

In summary, a population of patients exists (12.21% in our series) that evidence positive skin tests (intradermal tests in all our cases) or positive controlled challenge tests when these studies are repeated two or three weeks after the initial negative study. No statistically significant differences have been detected between these patients and the initially positive ones as regards age, gender, atopy, drug involved, day of therapy in which the reaction occurred, latency period, type of reaction, duration of the reaction or total or specific IgE levels. The only difference was a greater percentage of anaphylaxis cases among the patients diagnosed during the first phase of the study. As regards the time elapsed between the index reaction and the allergy study, and though there were no statistically significant differences in the overall sample, significant differences do exist in the case of the patients sensitised to aminopenicillins. The results reported stress the convenience of repeating the β -lactam antibiotic allergy studies after three weeks, particularly in the case of patients supposedly sensitised to aminopenicillins.

References

1. Patriarca G, Schivino D, Nucera E, Milani A. Positive allergological tests may turn negative with no further exposure to the specific allergen: a long-term, prospective, follow-up study in patients allergic to penicillin. *J Investing Allergol Clin Immunol* 1996; 6: 162-165.
2. Fernández Rodríguez C, Fiandor A. Seguimiento de pruebas cutáneas en pacientes con alergia a beta-lactámicos. *Rev Esp Alergol Inmunol Clin* 1997; 12: 5-6.
3. López L, Mateo B, Beristain A, Armisen M, Perelló, S, Álvarez-Cuesta E. Importance of reprovocation in penicillin allergy study. *Allergy* 1993; 48: 147.
4. Díaz Donado C, Armisen M, Quirce S, López L, Sánchez Cano M, Losada E. Importancia de la reevaluación diagnóstica en el estudio de la hipersensibilidad a betalactámicos. *Rev Esp Alergol Inmunol Clin* 1995; 10: 317-324.
5. López-Serrano MC, Caballero MT, Barranco P, Martínez-Alzamora F. Booster responses in the study of allergic reactions to beta-lactam antibiotics. *J Investig Allergol Clin Immunol* 1996; 6: 30-35.
6. Pamies R, Blanca M, García JJ, Torres MJ, Fernández J, Miranda A, et al. Evaluación seriada de las pruebas alérgicas en sujetos alérgicos a penicilinas. *Rev Esp Alergol Inmunol clin* 1997; 12:6.
7. Posadas S, Juárez C, Torres MJ, de la Fuente J, García JJ, Blanca M. Seguimiento de los valores del RAST en sujetos con anticuerpos IgE específicos a betalactámicos. *Rev Esp Alergol Inmunol Clin* 1997; 12: 7-8.
8. Blanca M, Torres MJ, García JJG, Romano A, Mayorga C, de Ramon E, et al. Natural evolution of skin test sensitivity in patient allergic to betalactams. *J Allergy Clin Immunol* 1999; 103: 918-924.

