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Safety and cost effectiveness of supervised ambulatory drug provocation tests in children with mild non-immediate reactions to beta-lactams

To the Editor,

Most reported drug hypersensitivity reactions (DHRs) to betalactams (BLs) in children are mild and delayed-onset, typically starting more than one hour after the first dose.[1] These reactions often include urticaria, maculopapular rashes (MPR), and/or edema.[2] Drug provocation testing (DPT) is the reference standard for confirming the diagnosis of DHR. A direct DPT, without prior skin or in vitro testing, has been proposed to explore nonimmediate nonsevere reactions in children,[3] and is safe.[4] However, optimal protocol (s) have not been standardized.[5,6] DPTs are generally started in daycare units (DCUs) and prolonged at home. Reactions that may occur during DPTs are easily controlled, and performing DPTs in DCUs is expensive and needlessly time-consuming. Thus, in 2015, we began to perform direct supervised ambulatory DPTs with the culprit drug in children with histories of mild delayed-onset reactions. A first therapeutic dose was given during consultation, and in the absence of an objective reaction within 1 hour, the DPT was prolonged at home. We aimed to assess whether this was safe and cost-effective.

Data from children consecutively referred between November 2015 and December 2018 for mild nonimmediate reactions to BLs and explored with direct supervised ambulatory DPTs in five pediatric allergy centers, including Necker Hospital, Créteil Intercommunal Medical Center, Ambroise Paré Hospital, Antoine Béclère Hospital, and Fontainebleau Hospital, were retrospectively collected. Inclusion criteria were delayed-onset (>1 hour after the first and last drug intake) and mild reactions (urticaria, MPR, unidentified skin reactions, and edema) to BLs, including amoxicillin, amoxicillin + clavulanate, cefpodoxime, cefixime, and cefuroxime.

Supervised ambulatory DPTs were performed without prior skin tests. The first dose was administered during consultation to healthy children. If no reaction occurred within 1 hour of simple monitoring in the waiting room, the DPT was prolonged at home at normal therapeutic doses (Table 1, online supplement). The duration of the DPT was 1-2 days more than the chronology of the index reactions, with a maximum of 8 days.[7] Should symptoms occur, parents were advised to stop the DPT, give H1-antihistamines and corticosteroids, seek medical advice, and send pictures of the reaction. DPTs were considered positive if objective symptoms occurred within 48 hour after the end of the DTP in the absence of a concomitant infection.

Data from 446 children (3.6 [1.9-6.4] years of age) were included (Table 2, online supplement). The general characteristics of the children and the index reactions are summarized in Table 1. The children had 456 reactions against one BL in 446 cases and two BLs in 10 cases. A total of 456 DPTs were performed: 39 were positive (8.6%) and 417 (91.4%) were negative. The characteristics of the reactions that occurred during the DPT are reported in Table 2. One was an immediate MPR that occurred at home nine hours after intake of the first dose and 30 minutes after the second. The reaction was benign and quickly resolved with H1-antihistamines. The 38 other reactions were nonimmediate. The reactions during the DPT occurred earlier or at the same time as the index reaction in 26 cases (66.7%), later in seven 17.9% ($P < 0.01$), and the chronology was undetermined in six (15.4%). The nature of the reactions was similar in 28 cases (71.8%) and different in 11 (28.2%) ($P < 0.01$). The extent of the reaction was lower or similar to that of the index reaction in 30 cases (76.9%), higher in six (15.4%), $P < 0.01$, undetermined in three (7.7%). There were no severe reactions, and all resolved spontaneously or were easily controlled with H1-antihistamines ± oral corticosteroids. Children who reacted to the DPT reported index reactions that occurred later than those reported for children who tolerated the DPT: 7 [4-8] vs 3 [1-6] days after the first intake of the drug, $P \leq 0.01$, and 9 [3.6-18] vs 9 [3.6-9] hours after the last, $P = 0.20$. The costs of these DPTs for the French National Health Insurance were €22800 (26,021 US Dollars). Starting 456 DPTs in a DCU would have cost €216,144 (246,690 US dollars). The cost saved was €193,344 (220,662 US dollars; online supplement).

