

Original article

Allergy to betalactam antibiotics in children: a prospective follow-up study in retreated children after negative responses in skin and challenge tests

Background: Up to 10% of the patients in whom suspected betalactam hypersensitivity (HS) has been excluded by skin and challenge tests report suspected allergic reactions during subsequent treatments with the same or very similar betalactams. It has been suggested that the reactions may result from a re-sensitization induced by the challenge performed at the time of the allergological work-up. However, most patients did not undergo a second allergological work-up, to determine if the reactions resulted from betalactam HS or not.

Objectives: We aimed to determine if children diagnosed nonallergic to betalactams have tolerated subsequent treatments with the initially suspected and/or other betalactams, and, in case of a reaction, if the reaction resulted from betalactam HS.

Methods: We sent a questionnaire concerning the clinical history of their children to the parents of 256 children previously diagnosed nonallergic to betalactams. A second allergological work-up was performed in the children reporting suspected allergic reactions during subsequent treatments with the same and/or other betalactams. Skin tests were performed with the soluble form of the suspected (or very similar) betalactams and other betalactams from the same and other classes. Skin test responses were assessed at 15–20 min (immediate), 6–8 h (semi-late) and 48–72 h (late). Oral challenge (OC) was performed in children with negative skin tests, either at the hospital (immediate and accelerated reactions), or at home (delayed reactions).

Results: A response was obtained from 141 children (55.3%). Forty-eight (34%) of those children had not been treated with the betalactams for whom a diagnosis of allergy had been ruled out previously. Seven (7.5%) of the 93 children who had been treated again reported suspected allergic reactions. Skin tests and OC were performed in six of those children, and gave negative results in five children. In one child previously diagnosed nonallergic to amoxicillin associated with clavulanic acid, we diagnosed a delayed HS to clavulanic acid and a serum sickness-like disease to cefaclor. Thus, the frequency of reactions resulting from betalactam HS in children with negative skin and challenge tests is very low, and does not exceed 2.1% (2/93) if we consider that the child which refused a second allergological work-up is really allergic to betalactams.

Conclusion: Our results in a very large number of children show that reactions presumed to result from betalactam HS are rare in children in whom the diagnosis of betalactam allergy has been ruled out previously. Moreover, they suggest that, as shown for the initial reactions, most of the reactions during subsequent treatments are rather a consequence of the infectious diseases for whom betalactams have been prescribed than a result of betalactam HS. Finally, they suggest that the risk of re-sensitization by OC is very low, and do not support the notion that skin testing should be repeated in children diagnosed nonallergic to betalactams.

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Abbreviations: AMX, amoxicillin; ID, intradermal; HS, hypersensitivity; MPR, maculopapular rash; OC, oral challenge; SSLD, serum sickness-like disease.

Ten to 20% of patients report suspected allergic reactions to betalactams (1–3). Studies based on positive responses in skin and oral challenge (OC) tests show that 2–60% of

the patients reporting reactions to betalactams are really allergic (4–10). However, 0.5–10% of the patients in whom suspected betalactam hypersensitivity (HS) has been excluded by skin and challenge tests report suspected allergic reactions during subsequent treatments with the same or closely related betalactams (11–15). It has been suggested that the reactions may result from a re sensitization induced by the challenge performed at the time of the allergological work-up (8, 14, 16–18). However, most patients did not undergo a second allergological work-up, to determine if the reactions resulted from betalactam HS or not. The aim of this prospective study was to determine if children previously diagnosed non-allergic to betalactams (9) had tolerated subsequent treatments with the initially suspected and/or other betalactams, and, in case of a reaction, if the reaction resulted from a true betalactam HS.

Methods

Patients

We sent a questionnaire enquiring the clinical history of their children to the parents of 256 children previously diagnosed nonallergic to betalactam antibiotics, based on negative skin test and OC results (9). The parents were asked if their children had been treated again with the betalactams for whom drug allergy had been ruled out, and if the treatments had been tolerated. In case of a reaction, the parents were asked for the type and chronology of the symptoms. Parents were also asked if their children had been treated with other betalactams, and if the treatments had been tolerated. A reminder was sent 2 months later to the parents who did not respond. The children were classified into four groups: nonresponders (group A), children that have not been treated with the suspected betalactams (group B), children tolerant to subsequent treatments with the initially suspected betalactams (group C), and children reporting suspected allergic reactions during subsequent treatments with the same and/or other betalactams (group D). Reactions to betalactams were classified as described by Levine (19). A second allergological work-up, based on a detailed clinical history and review of the patient's chart, skin tests and OC, was performed in the children of group D.