CYCLO-OXYGENASE 2 (COX-2) INHIBITORS AS ALTERNATIVE DRUGS IN NON-STEROIDAL ANTIINFLAMMATORY DRUG INTOLERANCE

A. L. Valero Santiago

Al·largo Centre. Barcelona, Spain

Non-steroidal antiinflammatory drugs (NSAIDs) are counted among the therapeutic groups with highest consumption. According to the National Health Service data, these agents occupied in 1997 the 7th place, with over 27 million packages sold. They are also the drugs that, in absolute terms, induce the greatest number of adverse events. Among the notifications received by the Catalan Institute of Pharmacology between 1983 and 1997, NSAIDs are the causative drugs in 19%. In one epidemiological study carried out in Spain, 24% of all consultations to Allergologists because of adverse drug reactions correspond to NSAIDs. From the point of view of the Allergologist, the most salient reactions are the respiratory (asthma rhinitis) and the cutaneous (urticaria, angioedema) ones. The pathophysiological mechanisms of these reactions may be specific, or IgE-mediated, or intolerance phenomena with an as yet obscure mechanism. With the discovery of the mechanism of action of acetylsalicylic acid and other NSAIDs through inhibition of the enzyme cyclo-oxygenase (COX) and the demonstration of a correlation between the severity of the reactions and the COX-inhibiting potency of the involved NSAID, the "pathophysiologic cyclo-oxygenase theory" was developed as an explanation for the intolerance reactions to NSAIDs belonging to different chemical structure groups. This theory achieved further support from the description of two COX isoforms (COX-1 and COX-2) and from the clinical confirmation that these patients tolerate better those NSAIDs with greater inhibition potency for COX-2. These facts have led to COX-1 inhibition being considered a primordial factor in the induction of such reactions. Studies with the new NSAIDs that are specific COX-2 inhibitors will further establish the possibilities of managing or avoiding NSAID-intolerance problems.

Key words: NSAIDs. Intolerance. Cyclo-oxygenase. Isoforms. COX-2. COX-2 inhibitors.

INHIBIDORES DE LA CICLO-OXIGENASA 2 (COX-2) COMO FÁRMACOS ALTERNATIVOS EN LA INTOLERANCIA A ANTIINFLAMATORIOS NO ESTEROIDEOS

Los antiinflamatorios no esteroideos (AINEs) son uno de los grupos terapéuticos de mayor consumo. Durante el año 1997, según los datos del Sistema Nacional de Salud, ocuparon el séptimo puesto con más de 27 millones de envases vendidos. Son también los que, en valores absolutos, producen mayor número de efectos adversos. De las notificaciones recibidas por el Institut Català de Farmacologia durante el período 1983-1997, el 19% se refieren a AINEs. En un estudio epidemiológico en España, el 24% de las consultas realizadas a alergólogos por reacciones adversas a fármacos son por AINEs. Desde el punto de vista alergológico, las reacciones que más nos interesan son las respiratorias (asma y rinitis) y las cutáneas (urticaria y angioedema). Los mecanismos fisiopatológicos de estas reacciones pueden ser específicos, o mediados por IgE, y de intolerancia, cuyo mecanismo no se conoce con exactitud. Con el descubrimiento del mecanismo de acción del ácido acetilsalicílico y de los AINEs a través de la inhibición de la ciclo-oxigenasa (COX), y a raíz de la observación de la relación entre la gravedad de las reacciones y la potencia de los AINEs en la inhibición de la COX, se formuló la "teoría fisiopatológica de la ciclo-oxigenasa" para explicar las reacciones de intolerancia a distintos grupos químicos de AINEs. Esta teoría se vio refrendada por la descripción de dos isoformas de la COX (COX-1 y COX-2) y por la verificación clínica de una mayor tolerancia en estos pacientes a los AINEs con mayor potencia de inhibición sobre la COX-2, hechos que hacen considerar la inhibición de la COX-1 como un factor primordial en el mecanismo desencadenante de estas reacciones. Estudios con los nuevos AINEs inhibidores específicos de la COX-2 delimitarán las posibilidades de tratar o evitar los problemas de intolerancia a los AINEs.

Palabras clave: AINEs. Intolerancia. Ciclo-oxigenasa. Isoformas. COX-2. Inhibidores de la COX-2.

In the classification of the most-consumed therapeutic groups and active molecules in the Spanish National

Health System for the year 1997, the non-steroidal antiinflammatory drugs (NSAIDs) take the seventh place with over 27 million packages sold.

The most frequent NSAID-associated adverse reactions are gastrointestinal complaints, blood dyscrasias, episodic asthma, urticaria and angioedema, and nephrotoxic and hepatotoxic phenomena. From the standpoint of the Allergologist, the most salient ones are the respiratory (asthma and rhinitis) and skin reactions (urticaria and angioedema, morbilliform rash, fixed pigmented erythema, vasculitis and toxic epidermal necrolysis).

