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Adverse Drug Reactions in Children – International Surveillance and Evaluation (ADVISE)

A Multicentre Cohort Study

Asia N. Rashed,[1] *Ian C.K. Wong*,[1] *Noel Cranswick*,[2] *Barbara Hefele*,[3] *Stephen Tomlin*,[4] *John Jackman*,[4] *Kenneth Lee*,[5] *Kam-Lun E. Hon*,[6] *Jeffrey Ong*,[2] *Maisoon Ghaleb*,[7] *Siew Siang Chua*,[8] *Tea Ming Hui*,[8] *Wolfgang Rascher*[3] and *Antje Neubert*[1,3]

1 Centre for Paediatric Pharmacy Research, UCL School of Pharmacy, London, UK
2 Pharmacology Research Unit, Royal Children Hospital, Parkville, VIC, Australia
3 Department of Paediatric and Adolescent Medicine, University Hospital Erlangen, Erlangen, Germany
4 Evelina Children's Hospital, Guy's & St Thomas' NHS Foundation Trust, London, UK
5 School of Pharmacy, The Chinese University of Hong Kong, Hong Kong
6 Department of Paediatrics, The Chinese University of Hong Kong, Prince of Wales Hospital, Hong Kong
7 Department of Practice and Policy, School of Pharmacy, University of Hertfordshire, Hatfield, UK
8 Department of Pharmacy, University of Malaya, Kuala Lumpur, Malaysia

Abstract

Background: A previous meta-analysis reported that 9.5% of hospitalized children suffered from an adverse drug reaction (ADR); however, reported incidences among studies varied.

Objective: To enhance the knowledge of ADRs in paediatric hospitalized patients at a global level we investigated the incidence and characteristics of ADRs in hospitalized children in European and non-European countries.

Methods: A prospective observational cohort study was conducted in academic and non-academic hospitals in five countries: Australia, Germany, Hong Kong, Malaysia and the UK. Children aged 0–18 years admitted during a 3-month period (between 1 October 2008 and 31 December 2009) were recruited. The main outcome measures were incidence, causality and outcome of ADRs.

Results: A total of 1278 patients (1340 admissions) were included [Australia n = 146 (149 admissions), Germany n = 376 (407), Hong Kong n = 143 (149), Malaysia n = 300 (314) and the UK n = 313 (321)]. The median age was 2 years (interquartile range [IQR] 0–7). Patients received a total of 5367 drugs (median 3; IQR 2–5) and median length of hospital stay was 4 days (IQR 3–7). A total of 380 ADRs were identified in 211 patients. The resultant ADR incidence of 16.5% (95% CI 14.5, 18.7) varied significantly between countries ($p < 0.001$). The highest incidences were observed in Malaysia and the UK. 65.3% (n = 248) of ADRs were found to be probable, and 24% of the ADRs were serious, with one being fatal.

Conclusions: By comparing data from five countries in Europe, Asia and Australia we have shown that the incidence of ADRs in hospitalized children is at least as high as incidences published in adults. However, the variation between countries was mainly due to different populations and treatment strategies. Particular attention should be given to opioid use in hospitalized children.

Background

Adverse drug reactions (ADRs) are an important global clinical problem and are a major contributor to mortality and morbidity.[1-3] Although most research to date has been confined to adults, the significance of ADRs in children has been increasingly recognized.[4] ADRs in children differ from those manifested in adults in terms of frequency, nature and severity due to the distinct pharmacokinetics and pharmacodynamics of drugs in children.[5] In addition, children are at a higher risk for ADRs, not least because many drugs are used without being studied properly in this population.[6,7]

A meta-analysis conducted in 2001 identified that the ADR incidence in hospitalized children is about 9.5%.[4] However, the confidence interval (CI) was large (95% CI 6.8, 12.3), indicating a wide variation among the studies. In 2009, a review of six prospective studies of ADRs in hospitalized children estimated that the incidence of ADRs was 10.9% (95% CI 4.8, 17.0).[8]

Major reasons for the differences in reported ADR incidences are the varying methods used for identifying ADRs and differing definitions of ADRs.[9,10] In the previous meta-analyses, lower ADR incidences were reported from studies using intensified spontaneous reporting[11,12] compared with studies using chart review.[13-15]

Most studies have been conducted at a national level, mainly in North America and Europe.[4] In Europe, a disproportionate number of studies came from the UK. No studies from Asia and Australia investigating ADRs in hospitalized children were found. A standardized methodology and the involvement of a wide range of countries in one cohort would significantly enhance the knowledge on ADRs in paediatric hospitalized patients at a global level.

The ADVISE (Adverse Drug Reactions in Children – International Surveillance and Evaluation) study was designed to investigate the incidence and characteristics of ADRs in paediatric hospitalized patients in five European and non-European countries. In addition, the incidence of ADRs in participating countries was compared and potential predictors of ADRs were identified.

Methods

Study Design

A multicentre cohort study was conducted in paediatric general medical wards in hospitals in five countries (Australia, Germany, China [Hong Kong], Malaysia and the UK). Details of participating hospitals and individual study wards are given in table I.

