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Prospective study of 5-day challenge with penicillins in children

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ABSTRACT

Objectives To examine if a 5-day challenge with penicillin improves the diagnostic sensitivity compared with a single full dose in children with mild skin reactions.

Design Subjects referred with suspected allergy to penicillin were consecutively included. Irrespectively of the morphology of the index reaction and the result of specific IgE, all subjects underwent a two-step titrated drug provocation test (DPT) with the culprit drug followed by a 5-day challenge at home.

Participants Children and adolescents aged 0–18 years referred to allergic workup for penicillin hypersensitivity at two paediatric Danish centres. Only subjects with non-severe skin reactions were included.

Results A total of 305 subjects were included and 22 (7%) of the DPTs were positive. Three subjects reacted within 1 hour of the first full dose and nine reacted 1–8 hours after the first full dose. Additional 10 positive reactions were observed during the prolonged provocation. Seven subjects reacted after the second full dose and three reacted after 3–6 days. Only mild skin rashes were observed. Eighteen subjects had a specific IgE to a penicillin >0.1 kU/L. Only one of these had a positive DPT.

Conclusion In children, a DPT with penicillins should include at least two full doses. In children with mild hypersensitivity reactions it may be safe to perform DPTs despite a low specific IgE.

Trial registration number NCT04331522

What is known about the subject?

- The vast majority of drug provocation tests with penicillins in children are negative. To perform prolonged provocations may pick up additional allergic reactions.

What this study adds?

- This study illustrates the value of prolonged provocation tests.
- Only 55% of the positive reactions appeared before the second full dose was administered.
- Interestingly, a specific IgE value between 0.1 kU/L and 1.01 kU/L was not associated with a positive provocation.

INTRODUCTION

Parent-reported prevalence of penicillin allergy in children is around 10%, but the real prevalence is considerably lower.[1 2] An erroneous penicillin allergy labelling leads to inappropriate prescription of broad spectrum antibiotics that are more expensive, may be less effective and often have more side effects than penicillins.[3] The optimal protocol for evaluating hypersensitivity reactions to penicillins in children is debated, and a recent survey illustrated significant heterogeneity in the diagnostic approach to β-lactam hypersensitivity.[4]

The European Network for Drug Allergy (ENDA), European Academy of Allergology and Clinical Immunology (EAACI) has recommended separate diagnostic algorithms for immediate and for non-immediate hypersensitivity reactions to β-lactams.[5 6] The distinction between the two types of reaction was previously based exclusively on the time interval from drug intake to the onset of a reaction, that is, immediate reactions appearing within 1 hour, and non-immediate reactions appearing more than 1 hour after drug intake.[7] In a recently published updated guideline from the EAACI Drug Allergy Interest Group (DAIG), a new classification of hypersensitivity reactions to β-lactams was introduced. This novel classification is based on both the chronology and the morphology of the index reaction with the time intervals overlapping.[8] An immediate reaction, typically urticaria, may occur up to 6 hours after the last administered dose, while non-immediate reactions can occur from 1 hour to several days after the initial drug administration and can present as maculopapular rash or delayed urticaria. The diagnostic workup should be differentiated, based on a risk stratification of the index reaction. The authors, however, conclude that further studies are needed to provide data supporting the standardisation of drug provocation test (DPT) protocols. Particularly, consensus is lacking concerning the optimal dosing schedules and whether extended DPTs are needed. In addition, it may be advisable to have separate protocols for children and adults.

In the present study performed at two Danish paediatric departments, we prospectively included children referred with a history of mild hypersensitivity reaction to oral penicillin. The same DPT protocol was used for all subjects irrespectively of the classification of the index reaction and the result of specific IgE.

The purpose of the study was to evaluate whether a prolonged DPT at home for 5 days picks up additional positive reactions compared with a two-step provocation test with a single therapeutic dose. In addition, we wanted to evaluate the ability of skin prick test (SPT), specific IgE and the morphology of the index reaction to predict the outcome of the DPT.

METHODS

Subjects

During a 5-year period from 2014 to 2019, all children aged 0–18 years with suspected allergy to penicillins were successively included in the study. The children were referred to the local paediatric department, depending on place of residence, the Regional Hospital Central Jutland or the Hans Christian Andersen Children's Hospital, Odense University Hospital. All included children had either developed a skin rash during oral treatment with penicillin leading to discontinuation of the drug or they had developed a rash within 48 hours after ended penicillin treatment. Subjects with a history of anaphylaxis and children with severe non-immediate reactions (Stevens-Johnson syndrome, toxic epidermal necrolysis and acute generalised exanthematous pustulosis) were excluded.

