Original Article

Natural History of Benign Nonimmediate Allergy to Beta-Lactams in Children: A Prospective Study in Retreated Patients After a Positive and a Negative Provocation Test

Aude Tonson la Tour, MD[a], Marine Michelet, MD[b], Philippe A. Eigenmann, MD[c], and Jean-Christoph Caubet, MD[c]

Geneva, Switzerland; and Toulouse, France

What is already known about this topic? Although it has been shown that the sensitivity to beta-lactams (BL) decreases over time in patients with an immediate hypersensitivity, data are lacking regarding the natural history of nonimmediate hypersensitivity to BL.

What does this article add to our knowledge? Our results showed that the vast majority of children (89%) with benign nonimmediate BL allergy become tolerant after 3 years. From another point of view, the negative predictive value of the drug provocation test (DPT) using a 2-day protocol was 96.7%.

How does this study impact current management guidelines? Our data strongly suggest that a follow-up DPT is safe and useful to assess tolerance acquisition in children with nonimmediate BL allergy. In addition, our data support the use of a 2-day protocol DPT.

BACKGROUND: The drug provocation test (DPT) is considered as the gold standard to diagnose drug allergy and is particularly important in the diagnosis of nonimmediate beta-lactam (BL) allergy in children. The natural history of BL allergy remains unknown.

OBJECTIVE: Our main aim was to evaluate the natural history of nonimmediate BL hypersensitivity and the long-term tolerance acquisition, and our secondary objective was to determine the negative predictive value (NPV) of the DPT following a 2-day protocol.

METHODS: Children developing a benign rash while treated by BL were prospectively recruited at the Emergency Department of the Geneva University Hospital from 2006 to 2011 and challenged with the incriminated BL (initial diagnostic drug provocation test [idDPT]) following a 2-day protocol. In case of a positive idDPT, the patients underwent a follow-up drug provocation test (fuDPT) 3 years later. In case of a negative idDPT, we sent a questionnaire to assess tolerance of a subsequent treatment with the incriminated BL.

RESULTS: Among the 18 children with a positive idDPT, 16 children (89%) had a negative fuDPT and 2 children developed a benign exanthema. Among those 16 children, 11 tolerated a subsequent treatment with the incriminated BL without any reaction, suggesting natural antibiotic tolerance acquisition. From another point of view, we found that the NPV of the DPT following a 2-day protocol was excellent at 96.7%.

CONCLUSIONS: Our data strongly suggest that a fuDPT is safe and useful to assess tolerance acquisition in children with a confirmed benign nonimmediate BL allergy. In addition, our results support the use of a short DPT protocol (2 days), which led to a high NPV of 96.7% in our population, with a favorable benefit-risk balance.

Key words: *Beta-lactam nonimmediate allergy; Drug provocation test; Negative predictive value*

Drug hypersensitivity reactions, particularly to beta-lactams (BL), represent a well-known major public health problem in children associated with a substantial morbidity and mortality.[1,2] The estimated prevalence in children ranges between 2.5% and 10.2%.[3] However, most of the studies overestimated the true prevalence due to incomplete diagnostic allergy workup not including a drug provocation test (DPT). This overdiagnosis is mainly due to the fear of life-threatening reactions during DPT, thus avoiding this procedure. This leads to unnecessary drug restriction, which contributes to increased

[a]Division of Pediatric Emergency, University Hospital of Geneva, Geneva, Switzerland
[b]Division of Pediatric Allergy, University Hospital of Toulouse, Toulouse, France
[c]Pediatric Allergy Unit, University Hospitals of Geneva, Geneva, Switzerland

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Corresponding author: Jean-Christoph Caubet, MD, Hôpitaux Universitaires de Genève, Département de Pédiatrie, 6 rue Willy-Donzé CH-1211 Genève 14, Switzerland. E-mail: jean-christoph.caubet@hcuge.ch.

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Abbreviations used
BL- Beta-lactams
DPT- Drug provocation test
fuDPT- Follow-up drug provocation test
idDPT- Initial diagnostic drug provocation test
NPV- Negative predictive value

resistance to antibiotics in the general population and high medical costs.

Exanthemas occurring during BL treatment are relatively common in children, ranging between 1% and 5%.[4] It has been shown that most of these benign skin rashes (ie, without symptoms suggestive of anaphylaxis or systemic reactions) are due to infectious diseases, or to interactions between drugs and infectious agents, rather than to real BL allergy.[5,6] According to recent international guidelines, the diagnosis of nonimmediate BL allergy (ie, occurring more than 1 hour after the last dose) in children is mainly based on a DPT, considered as the gold standard.[7,8] In addition, previous studies have shown that skin tests have a poor diagnostic value in nonimmediate benign reactions.[5,9,10]However, the DPT is not standardized in children, and there are a large variety of protocols currently used not only among various countries, but also among various centers in a given country. Particularly, the duration (number of days) of the DPT to diagnose a nonimmediate reaction is still a matter of debate.[8] There is a need for studies to determine the optimal duration of the DPT for nonimmediate reactions in children. In addition, the natural history of patients with a confirmed benign nonimmediate allergy to BL remains unknown. Only few studies, mainly performed in the adult population, have suggested a decreased sensitivity to BL over time, as shown by skin tests or *in vitro* tests becoming negative.[11,12] However, studies including a follow-up DPT (fuDPT) in patients with confirmed BL allergy are currently lacking in the literature, particularly in the pediatric population.