NSAIDs are the therapeutic drug that, in absolute terms, causes the greatest number of adverse events. They are involved in 25% of the adverse drug reactions reported to the Drug Safety Committee of the United Kingdom and, among the notifications received by the Catalan Institute of Pharmacology over the period from 1983 to 1997, 19% were related to NSAIDs and analgesics.

In the epidemiologic study on allergic conditions (Alergológica 95) carried out in Spain, with 4,000 patients surveyed, 12.6% of the patients reported adverse drug reactions of some type, and 24% of them had been caused by NSAIDs.

The NSAID-induced adverse drug reactions that demand the Allergologist's attention may be classified into two groups: IgE-dependent reactions, which are selective reactions to a single (structural) group of drugs, and intolerance-idiosyncrasy reactions, which involve all the different groups of NSAIDs. The mechanism whereby NSAIDs induce intolerance reactions in some individuals starting at a given moment in their lives is at present not precisely known.

Based on the discovery by Vane¹ that acetylsalicylic acid (ASA) exerts its antiinflammatory effects through the inhibition of the enzyme cyclo-oxygenase (COX), and that the remainder of the NSAIDs induce their effects through the same mechanism, the idea arose that COX inhibition might be an important phenomenon in the explanation of the NSAID-intolerance syndrome. Szczeklik² observed that a correlation existed between the in vitro COX-inhibiting potency of certain NSAIDs and the severity of the intolerance reactions they induced. On the basis of these observations, he formulated the "pathophysiologic cyclo-oxygenase theory" as the fundamental mechanism underlying these adverse reactions.

Over the last decade, a number of investigators have provided further experimental evidence. Increased generation of cysteinyl-leukotrienes through a derangement in

prostaglandin E₂ (PGE₂) modulation has been proposed, and the bronchodilator and bronchospasm-preventing effect of PGE₂ in ASA-intolerant asthmatics after an ASA challenge has been reported and documented^{3,4}. This suggests the possibility that the mechanism involved might not be a deflection of the arachidonic acid metabolism from the cyclo-oxygenase pathway to the lipo-oxygenase one, but the loss of the inhibitory mechanism of PGE₂.

Some authors⁵⁻⁷ have implicated the mast cells, the eosinophils and the platelets as the cellular elements involved in these abnormal responses and as the sources of leukotrienes in these adverse reactions.

Other pathophysiologic theories for NSAID intolerance have been put forward, such as a greater prevalence of a number of histocompatibility antigens in these patients⁸, persistent viral infection as an inductor of cytotoxic lymphocytes specific against the infected cells with ensuing release of inflammatory mediators, or complement activation and mediator release by specific basophil and mast cell populations.

The discovery of two distinct cyclo-oxygenase isoforms (COX-1 and COX-2) acting on arachidonic acid and generating prostaglandins, prostacyclins and thromboxanes has significant implications on the use of selectively COX-2 inhibiting NSAIDs in patients who are NSAID-intolerant with respiratory and cutaneous symptoms. The COX-1 isoform would appear to be the physiological or constitutive one and the one responsible for prostaglandin synthesis in the stomach, the kidney and the blood vessels, and thus the one responsible for maintaining normal function of these organs. Its inhibition would thus be related to the adverse effects of this drug family. Conversely, the COX-2 isoform would be the inducible one expressed in the course of an inflammatory process, so that its inhibition would correlate with the antiinflammatory activity of these drugs. From a clinical standpoint, these observations and findings have been corroborated by the observation that those NSAIDs with greater COX-2-inhibiting activity *in vitro* have the lesser ulcerogenic power.

There are at present three COX-2-selective NSAIDs in the Spanish pharmaceutical market: meloxicam, nabumetone and nimesulide. The latter one is the one most studied as regards tolerance in NSAID-intolerant patients, and the tolerance level observed in a number of studies ranges between 71 and 100%^{9,10}. There are two reported studies with meloxicam, showing tolerance in 80% and in 99% of the cases, respectively^{11,12}.

