

Original article

Clinical presentation and time course in hypersensitivity reactions to β -lactams

Background: β -lactam hypersensitivity reactions are classified as immediate or nonimmediate. Diagnosis is usually based upon skin tests and provocation challenges.

Objective: The time course of the reactions in proven β -lactam hypersensitivities was studied and then correlated with the symptoms to determine the relationship between the clinical presentations and the time course.

Method: All of the patients who consulted between 1996 and 2004 for a suspected β -lactam hypersensitivity reaction were studied. Two hundred and ten patients with a proven hypersensitivity reaction diagnosed according to the European Network on Drug Allergy were included in the present study.

Results: Of the patients, 36.7% had urticaria as a single symptom, 19.1% anaphylaxis without shock, 17.6% anaphylactic shock and 19.1% maculopapular exanthema. Anaphylactic shock and anaphylaxis mostly occurred within 1 h after drug administration. Exanthema mainly occurred after 24 h. Urticaria as a single symptom occurred at any time. A firm diagnosis was determined using immediate-reading skin prick (10.0%) and intradermal tests (38.1%), late-reading skin tests (19.1%) or provocation tests (32.9%).

Conclusion and clinical implication: Depending on the time course of the reaction, three clinical groups were identified: anaphylaxis and anaphylactic shock (immediate reaction); maculopapular exanthema (late reaction) as well as urticaria (immediate and late reaction).

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Drug hypersensitivity reactions are commonly classified as immediate or nonimmediate depending on their clinical presentation (1). Immediate reactions are usually induced by an IgE-mediated mechanism and occur within the first hour following the last drug administration (2). These reactions usually appear as urticaria, angioedema, rhinitis, bronchospasm or anaphylaxis. Nonimmediate reactions may occur at any time from 1 h to 48 h after the last drug administration and are often induced by a delayed T-cell-dependent type of allergic reaction (3, 4). Maculopapular exanthema is the most common nonimmediate reactions.

β -lactams are reported to induce both immediate and nonimmediate reactions (5–9). They represent one of the main causes of reported allergic reactions to drugs. However, the time course of the different clinical manifestations of allergic reactions to β -lactams has rarely been reported in detail for a large series of patients.

The diagnosis of β -lactam allergic reactions is now well established and can be determined using the standardized diagnostic procedures of the European Network on Drug Allergy (ENDA) (10–13). After examining clinical history

in detail, the diagnosis is usually based upon skin tests and provocation challenges (14). The measurement of serum β -lactam-specific IgE does not currently appear to have a high sensitivity in the diagnosis of allergic reactions. This is possibly due to methodological problems and also depends upon the availability of the relevant antigens (15, 16). The value of other biological tests such as histamine release and basophil activation in the diagnosis of β -lactam allergy is either insufficient or still under investigation (17–20).

In the present study carried out on 210 patients with a proven β -lactam allergy, we carefully analysed the time course of the different symptoms and assessed the diagnostic methods which were then correlated with the symptoms and their respective time courses.

Methods

Between September 1996 and December 2004, we prospectively studied all of the patients who consulted for a suspected allergic reaction to β -lactams in our center located in Montpellier, France.

This historic-prospective, dynamic, cohort study is part of a very large case and control cohort: the DAHD (Drug Allergy and Hypersensitivity Database).

Patients

This study included all of the patients with a diagnosis of drug hypersensitivity to β -lactams confirmed by skin tests (skin prick or intradermal) or a drug provocation test. However, the following cases were not included in the present study as challenge tests are contra-indicated: patients with very severe cutaneous reactions such as toxic epidermal necrolysis, Stevens–Johnson-Syndrome, drug reaction with eosinophilia and systemic symptoms and vasculitis, as well as those with organ involvements such as hepatitis and pneumonitis (21). Patients with an HIV infection were also excluded from the study because these cases usually represent a more complex problem (22). Atopic patients were defined as those having at least one positive skin prick test with the standardized battery of the most common aeroallergens of our region.

Clinical diagnosis of β -lactam allergy

At least 4 weeks after the resolution of clinical symptoms and far from any illness, all patients underwent the standardized ENDA diagnosis for drug allergy which included the ENDA questionnaire, skin tests to several β -lactam determinants and provocation tests when skin tests were negative (10–13, 23). Skin prick tests were carried out first and, if negative, intradermal skin tests were then performed. Both immediate and nonimmediate skin reactions were recorded. If the intradermal skin tests were negative, then an oral challenge was carried out.

