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The Utility of the World Health Organization-The Uppsala Monitoring Centre (WHO-UMC) System for the Assessment of Adverse Drug Reactions in Hospitalized Children

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SUMMARY Although the World Health Organization-The Uppsala Monitoring Centre (WHO-UMC) system has been suggested as a practical tool for classifying adverse drug reactions (ADRs), verification of such system has not been examined. The objective of this study was to evaluate the usefulness of the WHO-UMC classification for the diagnosis of ADRs. The gold standard was the results of drug challenges and serum tryptase in cases of anaphylaxis. Twenty-seven children had ADRs classified by the WHO-UMC system. The causality terms were 'certain' in 4/27, 'probable' in 6/27, 'possible' in 10/27 and 'unlikely' in 7/27 of the patients. Skin prick tests and intradermal tests were positive in 1/20 and 1/5 of the patients, respectively. Drug challenges and serum tryptase were positive in 8/26 and 1/3 of the patients, respectively. After complete evaluation, the positive and negative ADRs were documented in 9/27 patients (33.33%) and 18/27 patients (66.67%), respectively. The multi-level likelihood ratios for ADRs using the WHO-UMC system were ∞ in causality term 'certain', 2 in 'probable', 0.5 in 'possible', and 0 in 'unlikely'. In conclusion, causality term 'certain' and 'unlikely' of the WHO-UMC system had large impact on the likelihood of ADRs. In contrast, the causality term 'probable' and 'possible' had small impact on the likelihood of ADRs. Drug challenges and serum tryptase were helpful to confirm ADRs categorized by WHO-UMC system.

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Adverse drug reaction (ADR) is an important problem in pediatrics. The overall incidence of ADRs was 9.53% in hospitalized children and 1.46% in outpatient children.[1] Pediatric hospital admission due to ADRs was 2.09% and 39.3% of these events were life-threatening.[1] Drug allergy was the leading cause of anaphylaxis in hospitalized patients.[2]

There are some problems in determining ADRs since diagnostic tests are usually not available. The gold standard for the diagnosis of ADRs is drug challenge which is often impractical to be conducted in a normal setting. The causality assessment by The World Health Organization-The Uppsala

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Monitoring Centre (WHO-UMC) system has been considered a practical tool for classifying ADRs. Although this system gives general guidance to the classification of ADRs and has been widely accepted, the precision of this system to identify ADRs has not been systematically studied. Moreover, very few ADRs were classified as 'certain' or 'unlikely' due to the lack of re-challenge. As a result, most ADRs fall into categories of 'possible' or 'probable'.

The objective of this study was to evaluate the usefulness of the WHO-UMC classification as a diagnostic test for ADRs. The gold standard was the results of drug challenges and serum tryptase in cases of anaphylaxis.

MATERIALS AND METHODS

Subjects

The study was approved by the ethic committee, Siriraj Hospital, Mahidol University, Bangkok, Thailand. The medical records of pediatric patients (0-15 years of age) who were admitted to Siriraj Hospital from January 1st, 2005 to June 30th, 2006, and documented to have ADRs during the period of their admissions, were recruited. The ADRs were classified by causality assessment of the WHO-UMC criteria by two pharmacists who were well trained in WHO-UMC causality categories. The results of skin prick tests (SPT), intradermal (ID) skin tests, and drug challenges to suspect drugs were recorded. The serum tryptase was measured in cases of anaphylaxis. Informed consents were obtained prior to these procedures.

Definition of ADRs and the WHO-UMC causality categories

In this study, the term ADR was denoted as a response to a drug which was noxious and unintended, and which occurred at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function.[3]

The causality terms, 'certain', 'probable', 'possible' and 'unlikely' derived from The WHO-UMC causality categories of ADRs which were established by WHO International Drug Monitoring Program in 1991. The definitions of each category were as follows:[3] 1) certain: a clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which could not be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary; 2) probable: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which followed a clinically reasonable response on withdrawal (dechallenge). Rechallenge information was not required to fulfill this definition; 3) possible: a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug**,** but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal might be lacking or unclear; and 4) unlikely: a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which made a causal relationship improbable, and in which other drugs, chemicals or underlying disease provided plausible explanations.

SPT, ID test and drug challenge procedures

SPT and ID tests to suspect drugs were performed with 10 mg/ml of histamine phosphate and glycerinated saline as positive and negative controls. The suggested concentrations of drugs for SPT and ID tests by previous reports were used (Table 1).[4-9] A non-irritating concentration of 3 mg/ml of drugs was used if there was no previous reported protocol.[5] Amphotericin B had an irritative effect to skin and was not used for skin tests.[10] Antihistamines were discontinued for ≥7 days prior to skin tests. The size of wheal and flare reactions was recorded in millimeters (mm) and considered positive if the wheal was ≥ 3 mm compared to the negative control. Skin tests were not done in the patients who could not discontinue antihistamines.