Even though COX-1 inhibition has been considered

to represent a prime factor in the triggering mechanism of NSAID intolerance, other mechanisms of action of these new COX-2 inhibitors might conceivably play a relevant role. An example might be the various mechanisms of action described for nimesulide, such as its antioxidant action through superoxide anion synthesis inhibition and free oxygen radical scavenging or its actions as an histamine release inhibitor and histamine antagonist, as an adhesion molecule inactivator, tumour necrosis factor inhibitor and as an inhibitor of leukotriene and platelet aggregation factor synthesis.

A number of COX-2-inhibiting NSAIDs are presently under study, and they can be subdivided into selective and specific inhibitors. Selective ones would be those that inhibit COX-2 to a greater extent than COX-1, while specific COX-2 inhibitors would inhibit COX-2 exclusively. Two specifically COX-2-inhibiting NSAIDs, rofecoxib and celecoxib, are currently in the market in the USA; greater or total tolerance to these drugs might be expected in patients who are intolerant to (classical) NSAIDs.

Future research on the last aspect discussed, as well as on the value of leukotriene antagonists or on the use of the synthetic PGE₁ antagonist misoprostol may perhaps draw clearer perspectives regarding the possibility to treat or avoid the currently-occurring problems of NSAID intolerance.

References

1. Vane JR. The mode of action of aspirin and similar compounds. *J Allergy Clin Immunol* 1976; 58: 691-712.
2. Szczeklik A. Relationship of inhibition of prostaglandin biosynthesis by analgesics to asthma attacks in aspirin-sensitive patients. *Br Med J* 1975; 1: 67-69.
3. Sestini P, Armenti L, Gambaro G, Pieroni MG, Refini RM, Sala A, et al. Inhaled PGE₂ prevents aspirin-induced bronchoconstriction and urinary LTE₄ excretion in aspirin-sensitive asthma. *Am Respir Crit Care Med* 1996; 153: 572-575.
4. Szczeklik A, Mastalers L, Nizakowska E, Cmiel A. Protective and bronchodilator effects of prostaglandin E and salbutamol in aspirin-induced asthma. *Respir Crit Care Med* 1996; 153: 567-571.
5. Fisher AR, Rosenberg MA, Lilly CM, Callery JC, Rubin P, Cohn J, et al. Direct evidence for a role of the mast cell in the nasal response to aspirin in aspirin-sensitive asthma. *J Allergy Clin Immunol* 1994; 94: 1046-1056.
6. Nasser SM, Pfister R, Christie PE, Sousa AR, Barker J, Schmitz-Schumann M, et al. Inflammatory cell populations in bronchial biopsies from aspirin-sensitive asthmatic subjects. *Respir Crit Care Med* 1996; 153: 90-96.
7. Plaza V, Prat J, Rosello J, Ballester E, Ramis I, Mullol J, et al. *In vitro* release of arachidonic acid metabolites, glutathione peroxidase,

and oxygen-free radicals from platelets of asthmatic patients with the and without aspirin intolerance. *Thorax* 1995; 50: 490-496.

8. Quirarte J, Sanchez-García F, Torres MJ, Blanco C, Castillo R, Ortega N, et al. Association of HLA-DR11 with the anaphylactoid reaction caused by nonsteroidal anti-inflammatory drugs. *J Allergy Clin Immunol* 1999; 103: 685-689.

9. Morais M, Gaspar A, Carvalho F, Abreu J, Rosado J. Hipersensibilidades aos anti-inflamatórios não esteroides: Novas e velhas estratégias. *Rev Port Imunoalergol* 1998; 5: 335-343.

10. Valero AL, González Morales MA, Montoro J, Malet A. Nimesulina como tratamiento alternativo en pacientes con intolerancia a antiinflamatorios no esteroideos. *Rev Esp Alergol Inmunol Clin* 1998; 13: 336-338.

11. Kosnik M, Music E, Matjaz F, Suskovic S. Relative safety of meloxicam in NSAID-intolerant patients. *Allergy* 1998; 53: 1231-1233.

