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BRIEF COMMUNICATION

Experience with a new commercial skin testing kit to identify IgE-mediated penicillin allergy

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Abstract

Many patients who describe a history of allergy to penicillin do not prove to be allergic and can be treated safely with penicillin. After a period of 2 years where testing of penicillin allergy was not possible, a new commercial kit has recently become available. We report our initial experience with use of the kit with 29 patients and discuss one patient who experienced anaphylaxis during i.d. testing.

Up to 10% of patients attending hospital self-report a penicillin allergy,[1] although only 10% of these patients (1% total patients) prove to have a true immunoglobulin E (IgE)-mediated allergy.[2] All patients who report a penicillin allergy are denied penicillin-based antibiotics and are given broad-spectrum antibiotics that are more expensive and may contribute to development of antibiotic resistance.[3]

Exclusion of penicillin allergy is challenging. Detection of serum IgE specific for major penicillin determinants has a high positive predictive value but fails to identify many patients with a penicillin allergy.[4] Ideally, skin testing to major and minor penicillin determinants would improve diagnosis.[5–7] Unfortunately, in Australia, the availability of skin testing reagents (Allergopharma, Reinbeck, Germany) ceased in 2002, and these solutions expired in 2004.

A new manufacturer (Diater Laboratories, Madrid, Spain) has now made alternative penicilloyl poly-L-lysine (PPL) and minor determinant mixture (MDM) available. Preliminary results from Europe show a strong correlation to Allergopharma reagents.[8,9] Based on these results, we have recommenced testing of patients referred for investigation of penicillin allergy. We report our initial experience with the new reagents.

Patients who were actively avoiding penicillins because of a prior diagnosis of penicillin or cephalosporin allergy were recruited from private and public allergy clinics. All patients had negative (<0.35 kU_A/L) fluorescent enzyme immunoassay (FEIA) (Pharmacia, Uppsala, Sweden) for penicilloyl-specific and amoxycilloyl-specific IgE and were subsequently referred for penicillin testing. Exclusion criteria were pregnancy, beta-blocker medication or previous severe non-IgE-mediated reaction to penicillin.[2] Patients abstained from antihistamines for at least 5 days before testing.

Previous reactions to penicillins were classified according to historical symptoms and timing of onset of symptoms after exposure to first dose of medication with an immediate reaction occurring within 1 h of exposure and

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delayed reactions occurring after 6 h. There were no intermediate reactions (1–6 h). Immediate reactions were further defined as either isolated urticaria or anaphylaxis when accompanied by respiratory or cardiovascular compromise. Patients who could recall the nature of the reaction, but did not fulfil criteria for either urticaria or anaphylaxis were classified as possible IgE-mediated allergy. This included non-urticarial rash, gastrointestinal (GI) symptoms and other adverse effects. Informed consent was obtained before the testing within the drug allergy clinic and the study was approved by The Alfred Hospital Institutional Ethics Committee.

Solutions were prepared within 2 h of use. One millilitre of diluent supplied by Diater Laboratories (DAP kit; Madrid, Spain) was mixed with each vial of PPL and MDM (made up of sodium benzylpenicillin 0.5 mg, benzylpenicilloic acid 0.5 mg and sodium benzylpenicilloate 0.5 mg). Further dilutions of 1/10 and 1/100 (Figure 1) were carried out using normal saline (0.9% NaCl). Amoxycillin (Douglas Pharmaceuticals, Sydney, Australia) was prepared in sterile water for injection to a concentration of 20 mg/mL and benzylpenicillin (CSL, Melbourne, Australia) was prepared to 6 mg/mL for both skin and i.d. testing.

The protocol for testing was based on the manufacturer's suggested protocol of sequential testing starting with skin prick test (SPT) with PPL, then i.d. tests (IDT) with PPL 1/10 and PPL neat and if these were negative, to then proceed with SPT to MDM neat, then IDT with MDM 1/100, MDM 1/10 and MDM neat. However, to save time, testing was carried out in parallel. The manufacturer does not comment on testing with amoxycillin, but does suggest caution with patients who have had previous anaphylaxis by recommending starting 'cutaneous tests' with 1/1000 dilution. The final protocol for skin testing was amended after an early adverse reaction and is shown in Figure 1. SPT was carried out on the volar surface of the forearm using histamine and normal saline as the positive and negative controls, respectively. A positive SPT was defined as a wheal diameter of $\geq$3 mm with surrounding erythema at 15 min or an increase in wheal diameter $\geq$3 mm for IDT measured at 20 min. Any positive SPT or IDT was interpreted as confirmation of penicillin allergy and no further testing was carried out. Information was not collected on delayed reactions at site of IDT.

