

Parental-reported drug allergy in 6- to 9-yr-old urban schoolchildren

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Epidemiologic studies about the prevalence of adverse drug reactions in children are scarce compared to reports in adults. To assess the prevalence of parental-reported drug allergy in 6- to 9-yr-old urban school children, we performed a cross-sectional study of 6- to 9-yr-old urban children from the eastern Black Sea region of Turkey during the year 2004, using a self-administered questionnaire by parents. Response rate was 81.6% (2855/3500). The prevalence of parental-reported drug allergy was 2.8% (81/2855). The most common parental-reported drugs were penicillins and other β -lactams (59.3%), trimethoprim-sulfamethoxazole (11.1%), and acetylsalicylic acid and other non-steroidal anti-inflammatory drugs (NSAIDs) (9.9%). The most commonly reported clinical manifestations were cutaneous ($n = 76$, 93.8%) followed by gastrointestinal ($n = 17$, 21%) symptoms. In 19 (23.5%) children, the reaction involved more than one organ system. Of these 19 children, 14 used β -lactams. Systemic reactions were not reported with NSAIDs. Medications were taken by mouth in 88.9% of the reactions. Most of the reported allergic reactions occurred in the first day of treatment (61.7%). The reported time to reaction after the last intake of the drug was < 2 h in 35 (43.2%) children and 2–24 h in 45 (55.6%). Oral reactions occurred later than reactions to parentally administered drugs. Parents of 58 children (71.6%) reported that they completely avoided the suspected culprit drug following the reaction. Relapse occurred after re-administration of the drug in 21 (25.9%) children. A diagnostic approach for drug allergy was not undertaken in any of the children. This study may provide some information about the prevalence of drug allergy, although it is based on parental perception and results are unlikely to conform well to true prevalence.

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An adverse drug reaction (ADR) may be defined as any effect of the drug beyond its desired action. When immunologic mechanisms have been shown, these reactions should be classified as drug allergy (1).

Epidemiologic studies about the prevalence of ADRs in children are scarce compared to reports in adults. Impicciatore et al. (2) showed in a meta-analysis of 17 prospective studies that the overall incidence of ADRs in hospitalized children was 9.53% (range: 4.35–16.78%) while in outpatient children, this figure was 1.46% (range: 0.75–2.74%); the overall rate of pediatric hospi-

tal admissions related to ADRs was 2.09% (range: 0.59–4.10%).

Most studies concerning the incidence and prevalence of drug allergies involve only single classes of drugs (3–6), allergic reactions in certain diseases (7) or cutaneous reactions (8). Although the true incidence and prevalence are unknown, it has been estimated that drug allergy accounts for up to one-third of all ADRs (9, 10). In two cross-sectional studies, self-reported prevalence of drug allergy in university students and in a general adult population was found as 7.7% and 7.8%, respectively (11, 12).

In this study, we aimed to assess the prevalence of parental-reported drug allergy in 6- to 9-yr-old urban schoolchildren in the eastern Black Sea region of Turkey.

Methods

Study population

This is a cross-sectional study that was performed during the year 2004 in the eastern Black Sea region of Turkey, which is comprised six cities. The total population of 6- to 9-yr-old urban schoolchildren in these six cities is 33,552. Random sampling of 10% of children from the public primary schools in these six cities was performed in each age group and there were comparable numbers of boys and girls in all age groups.

Questionnaire

Each child took home a standard questionnaire to be completed by a parent or caregiver (parental report). The questionnaire began with questions on the child's demographics (age and sex). We then asked respondents the key question: 'In your opinion, does your child have a drug allergy?' If the answer was 'yes', parents/caregivers were then asked to indicate which symptoms occurred following drug intake from a list including cutaneous (eruption, itching, rash, swelling), nasal (sneezing, itching, secretion, blockage), ocular (redness, itching, secretion), bronchial (cough, wheezing, shortness of breath), gastrointestinal (stomachache, nausea, vomiting, diarrhea), laryngeal (difficulty in swallowing, difficulty in speaking), cardiovascular (palpitations/tachycardia, hypotension) and other (sweating, pallor, fainting, loss of consciousness) symptoms. Information about the name(s) of culprit drug(s), the route of administration, time between the last intake and the reaction, the managing and diagnostic procedure(s) carried out, and previous and subsequent administration of the culprit drug were obtained.