Study Population

The study population consisted of all children (0–18 years) admitted to the study ward for at least 24 hours over a 3-month study period in each country between 1 October 2008 and 31 December 2009 with the exception of Australia, where data were collected over a 1-month period only due to resource limitations.

Database and Data Collection

Data were collected using an online database application designed specifically for this project.[16] The data collected comprised patient demographics, medication details and admission diagnosis. For prescribed drugs, each chemical compound or combination of compounds (based on Anatomical Therapeutic Chemical [ATC) classification][17] was considered only once per patient irrespective of whether the dose was changed or

Table I. Characteristics of wards participating in the study

Characteristic	Australia	Germany	China	Malaysia	UK
City	Melbourne	Erlangen	Hong Kong	Serdang	London
Name of hospital	Royal Children's Hospital	University Hospital for Children & Adolescents, University of Erlangen-Nuremberg	Prince of Wales Hospital	Serdang Hospital	Evelina Children's Hospital
Type of hospital	Paediatric hospital	Paediatric hospital	General hospital	General hospital	Paediatric hospital
Total number of beds	~250	120	1200	620	180
Number of beds on study ward	36	24	30	28	40

prescriptions were repeated during the hospital stay. Fluid and electrolyte infusions and parenteral nutrition were not documented.

For standardization, the following established international terminologies were used: ATC[17] classification for medications, International Classification of Diseases, version 10 (ICD-10)[18] for diagnoses, and WHO Adverse Reaction Terminology (WHO-ART)[19] for ADRs.

A flowchart and checklist for chart review were provided (figures S1 and S2, Supplemental Digital Content [SDC], http://links.adisonline.com/DSZ/A68).

Identification of Adverse Drug Reactions (ADRs)

ADRs were identified by intensive chart review, which has been recognized as the gold standard in pharmacoepidemiology.[20,21] Unlike traditional spontaneous reporting, this method is less likely to miss common adverse reactions.[10,22]

One researcher in each team (a qualified pharmacist or a clinician) screened all patient records daily to identify all events potentially related to medications. All suspected ADRs were presented to the local research team, consisting of at least one clinical pharmacist and one paediatrician/paediatric pharmacologist. The team reviewed the patient record, including laboratory data, and assessed whether the event was an ADR as defined by the WHO.[23] A final decision was made by consensus after discussion within the group. The process is summarized in figures S1 and S2 (see SDC).

Assessment of ADRs

The causality of ADRs was estimated using the Naranjo algorithm[24] and severity was assessed using a weighted score (a total score of 1–4 indicates a mild ADR, 5–8 indicates a moderate ADR and >8 indicates a severe ADR) [see Dormann et al.[25]].

Whereas severity usually describes the intensity of an event (i.e. mild, moderate, severe), seriousness is based more on patient/event outcome or action criteria (fatal, life-threatening, requires inpatient hospitalization or prolongs existing hospitalization, results in persistent or significant disability/incapacity).[26] Widely established and accepted criteria to assess seriousness are provided by the International Conference on Harmonisation (ICH) with input from CIOMS,[26] which we used for our assessment. We also established the preventability of each ADR using the Schumock and Thornton[27] preventability criteria. All assessments of ADRs were carried out by the local research team in each country.

For each reported ADR, the time of occurrence, e.g. before, during or leading to admission, was documented.

All drugs that were likely to be involved in an ADR were documented. If there was more than one drug involved, the most likely one was considered as the main ADR causative drug. This decision was based on pharmacological properties and side effect profiles of the drug, which were obtained from the literature and the summary of product characteristics.

Reliability of ADR Detection and Assessment across Countries

The effectiveness of the methodology for ADR detection and its reliability across study sites was assessed. We randomly selected ten patients from

each site and a second reviewer (AN) assessed the patients with respect to the presence of an ADR. In order to assess the reliability of ADR assessment (causality/severity) we randomly selected 20 ADR cases from the study cohort and sent them to four raters for re-assessment.

Statistical Analysis

Statistical analyses were performed using Stata 11 (StataCorp, College Station, TX, USA). Since the data did not exhibit a normal distribution, Kruskal-Wallis analysis of ranks and Wilcoxon rank-sum tests were used to compare numerical variables. The chi-squared test was used to compare the proportions of categorical variables. Significant differences were considered at p-value <0.05.

Kappa statistics were used to assess the inter-rater reliability between the two reviewers for ADR detection and between the four raters for ADR assessment.[28]

ADR Incidence

The proportion of patients experiencing an ADR was defined as the number of patients with at least one ADR divided by the total number of patients in the study cohort. The proportion of patients experiencing an ADR in each country was defined as the number of patients with at least one ADR divided by the total number of patients in the individual country cohort.

The incidence of patients with ADRs was defined as the number of patients with an ADR divided by the number of patients receiving medications in either the total study cohort or in each country cohort.

The incidence of patients with ADRs during hospitalization was defined as the number of patients with at least one ADR during their hospitalization divided by the total number of patients receiving medications, similarly for serious ADRs. The proportion of all admissions that resulted from a drug taken prior to admission was calculated using the number of patients admitted due to an ADR divided by the total number of patients in the cohort receiving medications. All results were multiplied by 100 to give a percentage and stratified by country. For the purpose of incidence calculations and number of ADRs per patient, only the first patient admission was considered.

