

Questionnaire-based survey of lifetime-prevalence and character of allergic drug reactions in German children

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Data on the epidemiology of adverse drug reactions (ADR), especially allergic drug reactions, in children are rare. The reported prevalence of ADR in pediatric populations varies a lot, depending on type of the study and the country where the data were collected. In order to assess the prevalence of ADR and allergic drug reactions in a population of German children, we conducted a study in a German pediatric university hospital. A questionnaire concerning occurrence and character of ADR was distributed to all parents presenting their children in the hospital for planned admissions or in the emergency department from May 2004 to November 2004. Additional telephone interviews were conducted to specify the reported symptoms in ambiguous cases. One thousand four hundred forty-seven questionnaires were collected. The reported life-time prevalence of ADR according to the information given by the parents was 7.5% (108/1447). Six of the reactions were severe, three children had experienced anaphylactic reactions. In 4.2% (61/1447), the history was suspicious for a potential allergic mechanism because of an immediate or late phase cutaneous drug reaction. In this group, the suspected drugs were antibiotics in 85% (32.7% aminopenicillins, 29.5% other penicillins, 11.5% cefaclor, 8.2% macrolides and 18% others), antiphlogistic and respiratory drugs in 4.9% each and vaccines and contrast media in 3.3% each. There was a higher percentage of children under the age of four suffering from ADR. This trend was not significant when analyzing only the allergic reactions. Forty-four percent of the parents stated, their children suffer from drug allergy, although a clear non-allergic reaction was described. Both, ADR and allergic drug reactions are frequent phenomena in children. It is important to monitor drug therapy for any adverse reaction in order to inform the parents about the character of the adverse reaction, the necessary consequences and to initiate further diagnostic procedures.

Key words: children; drug allergy; adverse drug reaction; epidemiology

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The term 'drug allergy' covers a wide variety of immunologic mechanisms and clinical pictures. The World Allergy Organization recently defined drug allergy as a hypersensitivity reaction for which a definite immunologic mechanism, either IgE or T-cell mediated, is demonstrated (1). The more general term 'adverse drug reaction' (ADR)

is defined as 'a noxious and unintended response to a drug that occurs at a dose normally used in man' (2). A detailed classification of ADRs was published in the year 2000 (3). According to this definition, most reactions are dose dependent and predictable (type A reactions), whereas allergic reactions account for 10–30% of all

ADRs and are subsumed under the term 'type B reactions', which are categorized as non-dose dependent or bizarre.

Several studies investigated the incidence of ADR (4–16). Data on the epidemiology of allergic drug reactions are scarce (4–8). Even less is known about pediatric populations. Considering factors influencing the prevalence of allergic drug reactions like different prescription rates in different countries (9, 17) and the differences in the genetic background of a population (4), more detailed information about the rates of allergic drug reactions in children is needed.

In order to investigate the rate of allergic drug reactions in a German pediatric population, we conducted a questionnaire-based study in a tertiary, university children's hospital in Germany.

Materials and methods

A self-report questionnaire assessing occurrence and character of allergic drug reactions in children was distributed to all parents who presented their children in the children's hospital of the University of Cologne from May 2004 to November 2004 for planned admissions or in the emergency department (see in the appendix). The key question was: 'Has your child ever experienced an allergic drug reaction?'. If the parents stated 'yes', they were asked to name the culprit drug and answer additional questions. These regarded the date of the reaction and the symptoms (occurrence of skin reaction, pruritus, nausea/vomiting and/or others), the necessary therapies and consequences (no change, stop of the therapy/change to another medication, prescription of antiallergic medication, hospital admission and/or others) and the disease for which the drug was prescribed. For a clear differentiation between immediate and delayed drug reactions (later than 3 days after beginning of the therapy), we asked for the time course of the reaction and chose three time categories: reactions within 24 h, between 24 and 72 h and later than 72 h. These categories were chosen for two reasons: first for having a simple classification for parents even if the reaction occurred a longer time ago, second for increasing accuracy concerning the character of the reaction. Delayed reactions with skin manifestations are most probably T-cell mediated and immediate reactions with skin and systemic involvement are most probably IgE-mediated.

In cases of ambiguous answers, we conducted additional telephone interviews in order to specify the reported symptoms. In order to classify whether the reported reactions had a truly

allergic background, we reviewed their course and the symptoms. Those involving the skin or immediate systemic symptoms like anaphylactic reactions were classified as type B (allergic) reactions. Other reactions like exclusive gastrointestinal symptoms during antibiotic therapy or tachycardia and agitation during β -mimetic therapy were classified as type A (non-allergic) reactions.