Drug challenges were performed according to reported protocols.[4-12] In brief, ingesting (or injecting) increased doses of the suspect drug every 15 minutes (intravenous form) to 30 minutes (oral form) was done until the cumulative therapeutic dose was reached or until symptoms of a drug reaction occurred. The route of challenge was the same as the

route of reported reactions. The drug challenges were considered positive if there were symptoms or signs of ADRs such as anaphylaxis/anaphylactoid reaction, bronchospasm, rhinoconjunctivitis, laryngeal edema, urticaria, angioedema, and maculopapular eruption. Anaphylaxis was diagnosed by recent criteria.[13] Vital signs as well as patient's symptoms and signs were recorded every 15 minutes. Emergency resuscitation equipment and drugs were available in case of emergency.

Measurement of serum tryptase

The results of serial total tryptase levels were retrieved from the medical records of patients who developed anaphylaxis or anaphylactoid reactions after drug exposure. In brief, 2 blood samples were collected at 60 minutes after the onset of anaphylaxis and after the resolution of symptoms for more than 24 hours. After centrifugation at 1,500 x *g* for 10 minutes, the sera were frozen at –80 ºC until testing. Total tryptase levels were determined using the UniCAP Tryptase Fluoroenzymeimmunoassay according to the manufacturers' instructions (Pharmacia, Uppsala, Sweden).

Data collection and analysis

Data were expressed as individual values or the mean ± SD for group. Multilevel likelihood ratios were calculated to assess the value of the causality classification of The WHO-UMC system as a diagnostic test for ADRs. The gold standard was the results of drug challenges and serum tryptase in cases of anaphylaxis.

RESULTS

Demographic data of the patients

Twenty-seven patients (16 boys, 11 girls) were documented to develop ADRs by WHO-UMC criteria (Table 2). The mean age was 6.9 ± 4.4 years. Eleven patients (41%) had underlying diseases.

Drugs causing ADRs

The most common drugs causing ADRs in this study were antibiotics (44.5%), followed by acetaminophen (18.5%), Japanese encephalitis vaccine (11%), nonsteroidal anti-inflammatory drugs (NSAIDs, 7.4%), amphotericin B (3.7%), cyclophosphamide (3.7%), mepivacaine 3% (3.7%), budesonide/formoterol (3.7%), and cerezyme (3.7%). The most common antibiotics causing ADR was cotrimoxazole (18.5%), followed by amoxicillin (14.9%), ceftriaxone (3.7%), cephalexin (3.7%) and azithromycin (3.7%).

The clinical presentation of ADRs

The most common symptoms of ADRs in this study was isolated skin/mucosal system (85.2%) which included maculopapular rash (33.3%), isolated urticaria (25.9%), urticaria with angioedema (14.8%) and isolated angioedema (11.2%). None of the patient had isolated gastrointestinal, respiratory or cardiovascular symptoms. Four patients (14.8%) developed anaphylaxis or anaphylactoid reaction[13] as

Table 1 Non-irritating concentrations of skin prick tests (SPT) and intradermal (ID) tests

No.	Drugs	Concentration for SPT (mg/ml)	Concentration for ID tests (mg/ml)
1	Amoxicillin[4]	3	-
2	Cephalexin[5]	3	-
3	Cotrimoxazole[6]	3	3
4	Acetaminophen	3*	-
5	Diclofenac	3*	-
6	Japanese encephalitis vaccine[7]	Full strength gelatin**	1:100
7	Cyclophosphamide[8]	1, 10	1, 10
8	3% Mepivacaine[4]	Undiluted	-
9	Cerezyme[9]	40 U/ml	0.4, 4 U/ml

*Non-irritating concentration
**1 teaspoon of gelatin powder in 5 ml of normal saline
U, units.

shown in Table 2. Patient no. 5 developed generalized urticaria and hypotension at one hour after receiving intravenous ceftriaxone. Patient no. 13 had generalized maculopapular rash and hypotension at one hour after receiving intravenous amphotericin B. Patient no. 17 had urticaria, chest discomfort and decreased peak expiratory flow at 30 minutes after receiving oral acetaminophen. Patient no. 20 developed chest discomfort and palpitation at 15 minutes after receiving oral diclofenac.

