JPPT | Questionnaire Survey

Active Extraction of Experience of Adverse Drug Reactions in Children

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OBJECTIVE Safety information regarding the use of medication, over-the-counter drugs, and supplements for Japanese children is scarce. The aim of this study was to clarify adverse drug reaction (ADR) experiences in children and consider the method to collect ADRs efficiently.

METHODS We conducted a questionnaire survey regarding the ADR experiences of 20,412 children who were attending a preschool or kindergarten in the cities of Warabi and Toda, Saitama Prefecture, in May 2013.

RESULTS Responses were received from the guardians of 15,076 children (49.5% girls; 8.2 ± 3.5 yr). A total of 196 guardians (1.3%) responded that their children had experienced ADRs. Among them, a total of 243 suspected drugs and 284 ADRs were reported. Of the 243 suspected drugs, 2.5% were associated with a vaccine. The most frequently reported medication, reaction, and "medication–reaction pair" were antibacterials for systemic use, rash, and "antibacterials for systemic use and rash," respectively.

CONCLUSIONS In this study, we clarified that there were many potential ADRs among children, but all "medication–reaction pairs" reported were consistent with adverse events reported in the clinical trials available in the prescribing information of each medication. This study provides data respective to the frequency of these adverse events in the general pediatric population. Additional education is needed to enlighten guardians of the importance to report ADRs through the Direct Patient Reporting System.

ABBREVIATIONS ADR, Adverse drug reaction; ATC, Anatomical Therapeutic Chemical; OTC, over-the-counter drug

KEYWORDS adverse drug reactions; children; medication; medication safety; pediatrics; supplements; survey

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Introduction

Drugs must generally undergo extensive research, including preclinical testing and clinical trials, to ensure their safety, high quality, and effectiveness in target populations.[1] However, such studies have not often been undertaken for children because of the small profitability for pharmaceutical companies, the difficulty in obtaining consent, the wide range of ages from newborns to adolescents, and the various requests for different doses and dosage forms. Thus, safety information on the use of medications, OTCs, and supplements among children is scarce. This means that medication use among children could be more inappropriate than that among adults, and the lack of safety information and of available therapeutic options resulted in the use of off-label use in pediatrics.[2,3] In fact, according to a previous survey targeting children who had visited a hospital, about 70% of medications prescribed for children in Japan were reported to be off-label use.[4] It is important to use different approaches to exploring drug safety, including registries and also a careful review of the literature.[2]

Spontaneous reporting systems for adverse drug reactions (ADRs) are essential for post-marketing drug safety surveillance.[5] However, limited information has been collected on ADRs resulting from the use of medications, OTCs, and supplements, especially in children. Therefore, the Global Research in Paediatrics-Network of Excellence (the Global Research in Paediatrics network), which aims to facilitate the development and promote the availability of medication for children,[6] has started to collect safety information on the use of medications, OTCs, and supplements among children.

The safety evaluation system for marketed medications in Japan mainly consists of post-marketing clinical studies, such as post-marketing surveillance, and spontaneous reporting systems, such as the Drugs and Medical Devices Safety Information Reporting System, which is operated by the Pharmaceutical and Medical Devices Agency, established by the Ministry of Health, Labour and Welfare. Companies and health care professionals report ADRs through this system. As for patients, the Direct Patient Reporting System for ADR, in which patients and consumers report ADRs directly to the Pharmaceutical and Medical Devices Agency, was

Table 1. Medications Coded by the World Health Organization Anatomical Therapeutic Chemical (ATC)Code

