

cells. The patient is admitted into hospital and insulin is started subcutaneously, at first at very high dilutions and then at gradually increasing dosages until therapeutic doses are reached⁸. Table I presents a proposed rapid desensitisation protocol⁹. These protocols must be flexible, with modification of the doses and of the inter-dose intervals according to the local and/or systemic reactions that may arise. If insulin therapy is suspended, its later reintroduction entails a high risk of anaphylaxis.

The indications for insulin desensitisation include systemic reactions and severe local ones.

Desensitisation methodology

The less reactive insulin is used (skin tests), in the form of regular insulin; the initial dose is 1/100 of the one inducing a positive test. The administration route may be subcutaneous or intradermal. The blood glucose levels must be monitored throughout, and the desensitisation proceeds in dynamic fashion. Once the therapeutic dose is reached, desensitisation continues with retard insulin, under monitoring of the specific IgE and IgG levels.

In the case here reported, the desensitisation protocol suggested in Table I was used. The procedure achieved a reduction of the local reactions, and the specific serum IgE levels dropped to 1.3 PRU/ml.

Comments

Human insulin is less allergenic than non-human ones, but it may still induce IgE antibodies and cause allergic reactions. In such a case, desensitisation is the only possible therapy.

A number of alternatives have been proposed for patients in whom the desensitisation procedure has not achieved insulin tolerance: continuous subcutaneous insulin infusion¹⁰, subcutaneous administration of insulin, diphenhydramine and a corticosteroid in the same injection¹¹, and oral administration of insulin and acetylsalicylic acid¹².

References

1. Leonart R. Insulin allergy. Epidemiology and management. Clin Immunother 1994; 2: 7-12.
2. García-Ortega P, Knobel H, Mirada A. Sensitization to human insulin (letter). Br Med J 1984; 288: 1271.
3. Balsells M, Corcoy R, Leonart R, Pujol R, Mauricio D, García A,

et al. Primary allergy to human insulin in patient with gestational diabetes (letter). Diabetes Care 1991; 14: 423-424.

4. Kim R. Anaphylaxis to protamine masquerading as an insulin allergy. Del Med Jrl 1993; 65: 17-23.

5. Blanco C, Castillo R, Quirarte J, García I, de Pablos P, Carrillo T. Anaphylaxis to subcutaneous neutral protamine Hagedorn insulin with simultaneous sensitization to protamine and insulin. Allergy 1996; 51: 421-424.

6. Gin H, Aubertin J. Generalized allergy due to zinc and protamine in insulin preparation treated with insulin pump (letter). Diabetes Care 1987; 10: 789-790.

7. Kumar D. Lispro analog for treatment of generalized allergy to human insulin. Diabetes Care 1997; 20: 1357-1359.

8. Liñana JJ, Montoro FJ, Hernández MD, Basomba A. Reacciones adversas a la insulina. An Med Interna 1997; 14: 369-372.

9. Leonart R, Balsells M, Corcoy R. Primary hypersensitivity to human insulin (abstract). Clin Exp Allergy 1990; 20 Suppl.1: 208A.

10. Nagai T, Nagai Y, Tomizawa T, Mori M. Immediate-type human insulin allergy successfully treated by continuous subcutaneous insulin infusion. Intern Med 1997; 36: 575-578.

11. Loeb JA, Herold KC, Barton KP, et al. Systematic approach to diagnosis and management of biphasic insulin allergy with local anti-inflammatory agents. Diabetes Care 1989; 12: 421-423.

12. Haldoway IM, Wilson JD. Cutaneous insulin allergy responsive to oral desensitisation and aspirin. BMJ 1984; 289: 1565-1566.

RE-EXPOSURE TO β -LACTAM ANTIBIOTICS

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The diagnosis of hypersensitivity to β -lactam antibiotics is based on a sequence of steps comprising anamnesis, skin tests and/or specific IgE quantitation, and controlled exposure-challenge testing. The diagnosis of β -lactam hypersensitivity may be established at any of these steps, but most usually through the skin tests and/or the assessment of the specific IgE levels. However, a number of studies have reported that both the skin tests and the specific IgE may become negative over time^{1,2}. Other studies³⁻⁵ have shown that repetition of the tests and/or controlled exposure/challenge, ten to thirty days later, may establish the diagnosis in a number of patients who would have otherwise remained undetected. Considering this, a prospective study was initiated in order to establish the

usefulness of repeating the diagnostic tests in the assessment of β -lactam antibiotic hypersensitivity.