12. Di Fonso M, Romano A, Quarantino D, Papa G, Venuti A. Meloxicam as an alternative drug in patients reporting adverse reactions to non-steroidal antiinflammatory drugs (NSAIDs) (Abstracts). *J Allergy Clin Immunol* 1999; 103: 38.

BRONCHIAL INHALATION CHALLENGE WITH LYSINE ACETYLSALICYLATE IN PATIENTS WITH THE "ASA TRIAD". ASA DESENSITISATION PROTOCOL

J. Fraj Lázaro

Allergology Service
"Lozano Blesa" University Hospital
Saragossa, Spain

Our aim was to validate the specific inhalational bronchial challenge test with lysine acetylsalicylate (lysine-AS) in the diagnosis of ASA-induced asthma or of the ASA Triad. To that purpose, 45 asthmatic patients with a FEV1 ≥ 1500 ml and $\geq 60\%$ of the predicted value were studied. Three of these patients had required hospital admission after the administration of non-steroidal antiinflammatory drugs (NSAIDs). Six patients had tolerated some NSAID within the previous month and were therefore considered to be tolerant. A single-blind simple oral challenge test with ASA was performed on the remaining 36 patients with increasing ASA doses (30, 60 and 125 mg on the first day and, if no response was elicited, 250 and 500 mg on the second day). Patients with a positive response to the oral challenge underwent bronchial challenge testing with lysine-AS at increasing concentrations (11.25, 22.5, 45, 90, 180 and 360 mg/ml lysine-AS) using a Hudson 1720 nebuliser with the patients breathing at tidal vo-

lume. Patients who were tolerant underwent inhalational challenge with lysine-AS at the maximum test concentration. Sixteen patients evidenced a positive response to oral ASA, with a FEV1 fall $\geq 20\%$. Added to the three patients who had required admission, this represents 19 patients with a diagnosis of ASA-induced asthma. Out of these 19 asthmatics, 11 had a bronchospastic reaction upon bronchial challenge with lysine-AS. None of the 26 ASA-tolerant asthmatics evidenced a positive response in the inhalational challenge test. The diagnostic indices were: sensitivity 42%, specificity 100%, positive predictive value 100%, and negative predictive value 70%. Despite its low sensitivity, we consider the bronchial challenge test with lysine-AS to be indicated in patients with suspected ASA-triad. However, a negative test does not rule out the existence of ASA-induced asthma, and in those cases an oral challenge test should be performed. Our clinical experience in ASA desensitisation or ASA tolerance induction is restricted to two female patients with rheumatoid arthritis and ASA triad syndrome. In these two patients, the refractory period occurring in all these asthmatics after a bronchospastic response to ASA was taken advantage of; from that moment onwards, it is fundamental that the patients be treated with the corresponding NSAID on a daily basis, as desensitisation shows cross-activity for all NSAIDs. If this is not done, after the refractory period has elapsed (ca. 2-5 days) the patient might develop severe bronchospasm.

Key words: Acetylsalicylic acid (ASA). ASA-induced asthma. Oral ASA exposure. Bronchial lysine acetylsalicylate challenge. ASA desensitisation. Refractory period.

EXPOSICIÓN INHALATIVA BRONQUIAL CON ACETILSALICILATO DE LISINA EN PACIENTES CON ASA-TRÍADA. PROTOCOLO DE DESENSIBILIZACIÓN A LA ASPIRINA

En el presente trabajo nos planteamos como objetivo validar la prueba de exposición inhalativa bronquial específica con acetilsalicilato de lisina (ASA-lisina) en el diagnóstico del asma inducida por aspirina, o "ASA-tríada". Para ello, incluimos 45 pacientes asmáticos con un volumen espiratorio forzado en el primer segundo (FEV1) ≥ 1.500 ml e $\geq 60\%$ de su valor teórico. Tres de estos pa-