The originality of our procedure was as follows: a) to start DPTs during consultation and not in DCUs, b) to start the DPT with one therapeutic dose instead of gradually increasing doses, and c) to propose simple one-hour monitoring in the waiting room. We demonstrate that this procedure is safe and cost-effective.

The rationale for starting DPTs in DCUs is based on the risk of occurrence of potentially severe immediate reactions. In pediatric populations, immediate reactions during DPTs performed to explore nonimmediate reactions have been reported in some, but not all studies.[2,8] All such reactions were mild, most resolved spontaneously or with H1-antihistamines, and none occurred after a first low dose of antibiotic.[2,8] We thus started DPTs during consultation, rather than in a DCU, and a first therapeutic dose was given instead of gradually increased doses. As expected, we did not observe any immediate reaction after intake of the first dose. Only one child reported an immediate reaction after the second dose, at home. However, an IgE-mediated mechanism is unlikely because this reaction did not occur after the first dose and was mild. Thus, starting DPTs during consultation with a therapeutic dose of drug was safe. Our results extend previous data showing the safety of performing

TABLE 1 Demographic and clinical characteristics of the children and index reactions

	Total population	Hypersensitivity	No hypersensitivity	*P*
Characteristics of the patients				
Number, n (%)	446	39 (8.7)	407 (91.3)	
Female, n (%)	214 (48)	21 (53.8)	193 (47.4)	0.44
Age at the index reaction (y)	2.0 [1.1-3.9]	2.4 [1.3-4.0]	1.9 [1.0-3.9]	0.31
Age at workup (y)	3.6 [1.9-6.4]	3.6 [2.1-5.2]	3.6 [1.9-6.6]	0.87
Time before workup (y)	0.6 [0.3-1.6]	0.6 [0.3-0.9]	0.6 [0.4-1.7]	0.23
Characteristics of the index reactions				
Number, n (%)	456	39 (8.6)	417 (91.4)	
BL involved				
Amx, n (%)	316 (69.3)	27 (69.2)	289 (69.3)	0.99
Amx + clavulanate, n (%)	108 (23.7)	12 (30.8)	96 (23.0)	0.28
Cefpodoxime, n (%)	26 (5.7)	0 (0)	26 (6.2)	0.11
Cefixime, n (%)	4 (0.9)	0 (0)	4 (1)	0.54
Cefuroxime, n (%)	2 (0.4)	0 (0)	2 (0.5)	0.67
1 BL involved, n (%)	446 (97.8)	39 (100)	407 (97.6)	0.33
2 BLs involved, n (%)	10 (2.2)	0 (0)	10 (2.4)	0.33
Reason for prescription				
Otitis, n (%)	213 (46.7)	22 (56.4)	191 (45.8)	0.21
Angina and rhinopharyngitis, n (%)	142 (31.1)	9 (23.1)	133 (31.9)	0.26
Bronchopulmonary infection, n (%)	44 (9.7)	5 (12.8)	39 (9.3)	0.48
Other, n (%)	57 (12.5)	3 (7.7)	54 (13.0)	0.34
Chronology				
Onset after 1st dose (d)	3.0 [2.0-7.0]	7.0 [4.0-8.0]	3.0 [1.0-6.0]	<0.0001
D 1	102 (22.4%)	4 (10.3)	98 (23.5)	0.06
D 2-3	129 (28.3%)	4 (10.3)	125 (30.0)	0.009
D 4-6	72 (15.8%)	5 (12.8)	67 (16.1)	0.60
D 7 and more	114 (25.0%)	24 (61.5)	90 (21.6)	<0.0001
Unknown	39 (8.6)	2 (5.1)	37 (8.9)	0.43
After the last dose (h)	9.0 [3.6-9.0]	9.0 [3.6-18.0]	9.0 [3.6-9.0]	0.18
Symptoms				
Urticaria, n (%)	161 (35.3)	18 (46.2)	143 (34.3)	0.15
Maculopapular rash/erythema, n (%)	241 (52.9)	18 (46.2)	223 (53.5)	0.37
Unidentified rash, n (%)	43 (9.4)	3 (7.7)	40 (9.6)	0.70
Edema, n (%)	11 (2.4)	0 (0)	11 (2.6)	0.31
Pruritus, n (%)	124 (27.2)	13 (33.3)	111 (26.6)	0.40
Fever, n (%)	92 (20.2)	10 (25.6)	82 (19.7)	0.33
Extent of skin involvement, body surface area				
≥50%, n (%)	243 (53.3)	25 (64.1)	218 (52.3)	0.17
<50%, n (%)	198 (43.4)	13 (33.3)	185 (44.4)	0.17
Unknown, n (%)	15 (3.3)	1 (2.6)	14 (3.4)	
Duration of the index reaction, (days)	3.0 [2.0-5.0]	4.0 [2.0-5.0]	3.0 [2.0-4.0]	0.01