Statistics

All analyses were performed using SPSS statistical software version 10.0 (SPSS Inc., Chicago, IL, USA). A descriptive analysis was used for the characterization of the study population. Results were expressed as the mean $\pm$ s.e.m. or percentages of the responses to each question. The prevalence of responses was compared with Pearson chi-squared test (with the Yates correc-

tion when applied) or Fisher exact test when needed. The odds ratio (OR) and its 95% confidence interval (CI) were calculated. To compare age between two or more groups, Wilcoxon-Mann-Whitney test and Kruskal-Wallis one-way ANOVA were used. $p < 0.05$ was considered statistically significant.

Results

Of the 3500 children, 2855 (81.6%) returned a completed questionnaire. The prevalence of parental-reported drug allergy in our study group was 2.8% (81/2855). There were no significant differences in the prevalence of parental-reported drug allergy between age groups ($p = 0.457$) and gender (OR = 0.73, $p = 0.192$, 95% CI 0.46–1.16).

The most common parental-reported drugs were penicillins and other β -lactams (48/81, 59.3%), trimethoprim-sulfamethoxazole (TMP-SMZ) (9/81, 11.1%), and acetylsalicylic acid and other non-steroidal anti-inflammatory drugs (NSAIDs) (8/81, 9.9%). In seven (7/81, 8.6%) children, parents reported other drugs (two clarithromycin, two paracetamol, two pseudoephedrine and one eye drop) and in 11 (13.5%), parents did not recall the exact drug responsible for the reaction. In two (2.4%) children, parents reported more than one drug (pseudoephedrine and amoxicillin in one; paracetamol and amoxicillin in one) that caused the reaction. The reported prevalence of β -lactam, TMP-SMZ and NSAID allergy was not significant between age groups and gender. Twenty-one (25.9%) parents did not recall a previous contact with the drug suspected as responsible for the reaction.

The most commonly reported clinical manifestations were cutaneous ($n = 76$, 93.8%) followed by gastrointestinal ($n = 17$, 21%) and respiratory/ocular ($n = 8$, 9.9%). Isolated gastrointestinal symptoms were reported in two (2.4%) children. Collapse was reported only in one (1.2%) child. In 19 (23.5%) children, the reaction involved more than one organ system. Although not significant, systemic reactions were reported more in boys (12/41, 29.2%) than girls (7/40, 17.2%) ($p = 0.323$). All children with reported systemic reaction had cutaneous manifestations and 15 had gastrointestinal symptoms. Lower airway manifestations occurred in two children, one of whom reported to have collapse. Of these 19 children, 14 used β -lactams. Systemic reactions were not reported with NSAIDs.

Parents of 58 children (71.6%) reported that they completely avoided the suspected culprit drug following the reaction. Relapse was reported

in 21 children (25.9%) in whom the drug was given again. In two children, parents reported that the reaction did not occur following subsequent usage of the suspected culprit drug.

Of the 81 children, 47 (58%) were admitted to the emergency department. One child was treated with epinephrine, corticosteroid and antihistamine, while others were treated only with an antihistamine. Parents reported that they were advised by their doctors to avoid the culprit drug. However, a diagnostic approach for drug allergy was not undertaken in any of the children.

The route of administration was oral in 72 (88.9%) children and parenteral in nine (11.1%). The reported allergic reaction occurred in the first day of treatment in 50 (61.7%) children and in the second day of treatment in 24 (29.6%). In seven (8.6%) children, parents did not recall the exact day the reaction occurred. The reported time to reaction after the last intake of the drug was < 2 h in 35 (43.2%) children, 2–24 h in 45 (55.6%) children and more than 24 h in one (1.2%). The association between the route of administration and reported time to reaction (Table 1) was significant, with the parenteral route being responsible for more reactions occurring within the first 2 h (7/9, 77.7%, OR = 5.50, $p = 0.03$, 95% CI 0.94–56.77) and oral route for reactions occurring between 2–24 h (43/72, 59.7%, OR = 0.19, $p = 0.03$, 95% CI 0.02–1.13).

