Prevalence of drug allergy in Singaporean children

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ABSTRACT

Introduction: Adverse drug reactions (ADRs) are a common medical problem in children, affecting up to 15 percent of children, according to the literature. However, most studies on ADRs were performed in a hospital setting, and studies in the general population are limited. The current study aims to estimate the prevalence of ADRs in a large number of non-selected Singaporean children.

Methods: School children, aged 7–16 years, from 25 random schools were screened via a self-reported questionnaire on ADRs, and parents of the selected children were then followed up with a telephone interview to obtain additional information on specific manifestations, diagnosis and allergy testing.

Results: The prevalence of an ADR in children was 5.4 percent, with 56.7 percent of cases reporting an ADR to beta-lactam antibiotics. Dermal manifestations were reported in 60 percent of all ADRs, while multiple drug allergies accounted only for 3.8 percent. Only 6.9 percent of the children who experienced an ADR were referred to a hospital for further investigations.

Conclusions: ADRs were associated with a positive history of atopy, increased income level and Chinese and Indian ethnicity, but not with gender or age. It is striking that most children suffering from a clinical ADR were not investigated further or referred for diagnostic tests. Many parents were unaware of the availability of drug allergy tests and feared compromising their children's health. This certainly could attribute to the high incidence of the over-reporting of ADRs in the general population.

Keywords: adverse drug reaction, antibiotics, beta-lactam antibiotics, drug allergy, skin reactions

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INTRODUCTION

An adverse drug reaction (ADR) is defined by the World Health Organization (WHO) as any noxious, unintended and undesired effect of a drug that occurs at doses used for prevention, diagnosis or treatment.[1] The majority of ADRs fall under the category of Type A reactions, which are predictable, common, dose-dependent reactions, and are caused by known pharmacological actions of the drug, including drug toxicity and side effects.[2] Allergic (hypersensitivity) reactions to drugs or drug allergy (DA) belong to Type B reactions, which are uncommon and unpredictable.[2] Of all the ADRs, DA has the hallmark of being immunologically driven and is further distinguished from other types of ADR by the following features: (1) it requires prior exposure to the drug or chemically-related drug; (2) the onset of reaction can occur a few days after the first exposure or it can occur rapidly upon re-exposure to the drug; (3) the allergic reaction occurs at a dose far below the therapeutic range; (4) the allergic reaction usually subsides after discontinuation of the drugs; and (5) it is rare in the general population.[3,4]

ADR cases comprise 3%–6% of all hospital admissions and have an inpatient incidence of 10%–15%; DA is estimated to account for up to a third of all ADRs.[5,6] DA can affect any organ but the skin is most commonly involved, resulting in fatalities or great physical distress.[4,7] Unsurprisingly, studies on ADRs are often restricted to the inpatient population, which tend to be either of rather severe outcomes, directed to specific symptoms such as cutaneous reactions and anaphylaxis, or are drug specific.[3,8-14] Paediatric studies on ADR and DA are of similar designs.[15-18] In Singapore, one prospective survey of a hospital's population estimated a low incidence rate of DA at 4.2 per 1,000 patients and appeared to affect mainly adults, with the youngest patient reported to be 15 years of age.[5] Hence, this study aimed to estimate the prevalence of ADRs in a general population of children outside a hospital setting, where milder cases which did not require hospitalisation, were not excluded from analysis.

METHODS

School children aged 7–16 years, from 25 randomly-

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Table I. Multivariate comparison of self-reported adverse drug reaction/drug allergy prevalence.

Demographic	No. (%) of patient	% with ADR	p-value*	OR (95% CI)	Adjusted p-value*†	Adjusted OR (95% CI)†
Gender						
Male	2,096 (44.1)	5.5	0.6537	1.0 (0.8–1.4)	0.6715	1.0 (0.7–1.3)
Female	2,656 (55.9)	5.2		1		1
Ethnicity						
Chinese	3,483 (73.3)	6.0	0.0256	1.5 (1.0–2.4)	0.0278	1.4 (1.0–2.3)
Malay	894 (18.8)	3.6		1		1
Indian	375 (7.9)	4.8		1.4 (0.7–2.6)		1.2 (0.6–2.3)
Age (years)						
7	412 (8.7)	2.9	0.0552	–	0.0540	–
8	446 (9.4)	4.7				
9	496 (10.4)	5.2				
10	404 (8.5)	5.5				
11	523 (11.0)	5.0				
12	596 (12.5)	7.1				
13	574 (12.1)	6.3				
14	481 (10.1)	6.2				
15	446 (9.4)	4.9				
16	374 (7.9)	5.9				
Income group						
1	1,493 (33.1)	3.6	< 0.0001	1	< 0.0001	1
2	1,503 (33.3)	5.5		1.5 (1.0–2.1)		1.4 (1.0–1.9)
3	683 (15.1)	5.4		1.3 (0.8–2.0)		1.2 (0.6–1.7)
4	836 (18.5)	8.4		1.4 (0.9–2.1)		1.3 (0.8–1.8)
Self-reported history of allergy in:						
Father						
No	4,638 (97.6)	4.7	< 0.0001	1	< 0.0001	1
Yes	114 (2.4)	34.2		4.1 (2.6–6.7)		4.0 (2.3–6.4)
Mother						
No	4,721 (99.3)	5.3	< 0.0001	1	< 0.0001	1
Yes	31 (0.7)	29.0		2.9 (1.1–7.4)		2.7 (1.0–7.2)
Sibling						
No	4,697 (98.8)	5.0	< 0.0001	1	< 0.0001	1
Yes	55 (1.2)	43.6		4.6 (2.4–8.7)		4.3 (2.2–7.9)
Subject						
No	4,021 (84.6)	3.2	< 0.0001	1	< 0.0001	1
Yes	731 (15.4)	17.9		4.8 (3.6–6.5)		4.6 (3.2–6.1)