The primary objective of this prospective follow-up study was to evaluate the natural history of nonimmediate BL allergy in children by performing a fuDPT 3 years after a positive initial diagnostic DPT (idDPT). In addition, a follow-up phone call visit was performed to evaluate long-term tolerance in case of subsequent treatments with BL if this fuDPT was negative. Our secondary objective was to determine the negative predictive value (NPV) of the DPT following a 2-day protocol by means of a questionnaire evaluating the tolerance of the incriminated BL after a negative idDPT.

METHODS

Patients and study setting

The current study is a follow-up of a previously published prospective study. Inclusion and exclusion criteria are described elsewhere.[5] This study was approved by the Ethics Committee of the Geneva University Hospitals, Switzerland.

Briefly, children developing a benign rash while treated by BL were sequentially recruited at the Emergency Department of the Geneva University Hospital from 2006 to 2011. They were then challenged with the incriminated BL (idDPT) 2 months after the initial reaction. To increase the study's statistical power, additional children with a history of benign skin eruption during a BL treatment and challenged at our outpatient's clinic were prospectively included (without any restriction regarding the delay from the initial reaction).

Then, depending on the result of this idDPT, positive or negative, children were divided into 2 groups.

Assessment of the natural history of BL allergy

In the case of a positive idDPT, the patients underwent a second DPT 3 years later with the culprit BL antibiotic (fuDPT). The DPT was performed by administrating an initial dose of 10% of the whole dose (calculated by weight), and if this dose was well tolerated, the remaining 90% of the dose was given 30 minutes later. To identify reactions that may occur only at a higher dose, we used an initial dose of 25 mg/kg for amoxicillin, 23 mg/kg for cefprozil, and 23 mg/kg for cefaclor (which correspond to 150% of the usual therapeutic dose adapted to the weight). All patients were observed at least 1 hour after the last dose under strict hospital surveillance with full resuscitation backup. Then, the incriminated BL was prescribed for 48 hours at the standard therapeutic dose (50 mg/kg/day for amoxicillin, 45 mg/kg/day for cefaclor, and 30 mg/kg/day for cefprozil), to limit unnecessary exposure to a higher dose with potential side effects. In case of reactions, children were advised to stop treatment, to take oral antihistaminic, and to contact the research team to identify delayed reactions.

DPT was considered positive if any objective symptoms suggestive of an allergic reaction occurred during the treatment or within 48 hours after the last dose.

Finally, we organized a follow-up phone call visit for patients with a negative fuDPT to determine the tolerance of a subsequent full treatment for an infectious illness with the incriminated BL.

Questionnaire to assess the NPV of DPT

In case of negative idDPT, we sent a questionnaire to patients/parents and/or to their primary care physician, including questions about subsequent treatments and the tolerance to the culprit antibiotic. If the antibiotic was not tolerated, the patients were asked to describe the reaction.

Of note, the initial choice of a 2-day protocol for the idDPT was based on preliminary data suggesting that only a minority of allergic children will react after 2 days, and the potential side effects of a prolonged antibiotic treatment were taken into account.

RESULTS

fuDPT in patients with a BL allergy, confirmed by a positive idDPT

Characteristics of the included patients with a diagnosis of BL allergy as confirmed by a positive idDPT are shown in Table I. Eighteen patients with a positive idDPT have been included, 10 from the initial study (56%) and 8 recruited prospectively at our outpatient allergy clinic (44%). The reactions observed during the idDPT were maculopapular exanthema (n = 9, 50%), urticaria (n = 8, 44%), and vomiting/asthenia (n = 1, 6%). Although the initial reaction was nonimmediate (>1 hour), 5 children (28%) developed a reaction within the first hour after administration of the first challenged dose. None of the patients presented reactions after the third dose at home. The incriminated antibiotics were amoxicillin (n = 10, 55%), amoxicillin-clavulanic acid (n = 6, 33%), cefaclor (n = 1, 6%), and cefprozil (n = 1, 6%). The idDPT was performed at a median of 3 months after the initial reaction (range, 1 and 132 months).

To investigate the natural history of these BL allergies, a fuDPT was organized. The mean time elapsed between the