Material and Methods

The following systematic study protocol was applied to all patients referred because of suspected allergic reaction to a β -lactam antibiotic from April 1994 to April 1998:

(1) Detailed anamnesis and physical examination. The following variables were recorded: age, gender, time elapsed between the suspect reaction and the consultation, drug presumably involved, day of treatment in which the reaction occurred, latency period between the last dose of the suspect drug and the reaction, route of administration, and type and duration of the reaction.

(2) Skin tests with the β -lactam study panel: penicilloyl polylysine (PPL), minor determinant mix (MDM), penicillin G, amoxycillin, ampicillin and cefazoline) at the recommended concentrations and following the EAACI guidelines.

(3) Quantitation of the serum total IgE and specific β -lactam IgE antibody levels (Pharmacia CAP System; Pharmacia Diagnostics, Uppsala, Sweden).

(4) In those cases in which the above tests were ne-

Table II. Total and specific IgE concentrations in the patients diagnosed in Phase I and in Phase II of the study

	Phase I	Phase II	p
Total IgE (kU/l, $\bar{X} \pm SD$)	186.53 $\pm$ 228.67	98.91 $\pm$ 90.60	0,051
Penicillin G			NS
Class 0	54 (71.1)	8 (88.9)	
Class 1	9 (11.8)	0	
Class 2	10 (13.2)	0	
Class 3	3 (3.9)	1 (11.1)	
Amoxycillin			NS
Class 0	52 (75.4)	8 (100)	
Class 1	6 (8.7)	0	
Class 2	10 (14.5)	0	
Class 3	1 (1.4)	0	

The results for the different Classes are expressed as N (%). NS = non-significant difference.

gative, a placebo-controlled single-blind challenge test was performed with increasing doses of the presumably involved β -lactam antibiotic up to therapeutic doses.

The above four aspects constituted the first phase of the study. Phase II comprised the following:

(5) After 15 to 21 days, repetition of the skin tests as in point 2 above; if still negative, repetition of the controlled challenge test (as in point 4).

(6) Computer-supported statistical analysis of the data using the Statview 4.0 statistical software package.

Results

Over the study period, 477 patients were referred to our outpatient clinic for study of suspected β -lactam antibiotic allergy. A final positive diagnosis of β -lactam antibiotic allergy was established in 132 cases, in 115 of them (87.78%) during Phase I and in 16 (12.21%) during Phase II of the study. Among the patients diagnosed in Phase I, the diagnosis was established by the skin tests in 108 cases (93.91%), while in 7 cases (6.08%) the controlled exposure challenge test was required. The corresponding figures for the patients diagnosed in Phase II were 15 (93.75%) diagnosed through the skin tests and 1 (6.25%) that required the controlled exposure challenge. It is noteworthy that none of the patients diagnosed through the skin tests in Phase II had a positive prick test. No statistically significant differences were observed between the percentage ratios of cutaneous responses to a given determinant (Fig. 1).

The anamnestic data of the patients diagnosed in Phase I and in Phase II of the study were compared.

Table I. Comparison of the patient and reaction characteristics of the cases diagnosed in Phase I and in Phase II of the study

	Phase I	Phase II	p ^a
Gender			
Males	48 (41.7)	5 (31.3)	0.30
Females	67 (58.3)	11 (68.8)	
Age (years, $\bar{x} \pm DE$)	41.77 $\pm$ 17.39	39.94 $\pm$ 16.02	0.41
Atopy			
Yes	16 (14)	2 (12)	0.61
No	98 (86)	14 (87.5)	
Route of administration			
Oral	78 (69.6)	9 (56.3)	0.14
I.M.	29 (25.9)	7 (43.8)	
I.V.	4 (3.6)	1 (5.56)	
Other	(0.9% 1)	-	
Duration of the reaction (hours)	40.42 $\pm$ 59.34	22.85 $\pm$ 33.4	0.28
Life-threatening reaction			
Yes	38 (33)	2 (12.5)	0.07
No	77 (67)	14 (87.5)	
Time elapsed (months, $\bar{x} \pm SD$)	75.67 $\pm$ 111.17	121.87 $\pm$ 113.02	0.49

^a No statistically significant differences were detected between the patients diagnosed in Phase I and in Phase II for any of the data analysed.

