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

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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-

cientes habían precisado ingreso hospitalario tras la administración de antiinflamatorios no esteroideos (AINEs). Seis habían tolerado algún AINE en el mes previo, por lo que se les consideró tolerantes. A los 36 restantes se les practicó una prueba de exposición oral simple ciego con AAS a dosis crecientes de 30, 60 y 125 mg en el primer día y, en caso de no haber respuesta, 250 y 500 mg el segundo día. A aquellos pacientes con respuesta positiva en la prueba oral se les realizó prueba de exposición bronquial con ASA-lisina a concentraciones crecientes de 11,25, 22,5, 45, 90, 180 y 360 mg/ml mediante un nebulizador Hudson 1720, respirando a volumen corriente. A los tolerantes al AAS se les hizo inhalar ASA-lisina a la máxima concentración. Dieciséis pacientes presentaron respuesta positiva, con caída del FEV₁ $\geq 20\%$ tras la exposición oral al AAS, lo cual, sumando los tres pacientes ingresados, supone 19 pacientes con el diagnóstico de asma inducido por AAS. De estos 19 asmáticos, 11 reaccionaron con broncoespasmo tras la provocación bronquial con ASA-lisina. Ninguno de los 26 asmáticos tolerantes al AAS respondieron a la prueba inhalativa. Los índices diagnósticos fueron: Sensibilidad 42%, especificidad 100%, VPP 100% y VPN 70%. Pese a su baja sensibilidad, creemos indicada la prueba de exposición bronquial con ASA-lisina en pacientes con sospecha de ASA-tríada. Sin embargo, una prueba negativa no descarta la existencia de asma inducida por AAS, siendo necesario recurrir, en tales casos, a la prueba de exposición oral. Nuestra experiencia clínica en desensibilización o inducción de tolerancia al AAS se limita a dos mujeres con artritis reumatoide y síndrome de ASA-tríada. En ellas se aprovechó el periodo refractario que aparece en todos estos asmáticos tras una respuesta broncoespástica al AAS. A partir de ahí es fundamental que los pacientes se traten a diario con el AINE correspondiente, al ser la desensibilización cruzada para todos los AINEs. De lo contrario, una vez cesado este periodo refractario (2-5 días), el paciente podría sufrir un broncoespasmo grave.

Palabras clave: Ácido acetilsalicílico (AAS). Asma inducido por AAS. Exposición oral a AAS. Exposición bronquial a acetilsalicilato de lisina. Desensibilización al AAS. Periodo refractario.

Using the oral challenge test with acetylsalicylic acid, some 10% of the overall asthma patient population have been estimated to have an associated respiratory pseudo-allergy to non-steroidal antiinflammatory drugs (NSAIDs). This proportion increases to 35-45% in asthmatics eviden-

cing a highly characteristic clinical profile defined by intense symptoms of rhinosinusitis, nasal polyposis and (a symptom considered to be a herald one) hyposmia-anosmia, even among those without any past history of adverse respiratory reactions to NSAIDs. In the presence of this particular feature in the patients' clinical history, the prevalence of respiratory NSAID pseudo-allergy can exceed 90%. This clinical entity, which has recently been renamed "NSAID pseudo-allergy-associated airway disease", may achieve a considerable clinical transcendence, as there are a number of reports of fatal or near-fatal cases of respiratory failure secondary to severe exacerbation of asthma induced by the administration of a NSAID. This stresses the paramount importance of detecting this particular form of NSAID hypersensitivity at an early stage and turns the Allergologist into the adequate specialist for performing a truly preventive function.

There is at present no diagnostic procedure, either in vitro or in vivo, that is at the same time effective and innocuous for the patient. Thus, the only test that has been shown to be fully effective in the diagnosis of this particular condition is the oral challenge with acetylsalicylic acid (ASA) or with some other NSAID, with all the risk this entails for the patient. The oral challenge test with ASA is thus considered to represent the gold standard in the diagnosis of this disease. Any other in vitro or in vivo test that might be devised in the future will necessarily have to be validated against the oral ASA challenge one.

