

This section publishes the works presented at the scientific meetings organised by Autonomic or Regional Allergy and Clinical Immunology Societies. In this issue the section contains the communications presented at the XXII Scientific Meeting of the Castilian - Leonese Society of Allergy and Clinical Immunology, held in Valladolid (Spain) in November 1999.

Meeting Point

XXII SCIENTIFIC MEETING OF THE CASTILIAN-LEONESE SOCIETY OF ALLERGY AND CLINICAL IMMUNOLOGY

ADVERSE DRUG REACTIONS: UNEXPECTED RESULTS

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*The aim of this report is to stress the importance of carrying out challenge tests with drugs. The first case was a male referred to our outpatient clinic because of two adverse reactions, one with diclofenac and the other one with an unidentified NSAID. The initial working diagnosis was NSAID intolerance, but the study confirmed specific diclofenac hypersensitivity. The second case was a female who was referred to our unit twice within six months, the first time because of a reaction in the course of an infusion of cloxacillin, diclofenac and ranitidine, and the second one because of a new reaction with amoxicillin-clavulanate and Nolotil® (metamizole). The working hypothesis was that the patient had either *b*-lactam hypersensitivity or NSAID intolerance; the study confirmed full tolerance for *b*-lactams and non-pyrazolone NSAIDs, and hypersensitivity to ranitidine and pyrazolones. The third case was one of mild anaphylaxis two hours after the ingestion of the first tablet of an unidentified anti-influenza preparation. The working hypothesis was hypersensitivity to some of its components; the final diagnosis was hepatic echinococcosis. Finally, the fourth case was a 70-year-old female patient with rheumatologic problems referred because of three episodes of mild anaphylaxis: one after an unidentified drug, one after Dalamon® and one after Inzitan®. The latter two have three components in common: lidocaine, dexamethasone and cyanocobalamine. None of these three active components was responsible for the reactions. After the challenge studies the diagnosis was hy-*

persensitivity to thiamine, the fourth component in Inzitan®. In conclusion, we stress the importance of carrying out challenge test studies with drugs. Omitting these may lead to transcendent diagnostic errors and to the withdrawal of pharmacologic groups that are fully tolerated by the patient.

Key words: Adverse reactions. Drugs. Challenge studies.

REACCIONES ADVERSAS A FÁRMACOS: RESULTADOS NO ESPERADOS

El objetivo de este trabajo es apuntar la importancia de la realización de estudios de provocación con medicamentos. El primer caso se trata de un varón remitido a nuestra Unidad por dos reacciones adversas: una a diclofenaco y otra a un AINE no identificado. La sospecha diagnóstica fue una intolerancia a AINEs. Tras el estudio se confirmó una hipersensibilidad específica a diclofenaco. La segunda paciente fue remitida en dos ocasiones a nuestra Unidad en un plazo de seis meses, primero por una reacción durante la infusión de cloxacilina, diclofenaco y ranitidina, y después por una nueva reacción con amoxicilina-clavulánico y Nolotil®. La sospecha diagnóstica fue una hipersensibilidad a betalactámicos o una intolerancia a AINEs. El estudio diagnóstico confirmó tolerancia a betalactámicos y a AINEs no pirazolónicos e hipersensibilidad a ranitidina y pirazolonas. El tercer caso remitido se trataba de una anafilaxia leve dos horas tras la toma del primer comprimido de un antigripal. La sospecha diagnóstica fue de hipersensibilidad a alguno de

los componentes. El diagnóstico final fue una hidatidosis hepática. Por último, el cuarto caso fue una mujer de 70 años con problemas reumatológicos, remitida a nuestra Unidad por haber presentado tres episodios de anafilaxia leve tras un fármaco no indicado, tras Dalamon® y tras Inzitan®. Dalamon® e Inzitan® tienen tres componentes comunes: lidocaína, dexametasona y cianocobalamina. Ninguno de los tres principios activos comunes resultó ser el responsable. Encontramos, tras el estudio de provocación, una sensibilización a tiamina, el cuarto componente del Inzitan®. Para concluir, insistimos en la importancia de la realización de estudios de provocación con medicamentos. La no realización de los mismos puede conducir a errores diagnósticos de gran trascendencia y obligar a la retirada de grupos farmacológicos que son normalmente tolerados por el sujeto.

Palabras clave: Reacciones adversas. Fármacos. Estudios de provocación.

The aim of the present work is to highlight the importance of carrying out challenge studies with drugs. A number of cases are presented of adverse drug reactions (ADR), that are unrelated both as to causative agent and as to induced reaction. The common denominator of the cases selected is the surprising diagnostic result as compared with what would have been reasonably expected considering the patients' anamneses and the epidemiology of adverse drug reactions. In the four cases presented, if controlled challenge tests with drugs had not been performed, the diagnostic result would not only have been incorrect, but other highly relevant underlying disorders would have been missed.

Case 1

A male patient was referred to the Allergy Unit because of two adverse drug reactions, one of them with diclofenac and the other one with an unidentified non-steroidal antiinflammatory drug (NSAID). The initial diagnostic suspicion was NSAID intolerance. The study confirmed

Table I. Studies performed in Case 1

Challenge test with ASA: negative
Challenge test with indomethacine: negative
Skin tests with diclofenac: negative
Challenge test with diclofenac: positive

AS: acetylsalicylic acid.

specific hypersensitivity to diclofenac, so that the patient was able to use with safety all the remaining groups of NSAIDs (Table I).