Variables compared in the studies included gender, ethnicity, age, income group and self-reported history among family members.
* The p-value was calculated by using logistic regression analysis.
†Adjusted by means of multivariate logistic regression for gender, ethnicity, income group and self-reported family history.
ADR: adverse drug reaction; OR: odds ratio; CI: confidence interval

selected schools, were screened for self-reported ADRs using a parent-administered questionnaire, between April 2005 and April 2006. Self-reported ADRs were indicated by a "yes" or "no' question, e.g. "has your child ever had any unexpected and/or adverse reaction to any drug/medication?" Those who answered "yes" were asked to provide the name of the drug(s)/medication(s), age of the subject when the reaction first occurred, and how the subject was affected. Other information collected included history of asthma, eczema and rhinitis in the subject and his first-degree family members; demographics and socioeconomic status (grouped by lower, second, third and upper quartile of the national statistics for total monthly family income).

In the second phase, parents of subjects with a self-reported ADR were also asked for their consent to a follow-up phone survey. During this follow-up call, we inquired further about the signs and symptoms experienced by the subject during the reaction, whether they had sought a doctor's consultation for the reaction, and if so, for the doctor's diagnosis and whether the subject was tested for drug allergy. Data analyses were performed using the Statistical Analysis Software version 9.1 (SAS Institute Inc, Cary, NC, USA). Chi-square test was utilised to evaluate the effect of the selected risk factors on ADR. Fisher's exact test was used when necessary. Logistic regression was carried out to evaluate the risk factors of ADR and adjust for confounders as well. Missing values were excluded from the analysis.

RESULTS

In the screening survey (Table I), 4,752 (79.7%) valid responses were returned. The overall prevalence of

Table II. Types of medication reported.

Medication	No. (%) of cases
Antibiotics	161 (60.1)
Beta lactams	87
Macrolides	25
Co-trimoxazole	32
Others	2
Unknown	15
NSAIDs	52 (19.4)
Paracetamol	14 (5.2)
Others	17 (6.3)
Unidentified	24 (9.0)
Total	268 (100)

self-reported ADR was 5.4% (n = 263). No significant association with age and gender was observed ($p > 0.05$). In subjects with a self-reported ADR, a quarter experienced their first drug allergy below two years of age, while the median age of an ADR was five years of age, and the third quartile was ten years of age. Chi-square tests showed that ethnicity, income group and self-reported family history of allergy was associated with the occurrence of ADR ($p = 0.0256$, $p < 0.0001$, and $p < 0.0001$, respectively). ADR was least reported by Malays (3.6%) and most often by Chinese (6.0%), while the ADR occurrence rate was about 4.8% for Indians. The occurrence of an ADR followed an increasing trend according to the income group of the subject/family, where income group 1 refers to the lowest quartile and income group 4 to the top quartile of the national statistics of total monthly family income. Specifically, the reported ADR occurrence rate was 3.6% for Group 1, 5.5% for Group 2, 5.4% for Group 3 and 8.4% for Group 4. Subjects who had a history of allergy or familial history of allergy were also significantly more likely to report an ADR.