Skin tests

As previously described (9), skin tests [pricks and intradermal (ID)] were performed with the soluble form of the suspected (or very similar) betalactams and other betalactams from the same and other classes. The soluble betalactams used were benzylpenicillin (Penicillin G®; Panpharma, Fougères, France), amoxicillin (AMX, Clamoxyl®; Beecham, Philadelphia, PA, USA), ampicillin (Totapen®; Bristol, New York, NY, USA), cefazolin (Cefazoline®; Panpharma, Fougères, France), and ceftriaxone (Rocephine®; Roche, Burlington, NC, USA). The concentrations used were 250, 2500 and 25 000 IU/ml for penicillin G, and 0.25, 2.5 and 25 mg/ml for the other betalactams. Skin test responses were assessed at 15–20 min (immediate), 6–8 h (semi-late), and 48–72 h (late). A wheal ≥3 mm (prick) or 5 mm (ID) in diameter, present 15–20 min after the application, was defined as an immediate positive response if there was also a negative response to control solution (0.9% saline) and a positive response to histamine (prick: 10 mg/ml, ID: 0.1 mg/ml).

Semi-late and late responses to ID injections were classified as positive if wheals ≥5 mm in diameter were present.

Oral challenge

Oral challenge were performed in children with negative skin tests, either at the hospital for 24–48 h (immediate and accelerated reactions), or at home (delayed reactions), after informed consent of the parents. In the hospital, children received a first dose of 1–2.5 mg of the drug. The dose was increased gradually every 20 min until the appropriate cumulative dose per day for age and weight was reached. At home, daily therapeutic doses were prescribed for 5–7 days. Children were advised to stop treatment and to take oral antihistamines and/or corticosteroids if they experienced a reaction. OC were classified as positive if an adverse reaction of an allergic nature [e.g. urticaria and/or angioedema, maculopapular rash (MPR), erythema multiforme] occurred during the treatment or within 24–48 h of the end of the treatment.

Statistical analysis

Demographic and clinical differences between the groups of children were assessed by the *t*-test and χ^2 -test respectively. A *P*-value ≤ 0.05 was considered to be significant.

Results

Responses to the questionnaire

One hundred and fifteen children (group A, 44.7%) did not respond to the questionnaire and reminder, including 78 children who had moved towards an unknown address. Forty-eight of the 141 responder children (group B, 34.0%) had not been treated with the betalactams for whom a diagnosis of allergy had been ruled out. Nine of these children had tolerated treatments with other betalactams since the allergological work-up. Eighty-six of the 93 other children (92.5%; group C) had tolerated subsequent treatments with the initially suspected betalactams and other betalactams (*n* = 20), and seven children reported one (*n* = 5) or several (*n* = 2) suspected allergic reactions (7.5%; group D). The reactions were urticaria and/or angioedema (*n* = 7), MPR (*n* = 1), and unidentified rash (*n* = 1). The suspected betalactams were AMX alone (*n* = 3) or associated with clavulanic acid (*n* = 6). One child (no. 5) also reported a serum sickness-like disease (SSLD) associated with cefaclor treatment. The demographic characteristics of the children in the four groups are indicated in Table 1. The clinical characteristics of the children at the time of their first reactions are indicated in Table 2, and the clinical characteristics (first reactions and reactions to subsequent treatments with betalactams) of the children in the group D are indicated in Table 3.

The suspected betalactams and the type and chronology of the first (nonallergic) reactions were not significantly different between the children in groups A, B, and C. At the time of their first reaction, children in the group D were significantly younger than the children in group B

Table 1. Demographic characteristics of 255 children, including seven children investigated for suspected allergic reactions during subsequent treatments with betalactams after negative diagnostic work-up for suspected betalactam allergy

Group	A	B	C	D
Number of children	115	48	86	7
Ratio M/F	1.28	1.53	1.46	6
Age at the time of the first reaction: mean $\pm$ SD (range)	2.3 $\pm$ 2.15 years (2 months–9.6 years)	4.49 $\pm$ 4.0 years (3 months–16.4 years)	2.6 $\pm$ 2.75 years (4 months–12.2 years)	1.5 $\pm$ 1.13 years* (3 months–3.6 years)
Time between the first reaction and the first allergological work-up: mean $\pm$ SD (range)	2.0 $\pm$ 2.4 years (2 months–15.0 years)	2.5 $\pm$ 2.5 years (3 months–9.0 years)	2.4 $\pm$ 2.3 years (2 months–10.6 years)	1.6 $\pm$ 1.3 years (5 months–4.1 years)
Age at the time of the first allergological work-up: mean $\pm$ SD (range)	4.4 $\pm$ 3.0 years (10 months–16.6 years)	6.9 $\pm$ 4.3 years** (13 months–17.6 years)	5.0 $\pm$ 3.3 years (1–13.5 years)	3.1 $\pm$ 2.1 years (1–6.2 years)
Age at the time of present the investigation and second work-up: mean $\pm$ SD (range)	9.0 $\pm$ 3.3 years (3.7–21.1 years)	11.3 $\pm$ 4.5 years*** (3.7–23.1 years)	9.1 $\pm$ 3.5 years (3.7–17.6 years)	7.7 $\pm$ 2.6 years (4–10.7 years)

Group A: nonresponder children.