ATC Code	Name	Suspected Agent, n (%)*
J01	Antibacterials for systemic use	121 (49.8)
R03	Drugs for obstructive airway diseases	24 (9.9)
J05	Antivirals for systemic use	23 (9.5)
R06	Antihistamines for systemic use	12 (4.9)
S01	Ophthalmologicals	11 (4.5)
N02	Analgesics	8 (3.3)
R05	Cough and cold preparations	4 (1.6)
D07	Corticosteroids, dermatological preparations	3 (1.2)
C05	Vasoprotectives	2 (0.8)
M02	Topical products for joint and muscular pain	2 (0.8)
A03	Drugs for functional gastrointestinal disorders	1 (0.4)
B03	Antianemic preparations	1 (0.4)
C01	Cardiac therapy	1 (0.4)
D06	Antibiotics and chemotherapeutics for dermatological use	1 (0.4)
H02	Corticosteroids for systemic use	1 (0.4)
M01	Anti-inflammatory and antirheumatic products	1 (0.4)
N03	Antiepileptics	1 (0.4)
N05	Psycholeptics	1 (0.4)
R01	Nasal preparations	1 (0.4)
—	Vaccine	6 (2.5)
—	Others	18 (7.4)

* Percentages reflect a denominator of 243, which is the total number of suspected drugs that were reported.

started in 2019. Direct reporting of suspected ADRs by patients was well established in other countries.[7] The previous studies stated that patients report a suspected ADR when they consider that a health care professional has not paid attention to their concerns,[8] and patients provide much more detail and clearer descriptions of their experiences than health care professionals when reporting suspected ADRs.[9] Reports sent by patients tend to be less preconceived than those sent by health care professionals. Although relatively few reports have been sent through this system and some are of low quality, it is considered useful for identifying previously unknown ADRs. Therefore, with the aim of clarifying ADR experiences of children in Japan actively, we conducted a questionnaire survey on guardians regarding the occurrence of ADRs caused by medications, OTCs, and supplements.

Methods

We conducted a questionnaire survey on children attending kindergartens, nurseries, and schools in the cities of Warabi and Toda, Saitama Prefecture, in May 2013. The questionnaires were distributed once from teachers to the guardians and collected during a 1-month period. Guardians answered 1 questionnaire for each child. Although the questionnaire was not validated before it was used, the questionnaire was developed based on previous studies;[10,11] it was reviewed by the members of the working group, which included epidemiologists and pharmacovigilance professionals, to whom the purpose of the study was explained. Based on the comments received from the members, slight modifications to the wording of the questionnaire were made prior to its use in this study. The questionnaire (see Supplemental Material) was composed of items relating to the characteristics (e.g., age, sex, presence of siblings, underlying disease) and ADR experiences of children.

Medications were classified based on the World Health Organization Anatomical Therapeutic Chemical (ATC) Classification system.[12] Reactions were based on the Japanese version of the *Medical Dictionary for*

Table 2. Frequency of Adverse Reactions to Drugs and Others Reported in 2 or More Cases

Reaction (Preferred Term)*	n (%)†
Rash (details unknown)	76 (26.8)
Diarrhea	26 (9.2)
Urticaria	25 (8.8)
Vomiting/nausea	22 (7.7)
Eczema	21 (7.4)
Pruritus	14 (4.9)
Tremor	10 (3.5)
Pyrexia/hyperthermia	7 (2.5)
Hallucination	7 (2.5)
Lip erosion	6 (2.1)
Anaphylactic reaction	5 (1.8)
Hepatic function abnormal	4 (1.4)
Somnolence	4 (1.4)
Agitation	4 (1.4)
Abdominal pain	3 (1.1)
Status asthmaticus	3 (1.1)
Nasal discomfort/nasal mucosal hypertrophy	2 (0.7)
Skin erosion	2 (0.7)
Febrile convulsion	2 (0.7)

* The terms are described in reference 13.
† Percentages reflect a denominator of 284, which is the total number of ADRs that were reported.

Regulatory Activities[13] and were coded as "preferred terms" by health care professionals. Reactions described by guardians were difficult to classify according to existing international coding systems. Therefore, health care professionals examined whether those reactions were associated with those described in the prescribing information of each medication. Ethics approval for this study was obtained from the Toda City Central Hospital Ethics Committee. All participants were informed that participation in the survey was voluntary.