Results

Study Population

A total of 1278 paediatric patients (1340 admissions) were included [Australia n = 146 (149 admissions), Germany n = 376 (407), Hong Kong n = 143 (149), Malaysia n = 300 (314) and the UK n = 313 (321)]; 55% were male and the median age was 2 years (interquartile range [IQR] 0–7). Length of hospital stay in the cohort was 8347 days; median 4 days (IQR 3–7). 89.2% of children received 5367 drugs during hospitalization (median three drugs per patient; IQR 2–5) [table II]. The number of drugs prescribed per patient in the UK was found to be significantly higher than in the other countries ($p < 0.001$).

Based on the ICD-10 classification system, 'respiratory system' diseases were the most commonly reported diseases in all countries, followed by 'infectious and parasitic' diseases in Australia, Germany, the UK and Malaysia. In Hong Kong only a few infectious diseases were reported. Diseases of the nervous system were common in Germany, Malaysia and the UK. 'Endocrine, nutritional and metabolic' diseases occurred more frequently in Germany than Australia but none were reported in Malaysia and UK. Additional details of the diseases of the study population are shown in table SI (see SDC).

Drug Prescriptions

A total of 5367 prescribed drugs were recorded in the cohort. The highest number of prescriptions, for all countries, was for antibacterials (n = 1355; 25.3%), followed by analgesics (n = 903; 16.8%) and drugs for obstructive airway diseases (n = 472; 8.8%) [table III].

ADR Incidence

Two hundred and eleven of the 1278 patients experienced 380 ADRs. The proportion of patients experiencing an ADR was 16.5% (95% CI 14.5, 18.7). 129 patients experienced one ADR, 45 experienced two ADRs, 21 experienced three

Table II. Demographic characteristics of study population, proportions and incidences of patients with adverse drug reactions[a]

Patient characteristics	Country					Total
	Australia (–250/36[b])	Germany (120/24[b])	UK (180/40[b])	Hong Kong[c] (1200/30[b])	Malaysia[c] (620/28[b])	
No. of patients (no. of admissions)	146 (149)	376 (407)	313 (321)	143 (149)	300 (314)	1278 (1340)
No. of patients by age group, y [n (%)]						
0 to ≤2	81 (55.5)	133 (35.4)	176 (56.2)	62 (43.3)	225 (75.0)	677 (53.0)
>2 to ≤11	51 (34.9)	156 (41.5)	102 (32.6)	43 (30.1)	72 (24.0)	424 (33.2)
>11 to ≤18	14 (9.6)	87 (23.1)	35 (11.2)	38 (26.6)	3 (1.0)	177 (13.8)
Age, y [median (IQR)]	2 (0–8)	5 (1–10.5)	2 (0–6)	4 (0–13)	1 (0–2.5)	2 (0–7)
Sex [n (%)]						
Female	64 (43.8)	164 (43.6)	142 (45.4)	69 (48.3)	134 (44.7)	573 (44.8)
Male	82 (56.2)	212 (56.4)	171 (54.6)	74 (51.7)	166 (55.3)	705 (55.2)
Length of stay, days [median (IQR)]	4 (3–7)	4 (3–6)	4 (3–6)	6 (4–8)	5 (4–8)	4 (3–7)
No. of patients who received medications (%)	140 (95.9)	293 (77.9)	303 (96.8)	116 (81.1)	288 (96.0)	1140 (89.2)
Total no. of drugs prescribed	753	1343	2010	357	904	5367
No. of drugs prescribed per patient [median (IQR)]	4 (2–7)	2 (1–4)	5 (3–8)	2 (1–3)	3 (2–3)	3 (2–5)
No. of drugs prescribed per patient (only those with medication) [median (IQR)]	4 (3–7)	3 (2–5)	5 (3–8)	2 (2–4)	3 (2–4)	3 (2–5)
No. of patients with high-risk drugs [n (%)]	124 (88.6)	237 (80.9)	290 (95.7)	75 (64.7)	275 (95.5)	1001 (87.8)
ADR incidence[a] (95% CI) [n]						
Proportion of patients with an ADR	7.5 (3.8, 13.1) [11]	7.2 (4.8, 10.2) [27]	33.8 (28.6, 39.0) [106]	8.4 (4.4, 14.2) [12]	18.3 (14.1, 23.2) [55]	16.5 (14.5, 18.7) [211]
Age 0 to ≤2 y	3.7 (0.77, 10.4) [3]	4.5 (1.7, 9.6) [6]	30.1 (23.4, 37.5) [53]	11.3 (4.7, 21.9) [7]	19.1 (14.2, 24.9) [43]	16.5 (13.8, 19.6) [112]
Age >2 to ≤11 y	13.7 (5.7, 26.3) [7]	6.4 (3.1, 11.5) [10]	31.4 (22.5, 41.3) [32]	4.6 (0.57, 15.8) [2]	13.9 (6.9, 24.1) [10]	14.4 (11.2, 18.1) [61]
Age >11 to ≤18 y	7.1 (0.18, 33.9) [1]	12.6 (6.5, 21.5) [11]	60.0 (42.1, 76.1) [21]	7.9 (1.7, 21.4) [3]	66.7 (9.4, 99.2) [2]	21.5 (15.7, 28.3) [38]
Incidence[a] of patients with ADR	7.9 (3.9, 13.6) [11]	9.2 (6.2, 13.1) [27]	35.0 (29.6, 40.6) [106]	10.3 (5.5, 17.4) [12]	19.1 (14.7, 24.1) [55]	18.5 (16.3, 20.9) [211]
Incidence of ADRs as reason for admission	1.4 (0.17, 5.1) [2]	1.0 (0.21, 2.9) [3]	2.6 (1.1, 5.1) [8]	1.7 (0.21, 6.1) [2]	1.7 (0.57, 4.0) [5]	1.8 (1.1, 2.7) [20]
Incidence of ADRs during hospitalization	7.1 (3.5, 12.7) [10]	8.5 (5.6, 12.3) [25]	33.3 (28.0, 38.9) [101]	6.0 (2.5, 12.0) [7]	16.0 (11.9, 20.7) [46]	16.6 (14.5, 18.9) [189]
Incidence of serious ADRs	2.1 (0.44, 6.1) [3]	3.8 (1.9, 6.6) [11]	6.3 (3.8, 9.6) [19]	5.2 (1.9, 10.9) [6]	7.6 (4.8, 11.3) [22]	5.4 (4.1, 6.5) [61]