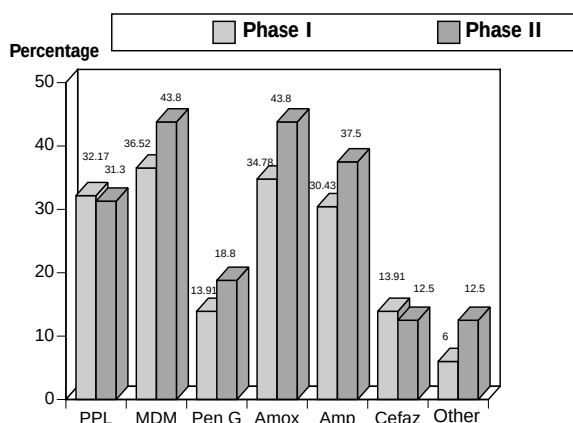


Fig. 1. Comparison of the percentages of positive tests to the various determinants in Phase I and in Phase II. No statistically significant differences were observed for any of them. PPL = penicilloyl polylysine; MDM = minor determinant mix; Pen G = penicillin G; Amox = Amoxycillin; Amp = ampicillin; Cefaz = cefazoline; Other = other types of β -lactam antibiotics.

No significant differences were detected between the two groups regarding patient characteristics (age, gender, percentage of atopsics) or the reaction characteristics (day of therapy, route of administration, life-threatening reaction, duration of the reaction) (Table I). There were also no statistically significant differences regarding the causative drugs, and particularly so when penicillins vs. aminopenicillins were considered (data not shown).

As regards the time elapsed between the reaction and the time of first consultation, and although the differences were not statistically significant, the mean elapsed time was 75.67 months for the patients diagnosed in Phase I and 121.87 months for those diagnosed in Phase II. However, when the time elapsed was analysed considering separately the patients who were sensitised to penicillins or to aminopenicillins (Fig. 2), the mean for those with penicillin sensitisation was 185.04 months for those diagnosed in Phase I and 240 months for those diagnosed in Phase II (NS), while in the patients with aminopenicillin sensitisation the corresponding mean values were 30.98 and 122.6 months ($p = 0.05$).

The comparison of the total and specific IgE concentrations (Table II) also failed to show statistically significant differences between the patients diagnosed in Phase I and in Phase II of the study. Finally, in the case of the type of reaction a statistically significant difference existed only for "anaphylaxis", which was significantly more frequent among the patients diagnosed in Phase I of the study (Fig. 3).

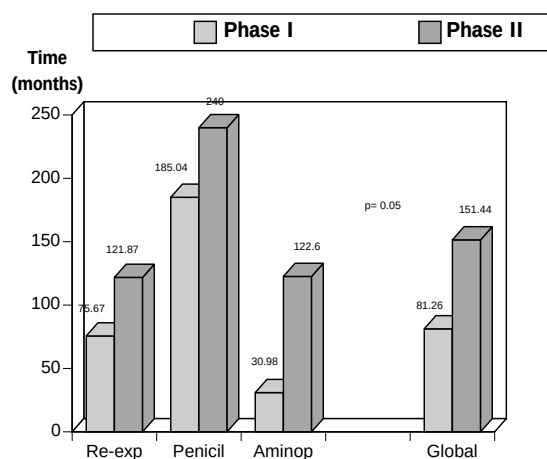


Fig. 2. Time (months) elapsed between the index reaction and the time of performing the allergy study. Statistically significant differences were observed upon separating the patients according to the drug involved: the elapsed time was much shorter in the patients diagnosed of aminopenicillin allergy in Phase I than in Phase II; no such differences were seen in the case of penicillin sensitisation. Re-exp = patients with penicillin and aminopenicillin allergy together; Penicil = patients with penicillin allergy; Aminop = patients with aminopenicillin allergy; Global = total patient sample.

Discussion

The course of the sensitising exposure to β -lactam antibiotics is quite different from that seen with other allergens, such as pollens or mites. Thus, in the case of mite allergy there is continuing exposure prior to and after the development of clinical symptoms, while in the case of the β -lactam antibiotics the usual course is one of multiple dis-

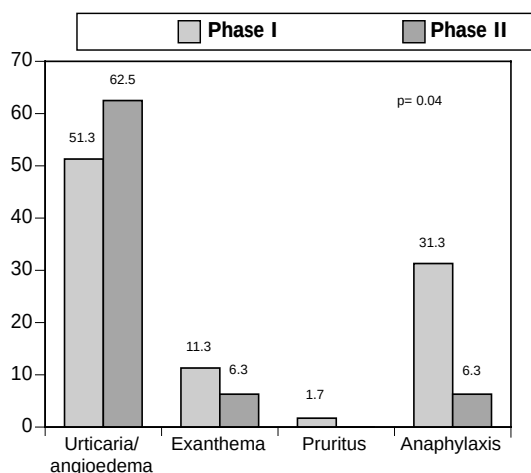


Fig. 3. Comparison of the incidence of the various reaction forms (percentages) in the patients diagnosed in Phase I and in Phase II. A greater percentage of anaphylactic reactions were observed in the cases diagnosed in Phase I of the study ($p < 0.04$).