The logistic regression confirmed that ethnicity, income group and self-reported history of allergy of any family member significantly affected the occurrence of ADR ($p = 0.0256$, $p < 0.0001$ and $p < 0.0001$, respectively). Compared to the Malays, the Chinese (odds ratio [OR] 1.5, 95% confidence interval [CI] 1.0–2.4) and the Indians (OR 1.4, 95% CI 0.7–2.6) were at a higher risk of reporting positive signs and symptoms of ADR. However, only the difference between the Chinese and Malays was statistically significant ($p = 0.0256$). The OR of Income groups 1–4 was 1, 1.5 (95% CI 1.0–2.1), 1.3 (95% CI 0.8–2.0) and 1.4 (95% CI 0.9–2.1), respectively. However, only the second income group remained significantly at risk. The OR of a child reporting a positive history of ADR when the child's father, mother and sibling had similar self-reported histories was 4.1 (95% CI 2.6–6.7), 2.9 (95% CI 1.1–7.4) and 4.6 (95% CI 2.4–8.7), respectively. Over half (60.1%) of the ADRs were associated with antibiotics (Table II), of which half belonged to the beta-lactam family. Nonsteroidal anti-inflammatory drugs (NSAIDs) (19.4%) were the next common pharmacological group of drugs involved. Multiple drug allergies to more than one pharmacological group was reported by ten (3.7%) subjects, while dermal signs were reported by 156 (58.2%), followed by facial occurrence in 62 (23.1%), and affected breathing in 13 (4.9%) subjects.

Parents of 174 subjects took part in the telephone interviews. 31.1% reported urticaria, 38.6% reported "spotty rash" and 32.9% reported swelling (angio-oedema) of various facial regions, including the eyes and lips. 156 (89.7%) parents sought a doctor's advice for their child's reaction, where the diagnoses were suspected DA (137 cases), the medicine was "too strong" for the child (2 cases), and the cause of the rashes could be due to the infection instead (3 cases). Only 12 (6.9%) subjects underwent clinical testing for DA, of which three had a positive result. Another 11 (6.3%) subjects, though not tested, had repeated exposures to the drug in question with the same kind of reactions. Only four parents mentioned that their child was sent to a hospital emergency department. Other than discontinuing the suspected medication, 106 (60.9%) subjects switched to an alternative medication successfully, 11 (6.3%) avoided similar types of drugs completely and seven (4.0%) switched to alternative therapies.

DISCUSSION

The data here provides an estimation to the burden of DA experienced in a large group of non-selected Singaporean children, and similarities with data from another local study were noted.[4] The results show that ADRs are mostly associated with antibiotics, especially penicillins, followed by NSAIDs, and are more prevalent in children from higher-income groups. Moreover, ADRs are significantly more prevalent in Chinese and Indian children and are significantly associated with a history of allergy in the subject and/or in the subject's family. In contrast, ADRs are not associated with gender and age. Furthermore, the results from this survey are very much in agreement with clinical experience in daily practice: the majority of children labelled as having an ADR had never been clinically verified, and were not referred to tertiary institutions for diagnostic tests. Also, very rarely did the doctors attempt to propose a possible alternative diagnosis for the ADR, such as a viral rash.

From our survey, it was also concluded that parents

were generally unaware that DA tests are available. However, when DA testing was proposed for their child, most parents found it unnecessary, mainly because alternative medicine is easily available and they did not want to risk having their child go through another ADR. Parents also held the misconception that ADR does not kill and hence, they were unwilling to pursue the matter further. Nevertheless, while it seems that ADRs are over-reported in the general population, there exists a group of children with relatively mild presentations of a true ADR, is adequately managed in the general clinic setting and is not represented in hospital-based studies.

There were a number of limitations in this study, such as over-reporting by patients and their family members due to recollection bias, as well as information bias from patients who responded to the telephone interviews. Also, the knowledge of ADRs from both patients and GPs could have affected the outcome of the studies. It is important to keep in mind that the "allergic signs and symptoms" reported could have been presentations of the disease itself and not true manifestations of allergic reactions to medications or treatments. Improvement in reporting could be enhanced with pictures explaining the different types of rashes during the questionnaire, instead of relying on the individuals' interpretation of various signs, symptoms and other medical terminologies.

Selection bias of children for the study was minimised through a randomised selection of schools across Singapore, with a randomised selection of student cohorts from classes within the school. This minimised the bias towards response only from children who have an allergic history and who understand what the signs and symptoms in the allergy history means. Hence, the selection of children who agreed to the survey could be said to be close to representing the general school-going population. The biggest limitation to the study, however, was the refusal by a majority of parents to validate the above-reported signs and symptoms in their children with a definitive provocation challenge test to the reported culprit drug or substance. It is understandable that parents do not want to subject their children to similar ordeals to past events, and the parents' final decisions and medical ethics held the study back to truly validate the reported signs and symptoms.

In conclusion, a prevalence of 5.4% of an ADR was found in a non-selected group of Singaporean children. Most of the reactions were induced by beta-lactam antibiotics and presented with skin manifestations. As diagnostic testing for an ADR was seldom performed, over-reporting and false-positive labelling of children with ADR are likely to occur.

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