The only presently available test with the potential capability to constitute an alternative in the diagnosis of asthma with associated NSAID pseudo-allergy is the inhalational bronchial challenge with lysine acetylsalicylate (lysine-AS). In previous studies performed over the last ten years on asthmatic patients undergoing bronchial challenge with lysine-AS, this test has been shown to be safer and quicker than the oral ASA challenge. However, there are still no convincing data regarding its diagnostic indices. With the fundamental aim of ascertaining these diagnostic indices we have recruited, over a period of 2 1/2 years, 45 asthmatic patients with a characteristic clinical profile of chronic asthma, rhinosinusitis, nasal polyposis and hyposmia/anosmia, with the further required feature of having a FEV₁ level $\geq 60\%$ of their predicted value and ≥ 1500 ml. Among these 45 asthmatic patients, six had tolerated one or more NSAIDs in the month preceding consultation, and were therefore automatically included in the "ASA-tolerant" group. Two patients had required admission into an Intensive Care Unit (ICU) because of severe asthmatic cri-

ses secondary to the ingestion of a NSAID (ASA and metamizole, respectively), and a further one had required hospital admission (but not into the ICU) for the same reason. These three patients were thus included into the "ASA-intolerant" group. There were a further nine patients with a past history of emergency ward care because of bronchospastic crises in relation to the ingestion of some NSAID, but it was deemed convenient to have them undergo an oral ASA challenge test. Thus, there were 36 patients out of the total population of 45 in whom ASA intolerance had to be ruled out or confirmed.

After securing their informed consent in writing, these 36 patients were first studied with a controlled progressive single blind oral challenge with ASA or placebo, with clinical and spirometric controls at hourly intervals. Twenty of them tolerated the maximal test dose (500 mg ASA) and were included into the "ASA-tolerant" group; the other 16 evidenced the classical positive response of bronchospasm with a FEV₁ drop $\geq 20\%$ and typical oculonasal symptoms. The mean ASA challenge dose inducing a 20% fall in the FEV₁ (PD₂₀-ASA) was 81.5 mg.

Thus, 19 asthmatic patients (42%) were also shown to be ASA-intolerant, while the remaining 26 (58%) tolerated this NSAID.

In a second phase of the study, and always while the patients were clinically and functionally stable, the specific inhalational bronchial challenge tests with lysine-AS were carried out, beginning with the 19 ASA-intolerant patients and following a pre-established protocol. When the test induced a positive response, the patient was re-scheduled for consultation one to two weeks later in order to assess the repeatability/reproducibility of the test.

The bronchial challenge test was initially negative in 11 ASA-intolerant patients, while the remaining eight had a positive response with a PC₂₀-lysine-AS level ranging from 30 to 283.4 mg/ml. The test was shown to be highly repeatable/reproducible, as in the second bronchial challenge positive results were observed in all cases and always with a PC₂₀-lysine-AS level lower than ± 2 concentration levels below the one having induced a positive response in the first challenge test. The bronchial challenge test with the maximal lysine-AS concentration (360 mg/ml) was negative in all cases in the 26 ASA-tolerant asthmatic patients.

The analysis of these data shows that the diagnostic indices for the bronchial challenge test with lysine acetylsalicylate in our series were as follows: (a) sensitivity 42%; (b) negative predictive value 70%; (c) specificity 100%;

(d) positive predictive value 100%, and (e) efficacy 75%. This means that, in clinical practice, any asthmatic patient in whom an associated NSAID pseudo-allergy is suspected might undergo a bronchial lysine-AS challenge study with an abbreviated protocol. If the results are positive, the unequivocal diagnosis of NSAID pseudo-allergy-associated airway disease can be established. However, if the test has negative results, an oral challenge test with ASA would be mandatory because of the low sensitivity and negative predictive value of the bronchial challenge test in our series.

As regards the ASA desensitisation procedures, or more precisely the procedures for induction of ASA tolerance, their indication is rather restricted in present times. For patients requiring life-long NSAID therapy (rheumatoid arthritis, lupus erythematosus, etc.), the introduction of the selective COX-2 inhibitor nimesulide appears to render an induction of ASA tolerance (which, once induced, would be universal for all NSAIDs) unnecessary. Besides being well tolerated by these patients, nimesulide has good antiinflammatory action. Other authors have induced ASA tolerance with therapeutic intent and have reported improvement of the nasal symptoms and, to a lesser extent, of the bronchial ones. However, the clinical availability of powerful inhalatory antiinflammatory agents and long-acting β_2 -adrenergic agonists render the induction of NSAID tolerance not altogether recommendable.