Results

Overall, 50,506 people in the area were younger than 15 years. Among these residents, questionnaires were distributed to 20,412. In total, 15,077 responses (73.9%) were received, collected from 66 facilities. Among the responses, 196 guardians (1.3%) replied that their child had experienced an ADR. The mean ages ± SDs of the children who had and had not experienced any ADRs were 8.2 ± 3.5 and 9.0 ± 3.3 years, respectively. About half of the children in both groups were girls. The percentages of children who had a primary disease (e.g., asthma, epilepsy) were 23.5% and 9.6% among children who had and had not experienced an ADR, respectively.

Among the 196 responses, a total of 243 suspected drugs were reported. There were 120 medications prescribed, 6 vaccines, and 18 others. According to the ATC therapeutic subgroup, about half of the reports were related to "antibacterials for systemic use," and about 10% to "drugs for obstructive airway disorder" and "antivirals for systemic use" (Table 1). In addition, 6 reports (2.5%) were associated with vaccines.

Among the 196 responses, a total of 284 ADRs involving 53 kinds of reactions were reported. The most frequently reported ADR was rash (26.8%), followed by diarrhea (9.3%) and urticaria (8.9%; Table 2). Although the number of reports was limited, some relatively serious reports were noted, such as anaphylactic reactions, hallucinations, febrile convulsions, and shock. The most frequently reported medication–reaction pair was "antibacterials for systemic use," such as amoxicillin and cefcapene and rash (Table 3). In total, 134 "medication–reaction pairs" were reported only once; among these, 37 reactions were not exactly the same

Table 3. Frequency of Medication–Reaction Pairs Reported in 2 or More Cases

Medication	Reaction (Preferred Term)*	n (%)†
Amoxicillin	Rash, drug eruption	15 (5.3)
Cefcapene	Rash, drug eruption	8 (2.8)
Oseltamivir	Hallucination	6 (2.1)
Clarithromycin	Rash, drug eruption	5 (1.8)
Cefaclor	Rash, drug eruption	4 (1.4)
Cefdinir	Rash, drug eruption	4 (1.4)
Tulobuterol	Rash, drug eruption	4 (1.4)
Cefdinir	Diarrhea	4 (1.4)
Cefditoren	Diarrhea	4 (1.4)
Minocycline	Vomiting/nausea	4 (1.4)
Vaccine	Pyrexia/hyperthermia	4 (1.4)
Azithromycin	Rash, drug eruption	3 (1.1)
Antibiotics	Diarrhea	3 (1.1)
Cefditoren	Urticaria	3 (1.1)
Cefpodoxime	Eczema	3 (1.1)
Cefcapene	Eczema	3 (1.1)
Clarithromycin	Eczema	3 (1.1)
Oseltamivir	Vomiting/nausea	3 (1.1)
Antibiotics	Vomiting/nausea	3 (1.1)
Formoterol	Tremor	3 (1.1)
Amoxicillin	Pruritus	3 (1.1)
Betamethasone	Rash, drug eruption	2 (0.7)
Other β-lactam antibacterials	Rash, drug eruption	2 (0.7)
Cefditoren	Rash, drug eruption	2 (0.7)
Erythromycin	Rash, drug eruption	2 (0.7)
Lysozyme	Rash, drug eruption	2 (0.7)
Amoxicillin and enzyme inhibitor	Diarrhea	2 (0.7)
Other β-lactam antibacterials	Diarrhea	2 (0.7)
Cefcapene	Urticaria	2 (0.7)
Clarithromycin	Urticaria	2 (0.7)
Azithromycin	Urticaria	2 (0.7)
Lysozyme	Urticaria	2 (0.7)
Paracetamol	Urticaria	2 (0.7)
Pranlukast	Urticaria	2 (0.7)
Amoxicillin	Eczema	2 (0.7)
Cefdinir	Eczema	2 (0.7)

Table 3. Frequency of Medication–Reaction Pairs Reported in 2 or More Cases

Medication	Reaction (Preferred Term)*	n (%)†
Azithromycin	Eczema	2 (0.7)
Azithromycin	Vomiting/Nausea	2 (0.7)
Theophylline	Vomiting/Nausea	2 (0.7)
Cefcapene	Pruritus	2 (0.7)
Tulobuterol	Tremor	2 (0.7)
Theophylline	Tremor	2 (0.7)
Cyproheptadine	Somnolence	2 (0.7)
Cyproheptadine	Agitation	2 (0.7)

* The terms are described in reference 13.
† Percent reflects a denominator of 284, which is the total number of ADRs that were reported.

as the description in the prescribing information of each medication. However, when health care professionals examined them, all "medication–reaction pairs" were associated with the description in the product information of each medication. Table 4 shows that "reaction described by guardians" and "reaction described in the prescribing information of each medication that healthcare professionals examined to be associated with the reaction described by guardians."