Clinical history. The ENDA questionnaire lists 43 symptoms possibly related to drug hypersensitivity as well as the time lapse between the last administration of the drug and the reaction (time course) (10). This standardized questionnaire associated to the expertise of a training doctor was the best way of characterizing the clinical history. Anaphylaxis was defined as a severe, life-threatening generalized or systemic hypersensitivity reaction (24). When urticaria/angioedema were associated with the other symptoms consistent with anaphylaxis (respiratory compromise, persistent gastrointestinal symptoms), the patient was classified as 'anaphylaxis'. The term 'anaphylactic shock' was utilized when there was a drop in blood pressure. Patients with urticaria as the only symptom were classified as 'urticaria'. All of this information was included in a DAHD using File Maker Pro® (Filemaker, Santa Clara, CA USA).

Skin tests to β -lactams. Skin prick tests and intradermal skin tests were performed as previously described and according to ENDA recommendations (12, 13). The following reagents were utilized: the major and minor determinants of penicillin G (Allergopharma, Darmstadt, Germany), PPL (penicilloyl polylysine) and MDM (minor determinant mixture), as well as penicillin G, amoxicillin, ampicillin and any other β -lactam suspected from the patient's history (if the injectable form was available). The full-strength concentrations of the tested β -lactams were: 35 g/ml for PPL, 1100 g/ml for MDM, 25 000 IU/ml for penicillin G, 25 mg/ml for other penicillins and 2 mg/ml for cephalosporins (25). The test sequence was as follows: (i) prick tests (1/10 concentration and full strength) at 15–20 min intervals, (ii) intradermal tests (ID) (1/100, 1/10 and full-strength concentrations) at 20–30 min intervals. The procedure was stopped if an immediate positive

skin test was observed. Prick tests were considered positive if the mean wheal diameter was larger than 3 mm and accompanied by erythema with a negative response to the control saline (13). Intradermal reactions were considered positive when the diameter of the initial wheal increased by more than 3 mm (13). A late reaction was recorded at 4–6 h, 24–48 h and at 1 week (12, 26) in patients with a nonimmediate clinical history. The validity of immediate and nonimmediate skin tests to β -lactams, including semi-synthetic penicillin/cephalosporin, has been published in separate documents (12–14).

Provocation tests. The oral provocation tests consisted of ingesting increasing doses of the suspected drug every 30 min until the usual daily dose was administered (11). These tests were carried out very progressively under strict hospital surveillance as previously described (23). In most cases, the same route of administration was used as the one in the clinical history. If the oral form of an injectable drug was available and identical, then the drug was administered orally. Administration was single-blinded and performed on the ward by a physician with full resuscitation back-up. Patients with a history of anaphylactic shock had intravenous catheters in place during the entire test. Physicians and nursing staff monitored the symptoms and cutaneous signs throughout the test. They also performed pulmonary function tests if bronchospasm was evident in the clinical history and monitored pulse and blood pressures. Oral challenges were considered positive if they reproduced the original symptoms or if an anaphylaxis or an anaphylactic shock occurred (11, 23). If the original reaction produced only subjective symptoms and challenge testing led to similar, nonverifiable symptoms, then placebo challenge steps were performed.

Statistical analysis

As this is a descriptive study, no statistical tests were performed. To describe qualitative variables such as symptoms, time course of reaction or proportion of positive tests, we calculated percentages. Moreover, the quantitative variable (age) was expressed in median 25th – 75th percentiles as the number of subjects included in this study was low and the distribution was not normal (using the Shapiro–Wilk normality test and the Skewness and Kurtosis tests).

Results

Demographic characteristics of the patients

Two hundred and ten (21.6%) patients of 973 tested for a suspicion of allergy to β -lactams during the 8-year period had a positive diagnosis and were included in the study. 67.1% were female, 46.2% were atopic and 22.9% had asthma. The median age at the time of the clinical reaction was 32.9 years (25–75% percentiles: 19.9 – 46.6 years). The median age at the time of the tests was 39.7 years (24.8 – 52.9).

Of the patients, 36.7% had urticaria as a single symptom, 19.1% anaphylaxis without shock, 17.6% anaphylactic shock, 19.1% maculopapular exanthema, 1.9% isolated respiratory symptoms, 0.5% other skin reactions and 5.2% other symptoms.

Time lapse between drug administration and clinical reactions

Of the patients, 39.5% reported their reaction within 1 h after the last drug administration, 9.5% between 1 and 6 h, 13.8% between 6 and 24 h, 24.8% after 24 h and 12.4% of the patients were unable to define the time lapse between the last drug intake and the clinical reaction.

