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Epidemiology of hypersensitivity reactions to penicillin in Slovenia

Peter Kopač[1]✉, Mihaela Zidarn[1], Mitja Košnik[1]

Abstract

Introduction: The incidence of allergy to penicillin is highly overestimated. Many patients are labeled as penicillin-allergic, which is often unconfirmed. We report an analysis of patients that were referred for evaluation of suspected penicillin allergy in 2007 and 2008.

Methods: In a 2-year period, 606 patients were referred: 460 (76%) female, average age 42 (14–85) years. The diagnostic procedure started with specific IgE (sIgE) measurement, followed by skin prick and intradermal tests with PPL, MDM, and the suspected antibiotic. If all tests were negative, a drug provocation test was performed (DPT). If more than 3 years had passed from the reaction and if the reaction was not severe, the DPT followed serological tests.

Results: In 49 (8%) patients, sIgE to penicillin was detected. Skin testing was performed on 274 (45%) sIgE-negative patients, with positive results in 14 (5%) patients. In 426 (70%) patients, DPT with the suspected drug was performed, which was positive in 19 (4.5%) patients. Diagnosis of penicillin allergy was established in 82 (13.5%) patients.

Conclusions: Tests of immediate hypersensitivity to penicillins were positive in a minority of patients referred. It is important to confirm or exclude suspected allergy to antibiotics because unnecessary use of more expensive broad-spectrum agents also contributes to the development and spread of certain types of drug-resistant bacteria.

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Introduction

Unwanted events are quite common during antibiotic therapy. Such events are often referred to as allergies. However, only 10 to 15% of side effects are actually due to immune-mediated hypersensitivity (1).

Penicillin antibiotics are the drugs most frequently suspected in drug hypersensitivity reactions. Clinically, drug allergies are divided into immediate and delayed reactions with different immunological mechanisms. Immediate reactions occur less than 1 hour after drug administration and clinical presentation varies from urticaria to life-threatening anaphylactic shock. The most common delayed reactions are maculopapular exanthema and delayed-onset urticaria, which are non-severe and self-limiting diseases. Severe delayed reactions such as acute generalized pustulosis, Stevens–Johnson syndrome or toxic epidermal necrolysis are rare and are accompanied by danger signs such as fever, bullous lesions, and mucosal and other organ involvement. A detailed clinical history and medical record of the reaction are essential because in vivo and in vitro tests are limited (2, 3). On the other hand, there are a large number of patients that report reactions that happened several years earlier and whose history is not always reliable. Therefore our diagnostic protocol mainly focused on excluding potentially life-threatening anaphylactic reactions. The diagnostic procedure consisted of history, serologic (specific IgE), skin prick, intradermal tests, and drug provocation tests (DPT) (1, 4–7).

We report on an analysis of all patients that were referred to our allergology department for evaluation of suspected penicillin allergy in 2007 and 2008.

Patients and Methods

All patients that were referred to our allergology department for evaluation of suspected penicillin allergy in 2007 and 2008 were included in this retrospective study.

The standard diagnostic procedure was as follows, but not all tests were performed in all patients. Diagnostics started with measurement of specific IgE (sIgE) to penicilloyl V, penicilloyl G, amoxicilloyl, and ampicilloyl (FEIA CA, Phadia, Uppsala, Sweden). According to the manufacturer's instructions, values over 0.35 kUA/L were regarded as positive. However, we regarded these results as questionable when total IgE (tIgE) was over 500 kU/L because it has been shown that in patients with high tIgE the results of sIgE to penicillin are most often falsely positive (8). If sIgE was negative or questionable, skin prick tests (SPT) were performed with the major determinant benzylpenicilloyl poly-L-lysine (PPL) (Diater Laboratorios, Madrid, Spain), the minor determinant mixture (MDM) formed by sodium-benzylpenicillin, benzylpenicilloic acid, and sodium-benzylpenicilloate (Diater Laboratorios, Madrid, Spain), and with the suspected antibiotic. The concentration for penicillin G was 10,000 IU/ml and for amoxicillin 20 mg/ml. In the case of negative SPT, skin intradermal tests (IDT) were made with dilutions at 1:100 and 1:10 and undiluted with PPL, MDM, and suspected antibiotic.

If all tests were negative, oral provocation was performed. An increasing amount of drug was administered at 1-hour intervals. Doses for phenoxymethylpenicillin were 50 mg, 150 mg, 300 mg, and 500 mg (cumulative dose 1,000 mg). Doses for amoxicillin were 5 mg, 50 mg, 250 mg, and 500 mg (cumulative dose 805 mg).

In patients that reported a history of a non-severe reaction more than 3 years earlier and were sIgE negative, DPT was performed without previous skin testing. In patients with a clinical history suggestive of delayed non-severe reaction and negative DPT, a prolonged oral provocation test (7 to 10 days with therapeutic dose) was proposed.

Skin and provocation testing were performed exclusively in a hospital setting. Data are present as mean and range.