Abbreviations: Amx, amoxicillin; BL, betalactam.

direct DPTs in DCUs with gradually increased dose of BLs and additionally show that DPTs for mild nonimmediate reactions can be safely started with a therapeutic dose during consultation, providing the first dose is given under medical supervision and the child followed for one hour before returning home. Our simplified procedure was well accepted. Very few parents preferred to start the DPT in DCU, and parents saved one day of work loss. Most of the parents were compliant, continued the DPT at home, and informed

TABLE 2 Results of positive DPTs

	Positive DPT	*P*
Number of positive DPTs	39	
Nature of the reactions		
Urticaria, n (%)	19 (48.7)	
Maculopapular rash/erythema, n (%)	19 (48.7)	
Unidentified rash, n (%)	1 (2.6)	
Similar to the index reaction, n (%)	28 (71.8)	0.0001*
Different from the index reaction; n (%)	11 (28.2)	
Chronology		
After the 1st dose (d)	6.0 [0.8-8.0]	
After the last dose (h)	9.0 [4.3-18.0]	
Earlier/same time as the index reaction, n (%)	26 (66.7)	<0.0001**
Later than the index reaction, n (%)	7 (17.9)	
Undetermined	6 (15.4)	
Extent		
Equal or inferior, n (%)	30 (76.9)	<0.0001***
Greater, n (%)	6 (15.4)	
Undetermined, n (%)	3 (7.7)	

Abbreviation: DPT, drug provocation test.
*Comparisons between similar vs different.
**Comparisons between earlier/similar vs later.
***Comparisons between equal/inferior vs superior.

the doctor of the test results. Our results should be interpreted with caution because: (a) We included young children in which benign skin rashes frequently coexist with infections, (b) the delay between the index reaction and the DPT was short, limiting memory bias, particularly concerning the presence of danger signals.

In summary, direct supervised ambulatory DPTs starting with a therapeutic dose of drug during consultation were safe and cost-effective. If confirmed, this simplified workup might be proposed by GPs, pediatricians, and allergists in consultation settings.[9]

CONFLICT OF INTEREST

None.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Age and early maternal smoking contribute to epithelial cell IL-13 responsiveness in a pediatric asthma population

To the Editor

Many asthma phenotypes are associated with excessive T helper type 2-like responses, and IL-13 is sufficient to induce pathological changes observed in asthmatic airways.[1] IL-13 signaling through a heterodimer of IL-13Rα1 and IL-4Rα induces the phosphorylation/homodimerization of the transcription factor STAT6.[1] IL-13/IL-13Rα1/STAT6 pathway activation in respiratory epithelial cells is required for the development of experimental asthma,[2] and polymorphisms in IL-13, IL-13Rα1, or IL-4Rα influence asthma susceptibility and/or severity.[3] As IL-13 "strength-of-signal" may influence allergic asthma development and/or severity, the goal of this study was to determine whether primary nasal epithelial cells (NECs) from children with asthma displayed cell-intrinsic variations in IL-13 responsiveness and to identify factors influencing the magnitude of IL-13-induced signaling.