Group B: children that have not been treated with the initially suspected betalactams.

Group C: children tolerant to subsequent treatments with the initially suspected betalactams.

Group D: children reporting allergic-like reactions during subsequent treatments with betalactams.

* $P < 0.05$ vs children in the group B.

** $P < 0.0005$ vs children in the groups A and C.

*** $P < 0.005$ vs children in the groups A and C.

Table 2. Clinical characteristics of 255 children, including seven children investigated for suspected allergic reactions during subsequent treatments with betalactams after negative diagnostic work-up for suspected betalactam allergy

Group (n)	A	B	C	D
Number of children	115	48	86	7
Initial reactions				
Number	152	63	106	10
Type, n (%)				
Severe anaphylaxis	9 (5.8)	5 (8)	1 (1)	
Urticaria $\pm$ angioedema	91 (60)	38 (60.3)	61 (57.5)	5 (50)
Others	52 (34.2)	20 (31.7)	44 (41.5)	5 (50)
Chronology, n (%)				
Immediate	13 (8.5)	7 (11.1)	3 (3.8)	1 (10)
Accelerated	65 (42.8)	34 (60)	51 (48.1)	2 (20)
Delayed	74 (48.7)	22 (28.9)	52 (48.1)	7 (70)
Suspected antibiotics, n (%)				
Amoxicillin $\pm$ clavulanic acid	98 (66)	37 (58.7)	72 (67.9)	7 (100)
Other penicillins	5 (1.8)	2 (3.3)	3 (2.9)	
Cephalosporins	49 (32.2)	24 (38)	31 (29.2)	

Group A: nonresponder children.

Group B: children that have not been treated with the initially suspected betalactams.

Group C: children tolerant to subsequent treatments with the initially suspected betalactams.

Group D: children reporting allergic-like reactions during subsequent treatments with betalactams.

($P \leq 0.05$). At the time of the first allergological work-up and at the time of the present investigation, children in the group B were significantly older than the children in groups A and C ($P \leq 0.0005$ and 0.005 respectively).

Results of the allergological work-up

Skin tests and OC were performed in six of the seven children in group D, and gave negative results in five

children. In one child (no. 5), initially diagnosed nonallergic to AMX associated with clavulanic acid, we diagnosed a delayed HS to clavulanic acid (based on positive OC with AMX associated with clavulanic acid, and negative responses in skin tests and OC with AMX alone) and a SSLD to cefaclor (based on clinical history, with negative responses in skin tests). Thus, the frequency of relapses resulting from HS to betalactams in children with previous negative skin tests and OC is very low, and does not exceed 2.1% (2/93) if we consider that the child that refused a second allergological work-up (no. 7) is really allergic to betalactams.

Discussion

To our knowledge, we report the first prospective study based not only on a questionnaire, but also on skin and OC tests. In this study, performed in a very large number of children, we aimed to determine if children diagnosed nonallergic to betalactams had tolerated subsequent treatments with the initially suspected and/or other betalactams, and, in case of a reaction, if the reaction resulted from betalactam HS.

We show that only 7.5% of the children diagnosed nonallergic to betalactams report suspected allergic reactions during subsequent treatments with the initially suspected and/or other betalactams. Our results agree with those of other studies showing that 0.5–10% of the patients in whom suspected betalactam HS has been excluded by skin tests and OC report suspected allergic reactions during subsequent treatments with the same or closely related drugs (11–15). The children reported reactions to AMX alone or associated with clavulanic acid. This is not surprising because this drug is the most

Table 3. Clinical characteristics of seven children reporting suspected allergic reactions during subsequent treatments with betalactams for whom drug allergy has been ruled out by a previous allergological work-up

