ORIGINAL ARTICLE

Assessment of a New Brand of Determinants for Skin Testing in a Large Group of Patients with Suspected β-Lactam Allergy

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Abstract

Background: Skin testing with major and minor determinants of benzylpenicillin is recommended standard practice for the evaluation of patients with immediate hypersensitivity reactions to β-lactams. However, commercial reagents for this purpose were recently dropped from the European market.
Objective: In the present study, we assessed a new brand of reagents for use in skin testing in patients with suspected penicillin allergy.
Methods: Prick tests and intradermal tests were performed with benzylpenicilloyl polylysine (PPL) and minor determinant mixture (MDM). Penicillin G, amoxicillin, and the culprit β-lactam were also tested. If skin tests were negative, a single-blind oral challenge test was performed with the culprit active principle or penicillin. If both skin tests and challenge tests were negative, the same procedure was repeated between 2 and 4 weeks later.
Results: A total of 636 patients were assessed. The allergy study was positive in 69 patients. Skin tests with PPL were positive in 30 patients (46.8%) and with MDM in 28 (43.7%). Sixteen patients displayed a positive reaction to both PPL and MDM (25%), while 42 patients (65.6%) had a positive reaction to either PPL or MDM alone. Thirty-two patients had positive skin test reactions to penicillin G or another β-lactam antibiotic. Five patients in whom a negative result was obtained in skin tests had a positive reaction to oral challenge.
Conclusions: Our results indicate that a new brand of determinants that is commercially available in Europe is a reliable and useful tool for the diagnosis of β-lactam allergy. The new reagents are a safe alternative to the previously available brand.

Key words: Penicillin allergy. Drug allergy. Major determinants. Minor determinant mixture. Benzylpenicilloyl polylysine.

Resumen

Antecedentes: Las pruebas cutáneas con determinantes mayores y menores de la penicilina se utilizan de forma habitual para el diagnóstico de reacciones de hipersensibilidad inmediata a los antibióticos betalactámicos. Estos extractos diagnósticos han sido recientemente retirados del mercado europeo.
Objetivo: Estudio de una nueva marca de determinantes para el diagnóstico de reacciones alérgicas a penicilina.
Métodos: Se realizaron pruebas cutáneas en prick e intradérmicas con una nueva marca comercial de PPL (benzilpeniciloil polilisina) y MDM (benzilpenicilina sódica, benzil peniciloato sódico y ácido benzilpeniciloico), penicilina, amoxicilina y el betalactámico implicado. Si las pruebas cutáneas resultaban negativas se realizaba test de provocación oral simple ciego con penicilina o el medicamento implicado. Si las pruebas cutáneas y la provocación resultaban negativas se repetían 2-4 semanas más tarde.
Resultados: Se estudiaron 636 pacientes con sospecha de alergia a betalactámicos. Sesenta y nueve presentaron un estudio positivo. Las pruebas cutáneas con PPL fueron positivas en 30 pacientes (46.8%) y 28 con MDM (43.7%). Dieciséis presentaron pruebas cutáneas positivas a PPL y MDM (25%) y 42 pacientes presentaron positividad a PPL o MDM (65.6%). Treinta y dos presentaron pruebas cutáneas a penicilina G u otro betalactámico. Cinco pacientes presentaron pruebas cutáneas negativas con prueba de provocación oral positiva.
Conclusiones: Se confirma la utilidad y fiabilidad de la nueva marca de determinantes comerciales disponible en Europa para el diagnóstico de reacciones de hipersensibilidad inmediata a betalactámicos. Se trata de una alternativa segura a la utilizada previamente.

Palabras clave: Alergia a penicilina. Alergia a medicamentos. Determinantes mayores. Determinantes menores. PPL. MDM.

Introduction

Allergic reactions are estimated to occur in approximately 2% of patients treated with penicillin [1,2]. Most of those reactions are maculopapular or urticarial rashes, while severe allergic reactions to penicillin such as anaphylaxis are much less common [2,3]. Nevertheless, severe reactions are potentially life threatening and can be fatal in a low percentage of individuals [3]. Although immediate allergic reactions to penicillin preparations can be caused by certain additives [4], they are usually mediated by immunoglobulin (Ig) E antibodies to either the major or minor determinants or both.

Skin testing demonstrates the presence or absence of specific IgE antibodies against major and minor penicillin determinants [5]. In the USA, IgE antibodies against major determinants could previously be tested with a benzylpenicilloyl-polylysine (PPL) product (Pre-Pen, Kremers Urban, Milwaukee, Wisconsin, USA) [6]. Although reagents for minor determinants are not commercially available in the USA, many clinicians use penicillin G at a concentration of 10 000 U/mL as a partial source of minor determinants [6,7] or use their own self-produced minor determinants, typically including both penicilloate and penilloate [7]. With this approach, around 85% of patients with a history of allergy to penicillin have negative reactions to skin tests either in adults [8] or in children [9], and those patients may therefore be able to receive penicillin safely.