Following Cincinnati Children's Hospital Medical Center (CCHMC) IRB approval, children (5-19 years old) with physician-diagnosed asthma were enrolled in the Pediatric Environmental Exposure Study (PEES).[4] Children and parents completed surveys to assess current secondhand smoke (SHS) exposure, early maternal smoking, asthma symptom frequency over the past 4 weeks (wheeze, shortness of breath, cough, and chest tightness), asthma control (childhood Asthma Control Test [ACT]), medication usage/treatment step, and exposure to air pollutants based on estimated mean concentration of elemental carbon attributable to traffic (ECAT) exposure using birth and current address.[4] Spirometry was performed, and asthma severity (mild, moderate, severe) was determined according to ATS guidelines. Children were currently taking asthma medication. Participants taking nasal steroids in the past 30 days were ineligible. Other medication usage was not restricted. Skin prick testing was not performed. NECs were collected from beneath the inferior turbinate using a cytology brush. NECs were passaged twice, treated with media or IL-13 (100 ng/mL) for 15 minutes, and levels of total and phosphorylated STAT6 (Tyr641) in cellular lysates were assessed by Western blot (Figure S1). IL-13-induced STAT6 activation (IL-13-stimulated pSTAT/STAT6 ratio, divided by medium-stimulated pSTAT/STAT6 ratio) was natural-log-transformed and used as the primary outcome variable in statistical analyses (SAS 9.4).

To determine whether IL-13 responsiveness varied with asthma severity in primary NECs, IL-13-induced STAT6 activation was assessed in nasal cells from children with mild (n = 12), moderate (n = 18), or severe asthma (n = 17). Asthma severity did not vary with age, sex, race, % predicted FEV1, environmental exposures, and total STAT6 expression (Table S1). Total IgE levels were significantly elevated in moderate (median: 318 IU/mL [IQR: 90-767]) and severe (384 IU/mL [116-598]) asthmatics compared with mild asthmatics (68 IU/mL; [29-148]) (P = 0.017) (Table S1). NECs responded to IL-13 (8- to >500-fold IL-13-induced STAT6 activation; Figure 1A); however, due to technical problems, samples from one participant failed to demonstrate IL-13-responsiveness and were excluded from subsequent analyses.

We performed a univariate analysis to examine the individual impact of potential factors on IL-13-induced STAT6 activation using Pearson correlation (continuous factors) and t test or ANOVA (categorical factors). Although not statistically significant, cells from children with moderate or severe asthma trended toward greater IL-13-induced STAT6 activation compared to children with mild asthma (P = 0.25; Table 1). Combining moderate and severe asthmatics, which demonstrated similar IL-13-induced STAT6 activation, did not improve this association (P = 0.105; Figure 1B). However, children whom had experienced asthma symptoms within the past 4 weeks (ie, Maximum Respiratory Symptom Score (MRSS) > 0; 89.4% of participants) had significantly more IL-13-induced STAT6 activation compared to those without recent symptoms (P = 0.040; Figure 1C, Table 1). IL-13-induced STAT6 activation was also marginally associated, albeit not significantly, with age and peripheral eosinophil count (Table 1). Interestingly, IL-13-induced STAT6 activation was significantly elevated in children exposed to early maternal smoking (25.5% of participants; P = 0.004; Figure 1D, Table 1). No associations were observed with primary smoking, current exposure to SHS, or ECAT exposure (current or pregnancy) (Table 1).

The univariate analysis suggested potential impacts of age, peripheral eosinophil count, and early maternal smoking; therefore, these factors were tested as co-variables using multiple linear regression (SAS GENMOD). In this model, eosinophil count did not