo nasal. Si el TNK era negativo, los pacientes se sometían a un TEC con 750 mg de aspirina (en dosis acumulativas).
Resultados: Veintiún pacientes presentaron una reacción nasoocular durante el TNK. Cuatro de ellos presentaron síntomas de asma bronquial (aunque solo uno mostró un descenso del FEV_1> 15%), pero no se produjeron otros acontecimientos adversos significativos. Los 15 pacientes restantes que tuvieron un TNK negativo, tuvieron una respuesta negativa durante el TEC con aspirina.
Conclusión: El TNK evaluado mediante rinómetro acústico es un método fiable para el estudio de pacientes con sospecha de EREA.

Palabras clave: Ketorolaco. Provocación nasal. Enfermedad respiratoria exacerbada por aspirina.

Introduction

A definitive diagnosis of aspirin-exacerbated respiratory disease (AERD) can only be made based on a single-blind placebo-controlled oral challenge (SBPCOC) with aspirin or another nonsteroidal anti-inflammatory drug (NSAID) carried out in patients with clinically suspected AERD [1-4]. However, SBPCOC is a time-consuming approach that can take at least 2 days to perform and result in severe reactions (mainly asthma exacerbations, laryngospasm, and even systemic symptoms in some cases). It may also require hospital admission, close monitoring, and emergency treatment to control respiratory and systemic reactions [5,6]. Thus, alternative methods have been developed to enhance safety and reduce the time needed for testing. Bronchial challenges [7] and nasal challenges [8-12] have been developed with various NSAIDs and assessment methods. Lee et al [8] recently presented a novel method using nasal ketorolac as the challenge drug and assessing the nasal response with a peak nasal inspiratory flow (PNIF) meter. Nasal challenge provided a rapid and safe means of confirming the diagnosis when it induced local reactions in the nasal airway of AERD patients and thus obviated the need for additional SBPCOC.

The aim of our study was to assess the diagnostic accuracy and safety of nasal ketorolac challenge (NKC) in patients with suspected AERD using acoustic rhinometry (acoR). A positive clinical response during NKC confirmed the diagnosis of AERD. A negative response, on the other hand, identified patients with suspected AERD who were candidates for increasing doses of oral aspirin until a cumulative dose of 750 mg was reached and thus established the true negative predictive value of this procedure.

Methods

Patients

The study population comprised 36 consecutive patients with AERD, moderate-to-severe asthma, and a past history of at least 1 episode of naso-ocular reaction, asthma exacerbation, or both after intake of NSAIDs [1,3]. The data collected were as follows: age, sex, type of NSAID-induced respiratory reaction, and the NSAID involved, as well as the presence of bronchial asthma and nasal polyps (Table 1). None of the patients had episodes of urticaria and/or angioedema before controlled challenge, and FEV_1 values were at least >70% predicted, with absolute values greater than 1.5 L. Patients with grade 3 or larger polyps were treated either medically with oral corticosteroids and fluticasone drops or surgically to reduce polyp size at least 30 days before NKC.

Drugs that could interfere with the results of NKC, such as H1 receptor antagonists and short-acting bronchodilator agents, were stopped 1 week and 6 hours before the procedure, respectively. However, all other asthma treatments (including montelukast, long-acting bronchodilator agents, and inhaled corticosteroids) were maintained.

Written informed consent was obtained from all patients, and the protocol was approved by the local ethics committee.

Table 1. Clinical Characteristics of AERD Patients

Case	Sex	Age	Nasal Polyps	Type of NSAID Reaction	NSAID Involved
1	M	48	Yes	BA	Ibu, Met
2	M	67	Yes	NOR + BA	Ket
3	F	65	No	NOR + BA	ASA, Met, D, Ket, Ibu
4	F	67	Yes	BA	ASA
5	M	70	Yes	NOR + BA	ASA
6	M	45	Yes	NOR	ASA
7	M	28	Yes	BA	ASA
8	F	54	Yes	NOR+ BA	ASA
9	F	52	Yes	BA	ASA, Ibu
10	M	56	Yes	NOR + BA	ASA, Met
11	F	41	Yes	NOR + BA	ASA, Ibu
12	F	68	Yes	BA	Ibu, Met
13	M	71	Yes	BA	Ibu
14	F	59	Yes	NOR + BA	ASA, Met, Ibu
15	M	51	Yes	NOR	ASA, Ibu
16	M	52	Yes	BA	ASA
17	M	53	Yes	NOR + BA	Ibu, Met
18	F	46	Yes	NOR + BA	ASA, Met
19	F	37	Yes	NOR + BA	ASA, Met
20	F	37	Yes	BA	ASA
21	M	51	Yes	NOR + BA	Ibu
22	F	55	Yes	NOR + BA	ASA, Met, Ibu, D
23	M	17	No	BA	Ibu, P
24	F	58	No	NOR + BA	Ibu
25	F	40	Yes	NOR + BA	ASA
26	F	37	No	NOR	D
27	F	31	No	BA	ASA, Ibu, P, Met
28	M	22	Yes	NOR+ BA	ASA, Ibu
29	M	54	No	BA	Ibu, K, D
30	M	36	Yes	NOR	Ibu
31	F	32	Yes	NOR + BA	Ket
32	F	43	No	NOR + BA	ASA, Ibu, Ket
33	F	39	No	BA	Ibu, Met
34	F	59	Yes	NOR	ASA, Met, Ibu
35	F	46	Yes	BA	Met
36	F	37	No	BA	ASA