Discussion

To our knowledge, this is the first large-scale comprehensive survey that collected ADRs actively from guardians and clarified the actual situation of ADRs among Japanese children. Among the 15,076 participants, the percentage of patients to report an ADR was 1.3%, and 284 ADRs in 196 children were reported.

The variability of ADRs based on the child's age may differ depending on whether they are able to complain about ADRs independently. However, no substantial age differences were seen in the frequency of medications and reactions reported. The reason for this may be that the present survey was based on the responses of guardians regarding their children's ADRs, not the overall incidence of ADRs. Whether guardians notice or provide accurate responses regarding the occurrence of ADRs in their children may depend on their child's complications. Therefore, it is considered desirable to establish a system capable of collecting and evaluating the occurrence of ADRs. In the previous review of pediatric ADRs from national pharmacovigilance databases in other countries, antibiotics were the most commonly reported medicines (7% to 33%), and the most frequently reported ADRs were skin disorders, including urticaria and rash, with rates ranging from 5% to 52% across studies.[14] In this study, nearly half of the reactions reported were associated with antibacterials, and approximately half of all reactions were related to skin symptoms. The most frequently reported "medication–reaction pair" was "antibacterials for systemic use and rash." This might be because antibacterials were found to be the most frequently used medication in children.[15] Additionally, antibacterials have been reported to be inappropriately prescribed for children in Japan compared with other countries.[16] Skin symptoms can be observed objectively by guardians and children themselves. Therefore, skin symptoms, which are not always caused by the use of medication, may appear frequently in children, and many parents may consider skin symptoms to be an ADR.

This comprehensive survey found that the guardians tended to report reactions in detail with various expressions, and there were many potential ADRs among children. Although all "medication–reaction pairs" were associated with the description in the prescribing information of each medication when health care professionals examined them in this study, patients' reports could be useful for signal detection of unknown ADRs that had not been previously reported by the preconceived ideas of health care professionals. However, some "medication–reaction pairs" reported by guardians often included reports that seemed to be influenced by reports in the media. In this study, "oseltamivir and hallucinations" could be the only pair influenced by the media, because there was no medication reported in the media except for oseltamivir among the medications reported. It is meaningful to conduct a comprehensive survey among children. However, a comprehensive survey was not always a means of collecting unknown "medication–reaction pairs" efficiently. Therefore, it was considered that it might be more important to enlighten guardians to report ADRs spontaneously through the Direct Patient Reporting System for ADR, rather than to collect ADRs actively from guardians. The patient reporting system has been started, but the number of reports has not increased sufficiently. More aggressive promotion of the Direct Patient Reporting System for ADR is needed in Japan.

Table 4. Thirty-seven Medication–Reaction Pairs That Were Not Exactly the Same as the Description in the Package Insert of Each Medication