The time lapse between the drug administration and the clinical reaction is presented in Table 1. Anaphylactic shock and anaphylaxis mainly occurred within the first hour after drug administration, whereas maculopapular exanthema occurred essentially after 24 h. On the other hand, urticaria as a single symptom occurred at any time. The other reactions were not analysed as there were too few patients.

Diagnosis of β -lactam allergic reactions

The diagnosis of drug allergy reactions was determined by positive history as well as by either immediate positive skin prick (10.0%) and intradermal tests (38.1%), late positive skin tests (19.1%) or by positive provocation tests (32.9%). The symptoms and time course of the reactions differed depending on the type of positive test (Table 2). The diagnosis of anaphylaxis and anaphylactic shock was determined mainly by immediate-reading skin prick and intradermal tests. On the other hand, exanthema was diagnosed by nonimmediate skin tests in 47.5% of the cases. Among the 12 (15.6%) patients who expressed a history of urticaria between 1 and 6 h after drug administration, 16.7% had an immediate positive skin prick test, 33.3% an immediate positive intradermal test and 50.0% a positive oral drug provocation.

Discussion

In the present study, we found that patients with a proven β -lactam allergy had variable symptoms and time courses. About one-third of the patients experienced an anaphylactic shock or anaphylaxis occurring within 1 h after the last drug intake, and skin tests were positive in two thirds of them. Maculo-papular exanthema occurred in <20% of the patients, usually after over 6 h following the last drug intake. Urticaria as a single symptom was present in one third of the patients but could occur at any time after the last drug administration. Other reactions were far less common.

One of the problems in the diagnosis of drug allergy is the validity of the reporting. There is no doubt that the patient is seen either at the acute phase or when a letter has been written by a physician who has observed the clinical reaction or when a photograph has been taken. However, this is not always the case. The results of this study suggest that the reporting of allergic reactions to β -lactams is adequate since, as expected: (i) anaphylactic shocks occurred in 83.8% of the cases within 1 h after drug administration on the first day of treatment and anaphylaxis without shock in 72.5% of the cases (ii) maculo-papular exanthema mostly occurred at least 6 h (95%) after the last drug intake and several days after the start of the treatment. Another interesting and expected point is that immediate positive skin tests led to the diagnosis when the reaction occurred within 1 h after drug administration (71.4%) and that nonimmediate positive skin tests were only found when the reaction occurred later (98.8%). Finally, 32.9% of truly allergic patients had negative skin tests but a positive provocation

Table 1. Description of the time course and the drug intake depending on the clinical reaction of patients with a proven allergy to β -lactams

	Anaphylaxis	Anaphylactic shock	Urticaria	Maculopapular exanthema	Other reactions
<i>n</i>	40	37	77	40	16
Age at history (year)	31.9 (19.9–45.5)	38.4 (29.1–50.5)	35.9 (19.4–48.5)	30.4 (8.9–39.9)	37.4 (19.9–49.9)
Sex (male, %)	16 (40.0)	17 (46.0)	22 (28.6)	11 (27.5)	3 (18.8)
Time course of reaction, <i>n</i> (%):					
<1 h	29 (72.5)	31 (83.8)	20 (26.0)	0	3 (18.8)
1–6 h	4 (10.0)	1 (2.7)	12 (15.6)	2 (5.0)	1 (6.3)
6–24 h	4 (10.0)	1 (2.7)	15 (19.5)	6 (15.0)	3 (18.8)
>24 h	2 (5.0)	1 (2.7)	20 (26.0)	24 (60.0)	5 (31.3)
Unknown	1 (2.5)	3 (8.1)	10 (13.0)	8 (20.0)	4 (25.0)
Drug involved, <i>n</i> (%):					
Amoxicillin	17 (42.5)	15 (40.5)	38 (49.4)	17 (42.5)	4 (25.0)
Ampicillin	4 (10.0)	2 (5.4)	4 (5.2)	4 (10.0)	2 (12.5)
Other penicillin	0	0	3 (3.9)	1 (2.5)	1 (6.3)
Cephalosporin 1G	9 (22.5)	15 (40.5)	13 (16.9)	2 (5.0)	0
Cephalosporin 2G	0	2 (5.4)	2 (2.6)	0	0
Cephalosporin 3G	4 (10.0)	1 (2.7)	3 (3.9)	2 (5.0)	4 (25.0)
Unknown	6 (15.0)	2 (5.4)	14 (18.2)	14 (35.0)	5 (31.3)

Cephalosporin 1G: cephalosporin first generation: cefaclor, cefadroxil, cefalexine, cefapirine, cefatrizine, cefazoline.

Cephalosporin 2G: cephalosporin second generation: cefamandol, cefuroxime.

Cephalosporin 3G: cephalosporin third generation: cefotaxime, cefotiam, ceftriaxone.