At both centres the allergy workup and the DPTs were supervised by a paediatric allergologist.

Allergy workup

Prior to the DPT, the index reaction was classified based on history, pictures on cell phones and medical records. Specific IgE (ImmunoCAP, Thermo-Fisher Scientific, Uppsala, Sweden) to benzylpenicillin, penicillin G, amoxicillin and ampicillin was measured with a cut-off value of 0.1 kU/L. At the university hospital, only, an SPT with the undiluted culprit drug was performed immediately prior to the DPT.[8] In case the culprit drug was amoxicillin–clavulanic acid, the SPT was performed with amoxicillin alone. Reactions to SPT were considered positive when the diameter of the weal was at least 3 mm compared with the negative control (saline).

Drug provocation test

All children and adolescents underwent an open oral DPT with the culprit drug. The in-hospital part of the DPT was performed in two steps: an initial dose of one tenth of a therapeutic dose and subsequently after 1 hour a full therapeutic dose according to weight. The used therapeutic doses were: phenoxymethylpenicillin: 15 mg/kg maximum 800 mg, amoxicillin: 15 mg/kg maximum 500 mg, dicloxacillin: 15 mg/kg maximum 1000 mg according to the Danish summaries of product characteristics.[9] The children were observed for 2 hours at the department and then continued with a 5-day provocation at home (figure 1). The first dose at home was administered in the evening, approximately 8 hours after the first full dose. The following 4 days, a therapeutic dose was administered three times a day. The DPT was considered positive if any objective allergic symptoms occurred during the DPT or the following 48 hours. The subjects were provided with the drug, a medication schedule to place a check mark for every taken dose and a prepaid envelope for returning the schedule to confirm adherence. The subjects were advised to return to the paediatric department in case of allergic reactions during the DPT.

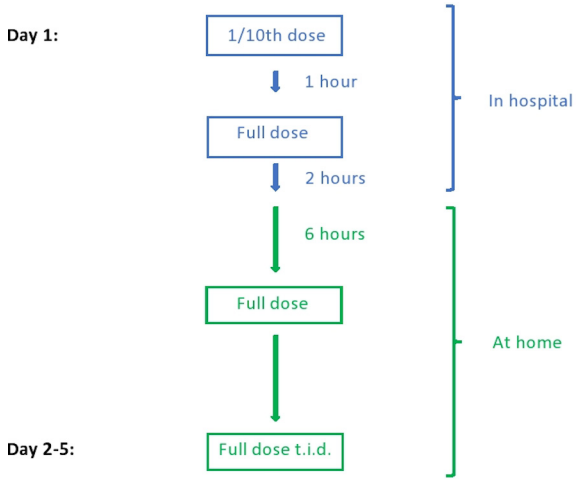

Figure 1 A schematic illustration of the drug provocation test. t.i.d, three times a day.

Written informed consent to include data in the database was obtained from all subjects or their parents in the case of age <15 years.

Patient involvement

Patients were not directly involved in the design of this study.

Statistical analysis

Data were expressed either as numbers and percentage or as medians with IQR. Comparisons were made using X^2 tests or Fisher's exact tests for categorical variables and Wilcoxon rank sum test for continuous data. $P<0.05$ was considered to be significant. Statistical analyses were performed using STATA V.16.1.

A sample size of 325 subjects was calculated based on alpha=0.05, power=80% and anticipated incidence of a positive DPT of 3% during 1-day challenge and 8% during 5-day challenge.

RESULTS

A total of 305 subjects, aged 8 months to 18 years, were included (table 1). None was excluded from the study. The delay from index reaction to DPT was less than 1 year in 133 (44%) of the subjects. A total of 264 (86%) subjects