Descriptive statistics were used to analyse demographic data and pattern of reactions and Chi-squared and Mann–Whitney test for age-related differences. All statistical analyses were performed with SPSS for Windows 14.0 (SPSS Inc, Chicago, IL, USA).

Results

One thousand four hundred forty-six questionnaires were analysed. The median age of the children was 43 month (0–211 month). Eight hundred forty-eight children were younger than 5 yr and 1225 younger than 10 yr. 49.9% were male.

The life-time prevalence of allergic drug reactions according to the information given by the parents was 7.5% (108 patients). After review of the reported symptoms, 61 (4.2%) reactions were classified as type B reactions, 25 as type A reactions and in nine reports, a classification was not possible (Table 1). In 13 cases, no obvious association between drug intake and reported symptoms was seen.

Six of the reported reactions were classified as serious, defined by the need for hospital admission or prolonged hospitalization because of the adverse event. Three parents (0.2%) described the reactions as anaphylactic. Two of these reactions involved the skin and respiratory system (Cefaclor and contrast medium), one the skin and the cardiovascular system (Vancomycin). Considering only allergic reactions, the culprit drugs were antibiotics in 85% (Tables 1

Table 1. Drug classes responsible for ADR divided in allergic (type B) and non-allergic (type A) reactions

Drug class	Type B reactions No. of patients (n = 61)	Type A reactions No. of patients (n = 25)
Antibiotics	52 (85%)	14 (56%)
Antiphlogistic drugs	3 (4.9%)	
Respiratory drugs	3 (4.9%)	3 (12%)
Vaccinations	2 (3.3%)	1 (4%)
Radio contrast media	2 (3.3%)	
Topical preparations		6 (24%)
Various		1 (4%)
Reactions to multiple drugs	6 (9.8%)	

Table 2. Antibiotics responsible for type B reactions

Antibiotic class	No. of reactions (n = 61)
Amoxicillin	20 (32.7%)
Other penicillins	18 (29.5%)
Cefaclor	7 (11.5%)
Macrolides	5 (8.2%)
Other cephalosporines	3 (4.9%)
Cotrimoxazol	1 (1.6%)
Vancomycin	1 (1.6%)
Multiple reactions	5 (8.2%)
Unspecified antibiotic	6 (9.8%)

and 2), respiratory drugs and non-steroidal anti-inflammatory drugs (NSAID) in 4.9% each, vaccines and contrast media in 3.3% each.

Twenty-two percent of patients discovered their reactions within the first 24 h of therapy, 47% between 24 and 72 h and 21% reported late phase reactions with presentation of the first symptoms more than 72 h after the start of the therapy.

The indication for antibiotic drug therapy in patients experiencing allergic drug reactions were airway infection and tonsillitis in 26% each, otitis media in 20%, urinary tract infection in 6.6% and various others in 4.9%. Concerning non-allergic reactions, 44.7% of the patients suffered from airway infection, 10.6% from otitis media, 8.5% from tonsillitis and 23% from various other diseases.

Sixty-four percent of the therapies were stopped after the ADR had occurred, 14% of the children received anti-allergic medication because of the event.

There was no difference in gender between the groups with or without history of ADR. The median age of the children having experienced an allergic reaction was higher (73 vs. 57 months, $p < 0.001$). We analyzed the risk of having experienced an ADR or allergic drug reaction during the last year in different age groups (Table 3). For ADR, there was a significant higher percentage of children under the age of 4 yr ($p > 0.05$), which was not significant looking only at the allergic reactions.

Table 3. Age distribution

Age group	Number of children	Number of ADR during the last year (% of children) ($p > 0.05$)	Number of allergic drug reactions during the last year n.s.
0–1	440	18 (4.1%)	9 (2%)
2–4	438	23 (5.3%)	14 (3.2%)
4–7	245	7 (2.9%)	4 (1.6%)
8–18	303	7 (2.3%)	7 (2.3%)

We also analyzed the parents error of estimation concerning the character of the reaction and found 44% misestimation of the described reaction as allergic when the symptoms clearly showed a type A reaction or no ADR at all (for instance therapy failure).