a Proportion takes into account all patients in the study cohort and in each individual country cohort; incidence takes into account only patients on medication in the study cohort and in each individual country cohort.

b Total no. of beds/no. of beds on study ward.

c General hospital.

ADR(s) = adverse drug reaction(s); **IQR** = interquartile range; **n** = no. of patients with ADRs.

Table III. Most frequently prescribed drugs for the three most common drug groups by country

Drug group (ATC classification)	Australia		Germany		UK		Hong Kong		Malaysia	
	Drug (no. of Rx)	Total no. of Rx (%)	Drug (no. of Rx)	Total no. of Rx (%)	Drug (no. of Rx)	Total no. of Rx (%)	Drug (no. of Rx)	Total no. of Rx (%)	Drug (no. of Rx)	Total no. of Rx (%)
Systemic antibacterials (J01)	Gentamicin (36), tobramycin (9)	45 (23.8)	Cefaclor (20), cefotiam (44), cefuroxime (2)	66 (22.7)	Amoxicillin and enzyme inhibitor (78), piperacillin and enzyme inhibitor (2)	80 (20.2)	Ampicillin (11), amoxicillin (2)	13 (21.3)	Cefuroxime (152)	152 (36.5)
	Benzylpenicillin (26), phenoxymethyl-penicillin (1)	27 (14.29)	Cefixime (3), cefotaxime (54), ceftazidime (6)	63 (21.6)	Cefotaxime (21), ceftazidime (3), ceftriaxone (49)	73 (18.4)	Cefuroxime (13)	13 (21.3)	Clarithromycin (69), azithromycin (6)	75 (17.99)
	Cefotaxime (21), ceftazidime (2), ceftriaxone (3)	26 (13.8)	Amoxicillin and enzyme inhibitor (34), piperacillin and enzyme inhibitor (1)	35 (12.0)	Azithromycin (12), clarithromycin (27), clindamycin (4), erythromycin (13)	56 (14.1)	Gentamicin (9), amikacin (1)	10 (16.4)	Cefotaxime (45), ceftazidime (3), ceftriaxone (14), cefoperazone, combinations (4)	66 (15.8)
	Others	91 (48.1)	Others	127 (43.6)	Others	189 (47.6)	Others	25 (40.9)	Others	124 (29.7)
Analgesics (N02)	Paracetamol (92)	92 (74.8)	Metamizole sodium (115)	115 (51.1)	Paracetamol (257)	257 (74.3)	Paracetamol (35)	35 (68.6)	Paracetamol (156)	156 (98.7)
	Morphine (12)	12 (9.8)	NA	NA	Morphine (53)	53 (15.3)	NA	NA	NA	-
Obstructive airways drugs (R03)	Salbutamol (25)[a]	25 (55.6)	Salbutamol (33)[a]	33 (55.0)	Salbutamol (65)[b]	65 (37.4)	Salbutamol (17)[a]	17 (60.2)	Salbutamol (86)[a]	86 (52.1)

a Route of administration: inhalation.

b Route of administration: inhalation and parenteral.

ATC = Anatomical Therapeutic Chemical; **NA** = not applicable; **Rx** = prescriptions.

ADRs and 16 experienced more than three ADRs. The incidence of patients with an ADR was 18.5% (95% CI 16.3, 20.9).

In the total cohort, there was no significant difference between sexes with regard to ADR occurrence (female: n = 97/573 [16.9%]; male: n = 114/705 [16.2%]; p = 0.717).

Overall, the incidence of patients experiencing an ADR was similar in Australia (7.9%), Germany (9.2%) and Hong Kong (10.3%) [p = 0.889]. The incidence was found to be significantly higher in Malaysia (19.1%) and the UK (35.0%) [p < 0.001].