Results of skin tests, drug challenges and serum tryptase levels

SPT and ID tests were performed in 20 (74.1%) and 5 patients (18.5%) who were not on antihistamines, respectively. SPT was positive in one patient (no. 3) to amoxicillin. ID test was positive in one patient (no. 27) to cerezyme. Drug challenges were performed in 26 patients (96.2%). The peak serum tryptase was measured in 3 patients with ana-

Table 2 Demographic data of the patients, WHO-UMC classification, skin tests and drug challenge results

No.	Age (years)	Underlying diseases	Suspect drugs	Reaction(s) to drugs	Onset	WHO-UMC category	SPT results	ID test result	Challenge test
1	7	None	Amoxicillin	Urticaria	45 min	Possible	Neg	ND	Neg
2	3	IgG3 subclass deficiency	Amoxicillin	Urticaria	1 h	Possible	Neg	ND	Neg
3	2	None	Amoxicillin	Urticaria, periorbital angioedema	2 h	Probable	Pos	ND	Pos
4	8	None	Amoxicillin	MP rash	3 h	Unlikely	Neg	ND	Neg
5	2	UTI	Ceftriaxone	Anaphylactic shock	1 h	Probable	ND	ND	ND
6	12	None	Cephalexin	MP rash	4 h	Unlikely	Neg	ND	Neg
7	2	Thalassemia	Cotrimoxazole	Urticaria, angioedema	10 h	Certain	Neg	ND	Pos
8	2/12	CGD	Cotrimoxazole	MP rash	2 h	Unlikely	Neg	Neg	Neg
9	15	Malignant lymphoma	Cotrimoxazole	MP rash	3 days	Unlikely	Neg	ND	Neg
10	9	Leukemia	Cotrimoxazole	MP rash	2 days	Certain	Neg	ND	Pos
11	9	Neuroblastoma	Cotrimoxazole	MP rash	3 days	Possible	Neg	ND	Neg
12	2	None	Azithromycin	Urticaria	6 h	Possible	ND	ND	Neg
13	9	Leukemia	Amphotericin B	Anaphylaxis/ anaphylactoid	1 h	Probable	ND	ND	Pos
14	11	None	Acetaminophen	Urticaria angioedema	30 min	Certain	ND	ND	Pos
15	4	None	Acetaminophen	Urticaria	15 min	Possible	Neg	ND	Pos
16	8	None	Acetaminophen	Urticaria angioedema	30 min	Possible	ND	ND	Neg
17	12	None	Acetaminophen	Anaphylaxis/ anaphylactoid	30 min	Certain	Neg	ND	Pos
18	11	None	Acetaminophen	Periorbital angioedema	15 min	Unlikely	Neg	ND	Neg
19	8	None	Ibuprofen	Angiodedma	30 min	Possible	ND	ND	Neg
20	15	None	Diclofenac	Anaphylaxis/ anaphylactoid	15 min	Possible	Neg	ND	Neg
21	1	None	JE vaccine	Angioedema	10 h	Unlikely	Neg	ND	Neg
22	2	None	JE vaccine	Urticaria	2 days	Unlikely	Neg	Neg	Neg
23	1	None	JE vaccine	Urticaria	5 days	Probable	Neg	Neg	Neg
24	11	SLE	Cyclophos-phamide	MP rash	2 h	Probable	Neg	Neg	Neg
25	8	None	3% Mepi-vacaine	Urticaria	1 h	Possible	Neg	ND	Neg
26	8	Asthma	Budesonide/ Formoterol	MP rash	8 h	Probable	ND	ND	Neg
27	7	Gaucher's disease	Cerezyme	MP rash	2 days	Possible	Neg	Pos	Pos

UTI, urinary tract infection; SLE, systemic lupus erythematosus; CGD, chronic granulomatous disease; JE vaccine, Japanese encephalitis vaccine; MP rash, maculopapular rash; SPT, skin prick test; ID, intradermal test; Neg, negative; ND, not done; Pos, positive; h, hour(s); min, minute(s).

phylaxis/anaphylactoid reactions (no. 5, 13 and 17) and was shown to be 3.97 times higher than baseline in patient no. 5. In patient no. 13 and 17, serum tryptase was not higher than baseline. Overall, ADRs categorized by WHO-UMC system classified patients to 'certain' in 4/27 (14.8%), 'probable' in 6/27 (22.2 %), 'possible' in 10/27 (37 %), and 'unlikely' in 7/27 (26%). After drug challenges and serum tryptase were determined, the positive ADRs were documented in 9/27 patients (33.33%) and negative ADRs were documented in 18/27 patients (66.67%). The multi-level likelihood ratios for ADRs using the WHO-UMC system were ∞ in causality term 'certain', 2 in 'probable', 0.5 in 'possible', and 0 in 'unlikely' (Table 3).