Discussion

Several surveys investigated the prevalence of ADR in children. In general, the risk for pediatric outpatients to suffer from an ADR is much lower (0.67–7.3%) (4, 8–10) compared with hospitalized children (1.6–16.8%) (4, 9). The risk of experiencing an ADR is increased when off-label drugs are taken (13) and when suffering from serious disorders (7). The group of patients we examined in our study was a pediatric population consisting of outpatients that came to the emergency department because of an acute illness as well as children with chronic diseases who are regularly seen in specialized outpatient departments of our hospital. The high number of chronically sick children could be an explanation for the higher incidence of reported ADR in the population we examined compared with general pediatric practices.

We found two comparable questionnaire-based studies concerning adverse and especially allergic drug reactions in the literature (5, 6). The first survey evaluated an adult population in Portugal. The prevalence of self-reported drug allergy was 7.8%, with 53% of the patients stating to be allergic to β -lactams and 20.4% to NSAIDs. Most of the reactions occurred on the first day of therapy and showed a more severe course with 35.9% cardiovascular and 14.4% respiratory symptoms. In this study, there was no retrospective differentiation between type B and type A reactions. The observed differences between this study and our results are most likely due to the different age groups investigated. Children are more likely to react with delayed skin reactions and are consuming less NSAIDs.

The second study was recently published and investigated the rate of allergic reactions in 6- to 9-yr-old schoolchildren in Turkey (6). The parental-reported prevalence of drug allergy was 2.8% reflecting the lower incidence in a general population. In contrast to our results, 98.8% of the reactions were immediate type reactions. The drug classes were largely comparable: β -lactam antibiotics, followed by trimethoprim-sulfamethoxazol and NSAIDs. The explanation for the completely different pattern of reported reactions with virtually no delayed type reactions

is not clear. One possible explanation could be different information of the parents by their physicians. Delayed drug reactions might have been regarded as caused by an infectious rather than an allergic mechanism. Furthermore, the different genetic background might be a relevant factor.

Most of the reported ADR in our study were type B reactions to antibiotics. The majority of these reactions occurred during aminopenicillin-therapies followed by other penicillins and cefaclor. These results are comparable with other reports with slight differences most likely depending on drug usage patterns of the countries where the studies were conducted (8–10). The pattern of ADR-related symptoms caused by antibiotics is different compared with studies in adult populations. In adults, skin reactions are most often observed during therapy with trimethoprim-sulfamethoxazol, fluoroquinolones and penicillins (14). It is well known, that the occurrence of rash during an antibiotic therapy in children is a frequent phenomenon and that only a minority of these children are truly allergic on re-exposure (10, 18–21). For establishing the diagnosis 'drug allergy', further testing including skin testing and drug challenge is mandatory. In our study, the parents were informed about the necessity of further diagnostic procedures, but only four patients were referred by their pediatricians for the testing procedures. Of these, only in two, a reproducible allergic reaction was proven (Clarithromycin, Amoxicillin).

To our knowledge, only one study investigated the age-related risks of experiencing an ADR to date (9, 11) and there is no information about allergic drug reactions in different age groups. In our population, the risk for having experienced an ADR during the last year was higher in the group of children under 4 yr. Analyzing only the allergic reactions, the age-related differences were not significant.

Younger children suffer more frequently from viral infections and receive more antibiotic therapies than older children. The higher exposure to drugs contributes to a higher probability of ADR.

Another important finding of this study is the high level of misestimation (44%) of the parents who believed their children were allergic to drugs after a non-allergic adverse drug reaction. This is the consequence of incomplete information of these parents by their physician after the ADR had occurred. The fear of further reactions will lead to unnecessary avoidance of the suspected drugs and parental malcompliance. It is one of our responsibilities as pediatricians and allergol-

ogists to assess adverse drug reactions in the single patient in order to establish the correct diagnosis and inform the patients how to deal with the suspected drug further in life.

There are several limitations in this study. The main problem is the retrospective approach. The definitions of the terms may be vague for parents and the exact clinical course is difficult to remember in some cases. The retrospective classification of the reactions as allergic or non-allergic based on differentiation between cutaneous and gastrointestinal symptoms may be wrong in some cases. Diarrhea is a common side effect of antibiotic therapy and vomiting is a known immediate side effect of erythromycin, but it may be, in rare cases, the only symptom of a mild anaphylactic reaction even without skin reaction. It is also obvious, that not every cutaneous eruption associated with a medical therapy indicates a drug allergy. Nevertheless only a retrospective, questionnaire-based study offers the possibility to evaluate a large group of patients and to generate epidemiologic data about the extent of drug allergy as a problem in childhood. Large prospective studies with complete diagnostic procedures in all patients and in different parts of the world are necessary to elucidate the complex epidemiology of drug allergy.

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