Approximately 2% of the patients were admitted due to an ADR, varying between 1.0% in Germany and 2.6% in the UK. Of the 380 ADRs, 26 (7.0%) were responsible for the admission of 20 patients (table II).

The total of 380 ADRs was related to 488 drugs (9.1% of all prescribed drugs). 272 adverse reactions were due to single drugs and 108 reactions had multiple drug involvement.

ADR Characteristics

The five WHO system organ classes most commonly involved in the 380 identified ADRs were gastro-intestinal system disorders (n = 183), skin and appendages disorders (n = 59), metabolic and nutritional disorders (n = 47), heart rate and rhythm disorders (n = 41) and psychiatric disorders (n = 28) [figure 1].

By comparing the most frequent clinical manifestations of ADRs, gastro-intestinal system disorders (e.g. diarrhoea, vomiting, nausea) occurred in all countries, while heart rate and rhythm disorders (such as tachycardia) were reported more frequently in the UK compared to other countries (n = 34/41 cases).

In the overall study cohort, antibacterials were the drug group most frequently involved in ADRs (n = 200). The second most frequently involved drug group was analgesics (n = 83 ADRs), of which morphine (n = 64) was the drug most often causing ADRs.

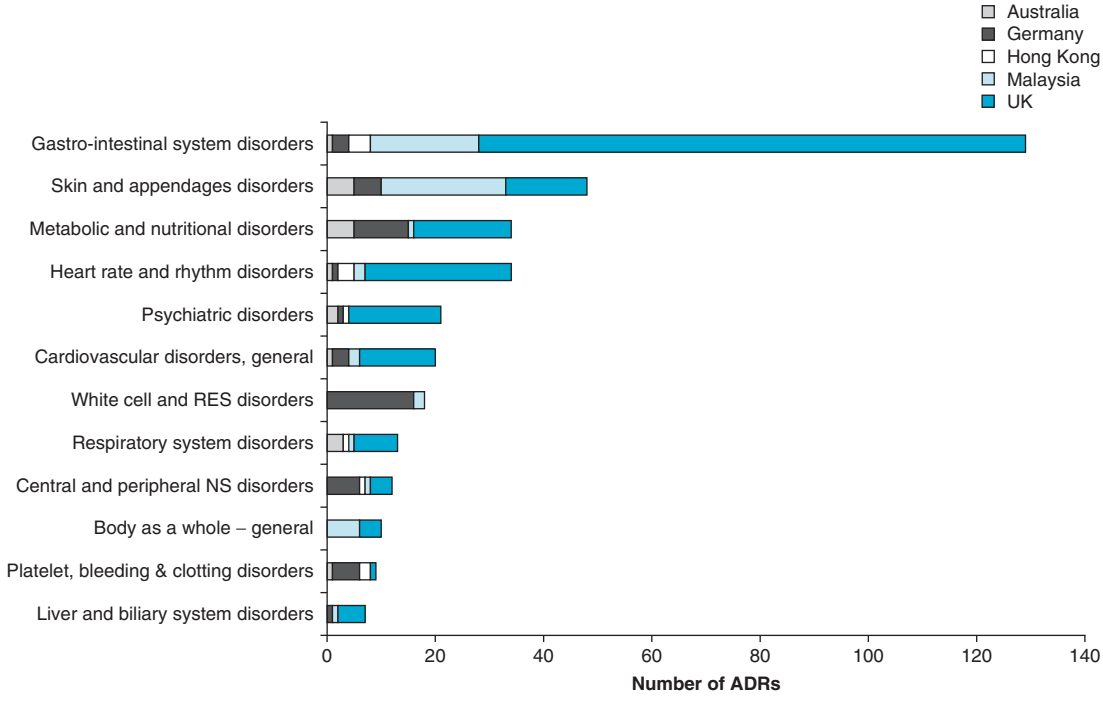

Fig. 1. Number of adverse drug reactions in major WHO system organ classes affected, in each country. **ADR** = adverse drug reactions; **NS** = nervous system; **RES** = reticuloendothelial system.