The best approach to assessment of penicillin allergy involves performing skin tests with major and minor penicillin determinants [5,10]. Between 1% and 4% of patients who test negative with this approach will have non-life-threatening urticarial reactions [3]. A product containing major and minor determinants (Allergopharma kit) was available on the European market until 2004, when it was withdrawn by Merck worldwide [11,12]. To address this problem, major and minor penicillin determinants have begun to be produced in Spain by a new company (Diater S.A., Madrid, Spain). We undertook a prospective study in which skin tests were performed with this product in a group of patients referred to our hospital with suspected penicillin allergy. Our results show that the tested product has a similar efficacy to that found in previous studies with older brands of determinants [1,13].

Methods

Patients

The study included all patients with suspected penicillin allergy referred for assessment in the Allergy Service of University Hospital NS Candelaria, Tenerife, Spain, by general practitioners, pediatricians, and other specialists from the referral area (980 000 inhabitants) between January 2004 and June 2006. All patients had suffered immediate symptoms, which were classified as rash, urticaria, angioedema, and anaphylaxis. Studies with the offending drug, or several drugs if more than 1 had been used, were performed as described below. All procedures were approved by the institutional review board and both written and verbal informed consent was obtained. In the case of children, written and verbal informed consent was obtained from the parents.

Skin Prick Test

Skin prick test (SPT) was performed with commercial PPL as the major determinant at a concentration of 0.04 mg/mL with 20 mg mannitol in buffer (137 mM NaCI, 2.7 mM KCI, 4.3 mM Na_2HPO_4, 1.4 mm KH_2PO_4, pH 7.3), and minor determinant mixture (MDM) including sodium benzylpenicillin (0.5 mg/mL), disodium benzylpenicilloate (0.5 mg/mL), and benzylpenicilloic acid (0.5 mg/mL) in the same buffer. Both major and minor determinants were purchased from Diater S.A. (Madrid, Spain). SPT was also performed with penicillin G at a concentration of 250 000 U/mL, amoxicillin at 20 mg/mL, and the offending β-lactam drug if it differed from those drugs at previously published concentrations [5,14] . Histamine phosphate and saline solution were used as positive and negative controls, respectively. Then, intradermal tests were performed with PPL and MDM at the same concentrations and penicillin G at a concentration of 100 000 U/mL. Both SPT and intradermal tests were assessed 20 minutes after application and the results were considered positive if a wheal and flare reaction larger than the negative control was present during SPT or 3 mm higher than the injected papule in intradermal testing.

Oral Challenge and Reevaluation

If the results of skin tests were negative, a single-blind oral challenge test was performed with the offending agent, or if this was not known by the patient, with penicillin. Challenge was started at 10% of the total dose of the active principle and doses were increased 2-fold every 60 minutes until the total dose of the offending active principle was reached. Patients who displayed no symptoms remained in hospital for at least 2 hours after last challenge and maintained contact with the hospital to report any delayed drug reaction.

If SPT, intradermal tests, and oral challenge tests were all negative, the same procedure was followed including SPT, intradermal test, and open oral challenge between 2 and 4 weeks later, as recommended by the European Network for Drug Allergy (ENDA) [5].

Results

Between January 2004 and June 2006, 709 patients with suspected penicillin allergy were referred to the allergy department of University Hospital NS Candelaria. Forty patients refused to participate in the study. In those patients, avoidance of β-lactam drugs was recommended. The remaining 669 patients with an immediate reaction and suspected penicillin allergy were included in the study.

Amoxicillin was the culprit drug in 68% of patients, benzylpenicillin in 14%, and ampicillin in 6%, while in 22% of cases patients did not clearly recall the culprit drug but claimed to be allergic to penicillin. The symptoms were rash, urticaria, or angioedema in 677 patients (95.5%) and anaphylaxis in 32 patients (4.5%). The time interval between the last reaction and

the allergy study ranged from 90 days to 7300 days (median, 1095 days).

A positive diagnosis of penicillin allergy was given in 69 patients (10.3%). A positive reaction in skin test with PPL was obtained in 30 patients (43.5% of positive patients), MDM in 28 patients (40.5%), and PPL and MDM in combination in 16 patients (23.2%). In total, 42 patients (60.9%) had a positive reaction to skin tests with PPL, MDM, or both. Skin tests with penicillin, amoxicillin, ampicillin, and/or cephalosporin were positive in 32 patients (46.4%). In 12 patients the only positive result was obtained with PPL, in 8 only with MDM, and in 10 only with PPL and MDM. In 17 patients, the only positive result was with penicillin, amoxicillin, ampicillin, or cephalosporin.