[1]Golnik University Clinic of Respiratory and Allergic Diseases, Golnik 36, SI-4204 Golnik, Slovenia. ✉ **Corresponding author: peter.kopac@klinika-golnik.si**

Results

In the 2-year period, 606 patients–460 (76%) female, average age 42 (14–85) years–were referred for evaluation of penicillin allergy. The procedure is summarized in Figure 1.

A history of immediate reaction was reported by 279 (46%); among these, 36 (6% of all patients) reported symptoms suggestive of anaphylaxis. A history of delayed reaction was reported by 121 (20%), and 206 (34%) did not recall the reaction. In 49 (8%) patients, specific IgE to at least one beta-lactam antibiotic was detected. In 11 of these patients, total IgE (tIgE) level was measured and in four patients it was higher than 500 kU/l. These four patients underwent DPT, which was negative. The other 45 patients were regarded as penicillin-allergic and no further tests were performed.

The remaining 571 patients were invited for further testing, of whom 117 (19%) refused further testing.

Skin testing was performed on 274 (45%) patients, with positive results in 14 (5%) patients (six SPT, eight IDT). In eight patients, skin tests were positive with PPL and in six with MDM. None were positive with the culprit drug. Those patients were regarded as penicillin-allergic and no further tests were performed.

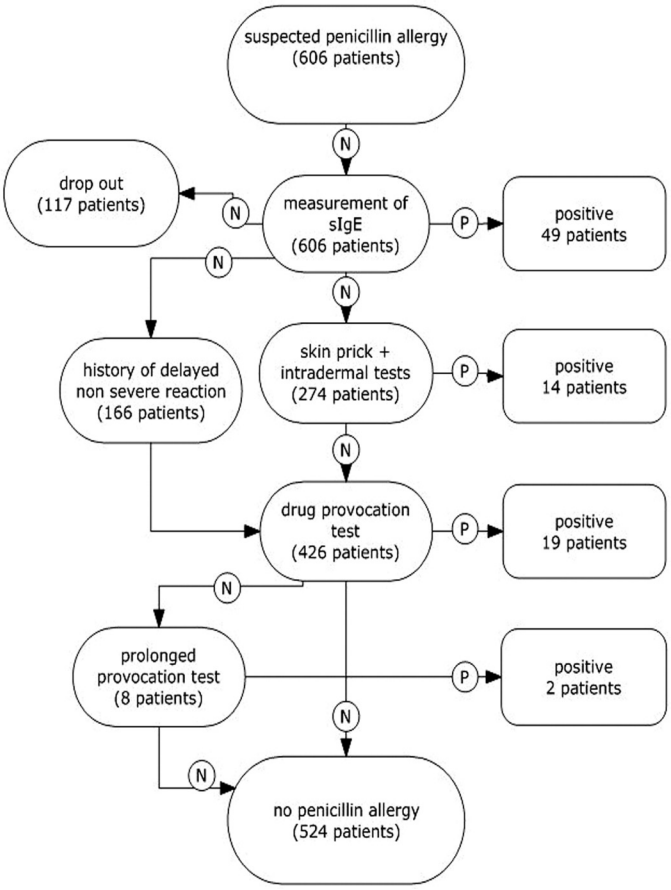

Figure 1 | Trial profile.

In 426 (70%) patients, DPT with the suspected drug was performed. DPT was carried out with phenoxymethylpenicillin in 227 (53%) patients, with amoxicillin in 126 (30%) patients, and with amoxicillin-clavulanic acid in 72 (17%) patients. The 166 patients that reported non-severe reaction more than 3 years ago proceeded to DPT without previous skin testing and all of these patients were DPT-negative. In 19 (4.5%) out of 260 skin prick test–negative patients, hypersensitivity was confirmed in DPT. Eight DPTs were positive with phenoxymethylpenicillin, seven were positive with amoxicillin, and four with amoxicillin-clavulanic acid.

One patient experienced shortness of breath after the first dose of amoxicillin. All of the other patients experienced only skin symptoms with erythema, urticaria, and/or angioedema. Provoked reactions were immediate in 16 patients and delayed in three patients. In 13 patients, the provoked reaction was similar to that reported in clinical history; however, three patients that reported delayed reaction suffered an immediate reaction in DPT.

Prolonged DPT was proposed to all patients with negative DPT and a history suggestive of delayed non-severe reaction. However only eight prolonged DPTs were performed, and were positive in two patients with amoxicillin-clavulanic acid.

Based on our protocol, drug allergy was confirmed in 82 (13.5%) of all patients referred: 14 (20%) male, 54 (80%) female, age 16 to 79, average age 44. In 49 (72%), the hypersensitivity reaction was immediate with erythema and urticaria. In 19 (28%), the reaction was delayed with urticaria and/or maculopapular rash.

Discussion

Immediate hypersensitivity to penicillin was confirmed only in a minority (13.5%) of all patients referred, with a higher incidence in female patients, which is consistent with data from the literature (9).