Table IV. Drugs most frequently associated with adverse drug reactions

Drug group (ATC classification)	Total no. of Rx	No. of patients with ADRs	No. of ADRs (% per Rx)	Drugs (no. of ADRs for each causative drug)	Examples of ADRs
Immunosuppressants (L04)	45	4	15 (33.3)	Azathioprine (2), ciclosporin (2), mycophenolic acid (1), tacrolimus (9)	Hypertrichosis (ciclosporin), hyperkalaemia (tacrolimus)
Antivirals (J05)	54	8	11 (20.4)	Aciclovir (6), foscarnet (2), ganciclovir (1)	Bradycardia (foscarnet), nephropathy toxic (aciclovir)
Diuretics (C03)	67	6	10 (14.9)	Furosemide (7), spironolactone (3)	Hypokalaemia (furosemide), hyperkalaemia (spironolactone)
Antibacterials (J01)	1355	113	200 (14.8)	Penicillins (70), macrolides (41), aminoglycosides (8), ciprofloxacin (1), cephalosporins (67), carbapenems (2), vancomycin (3), sulphonamides and trimethoprim (7), linezolid (1)	Diarrhoea (amoxicillin), ALT increased (clarithromycin), leukocytosis (vancomycin)
Corticosteroids (H02)	238	16	34 (14.3)	Systemic corticosteroids (34)	Hyperglycaemia (methylprednisolone), Cushing's syndrome (prednisone)
Anaesthetics (N01)	63	6	8 (12.7)	General anaesthetics (5), local anaesthetics (3)	Airways obstruction (propofol), respiratory distress (bupivacaine, combinations)
Antiepileptics (N03)	153	13	19 (12.4)	Antiepileptics (19)	Thrombocytopenia (valproic acid), nystagmus (phenytoin)
Cough and cold preparations (R05)	66	7	7 (10.6)	Bromhexine (1), codeine (6)	Constipation (codeine), cyanosis (bromhexine)
Analgesics (N02)	903	41	83 (9.2)	Acetylsalicylic acid (4), clonidine (13), metamizole sodium (1), morphine (64), tramadol (1)	Hypoventilation (morphine), pulmonary oedema (acetylsalicylic acid), bradycardia (clonidine)
Drugs for obstructive airway disease (R03)	472	31	45 (9.5)	Salbutamol (44), epinephrine (1)	Tachycardia, hypokalaemia and tremor (salbutamol)
Psycholeptics (N05)	126	4	7 (5.6)	Midazolam (2), diazepam (1), clobazam (3), chloral hydrate (1)	Bradycardia (midazolam), drowsiness (clobazam)
Others	789	32	49 (6.2)	Others	Others

ADRs = adverse drug reactions; **ALT** = alanine aminotransferase; **ATC** = Anatomical Therapeutic Chemical; **Rx** = prescriptions.

Heart rate and rhythm disorders (n = 41) were mainly caused by respiratory drugs, with salbutamol (n = 32) being the causative drug most often.

Looking at the proportion of the number of prescriptions involved in an ADR, immunosuppressants, antivirals and diuretics were the three groups most frequently associated with ADRs (33.3%, 20.4% and 14.9% of prescriptions, respectively) [table IV].

Causality

Overall, 7.9% of ADRs were assessed as 'definite', 65.3% as 'probable' and 26.8% as 'possible' [table V]. Most of the ADRs were judged to be 'probable' in three countries except Hong Kong where all ADRs identified were classified 'possible' and Australia where the majority were 'possible'. ADRs assessed as definite were particularly high in Malaysia (24.3%).

Preventability

Of the ADRs identified, 16.6% were classified as preventable.

Severity

Most of the ADRs (63.4%) were found to be mild, 35.5% were moderate and 1.1% were severe. This was similar in all countries except Malaysia where more ADRs (54.3%) were assessed as moderate.

Table V. Classification of adverse drug reactions identified in the study cohort

ADR characteristics	No. of ADRs					Total (n = 380)
	Australia (n = 21)	Germany (n = 53)	UK (n = 223)	Hong Kong (n = 13)	Malaysia (n = 70)	
Severity [n (%)][a]						
Mild	15 (71.4)	48 (90.6)	136 (61.0)	10 (76.9)	32 (45.7)	241 (63.4)
Moderate	5 (23.8)	4 (7.5)	85 (38.1)	3 (23.1)	38 (54.3)	135 (35.5)
Severe	1 (4.8)	1 (1.9)	2 (0.9)	0	0	4 (1.1)
Causality [n (%)][b]						
Definite	2 (9.5)	10 (18.9)	1 (0.44)	0	17 (24.3)	30 (7.9)
Probable	6 (28.6)	27 (50.9)	167 (74.9)	0	48 (68.6)	248 (65.3)
Possible	13 (61.9)	16 (30.2)	55 (24.7)	13 (100)	5 (7.1)	102 (26.8)
Preventability [n (%)][c]						
Preventable	7 (33.3)	10 (18.9)	40 (17.9)	3 (23.1)	3 (4.3)	63 (16.6)
Not preventable	14 (66.7)	43 (81.1)	183 (82.1)	10 (76.9)	67 (95.7)	317 (83.4)

a Severity scale according to Dormann et al.[25]

b Causality according to Naranjo algorithm.[24]

c Preventability according to Schumock and Thornton.[27]

ADR(s) = adverse drug reaction(s); **n** = no. of ADRs.

Seriousness

Overall, 24% (n = 91) of the ADRs were found to be serious and, of these, one ADR had a fatal outcome, four were life-threatening and one led to persistent incapacity (tables VI and VII). Of the 91 serious ADRs, 18.7% (n = 17) were preventable. The incidence of patients with serious ADRs in the study cohort was 5.4% (95% CI 4.1, 6.5), being highest in Malaysia (7.6%) and lowest in Australia (2.1%) [table II].

Inter-Rater Reliability Analysis

The inter-rater agreement between the two reviewers for identifying patients with ADRs was 'almost perfect', with k = 0.89 (95% CI 0.75, 1.0) and the agreement on the number of ADRs per patient was 'substantial', with k = 0.77 (95% CI 0.60, 0.94).[28]

However, the inter-rater agreement between the four raters for ADR causality assessment using the Naranjo algorithm was 'fair', with k = 0.30, while the agreement on ADR severity using a previously reported scale[25] was 'moderate', with k = 0.55.