Child	First reactions (suspected betalactams)	Betalactam treatments tolerated between the first work-up and the reaction during subsequent treatment with betalactams	Time between the first work-up and the (first) subsequent reaction	Suspected allergic reactions to subsequent treatments (suspected betalactams)
1	2 delayed MPR (AMX associated with clavulanic acid)	2 treatments with AMX alone or associated with clavulanic acid	3.3 years	1 accelerated urticaria and angioedema (AMX)
2	1 accelerated unidentified rash (AMX associated with clavulanic acid)	No treatment	9 months	1 delayed MPR and 1 accelerated urticaria (AMX associated with clavulanic acid)
3	1 delayed MPR (AMX associated with clavulanic acid), and 1 urticaria and angioedema (AMX)	No treatment	5.2 years	1 delayed urticaria (AMX)
4	1 delayed unidentified rash (AMX associated with clavulanic acid)	7 treatments with AMX alone or associated with clavulanic acid, and with cephalosporins	1.3 years	1 accelerated unidentified rash (AMX associated with clavulanic acid)
5	1 delayed urticaria (AMX associated with clavulanic acid)	2 treatments with AMX alone or associated with clavulanic acid	3.7 years	1 delayed urticaria (AMX associated with clavulanic acid), and 1 SSLD (cefactor)
6	1 delayed urticaria (AMX)	No treatment	3.2 years	1 accelerated urticaria (AMX) and 1 accelerated urticaria (AMX associated with clavulanic acid)
7	1 delayed urticaria and angioedema (AMX associated with clavulanic acid), and 1 immediate urticaria (cefadroxyl)	1 treatment with AMX alone	3.6 years	1 accelerated urticaria and angioedema (AMX associated with clavulanic acid) (not explored)

AMX, amoxicillin; MPR, maculopapular rash; SSLD, serum sickness-like disease.

prescribed betalactam in France and was the most frequently suspected cause of the initial reaction in all groups of children (Table 2).

The differences for age at the time of their first reaction, the time at the first allergological work-up and the time of the present investigation between the four groups of children are probably coincidental, and suggest that the age of the patients should not be a determinant factor for the indication of an allergological work-up.

Several studies have suggested that, although well-tolerated, the challenge performed at the time of the allergological work-up may induce a « resensitization » (8, 14, 16–18), and may be responsible for allergic reactions during subsequent exposures to betalactams (16). Those results suggested that skin testing should be repeated in patients with negative skin and challenge tests.

The reactions in those patients may be nonallergic, as suggested by the studies of Bittner and Macy (11, 15, 20), showing that numerous patients reporting suspected allergic reactions after they have been diagnosed nonallergic to betalactams tolerate subsequent treatments with the suspected and/or closely related betalactams. Moreover, IgE-dependent (immediate) and non-IgE-dependent (nonimmediate) sensitizations have been detected by means of *in vivo* tests in 1–20% of subjects tolerant to betalactams (1, 18, 21–24). By means of *in vitro* tests (Lymphocyte Transformation Test, Leukocyte Migration Test, and specific IgM, IgG and IgE determinations), it has been shown that a large number of subjects tolerant to betalactams develop a transient and nonpathogenic sensitization when they are treated with these antibiotics (25).

We clearly show that, in children diagnosed nonallergic to betalactams, most reactions during subsequent treatments are not a consequence of betalactam HS. Five of the six children who underwent a second allergological work-up were diagnosed nonallergic to betalactams. In the sixth child, initially explored for a suspected HS to AMX associated with clavulanic acid, we diagnosed a nonimmediate HS to clavulanic acid and a SSLD to cefactor. Thus, if we consider that the child that refused a second allergological work-up is really allergic to betalactams, our results show that only two of 93 children (2.1%) may have been « resensitized » by the OC performed at the time of the first allergological work-up or by well-tolerated subsequent treatments with betalactams. Our results agree with those of Solensky et al. (26), who showed no sensitization and no reaction in 46 adult patients diagnosed nonallergic to penicillins and who underwent repeated treatments and skin testing with the initially suspected drugs. They also agree with the results of Bittner and Greenberger (11), who showed negative responses in skin tests and OC in three patients reporting suspected allergic reactions to betalactam treatments after they had been diagnosed nonallergic to betalactams.

Conclusion

Consistent with other studies (11–15), the results of this follow-up prospective study in a very large number of patients show that reactions presumed to result from betalactam HS are rare in children in whom the diagnosis of betalactam HS has been ruled out previously. They also suggest that, as shown for the initial reactions, most

reactions occurring during subsequent treatments are rather a consequence of the infectious diseases for whom betalactams have been prescribed than a result of betalactam HS. Finally, they agree with those of other studies showing that the risk of resensitization by OC is very low (11, 14, 26), and do not support the notion that skin testing should be repeated in children diagnosed nonallergic to betalactams.

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