Table 1 Patient characteristics

	N (%)	Positive	Negative
Subjects	305	22	283
Sex			
Female	127 (42)	8 (36)	119 (42)
Male	178 (58)	14 (64)	164 (58)
Age, years, median (quartiles)	5.4 (2.0;11.4)	4.5 (1.8;13.3)	5.5 (2.0;11.4)
Setting			
University hospital	127 (42)	6 (27)	121 (43)
Regional hospital	178 (58)	16 (73)	162 (57)
Culprit drug			
Penicillin V	122 (40)	7 (32)	115 (41)
Amoxicillin	151 (50)	13 (59)	138 (49)
Dicloxacillin	17 (6)	1 (5)	16 (6)
Amoxicillin+clavulanic acid	15 (5)	1 (5)	14 (5)
Index reaction			
Urticaria	152 (49.8)	16 (73)	136 (48)
Maculopapular rash	151 (49.5)	6 (27)	145 (51)
Erythema multiforme	2 (0.7)	0 (0)	2 (1)
Time from index reaction to DPT			
<1 year	133 (44)	13 (59)	120 (42)
1–2 years	18 (6)	2 (9)	16 (6)
>2 years	53 (17)	3 (14)	50 (18)
Unknown	101 (33)	4 (18)	97 (34)
Skin prick test	Positive/negative		
	0/123	0/6	0/117
Specific IgE	Positive/negative		
Penicillin V	13/286	1/120	12/266
Benzylpenicillin	9/284	1/19	8/265
Ampicillin	8/230	1/15	7/215
Amoxicillin	11/120	01/10/20	5/110

DPT, drug provocation test.

returned the challenge schedule confirming adherence with the prolonged DPT.

A total of 22 (7%) of the DPTs were positive (figure 2). The reactions were all non-severe skin rashes either urticaria or maculopapular rash. Three children with urticaria had accompanying mild angioedema and two complained of itching palms. None reacted on the initial 1/10 of a full dose. Three (14%) of the 22 positive subjects reacted within 1 hour after the first full dose and additional three subjects reacted during the second hour of observation. In all, 12 children reacted before the second full dose was administered. The three children who reacted more than 24 hours after the first full dose reacted at day 3, 5 and 6 of the DPT, respectively.

The two children with an index reaction of erythema multiforme both had a negative DPT.

The subjects with a positive DPT did not differ from the negative group with respect to age (median 4.5 vs 5.5 years, p=0.75), gender (male: 64% vs 58%, p=0.60), culprit drug (amoxicillin: 59% vs 49%, p=0.35) or time

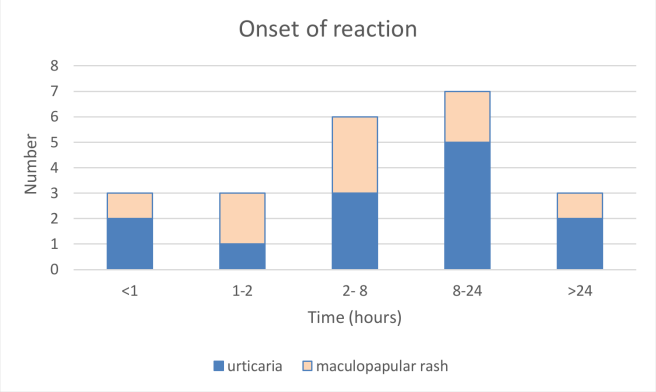

Figure 2 The time interval from first full dose to the appearance of a reaction and the morphology of the rash.

interval from index reaction to DPT (delay <1 year: 59% vs 42%, p=0.13).

Only the morphology of the index reaction differed significantly between groups. In 73% (n=16) of the positive DPTs, the indication for diagnostic workup was urticaria vs 48% (n=136) in the negative group (p=0.026). Thirteen of the 16 positive children with an urticarial index reaction also had urticaria during the DPT. In all six positive DPTs where the index reaction was a maculopapular rash a similar reaction was observed during the DPT.

The number of positive DPTs did not differ significantly between the two centres (positive DPT: university hospital 5% vs regional hospital 9%, p=0.16).

All SPTs were negative, while 18 children (6%) had at least one positive specific IgE measurement. Of the 41 positive IgE measurements, only nine were >0.35 kU/L. The highest measured specific IgE was 1.01 kU/L. This subject, a 13-year-old boy, had a negative DPT. Median (quartiles) time from measurement of specific IgE to the DPT was 75 days (45;132). Only one of the children with a positive specific IgE had a positive DPT.