Discussion

This study found that 211 of the 1278 (16.5%) hospitalized children from five European and non-European countries observed in the study cohort experienced at least one ADR during the

Table VI. No. of adverse drug reactions with serious outcome[a] in each country [n (%)]

ADR outcome	Australia (n = 21)	Germany (n = 53)	UK (n = 223)	Hong Kong (n = 13)	Malaysia (n = 70)	Total (n = 380)
Fatal	1 (4.8)	NA	NA	NA	NA	1 (0.3)
Involved persistence or significant disability or incapacity	NA	NA	1 (0.4)	NA	NA	1 (0.3)
Involved or prolonged inpatient hospitalization	3 (14.3)	18 (34.0)	24 (10.8)	6 (46.2)	34 (48.6)	85 (22.4)
Life threatening	NA	1 (1.9)	3 (1.3)	NA	NA	4 (1.1)
Total serious ADRs	**4 (19.0)**	**19 (35.8)**	**28 (12.6)**	**6 (46.2)**	**34 (48.6)**	**91 (23.9)**

a International Conference on Harmonisation/CIOMS criteria.[23]

ADR(s) = adverse drug reaction(s); **n** = no. of ADRs; **NA** = not applicable.

Table VII. Fatal and life-threatening adverse drug reactions

ADR outcome	ADR causative drug
Life threatening	
Hypotension	Morphine
Hypoventilation	Morphine
Liver cell damage	Clarithromycin
Pseudotumor cerebri	Normal human immunoglobulins for intravascular administration
Fatal	
Hypomagnesaemia	Tacrolimus

ADR = adverse drug reaction.

study period. Amongst those receiving at least one medication, the incidence of ADRs is 18.5% (95% CI 16.3, 20.9) and thus higher than in previously reported meta-analyses.[4,8]

Incidences of ADRs

One reason for the higher incidence of ADRs may be the use of intensive chart review as the detection method.[10,20,21] Not all of the studies included in previous meta-analyses used this method, which may explain their lower incidences of ADRs.[4,8]

The incidence of ADRs was highest in the UK when compared with other participating countries. The number of drugs prescribed per patient was also highest in the UK, and this may be a major contributing factor to the higher incidence. Furthermore, one of the drugs frequently associated with ADRs in the UK was morphine. 81.5% (53/65) of all morphine prescriptions in the study cohort were prescribed in the UK and 28% (n = 63/223) of ADRs were caused by morphine in the UK. Morphine was not prescribed in the other countries in our study except Australia (18.5% of all morphine prescriptions). Higher use of opioids in the UK compared with other EU countries has previously been reported.[29] Morphine prescribing in hospitalized children is also common in other western countries such as the US. A recent study conducted in the US by Lasky et al.[30] reported that morphine was among the top ten drugs administered to children during hospitalizations. Nevertheless, the question as to whether the guidelines for using morphine in children and adolescents in UK hospitals are appropriate or not remains to be investigated.

The frequent use of this high-risk drug may be another factor contributing to the higher incidence of ADRs in the UK. Other studies in hospitalized children from the UK and the US also showed that morphine was among the drugs most commonly associated with ADRs.[12,31]

A very recent evaluation of voluntary safety reports in a paediatric hospital revealed that about 10% of all reports were related to opioids, with morphine being the drug most often involved.[32]

Another drug frequently prescribed in the UK was salbutamol, which was given to 18.2% (n = 55) of all UK patients and related to 15.2% (n = 34/223) of ADRs observed in the UK. In Malaysia however, 27.8% (n = 80) of patients received this drug but it was associated with only two ADRs (n = 2/70). Salbutamol was also frequently prescribed in the other participating countries, but rarely related to ADRs. One reason for the higher number of ADRs seen in the UK may be that salbutamol was also administered intravenously (about 11% of all salbutamol prescriptions in the UK) while in other countries it was only administered by inhalation. Overall, 43.5% (n = 97/223) of ADRs in the UK were associated with morphine and salbutamol.

Another possible explanation for the high incidence of ADRs in the UK is the inclusion of observations reported by parents in the nursing notes, which did not happen in other countries. Patient reporting of potential ADRs has been found to be an enhancement for the detection and reporting of ADRs.[33] In paediatric patients, the parents pay close attention to their children and any troublesome symptoms. Documentation of this information may have led to increased observation of ADRs in the UK cohort. This might also explain the high percentage of non-serious ADRs reported in the UK.