crete exposures to the drug(s) prior to the development of sensitisation, with absolute avoidance of any contact with the drug(s) after that moment. Furthermore, in a considerable number of the cases a rather long time has elapsed from the moment of the reaction to that of consultation. It is thus at least theoretically possible for a patient to have negative skin tests and even to tolerate a single exposure to the causative drug at the time of the study and then develop a new reaction during a later therapy course. This has been observed in a number of studies⁵. Obviously, this observation is of prime importance for establishing the diagnosis and for the ensuing recommendations regarding the future use of such drugs.

It has been reported that skin tests with β -lactam antibiotics may become negative with the passage of time. Patriarca et al.¹, in a six-year follow-up of patients with positive skin tests or specific IgE antibodies to penicillin, show that positive skin tests persisted in 75.6% of the patients after two years, in 40.3% after four years, and in only 20% after six years; a similar evolution was seen for the specific IgE antibodies. In Spain, Fernández and Fiandor² demonstrated that the skin tests with β -lactam antibiotics turned negative in 48% of the patients after two years, and Pamies et al.⁶ reported a reduction of the positive tests, already after the first month, by 13% among patients sensitised to bencyl-penicillin and by 34% in those sensitised to aminopenicillins. Posadas et al.⁷ followed 25 patients with positive specific IgE to bencyl-penicillin and 24 with positive specific IgE to amoxycillin and observed that in the first group 21% of the patients were IgE-negative after one year and 82% were negative after five years, while the corresponding figures for the second group were 42% and 100%, respectively.

In the present study, the repetition of the diagnostic tests allowed us to establish a positive diagnosis in 12.21% more patients: 16 patients who had had negative skin tests yet had tolerated a full therapeutic dose of the β -lactam antibiotic that had caused the index reaction then had, in Phase II of the study, either a positive skin test or a positive controlled challenge test.

There are few similar studies published in which the diagnostic tests are repeated within a short time. In one of them, López-Serrano et al.⁵ found a positive reassessment in 10 out of 52 patients (19.23%). Díaz Donado et al.⁴ similarly found that 17.3% of their patients (13/75) had a positive skin test or a positive challenge upon reassessment. In the present study, with a larger patient population, the proportion of positive reassessments is 12.21%.

We have further examined whether there were any differences in the patient or reaction characteristics between the cases diagnosed in Phase I and those diagnosed in Phase II of the study. No differences were seen in the patients' age or gender, or in the percentages of atopic cases. Upon analysing the characteristics of the reactions, there were also no significant differences concerning the involved drug, the route of administration, the moment at which the reaction occurred, the latency period or the duration of the reaction. The only statistically significant difference observed concerned the type of reaction that had initially occurred. Thus, the patients diagnosed in Phase I of the study had a greater percentage of anaphylaxis reactions than those diagnosed in Phase II. Furthermore, none of the patients had a positive prick test in Phase II. This particular observation might perhaps have its explanation in the fact that the -more intense- anaphylactic reactions maintain skin reactivity over longer periods. In fact, those patients who had experienced anaphylactic reactions had a higher percentage of positive prick tests ($p = 0.006$; data not shown). No significant differences were observed in the times elapsed between the index reaction and the moment of the allergy study. However, Díaz Donado et al.⁴ observed that in the patients diagnosed in phase II of their study the time elapsed until the allergy study was performed had been longer. In the present study, the mean elapsed time in the cases diagnosed in Phase II was ca. 46 months longer than in those diagnosed in Phase I.

In a recent communication, Blanca et al.⁸ have prospectively studied the evolution of the skin tests in patients with β -lactam hypersensitivity, finding a different evolution course in those sensitised to aminopenicillins and those sensitised to bencyl-penicilloyl or MDM, the former losing their skin reactivity much earlier than the latter. In our own series, the analysis of the time elapsed until the allergy study considering the penicillin- and aminopenicillin-sensitised patients separately shows that in the latter case the elapsed time had been much longer for those diagnosed in Phase II than for those diagnosed in Phase I, in coincidence with the report of Blanca et al.⁸. Regarding the IgE levels, no statistically significant differences were observed either for the total IgE or for the specific IgE antibody concentrations to any of the four β -lactam antibiotics tested. As a matter of fact, this technique had but scarce diagnostic value (data not shown), and this might have influenced this result.

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

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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.