The symptoms and signs upon drug challenges were the same as those reported for ADR classification but with milder reactions. None of the patients developed anaphylaxis upon drug challenges.

DISCUSSION

The WHO-UMC system has been used worldwide to evaluate ADRs. Our study attempted to assess the usefulness of WHO-UMC causality assessment system for the diagnosis of ADRs in hospitalized pediatric patients. The gold standard was the results of drug challenges and serum tryptase in cases of anaphylaxis.

In this study, 40% of the patients had underlying diseases. Such diseases increase exposure to drugs such as antibiotics, antifungal, and chemotherapeutic drugs. Cotrimoxazole was found to be the most common antibiotic causing ADR. This could be due to several hematologic patients required prophylaxis for *Pneumocystis carinii* pneumonia (PCP) infections. The most common clinical presentation of ADRs in our study was maculopapular rash (33.3%) which was similar to other reports.[14] Anaphylaxis/anaphylactoid was reported in 4 patients (no. 5, 13, 17 and 20). Two of these patients (no. 13 and 17) had positive drug challenges and one patient (no. 5) had elevated serum tryptase. Therefore, these 3 patients had positive ADRs. Patient no. 20 had a negative drug challenge despite the history of anaphylaxis/anaphylactoid and was re-classified as negative ADRs.

The serial total serum tryptase levels were considered a serologic marker to confirm anaphylaxis. Enrique *et al.*[15] demonstrated that reaction-trypatse/baseline-tryptase ratio was 2.85 in anaphylactic and 1.29 in non-anaphylactic groups. The patient no. 5 developed anaphylaxis and had elevated reaction-trypatse/baseline-tryptase ratio (3.97) from ceftriaxone which could be due to massive mast cell degranulation. In patients no. 13 and 17, serum tryptase levels were not elevated despite anaphylactic symptoms. This could be due to non-IgE mediated drug reactions from amphotericin B[10] and acetaminophen.[16]

In our study, SPT was positive to amoxicillin in one patient (no. 3). ID test was positive to cerezyme in one patient (no. 27). Drug challenges in these patients were positive and positive ADRs were documented. The small number of positive SPT was confirmed by the previous report of Lammintausta *et*

Table 3 Numbers of patients with adverse drug reactions (ADRs) categorized by WHO-UMC criteria and ADR classification after further tests were done

WHO-UMC criteria (n = 27)	ADRs after drug challenges and serum tryptase were done (n =27)		Likelihood ratio
	Positive ADRs	Negative ADRs	
Certain	4	0	∞
Probable	3	3	2
Possible	2	8	0.5
Unlikely	0	7	0
Total	9	18	

al.[17] who demonstrated that positive SPT was documented in only 1.1% of 935 patients manifesting cutaneous ADRs. This might imply that most ADRs were non-IgE mediated reactions.

In IgE-mediated ADRs from drugs such as amoxicillin and cephalexin, the results of SPT and drug challenges correlated well with each other (Table 2). In contrast, in non-IgE mediated ADRs from drugs such as cotrimoxazole, challenge tests were done in 5 patients and the results were positive in 2 patients despite negative SPT in all patients. Therefore, drug challenges remained a useful procedure to confirm ADRs, especially in non-IgE mediated drug reactions. Within the protocol of progressive administration of drug with a small starting dose,[4-12] drug challenges were considered safe and provided useful information.

After complete evaluation, the multi-level likelihood ratios for ADRs using the WHO-UMC system were ∞ in causality term 'certain', 2 in 'probable', 0.5 in 'possible', and 0 in 'unlikely'. This indicated that if the WHO-UMC system classified ADRs into 'certain' or 'unlikely', the impacts on likelihood to be positive ADRs (for 'certain') or negative ADRs (for 'unlikely') were large. However, if the WHO-UMC system classified ADRs into 'probable' or 'possible', the impacts on likelihood to be positive or negative ADRs were small. Therefore, further tests such as drug challenges or serum tryptase might be useful to document ADRs especially in patients who had no alternative drugs.

In conclusion, the WHO-UMC system had large impact on the likelihood of ADRs if the causality assessment were 'certain' or 'unlikely'. However, if the causality assessment were 'probable' or 'possible', further tests such as drug challenges or serum tryptase should be done to provide additional information for proper drug management.

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