Medication	Reaction Described by Guardians*	Reaction (Preferred Term) Described in the Prescribing Information†
Acetaminophen		
Patient 1	There was a little bit of a feeling of dream walking.	(Symptoms related to present illness)
Patient 2	Eczema	Hypersensitivity, urticaria
Adrenaline	Anaphylaxis	(Symptoms related to present illness)
Amoxicillin hydrate	Breathe unsteadily	Dyspnea
Azithromycin hydrate		
Patient 1	Stomach pain	Abdominal pain, Abdominal discomfort
Patient 2	The face swelled in red	Localized swelling
Patient 3	The pressure of the chest and the vomiting motion	Chest pain, nausea
Cefcapene pivoxil hydrochloride hydrate		
Patient 1	Anemia, immune, and hemolytic	Hemolytic anaemia
Patient 2	Swollen gums	Periodontitis
Patient 3	Sores on the lips	Stomatitis
Patient 4	The red spots came out	Rash, urticaria
Cefdinir	Discomfort in the nasal cavity	Skin disorder, burning sensation on the mucous membrane
Cefditoren pivoxil	Convulsion	Seizure
Cefotaxime sodium	It turned red in the patch test	Hypersensitivity
Clarithromycin		
Patient 1	The red spots came out	Rash, urticaria
Patient 2	Sores on the lips	Stomatitis
Cyproheptadine hydrochloride hydrate	Eczema	Rash
d-Chlorpheniramine maleate	Hallucinations appeared when suffering from influenza	(Symptoms related to present illness)
Dexamethasone propionate	Sores on the skin	Contact dermatitis, hypersensitivity
Dimethyl Isopropylazulene	Rash	(Symptoms related to present illness)
Erythromycin ethylsuccinate	Sores on the lips	Roughness in the mouth
Faropenem sodium hydrate	Eczema	Hypersensitivity, rash, urticaria
Faropenem sodium hydrate	Sores on the lips	Cheilitis
Formoterol fumarate hydrate	Extrapyramidal path	Tremor

Table 4. Thirty-seven Medication–Reaction Pairs That Were Not Exactly the Same as the Description in the Package Insert of Each Medication

Medication	Reaction Described by Guardians*	Reaction (Preferred Term) Described in the Prescribing Information†
Fosfomycin calcium hydrate	Being tired	Malaise
Gentamicin sulfate	Sores on the skin	Hypersensitivity, rash
Lysozyme hydrochloride	Red swelling around the mouth	Face oedema, redness
Methyl salicylate	Induction of asthma	(Symptoms that might be caused by smell of methyl salicylate)
Minocycline hydrochloride	Turned white in a mouth	Oral candidiasis
Norfloxacin	Sores on the lips	Cheilitis
Oseltamivir phosphate Patient 1 Patient 2 Patient 3	 Having nightmares, talking in a delirium, and tried to get up. Dilated pupils, tried to move. Easy to cause a tantrum	 Abnormal behavior Abnormal behavior Agitation
Potassium clavulanate and Amoxicillin hydrate	Swollen the nasal cavity like a ripe tomato	Angioedema
Theophylline	Febrile convulsion	Seizure
Tipepidine hibenzate	Drowsiness	Somnolence
Tulobuterol	Discomfort in the hands	Tremor

* Some of the reactions described in Japanese were difficult to translate faithfully in English.
† Reaction (preferred term) described in the package insert of each medication that health care professionals examined to be associated with the reaction described by guardians.

Limitations of Study

The survey was region specific in Japan; therefore, the findings cannot be generalized to all children in Japan or other countries, such as United States. However, because the response rate in this study was high (73.9%), the results appeared to reflect Japanese children's actual situation of ADRs. Because we asked guardians about their children's experience of ADRs, recall bias could have occurred. The judgment by health care professionals is not strictly a valid reference as to whether those reactions were associated with those described in the prescribing information of each medication, so multiple pharmacists were used in the reviewing the reports, including a pharmacist who qualified as a pharmacovigilance specialist. Because of some changes occurring in medication treatments from 2013 to 2020, such as the introduction of new medications, there might have been some changes in health care specialists' attitude toward the spontaneous ADR reporting. However, the aim of the present study was to clarify the actual situation of ADRs among Japanese children based on the large-scale comprehensive survey that collected ADRs actively from guardians, which would not seem to be significantly affected by these changes occurring in medication treatments from 2013 to 2020.

Conclusion

In this study, we clarified that there were many potential ADRs among children, but all "medication–reaction pairs" reported were consistent with adverse events reported in the clinical trials available in the prescribing information. This study provides data respective to the frequency of these adverse events in the general pediatric population. Additional education is needed to enlighten guardians of the importance to report ADRs through the Direct Patient Reporting System.

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