Abbreviations: AERD, aspirin-exacerbated respiratory disease; ASA, aspirin; BA, bronchial asthma; D, diclofenac; Ibu, ibuprofen; Ket, ketoprofen; Met, metamizole; NOR, naso-ocular reaction; NSAID, nonsteroidal anti-inflammatory drugs; P, paracetamol.

Nasal Ketorolac Challenge

All patients were included in a previously established NKC whose diagnostic safety and accuracy were assessed using acoR (A1-Compact, Optomic) [8,13] at least 1 month after resolution of the NSAID-induced respiratory reaction. Each patient assessed nasal blockage, rhinorrhea, itching, and sneezing before and after nasal challenge using a 100-mm visual analog scale (VAS) with a total range of 0 to 400 mm. Lower respiratory function was also evaluated using a spirometer (Sibelmed). The prechallenge nasal symptoms according to the VAS are shown in Table 2.

An initial single-blind challenge with saline as placebo was performed to rule out nasal hyperreactivity. If the sum of the volumes of both nasal cavities 2-8 cm from the nostril (Vol_{2-8}) declined by <25% after administration of saline, the patient underwent nasal challenge up to a total dose of 13 mg of ketorolac (Laboratorios Vita), which was sprayed into both nostrils. The placebo was 0.9% fresh saline solution at room temperature. A solution of 10 mg/mL of ketorolac was prepared at the beginning of the procedure by dissolving the content of 1 ampoule (volume, 1 mL) of 30 mg of ketorolac in 2 mL saline. One spray nebulized approximately 0.1 mL, which is equivalent to 1 mg of ketorolac.

The single-blind challenge was started with saline solution by spraying 2 puffs into each nostril. A graduated challenge with ketorolac solution was then performed using an initial dose of 1 mg (1 puff). If no clinical response occurred and if Vol_{2-8} declined by <30%, incremental doses of ketorolac were administered every 30 minutes and monitored using acoR and spirometry before each dose, as follows: 2 mg (1 spray in each nostril), 4 mg (2 sprays in each nostril), and 6 mg (3 sprays in each nostril). Thus, the maximum cumulative dose in the NKC was 13 mg of ketorolac. If the patient showed any symptoms or signs during incremental exposure to ketorolac, the challenge was interrupted and the reaction treated.

A positive nasal challenge was defined as an increase of ≥30% in total nasal symptoms recorded by VAS and as a ≥30% decline in the nasal airway volume (Vol_{2-8}) compared with that obtained after instillation of saline solution. Lower airway signs and symptoms, such as asthma exacerbation or laryngospasm, were also recorded (if any). A 15% decline in baseline FEV_1 values during NKC was considered a positive asthmatic response. Laryngospasm was defined as crowing sounds over the trachea with an flattened inspiratory loop in the flow/volume curve.

The nasal challenge response was considered negative when no symptoms or a decrease of <30% in Vol_{2-8} was observed or when no change in nasal volume or an increase of <30% measured by VAS was recorded during the 3-hour period following instillation of the last dose of ketorolac.

Oral Aspirin Challenge

All patients with suspected AERD and a negative NKC result were included in a previously established 3-day single-blind placebo-controlled oral aspirin challenge [6]. Oral aspirin challenge was performed at least 1 week after a negative NKC result was obtained in a patient with suspected AERD and after withdrawal of montelukast at least 5 days before in order to avoid the possibility of silent desensitization [14]. On the first day of placebo challenge, airway stability was monitored based on lung function, which was measured after each observation period (variability in FEV_1 <10% from baseline). The first 2 aspirin doses (50 and