To our knowledge there are no previously published data on the occurrence of ADRs in hospitalized children in Australia, Hong Kong and Malaysia. In Australia, paediatric medication safety research has been conducted previously, but these studies investigated drug related problems or adverse events identified by spontaneous report-

ing only.[34-36] Malaysia is a tropical country and infectious diseases are common in children. Consequently, almost 50% of prescribed drugs were antibacterials for systemic use, and 75.7% of the reported ADRs were related to this drug group, which is known to be frequently associated with ADRs.[31,37]

In our study, the incidences of ADRs were similar for Australia, Germany and Hong Kong (7.9%, 9.2% and 10.3%, respectively). For Germany, previously reported incidences using a comparable method were 14.1% and 17.4%, which are both clearly above the incidence found in our study.[6,9] However, the length of hospital stay and the number of drugs prescribed was lower in our study, which may explain the lower incidence of ADRs. Furthermore, one of the studies was conducted on an infection ward where the use of more high-risk drugs such as antibacterials was apparent.[6] Antibacterials have been shown to be more often related to ADRs.[20,31,37]

Similar to the findings in our paediatric study, data reported from the adult population in previous studies suggest that between 12% and 20% of patients experience an ADR.[25,38] A more recent study from the UK in adults, which used a similar approach to that used in this study, reported that 14.7% (95% CI 13.6, 15.9%) of 3695 patient episodes experienced one or more ADRs during hospitalization.[39] Whereas in the adult literature there is evidence that ADRs are more common in women compared with men, our study did not show a difference in proportion of girls and boys who had an ADR (16.9% vs 16.2%).[40,41]

ADRs Leading to Hospital Admission

We found that 1.8% (95% CI 1.1, 2.7) of patients were admitted to hospital as a consequence of an ADR. This means that almost one in every 60 admissions was due to an ADR. This proportion is similar to other paediatric studies, whereas higher proportions have been reported in adults.[3,8,42,43]

Severity and Seriousness of ADRs

We classified the majority of ADRs as mild (63.4%) in line with many previously published studies.[12,13,15,20] Also, in our study the results of the inter-rater analysis with respect to the severity assessment varied between countries and achieved moderate agreement only. This confirms that the currently available ADR assessment scales are subjective and no single algorithm is accepted universally.

Using the ICH/CIOMS criteria, in our study serious ADRs accounted for 24% of ADRs. Both a similar percentage of serious ADRs (19%) and a higher percentage (37.5%) have been reported.[31,44] In our study, 18.7% of serious ADRs were preventable; thus, treatment strategies need to be optimized in order to improve patient outcome.

One ADR had a fatal outcome, which accounted for 0.3% (95% CI 0.01, 1.5) of the ADRs in our study. Similar proportions have been reported previously for children and adults,[1,45] although higher numbers were reported in more recent studies in both populations.[31,43]

Economic Impact

We did not investigate the economic impact on healthcare systems. However, we have shown that about 2% of patients were admitted because of ADRs, accounting for a total of 114 days of hospital stay, and 22.4% of ADRs resulted in a prolonged hospital stay. Thus, ADRs have a considerable economic burden since they lead to additional days of hospitalization and therefore treatment costs.[2,3]

Study Strengths and Limitations

This is the first multinational study including European countries, Asian countries and Australia to investigate the incidence of ADRs in hospitalized children. The study used the gold-standard method for ADR detection. The inter-rater agreement for ADR detection was 'almost perfect', indicating good and homogeneous ADR detection across the countries. Hence, variances in reported incidences of ADRs are unlikely to be due to the ADR detection method and may reflect population differences and/or prescribing practices.

However, this study has several limitations. The sample size from two hospitals, Australia and Hong Kong, was small. This was due to resource limitations in Australia which resulted in

only 1 month of data collection. The spread of pandemic flu (influenza A H1N1) during the second half of 2009 in Hong Kong led to restrictions in ward visits for research, thus a smaller number of patients were reviewed. Consequently, variation in the number of patients from each country makes comparison between countries more difficult.

Differences in the documentation in patients' medical records may have had an influence on the detection of ADRs in our study. If important information is not documented adequately, ADRs are unlikely to be identified by the research team. This might apply mainly to mild and clinically less serious ADRs; however, they may indicate the early sign of a potentially serious ADR.

Also, we did not investigate the possible association between the underlying disease(s) and the incidence of ADRs. However, this study has shown that the most common diagnoses were similar in all countries, with respiratory system diseases being the most frequent.

Conclusions

This international paediatric study provides important information about the nature of ADRs in the paediatric populations across different countries around the world. Comparing data from five countries in Europe, Asia and Australia we have shown that the incidence of ADRs in children is at least as high as in adults. However, there was great variation between countries, which were likely to be due to different populations and treatment strategies.

The study found that 1.8% of children were admitted to hospital over the study period as a result of an ADR. Furthermore, it also confirms that ADRs remain a considerable risk for children admitted to hospital, i.e. on average every sixth child in hospital experiences an ADR and every eighteenth child has an ADR with serious consequences. Moreover, the number of drugs per patient is a major contributor to the occurrence of ADRs in all countries. The use of morphine and intravenous salbutamol contributed to the higher ADR incidence in the UK. Opioids were found to be of particular concern regarding their use in hospitalized children. Therefore, optimizing treatment strategies and reducing drug use are important in order to maximize patient safety.

The findings from this study can act as a baseline to which other paediatric services around the world can compare their practice. Sharing safety information is essential to enhance the benefit-risk profile of drugs used in children. Furthermore, these data can be used to support evidence-based protocols for healthcare professionals and policy makers to improve awareness towards the safety of drug use in children.

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Correspondence: Dr *Antje Neubert*, Department of Paediatric and Adolescent Medicine, University Hospital Erlangen, Loschgestr. 15, 91054 Erlangen, Germany.
E-mail: antje.neubert@uk-erlangen.de