DISCUSSION

The present study illustrates that the classification of drug hypersensitivity reactions as immediate or non-immediate reactions poses difficulties. Allergic urticaria is considered as an immediate IgE-mediated reaction[5] but in case of drug allergy, urticaria can occur several hours or even days after drug consumption.[8] Likewise, maculopapular rash considered to be a non-immediate reaction[6] can appear immediately after drug intake. The majority of the parents were not able to recall sufficient details about the index reaction to determine if the reaction appeared within 6 hours of the last administered dose. Consequently, we could only classify the index reaction based on the morphology. As the classification of the rash was based on photographs, history and medical records, an element of incorrectness and recall bias is possible.

The purpose of this study was to investigate if it is necessary to perform extended DPT. Only 6 of the 22 positive reactions appeared during the 2 hours of observation.

Apparently, at least seven positive reactions (32%) would have been missed if a second full dose had not been administered after 8 hours. Although, it is possible that some of these subjects would have had a reaction after the first full dose after a time interval of more than 8 hours. While the second full dose seems important, the subsequent 4 days of drug consumption only contributed an additional three (14%) positive reactions. Mori *et al* performed 177 five-day provocations in children with suspicion of allergy to amoxicillin. In total, 17 (9.6%) of the DPTs were positive, thereof four on day 5 of the DPT.[10] These paediatric data differ from the results in adult studies. Fransson *et al* reported that 47% and 51% of the positive reactions in adults appeared after three or more days of prolonged provocation with aminopenicillins and penicillin V, respectively.[11]

Prolonged DPTs thus seems to increase the diagnostic sensitivity. In addition, prolonged DPTs may also increase the proportion of subjects who subsequently ingest penicillin in real-life conditions because parents and physicians are more convinced that the drug will be tolerated.[8 12 13]

The sensitivity of skin test may be less in children than in adults.[14] In Denmark, we do not have access to minor and major benzylpenicillin determinants. Consequently, the sensitivity of the SPT is very low. Several authors have found DPT with penicillins without any prior allergy workup to be safe in patients with mild reactions.[3 15–19] Also, the DAIG Paediatric Task Force suggests that in children with non-immediate mild exanthema a DPT without previous skin test or in vitro testing can be performed.[20]

In the present study, a DPT was performed irrespectively of the specific IgE results. However, all specific IgE levels were low. Therefore, we can only conclude that in the present study, positive specific IgE values between 0.1 kU/L and 1.01 kU/L were not associated with a positive DPT. This is, however, in accordance with the growing evidence that both the sensitivity and the specificity of specific IgE penicillin assays is low.[21]

The main weakness of the study is the time interval from the index reaction to the diagnostic workup. The delay was more than 1 year in approximately half of the subjects. Although this reflects clinical practise at the two Danish centres primarily due to a delay in referral, the sensitivity of the allergy tests decreases over time.[22] SPT and measurement of specific IgE should ideally be performed 4–6 weeks from the reaction.[6] Moreover, clinical penicillin tolerance acquisition can occur in both children and adults.[23 24] Therefore, in clinical trials it is important to perform the DPT shortly after the allergy tests. In case of a positive DPT, one should consider to rechallenge the child after a few years as this may reduce the number of children going into adulthood labelled penicillin allergic. Rechallenge, however, may impose a risk of re-sensitisation.

The present study population seems representative for children suspected of being penicillin allergic. The 305 children reside in two different Danish regions, they were consecutively included when referred for penicillin allergy workup and none was excluded.

A DPT with penicillin is a relatively simple and low-risk procedure with important consequences both on an individual and a society level. Due to paucity of data in children, recommendations for adults have been applied. However, children generally have no or only mild reactions in DPTs with penicillin.[20] SPT has low sensitivity, and we find intradermal tests too painful to be part of the routine workup in children. Consequently, skin tests may be omitted in children with mild reactions. It is likely that it is safe to perform DPTs in children without knowing the specific IgE level. However, we find it necessary to evaluate DPTs in children with a recently measured positive specific IgE to penicillin before a decision to exclude specific IgE-measuring from DPT protocols can be made.

CONCLUSION

Based on the present study, we suggest that children with mild cutaneous reactions should undergo an in-hospital DPT with penicillin, followed by at least one additional full dose at home. Further studies are needed to investigate the diagnostic value of a positive-specific IgE to penicillin.

Contributors Both authors have contributed to the design of the study, collection of data and drafting of the manuscript. JG conducted the statistical analysis.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval According to The Danish National Committee on Health Research Ethics the study was not subject to notification because all procedures were part of routine medical care and the study did not include any extra diagnostic procedures. Data were prospectively included in a database approved by The Danish Data Protection Agency.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as online supplementary information.

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