Discussion

In the present study, we found that the prevalence of parental-reported drug allergy in 6- to 9-yr-old schoolchildren was 2.8%. To our knowledge, this is the first study in the literature concerning the prevalence of parental-reported drug allergy in childhood. In our survey, it was lower than the prevalence previously reported for adults (11, 12). This may be due to lower drug

consumption in children compared with adults or because some parents may not have considered the reactions to be allergic.

Similar to the other studies (3, 11, 12), cutaneous manifestations were the most commonly reported reactions. The majority of children (91.3%) in whom the same drug was subsequently administered had another reaction, increasing the likelihood of drug hypersensitivity. Another finding indicating most of the children in our study might have true hypersensitivity is that isolated gastrointestinal symptoms which are generally attributed to drug intolerance instead of drug allergy (13) were rarely reported in our study group. It seems that immediate type hypersensitivity reactions are more frequent than delayed type, since the reactions occurred in the first day of treatment in the majority of children, and in approximately half of the children, the reported time to reaction after the last intake of the drug was within 2 h.

β -Lactams, TMP-SMZ and NSAIDs were the most often reported drugs suspected to be responsible for drug hypersensitivities. Apart from the previous studies in which β -lactams and NSAIDs were the most commonly reported drugs that caused hypersensitivity reactions (11, 12, 14, 15), TMP-SMZ was the second most frequently reported drug suspected to be allergic in our population. In Turkey, β -lactams and TMP-SMZ are the two most often prescribed antibiotics for children, and although not the case for antibiotics, NSAIDs are easily obtained over the counter.

Over one-third of the children were not attended to the emergency department. Moreover, the culprit drug was administered again in approximately 25% of children, implying that most of the parents did not take into consideration or were unaware of the importance of the reactions.

Parents were advised by their doctors to avoid the drug that caused the reaction but neither diagnostic approach was carried out nor was any child referred to an allergist. This may be due to the few standardized validated diagnostic tests available. Diagnosis of drug allergy often relies on the clinical history alone, and treatment, in many instances, is based on an absolute avoidance of the culprit drug. However, most of patients who visit a doctor for a reaction that is diagnosed as drug allergy are not allergic (9). Most reactions that coincide with drug intake in children are cutaneous eruptions due to the underlying disease (11). The gastrointestinal symptoms may represent intolerance rather than allergy (13), or syncope following administration of parenteral drugs (i.e. procaine penicillin,

Table 1. Association between the route of administration and reported time to reaction

	n (%)	OR (95% CI)	p-value
<2 h			
Oral	28/72 (38.9)	5.50 (0.94–56.77)	0.03
Parenteral	7/9 (77.7)		
2–24 h			
Oral	43/72 (59.7)	0.19 (0.02–1.13)	0.03
Parenteral	2/9 (22.3)		
>24 h			
Oral	1/72 (1.4)		
Parenteral	0		

lidocaine) may represent a vasodepressor reaction rather than anaphylaxis (16). This may cause an unnecessary avoidance of the drug, especially, when its usage is essential, which may in turn lead to the prescription of less-effective drugs, a delay in treatment and an increase in costs. Therefore, patients with a history or suspicion of drug allergy should be evaluated by an allergist to make a proper diagnosis.

This study may provide some information about the prevalence of drug-induced anaphylactic reactions in a general pediatric population. Although the exact incidence of anaphylaxis is unknown, an incidence of 7.9–21 per 100,000 persons per year has been estimated in different studies (17, 18). In different series, drugs are reported as the first (19, 20) or second (13) most frequent cause of anaphylaxis. If we consider that all reported reactions were true allergy, the prevalence of drug-induced anaphylaxis in our study group would be six per 100,000 (19/2855); for severe anaphylaxis, this rate would be seven per million (2/2855).

This study is based on parental perception and results may not conform well to true prevalence of drug allergy. Epidemiologic studies assessing the true prevalence of drug allergies are difficult to perform and data are lacking in this field of allergy. Constituting a protocol in cooperation with primary care physicians and arranging studies in collaboration with national–international allergy centers using the same methodology may help to overcome this problem.

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