Case 2

A female patient was referred to our Unit twice within six months. In the first occasion the cause was an adverse reaction during the infusion of cloxacillin, diclofenac and ranitidine; at this time the diagnosis was ranitidine hypersensitivity. Five months later she was again referred to the Unit because of an episode of urticaria/angioedema and dyspnoea during the intravenous infusion of amoxycillin-clavulanate and Nolotil® (metamizole). The diagnostic suspicion was that perhaps a case of β -lactam hypersensitivity or one of NSAID intolerance had been overlooked. The diagnostic study confirmed tolerance for β -lactams and for non-pyrazolone NSAIDs, and hypersensitivity to ranitidine and pyrazolones (Table II). If challenge tests with drugs had not been performed, the use of β -lactam antibiotics, NSAIDs and H_2 antagonists would have been forbidden to this patient.

Case 3

This was a case of mild anaphylaxis occurring two hours after taking the first tablet of Coricidin®, an anti-influenza drug containing paracetamol, phenylpropanolamine and dexchlorphenyramine. The diagnostic suspicion was

Table II. Studies performed in Case 2

FIRST VISIT:

Skin tests with β -lactams: negative
Skin tests with diclofenac: negative
Skin tests with ranitidine: positive
Zantac® iv 10 mg/ml: 11x11 mm
1 mg/ml: 6x6 mm

Challenge tests with penicillin G, amoxycillin and cloxacillin: negative
Re-challenge with β -lactams: negative
Challenge tests with diclofenac: negative
Challenge test with omeprazole: negative

SECOND VISIT:

Skin tests with β -lactams: negative
Skin tests with Nolotil® (metamizole): positive
Nolotil® iv (4 mg/ml): 8x8 mm
Challenge tests with penicillin G, amoxycillin and amoxycillin-clavulanate: negative
Re-challenge with β -lactams: negative
A challenge test with Nolotil® was not performed

Table III. Studies performed in Case 3

Challenge test with Polaramine®: negative	
Challenge test with Coricidin®: negative	
Results of the urticaria protocol:	
Eosinophil count:	700 cells/ μ l
Total serum IgE:	183 kU/l
Skin tests, latex and <i>Anisakis</i> :	2 mm
Anti- <i>Anisakis</i> IgE:	5.2
Anti- <i>Echinococcus</i> IgE:	0.44
<i>Echinococcus</i> serology:	> 1/1280
Abdominal ultrasound scan: hepatic cyst, 16.8 x 15.6 x 9.5 cm	

Coricidin®: paracetamol, dexchlorphenyramine, phenylpropanolamine.

Table IV. Studies performed in Case 4

Skin tests with lidocaine, mepivacaine, Benadon®, Benerva®, Inzitan®, Urbason®, Actocortina® and Optovite B12®: negative	
Challenge test with Urbason® (6-methyl-prednisolone): negative	
Challenge test with lidocaine: negative	
Challenge test with dexamethasone: negative	
Challenge test with thiamine: positive	
Challenge test with pyridoxal phosphate: negative	
Challenge test with cyanocobalamine: negative	

hypersensitivity to one or more of the components. The drug challenge tests confirmed tolerance for Coricidin®; the anaphylaxis episode was therefore not attributed to any drug, and the study of the patient had to be continued. The final diagnosis was hepatic echinococcosis (Table III).

Case 4

A 70-year-old woman with rheumatologic problems was referred to the Allergy Unit because of three episodes of mild anaphylaxis, one after taking an unidentified drug, one after taking Dalamon® and one after taking Inzitan®. Dalamon® and Inzitan® have three components in common: lidocaine, dexamethasone and cyanocobalamine. None of these three active components was demonstrated to be responsible for the clinical manifestations. The challenge studies disclosed sensitization to thiamine, the fourth component in Inzitan® (Table IV). The causative agent in the reaction to Dalamon® could not be identified; it was in all probability one of the remaining components of the preparation, but we did not consider it to be ethical to continue the study. The drug challenge tests performed will allow this patient the safe use of corticosteroids and lidocaine should she again require them.

It is concluded that refraining from performing challenge tests with drugs may under certain circumstances lead to overlooking other diagnoses, which may occasionally be highly transcendent. Furthermore, when several drugs appear to be involved in the adverse reactions, in the best of cases too many pharmacological groups are thenceforward forbidden to the patient; in the worst case, if on the basis of what is epidemiologically most likely only one such therapeutic group is withdrawn, the ensuing consequences may be truly severe.

A NATURAL HISTORY OF ALLERGY TO PENICILLIN?

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Antibiotics of the β -lactam group are those most extensively used in Spain. Allergic reactions are estimated to occur in 1 to 10% of the treated patients. The manifestations of penicillin allergy are in the majority of the cases those of a type I reaction.

Skin tests with β -lactams are a reliable, fast and low-cost method for the diagnosis of allergic reactions. According to the reviewed literature, the skin tests are positive in 50 to 60% of the patients with a clinical history suggestive of allergic drug reaction; in the remainder of the cases, the diagnosis would have to be established through challenge or re-challenge tests. Usually, when the skin test is positive the challenge test follows suit, and only in 5% of the cases with negative skin tests does the challenge test have a positive result.

A number of studies have been performed on the natural evolution of the sensitivity of skin tests in patients with β -lactam allergy over time, but no studies have been published regarding induction or loss of β -lactam sensitization.

In clinical practice it is quite frequent to see patients with a history suggestive of immediate penicillin hypersensitivity. After having ruled out that possibility in a number of cases, it was decided to assess a larger sample in order to ascertain the evolution of the diagnostic tests.