Table 2. Clinical presentation of patients with a proven allergy to β -lactams

	<i>n</i>	Immediate positive prick tests	Immediate positive ID tests	Nonimmediate positive skin tests	Positive provocation tests
Sex (male, %)	69	29 (36.3)	11 (27.5)	7 (33.3)	22 (31.9)
Delay between drug reaction and test (months)		7.9 (3.3–169.3)	9.7 (3.7–57.3)	62.3 (8.8–185.4)	11.8 (5.1–66.1)
Clinical reaction, <i>n</i> (%)					
Anaphylaxis	40	4 (10.0)	22 (55.0)	2 (5.0)	12 (30.0)
Anaphylactic shock	37	6 (16.2)	20 (54.1)	0	11 (29.7)
Urticaria	40	9 (11.7)	27 (35.1)	14 (18.2)	27 (35.0)
Exanthema	77	2 (5.0)	6 (15.0)	19 (47.5)	13 (32.5)
Other reaction	16	0	5 (31.3)	5 (31.3)	6 (37.5)
Time course of reaction, <i>n</i> (%)					
<1 h	83	15 (18.1)	47 (56.6)	1 (1.2)	20 (24.1)
1–6 h	20	3 (15.0)	6 (30.0)	4 (20.0)	7 (35.0)
6–24 h	29	0	8 (27.6)	8 (27.6)	13 (44.8)
>24 h	52	0	14 (26.9)	22 (42.3)	16 (30.8)
Unknown	26	3 (11.5)	5 (19.2)	5 (19.2)	13 (50.0)
Drug involved, <i>n</i> (%)					
Amoxicillin	91	9 (42.9)	34 (42.5)	20 (50.0)	28 (40.6)
Ampicillin	16	0 (0)	6 (7.5)	8 (20.0)	2 (2.9)
Other penicillin	5	1 (4.8)	2 (2.5)	1 (2.5)	1 (1.4)
Cephalosporin 1G	39	2 (9.5)	20 (25.0)	1 (2.5)	16 (23.2)
Cephalosporin 2G	4	2 (9.5)	0 (0)	0 (0)	2 (2.9)
Cephalosporin 3G	14	1 (4.8)	4 (5.0)	3 (7.5)	6 (8.7)
Unknown	41	6 (28.6)	14 (17.5)	7 (17.5)	14 (20.3)

Cephalosporin 1G: first generation cephalosporin 1: cefaclor, cefadroxil, cefalexine, cefapirine, cefatrizine, cefatrizine, cefazoline.

Cephalosporin 2G: second generation cephalosporin 2 generation: Cefamandol, cefuroxime.

Cephalosporin 3G: third generation cephalosporin 3 generation: cefotaxime, cefotiam, ceftriaxone.

Per cent in row

test. This rate was especially high with urticaria (67.5%) and lower in anaphylaxis and anaphylactic shock (30.0 and 29.7% respectively) (23). These results show that the ENDA procedure can be used reliably in the diagnosis of allergic reactions to β -lactams (10, 13).

As previously reported, β -lactams can induce a series of allergic reactions, but there was no clearly-described time course analysis (5–9). This study shows that three types of reaction account for over 88% of the allergic reactions to β -lactams: early-onset anaphylactic shock and anaphylaxis, late-onset maculopapular exanthema and isolated urticaria. In this study, urticaria appears to be either an IgE-mediated allergic reaction (i.e. with positive immediate reading skin tests) occurring within 1 h after drug administration or a nonimmediate reaction occurring between 1 and 6 h or even later (after 24 h). The study suggests that nonimmediate urticaria occurring between 1 and 6 h after the last drug administration resembles the nonimmediate reactions following peptide immunotherapy. These reactions started within 2 to 6 h after the injection of cat peptides and were in the form of urticaria or bronchospasm (27–29). Usually, these reactions were

not very severe and tended to subside with subsequent injections. They were ascribed to a direct T-cell activation induced by the injected peptide (30–33). β -lactams could well act as T-cell epitopes causing a reaction which has never been fully described in drug allergy and this may represent the type IVe drug allergic reaction (4). This hypothesis should however be confirmed by appropriate tests including skin biopsies during the nonimmediate reaction and *in vitro* T-cell activation markers (32, 34).

In conclusion, most β -lactam hypersensitivity reactions can be divided into three groups: anaphylaxis and anaphylactic shock (immediate reaction); maculopapular exanthema (late reaction) and urticaria (which can occur at any time). For the diagnosis of β -lactam hypersensitivity in clinical practice, skin tests and oral provocation tests are the most efficient.

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