Table 2. Baseline Nasal Symptoms of Patients Recorded by Visual Analog Scale

Case	Nasal Blockage	Rhinorrhea	Itching	Sneezing	Total Nasal Score
1	81	35	12	41	229
2	65	52	11	27	155
3	63	66	53	68	250
4	21	54	21	61	157
5	66	48	18	52	184
6	32	71	0	41	144
7	54	39	22	66	181
8	59	57	10	42	168
9	47	52	18	18	135
10	83	70	0	31	184
11	77	51	22	56	206
12	56	40	31	25	152
13	58	45	41	50	194
14	80	0	20	0	100
15	70	75	0	0	145
16	49	22	0	25	96
17	72	76	0	78	226
18	68	68	12	40	188
19	75	56	21	32	184
20	79	54	31	76	240
21	69	67	40	40	216
22	88	75	61	62	286
23	55	52	61	48	216
24	50	50	38	36	174
25	72	67	0	21	160
26	49	51	0	38	138
27	61	60	12	22	155
28	85	70	67	80	302
29	44	31	28	20	123
30	85	36	0	36	157
31	81	67	21	44	213
32	69	56	10	21	156
33	56	39	0	31	126
34	65	58	0	33	156
35	51	60	0	12	123
36	21	30	0	0	51

100 mg) were administered on day 2, and the remaining doses (250 and 500 mg) were administered on day 3. Placebo and aspirin were administered in an opaque gelatin capsule at a 180-minute interval from each dose.

Table 3. Results of Nasal Ketorolac Challenge in Patients With Aspirin-Exacerbated Respiratory Disease

Case	Cumulative Provoking Dose, mg	Time Elapses, min	Decline in Vol_{2-8}, %[a]	Respiratory Symptoms	Result
1	13	45	34.6	NOR + BA	Positive
2	13	180	16		Negative
3	1	30	53.7	NOR	Positive
4	7	30	34	NOR	Positive
5	13	180	10.2		Negative
6	13	50	33.8	NOR	Positive
7	13	180	6.5		Negative
8	13	180	15.7		Negative
9	3	20	39	NOR	Positive
10	13	55	45	NOR	Positive
11	13	30	40.5	NOR	Positive
12	13	180	15.4		Negative
13	13	180	13.7		Negative
14	3	20	32.8	NOR + BA	Positive
15	13	120	49.7	NOR + BA	Positive
16	13	55	31.6	NOR	Positive
17	13	40	30.3	NOR	Positive
18	13	90	55.4	NOR + BA	Positive
19	13	50	30.9	NOR	Positive
20	1	30	36.6	NOR	Positive
21	7	20	30.4	NOR	Positive
22	13	60	49.9	NOR	Positive
23	13	180	18.9		Negative
24	13	180	12.3		Negative
25	13	180	7.4		Negative
26	13	180	13.4		Negative
27	13	90	33.5	NOR	Positive
28	3	30	30.3	NOR	Positive
29	13	180	6.8		Negative
30	13	180	15.6		Negative
31	3	30	53.5	NOR	Positive
32	1	30	45.4	NOR	Positive
33	13	180	19.2		Negative
34	13	120	30.8	NOR	Positive
35	13	180	12.1		Negative
36	13	180	1.9		Negative

Abbreviations: BA, bronchial asthma; NOR, naso-ocular reaction.
[a]Vol_{2-8}, the sum of the volumes of both nasal cavities 2-8 cm from the nostril.

The challenge was considered positive if it fulfilled at least 1 of the following criteria: pruritus and wheals; macular and/or papular areas at any location; edema of the skin and/or external mucosa and naso-ocular and/or lower airway signs and symptoms, including bronchospasm with a fall in FEV_1 >15%; or laryngospasm. The clinical characteristics of each SBPCOC (symptoms, dose, and time elapsed) were recorded. During the challenge procedure, patients were clinically monitored at 15 minutes, 30 minutes, and every hour after administering the NSAID or placebo, or at any time symptoms were reported by the patient.

Results

Nasal Ketorolac Challenge

NKCs were carried out in 36 consecutive patients with suspected AERD. The result was positive in 21, with isolated nasal and ocular symptoms (Table 3). Four patients also developed lower respiratory tract symptoms, including mild bronchospasm and/or chest tightening, which were treated with short-acting ß-agonists and oral corticosteroids. The fall in FEV_1 values during NKC in patients with asthma symptoms was 17.83%, 8.96%, 5.46%, and 12.26% in patients 1, 14, 15, and 18, respectively. No significant changes in FEV_1 values were observed in patients who experienced a naso-ocular reaction alone. Twelve patients reacted after exposure to 13 mg of ketorolac (57% of cases), 3 patients reacted at 1 mg, 4 at 3 mg, and 2 at 7 mg.