Allergy to penicillin was diagnosed in 11 out of 69 positive patients on re-examination, 9 of them by skin test. Finally, in 5 patients the results of skin tests were negative but the single-blind oral challenge test was positive in retest (7.2%). Four of those patients had reactions within the first 30 minutes of drug challenge. In the fifth patient, the first and second examinations including skin tests and oral challenge were negative but, because of a very convincing but also old history of allergic reaction, we performed a third examination and a positive result was obtained in intradermal test with PPL and MDM.

Discussion

Guidelines on the assessment of individuals with immediate hypersensitivity reactions to β-lactam drugs recommend skin test with PPL and MDM of benzylpenicillin [5,15]. Fortunately, while commercial reagents were dropped from the market in the USA and, more recently, Europe [11], a new commercial kit was introduced in Spain in 2004. Following the introduction of that product, we compared the old withdrawn kit Allergopen (Reinbeck, Germany) and the new product (Diater, Madrid, Spain) in 20 patients diagnosed with penicillin allergy [12,16]. Since we observed an optimal clinical concordance in the performance of the 2 preparations, we continued testing our patients with Diater determinants [16,17]. Subsequently, other authors have confirmed our findings in a group of 22 patients [18,19]. Rodriguez-Bada et al [18] also performed in vitro analysis by high-performance liquid chromatography to examine the composition of the products and by radioallergosorbent test (RAST) inhibition to observe potential differences in 22 selected cases. RAST inhibition assays showed similar results in the inhibition of PPL and MDM with both kits. Romano et al [19] performed skin tests in 148 patients with either immediate or nonimmediate reactions to β-lactams and 47 control individuals. MDM reagents produced identical results in all 195 patients, while the results of skin testing with PPL reagents were concordant in 190 (97.4%) of them.

Our findings revealed that nearly half of the subjects would be misdiagnosed without PPL and MDM determinants and would be subjected to an open oral challenge. Because we did not perform challenges in subjects with positive skin tests to PPL and MDM, we cannot provide exact data about specificity. However, the rate of positive results (10.9%) was similar to most published series [1,20,21] and we may speculate that specificity was high. Since only 5 subjects had a negative skin test result followed by a positive oral challenge (7% of positive studies), our results suggest a high sensitivity and negative predictive value for skin testing. Thus, our data suggest that the new brand of determinants that is commercially available in Europe is a reliable and useful tool for the diagnosis of penicillin allergy.

Penicillin and its derivatives (semisynthetics and cephalosporins) are the most prescribed antibiotics for common infections. Along with their widespread use, these antibiotics are the most frequently reported by both patients and physicians to induce allergic reactions ranging from skin rashes to systemic anaphylaxis [22,23]. As adverse drug reactions affect daily clinical practice (rising morbidity and mortality) and health care spending (direct and indirect costs) a precise diagnosis of drug allergy is mandatory. The medical history is not always conclusive but a combination of a positive clinical history and skin testing [20] has been shown as the most reliable approach [21] to evaluate immediate adverse reactions to β-lactams according to the ENDA/EAACI reports [5]. ENDA also recommends measuring specific IgE in vitro [5]. However, since our hospital had a large waiting list and outpatients could wait for at least 2 years for an allergy study, IgE determination was not worthwhile in most patients. It is well known that specific IgE levels decrease over time [10]. Moreover, Fontaine et al [24] have recently proposed that IgE measurement should be limited to patients with a clinical history of anaphylactic shock and negative skin test.

Skin testing with penicillin is known as a safe diagnostic procedure in trained/experienced hands [25] and should always be performed prior to drug provocation testing, which is considered the gold standard to confirm or rule out drug allergy but is not free from potential severe reactions. As with any diagnostic procedure, the sensitivity and specificity of skin testing are critical to evaluate the method. While specificities of up to 99% have been reported for diagnosis of penicillin allergy [26], large differences have been described in terms of determinant sensitivity [26,27]. For instance, Torres et al [26] published a study involving 290 patients selected on the basis of genuine penicillin allergy revealed by either skin test, positive serum specific IgE, or drug challenge, and obtained a positive skin test in 70% of the patients. The development of common guidelines for methods used in the diagnosis of immediate allergic reactions to β-lactams may help to understand the variability in drug sensitization among populations, which could be influenced by genetic factors and the prescription/consumption habits in different geographic areas. The usefulness of skin testing should not be restricted to diagnosis, as it may also contribute to establishing clinical follow-up of those allergic patients who eventually lose sensitization [2] and may subsequently benefit from use of the drug.

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