Patients with negative SPT and IDT were challenged immediately after skin testing with 250 mg of whichever penicillin was taken at initial reaction, if known. Patients who could not recall the drug to which they reacted received amoxicillin, as this is the most common penicillin prescribed.[10] Patients were observed for at least 1 h after the oral challenge and asked to continue taking 250 mg of the antibiotic b.i.d. for the next 5 days.

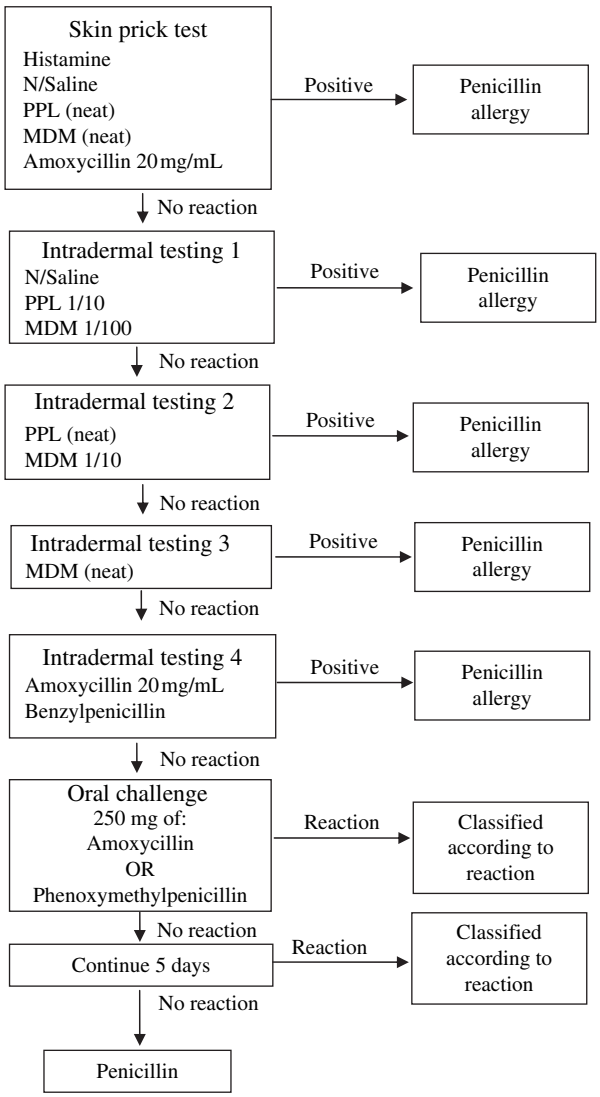

Figure 1 Protocol used for skin prick and i.d. testing of patients to assess allergy to penicillin-based antibiotics. MDM, minor determinant mixture; PPL, penicilloyl poly-L-lysine.

Patients were contacted by telephone at 48 h and 7 days after testing to determine adverse events. If patients reported symptoms, they were asked to return for a formal assessment and their reaction was classified as rash, GI upset, nausea, headaches or other. As many patients could not return, it was not possible to clearly define the type of rash.

A total of 46 patients was invited to participate in testing for penicillin allergy; of these, 15 patients declined and 2 did not proceed because of unstable asthma, leaving 29 patients who underwent testing for penicillin allergy according to

the protocol (Figure 1). The median age of these 29 patients was 47 years (range 22–80 years); 9 were men.

Original reactions are listed in Table 1. Classification according to the history of previous reactions showed that patients could be classified into one of three clinical categories: (i) anaphylaxis after taking either a penicillin or a cephalosporin, (ii) delayed urticaria occurring >6 h after the first dose or (iii) a possible IgE-mediated penicillin allergy with subsequent avoidance of penicillin-based antibiotics.

Four patients had a positive skin test to one of the reagents. The results are stratified in Table 1 according to the presenting reaction. No patient had a positive SPT. All four positive results followed i.d. testing.

There was one serious adverse event during testing, which occurred on the first day. The patient was a 25-year-old man who developed anaphylaxis on i.d. testing with positive reactions to all four reagents (PPL (1/10), MDM (1/100), amoxycillin and benzylpenicillin). He had a history of asthma and had reacted to amoxycillin/clavulanate 3 months earlier with bronchospasm 20 min after exposure. His FEIA to ampicilloyl was 0.34 kU_A/L with penicilloyl-G, penicilloyl-V and amoxycilloyl all <0.10 kU_A/L and a negative SPT.

The protocol was adjusted after this reaction, so that PPL and MDM were first tested and then amoxycillin and benzylpenicillin only after IDT to major and minor determinants were negative (Figure 1). No further serious adverse events occurred.

Of the remaining 25 patients with negative skin tests, 18 were challenged with amoxycillin and 7 were challenged to penicillin. There were no immediate reactions. However, four patients developed delayed reactions at 6 h or more after the challenge, in all cases classified as rash.