The only currently valid relative indication for ASA tolerance induction would be that of asthmatic patients with NSAID pseudo-allergy who require lifelong administration of platelet aggregation inhibitors because of cardiovascular disease.

In the modest experience of this author, only two patients, both of them asthmatic women with NSAID pseudo-allergy and rheumatoid arthritis, have undergone a tolerance induction protocol based on taking advantage of the so-called refractory period. During this period, which lasts for two to five days after a reaction, the patients becomes refractory to this particular side effect of NSAIDs. In these two patients, and after induction of a bronchospastic reaction with 125 mg doses of ASA, a tolerance induction protocol was initiated on the following day by administering progressively increasing doses of (again) 125 mg, 250 mg and 500 mg, which they perfectly tolerated. As the tolerance induction is universal for all members of this therapeutic group, tolerance to the other NSAIDs is also quite good. It is of paramount importance to advise the patients that they must continue to take their daily dose of the NSAID concerned indefinitely, as an interruption of this therapy inde-

fectively induces, once the refractory period has ended, a return to the previous hypersensitivity state.

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DRUG HYPERSENSITIVITY REACTIONS IN HIV-INFECTED PATIENTS. INDUCTION OF COTRIMOXAZOLE TOLERANCE

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Adverse drug reactions are frequent in patients with HIV infection. Toxic-infective exanthemas may be indicative of an immunopathogenic effect of HIV or of other viruses. The products resulting from the metabolism of the administered drugs may act favouring the hypersensitivity response. T lymphocytes are important in these reactions. The increased frequency of reactions in patients with CD4⁺ counts ranging between 50 and 350 cells/ μ l might be due to a coincidence with the acme of the derangement of metabolic and immunologic mechanisms described in this paper and acquired in the course of HIV infection. It has been suggested that the side effects occurring during treatment with trimethoprim/sulfamethoxazole (cotrimoxazole) might be explained through the

formation of toxic hydroxylamines. Formation of these metabolites occurs preferently in the cytochrome P-450-induced hepatic microsomal metabolic pathways. Slow acetylation is more common in HIV-infected patients, who are moreover frequently polymedicated; this may lead to an accumulation of toxic metabolites such as hydroxylamines, which may in turn influence hypersensitivity. Glutathione is an antioxidant co-factor in the acetylation pathway that is decreased in HIV patients, and the cytotoxicity of hydroxylamines is increased in glutathione-depleted lymphocytes. Furthermore, hydroxylamines may act as haptens and be covalently bound to proteins, inducing the generation of toxic free radicals or the release of cell mediators. Cotrimoxazole represents a particular problem in this context, as about 50% of the patients require a change in their therapy after a reaction. Many patients may be treated with an alternative drug; for the remainder, the options are continuation of cotrimoxazole therapy with treatment of the reaction, reintroduction of the drug after withdrawal, and desensitisation. Success in desensitisation protocols (tolerance induction) appears to be more likely with protocols lasting for five or more days in patients with low CD4⁺ counts. In our study, the patients were to be entered into a desensitisation protocol or into slow reintroduction, according to their previous symptoms. The desensitisation protocol lasted six days and was carried out in-hospital. Forty-three patients were studied; 12 underwent controlled reintroduction of the drug, and 10 of them tolerated such reintroduction. Thirty-three patients were then selected (31 of them directly, plus the two who reacted upon reintroduction) for administration of the slow reintroduction (desensitisation) protocol. Overall, 32 of these 33 patients tolerated the drug. In the light of the results of our study and of other previous ones, it is very important to carry out an allergologic assessment in order to select the most adequate procedure. Even so, a "best and most effective" desensitisation procedure has not yet been established. Desensitisation or reintroduction of tuberculostatics is required when there is no effective alternative treatment available. Desensitisation protocols with other drugs have been sporadically reported in the case of HIV patients.

Key words: Drug reactions. Reintroduction. Desensitisation. Cotrimoxazole. HIV.