Serologic tests were positive in 8%. The specificity of commercially available serologic tests is reported to be as high as 86 to 100% (5), but specificity declines rapidly if tIgE is higher than 500 kIU/l (8). Nevertheless, the diagnostic value of sIgE in diagnostics of penicillin allergy is limited due to low sensitivity (40–70%), which also diminishes over time (5). In our group, tIgE was determined in only 11 patients (22% of sIgE-positive patients), and in four of these patients sIgE was found to be falsely positive due to high tIgE, which was proved with negative DPT. However, at the time of our study data on the low reliability of sIgE against penicillin in subjects with high tIgE had not been published yet. Overall, we can speculate that proper evaluation of serologic tests would have decreased the final number of patients designated as penicillin-allergic by approximately 10%.

Skin tests were diagnostic in a further 5% of patients. The specificity of skin tests is reported to be 98%, and sensitivity ranges from 22 to 70% (5). Although systemic reaction in IDT is reported in up to 10% of patients with immediate hypersensitivity to antibiotics, we did not experience any. However we did not perform in vivo tests in patients with positive sIgE.

Serologic and skin tests both have comparable good specificity but low sensitivity, but from the financial point of view skin tests are far more favorable. However, in a study on patients with negative skin tests and positive DPT, commercial serologic tests were positive in 3/15 patients. The positive predictive value (PPV) of serologic tests was 45% and the negative predictive value (NPV) 77.1%, with much better results in patients presenting as anaphylactic shock (PPV 100%, NPV 17.8%) than in those with urticaria (PPV 70.9%, NPV 82.2%). Based on this study, serologic tests should at least be performed in patients with a clinical history of anaphylactic shock and negative skin tests in order to avoid severe reactions during drug provocation tests (10).

DPT was diagnostic in a further 4.5% of patients with negative

sIgE and skin tests. DPT is currently still the most specific test for establishing or excluding drug hypersensitivity. The negative predictive value of DPT was estimated to be 94.1% (89.8–98.3%) (11). None of the DPT reactions that occurred in skin test false-negative patients were severe (11). However, it does have limitations: it is time consuming, could induce dangerous reactions, and has the potential to sensitize the patient. Moreover, it could be false negative. Short-term tolerance could be induced during an incremental provocation test, or cofactors such as immune status in the state of the illness (such viral infection) or additional drugs could be missing (12). In addition, the duration of DPT is important because many patients with delayed hypersensitivity react only after prolonged consumption of antibiotics. Even prolonged follow-up after intake of a single daily dose of antibiotics does not significantly improve the diagnostic value of the test because a higher cumulative dose is probably needed in most patients to elicit a delayed hypersensitivity reaction. In a study by Borch, 50% of patients with a convincing history of delayed reaction to penicillin actually reacted if DPT was prolonged to up to 10 days (13).

Only one potentially severe reaction with shortness of breath occurred during the study period. In fact, a low positive rate of DPT was expected because many patients reported a clinical history that was not suggestive of immediate hypersensitivity.

An in vitro test with a high negative predictive value would be useful. The basophile activation test is the most promising and is a highly useful cellular in vitro test in diagnostics for immediate hypersensitivity to protein allergens–for example, in Hymenoptera venom hypersensitivity (14). However, in patients allergic to small allergen compounds (haptens) such as antibiotics it has high specificity (80–100%), but its sensitivity (30–50%) (15) is low, as in serological tests. A lymphocyte transformation test is a useful test for diagnosing delayed hypersensitivity reactions with high specificity (85–93%) and sensitivity (60–70%) (16), but it is cumbersome and it involves radioactivity and expensive equipment. Other promising tests for diagnosing delayed hypersensitivity reactions such as the CD 69 up-regulation test, measurement of cytokine production, and granzyme immunospot assay are still being studied (17). All of these tests have several limitations: a fresh blood sample must be processed within 24 hours, they require a trained and experienced immunological laboratory, and they are expensive. Therefore these in vitro tests are currently still not useful for everyday clinical practice and are limited to specialized research centers.

In 20% of patients with negative sIgE, the diagnostic protocol was not carried out completely. If the prevalence of penicillin hypersensitivity was equally distributed among the study group, this would mean seven missed penicillin-allergic patients. In addition, there was a low adherence to the suggested prolonged DPT, which is most probably due to the fact that prolonged DPT is time-consuming and patients were supposed to be hospitalized.

Based on experience and these data, we have already modified our diagnostic protocol to reduce time and expenses and to improve adherence. We use serological tests more cautiously and economically, only when an immediate (IgE) mechanism is suspected and only with the culprit antibiotic. Because PPL and MDM reagents are no longer commercially available and other studies have also shown their limited usefulness (18), we use commercial penicillin G and the culprit drug in intravenous form for skin tests. DPT is mainly performed in a 1-day hospital setting and prolonged DPT on an outpatient basis. In patients with a non-suggestive history, often only open DPT with a single full dose of the culprit drug is performed to exclude immediate reaction.

In conclusion, each year a diagnosis of penicillin hypersensitivity is invalidated in approximately 200 to 250 patients. It is important to raise the awareness of patients and doctors that it is necessary to confirm or exclude suspected penicillin allergy and to advise penicillin treatment in the case of indications to patients with negative tests. Unnecessary use of more expensive board-spectrum agents with more side effects burdens the healthcare system and also contributes to the development and spread of certain types of drug-resistant bacteria.

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