A post hoc analysis was performed to compare the differences in clinical reaction in relation to the dose of ketorolac in 4 patients (9, 10, 11, and 22), who were successfully desensitized with aspirin owing to suboptimal control of nasal and sinus symptoms and anosmia and were twice challenged with nasal ketorolac during the process (Table 4). The Vol_{2-8} values obtained during the first clinical reaction and the challenge dose of ketorolac did not differ significantly from those observed in a subsequent challenge.

Table 4. Reproducibility of Response to Nasal Ketorolac Challenge in 4 Patients With Aspirin-Exacerbated Respiratory Disease

Case	Ketorolac Provoking Dose, mg	Vol_{2-8} Decrease After Clinical Reaction[a,b] First NKC	Second NKC[c]
9	3	39.0	31.8
10	13	45.0	48.4
11	13	40.5	31.6
22	13	49.9	41.3

Abbreviation: NKC, nasal ketorolac challenge.
[a]Vol_{2-8}, the sum of the volumes of both nasal cavities 2-8 cm from the nostril.
[b]Maximum decline in the nasal airway measured as Vol2-8 compared with that obtained after instillation of saline solution (%).
[c]The time elapsed between the first and second nasal ketorolac challenge was at least 6 months for each patient.

The remaining 15 patients experienced no clinical reactions during NKC and underwent an additional controlled oral challenge in order to confirm or rule out AERD.

Oral Aspirin Challenge

Fifteen patients with a convincing history of AERD and negative NKC results underwent SBPCOC with aspirin and tolerated a cumulative dose of 750 mg (Table 3).

Discussion

Moderate-to-severe, unstable, and poorly controlled asthma is common in AERD patients and induces many clinicians to bypass oral challenge with NSAIDs owing to the increased risk of adverse reactions and to the fact that it is time-consuming. Therefore, challenges with NSAID are rarely performed for diagnostic purposes outside research units [2-4,6].

We demonstrated that using NKC assessed with acoR was a safe, effective, and reproducible method for diagnosis of AERD. Unlike oral challenges, NKC caused fewer adverse extrapulmonary effects or bronchospasms and induced mainly isolated naso-ocular reactions. With the exception of 1 patient who developed asthma symptoms with a >15% drop in FEV_1, no other severe adverse events occurred. In addition, all of the study patients continued with their asthma treatment (including montelukast, a leukotriene modifier) during the NKC, thus decreasing the likelihood of severe lower respiratory reactions without significantly masking naso-ocular symptoms [15]. The patients experienced the symptoms after a mean of 49 minutes, ie, between the 2-fold and 4-fold doses of ketorolac in 85% of cases.

We also explored the ability of NKC assessed by acoR to predict responses to the oral aspirin challenge. In the present study, we showed that a negative nasal response to 13 mg of ketorolac (cumulative dose) is always followed by a negative response to aspirin oral challenge. This finding would allow the clinician to perform an SBPCOC with aspirin with the certainty of a safe outcome and—possibly—shorter protocols. However, in a recent study, up to 10% of patients with a negative NKC result experienced respiratory reactions during a subsequent oral aspirin challenge. The authors evaluated 100 patients with AERD (by clinical history and positive oral aspirin challenge) who were rechallenged with intranasal ketorolac [8]. A positive reaction (defined as rhinitis, conjunctivitis, and/or bronchospasm with a significant decrease in the PNIF rate and/or FEV_1 values) was observed in 90%. These observations were confirmed in a recent study on the feasibility of PNIF as an objective measurement in the assessment of a reaction to nasal ketorolac [9]. The fact that all of the patients in the present study tolerated aspirin challenge after a negative NKC result could be because of the use of acoR instead of a PNIF. Recently, Miller at al [10] also reported a high percentage of positive challenge results (45%) with 325 mg of aspirin in patients who had previously experienced a negative acoR-monitored nasal challenge with aspirin-lysine [10]. Anterior active rhinomanometry used as an objective assessment method revealed that only 16 of 20 patients with oral challenge–proven AERD (80%) had a positive nasal response to the nasal challenge with aspirin-lysine [11]. These different clinical outcomes suggest that the NSAID, the objective method used to measure the changes in nasal airways, or both might have a relevant effect on the results of nasal NSAID challenges.

In conclusion, NKC assessed by acoR was characterized by a lower incidence of adverse effects during the procedure, and, although the present sample was not large enough to fully determine the negative predictive value of acoustic rhinometry, our data seem to suggest that the combination of NKC assessed with acoR was a safe and useful procedure for selection of candidates to undergo safe oral aspirin challenge.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

Previous Presentation

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