We present our experience with skin testing using the newly available commercial PPL and MDM (Diater Laboratories) in patients who had previously been advised to avoid penicillin. Our experience supports a high negative predictive value for excluding IgE-mediated allergy with no immediate reactions occurring after challenge to amoxycillin, or penicillin after negative skin testing. Although safe in low-risk patients, one patient with a history of anaphylaxis developed anaphylaxis on testing.

After the episode of anaphylaxis, only patients without an immediate reaction to penicillin were offered testing. Patients with a highly probable history of immediate penicillin sensitivity were deemed to have penicillin allergy. A review of reactions to skin testing for penicillins up to the year 2000 showed that systemic reactions only occurred in 0.11% of 7539 patients.[11] However, this rate seems to reflect the pretest probability of positive results with approximately 9% of 147 patients with positive skin tests developing a systemic reaction in two studies since 2000.[12] The two important risk factors were previous anaphylaxis (9 of 13 reactors) and onset of symptoms within 1 h of initial drug exposure (12 of 13 reactors).[12] Asthma was not associated with systemic reactions.[12]

We could not determine whether amoxycillin, benzylpenicillin, PPL or MDM caused our patient's reaction. However, amoxycillin was responsible for 50% of the adverse skin test reactions in another cohort where the drugs were tested in isolation.[5] In the recently published cohort using the Diater Laboratory PPL and MDM, and amoxycillin, no systemic reactions were seen among 195 patients, including 102 patients with positive skin tests.[9]

After the adverse reaction, testing was only carried out on patients with a reaction suggestive of IgE-medicated allergy occurring >1 h after exposure; a possible or unknown history of penicillin allergy or an allergy to cephalosporins. With these restrictions, no further IgE-mediated reaction to challenge occurred. Approximately

Table 1 Results of skin tests and oral challenge

Initial event			Skin test Positive†					Skin test Negative, oral challenge			
Classification	*n*	Drug	*n*	PPL	MDM	BP	AMX	*n*	Immediate	Delayed	Reaction type
Anaphylaxis	1	AMX	1	+	+	+	+	0			
	4	CEPH	1		+			3	0	0	
Delayed urticaria	3	AMX	0					3	0	2	Rash
	2	BP	0					2	0		
	1	CEPH	0					1	0		
	1	UNK	0					1	0		
Possible IgE-mediated allergy	6	AMX	0					6	0		
	7	BP	1	+				5	0	1	Rash
			1		+						
	4	UNK	0					4	0	1	Rash
Total, *n*	29		4					25			

†All positive skin tests were i.d. AMX, amoxycillin; BP, benzylpenicillin; CEPH, any cephalosporin; IgE, immunoglobulin E; UNK, unsure of potential cause, but told to avoid penicillins.

16% of patients with an IgE-mediated penicillin allergy defined by challenge can have negative skin tests and blood specific IgE test.[5,13] If only those who are unlikely to have an IgE-mediated allergy are tested and challenged, the negative predictive value of our testing should remain high and the likelihood of a systemic reaction on challenge should be low, optimizing the protocol.

The protocol we used was adapted from the manufacturer's recommendations and differs from that recommended by the European Network of Drug Allergy (ENDA),[14] which suggests sequential SPT and IDT to the maximum concentration of solutions in patients with reactions that have not occurred within 1 h of exposure. In those with prior severe reaction or those with a previous mild reaction, but are at special risk, it recommends carrying out tests starting at 1/1000 dilution. It also suggests repeat testing 2–4 weeks later in some patients who have not been pursued. As a result of our experience with penicillin skin testing, we now conform to the ENDA guidelines and use greater dilutions (to 1/1000) in patients at fulfilling the high-risk categories requiring penicillin skin testing. Although we have not had any patient with immediate reactions on challenge, we also exercise caution in challenging the high-risk patients and do so by administering to 1/10 initial dose.

We continued the penicillin (or amoxycillin) for 5 days after the challenge to determine whether the patient would develop a delayed-type hypersensitivity reaction. This protocol differs from others and does not reflect on performance of SPT but improves prediction of future reactions to penicillin that are not mediated by IgE-dependent mechanisms.[5,10]

Patients who are allergic to penicillins are frequently advised to avoid cephalosporins, but recent papers suggest that this may not be necessary.[15] We carried out skin testing on cephalosporin-allergic patients as recommended and found one patient out of five who was skin test positive to penicillin determinants.[16]

As this is the first reported experience with this product outside of Europe, we believe that this information will be useful for clinicians testing for penicillin allergy and for all clinicians with penicillin-allergic patients.

Our experience with the new commercial PPL and MDM (Diater Laboratories) shows the reagents to be useful, particularly in exclusion of allergy in patients who have not had an immediate reaction to penicillin antibiotics or who have a documented allergy to cephalosporins.

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