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Suspected Adverse Drug Reactions Reported For Children Worldwide

An Exploratory Study Using VigiBase

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Abstract

Background: As a first step towards implementing routine screening of safety issues specifically related to children at the Uppsala Monitoring Centre, this study was performed to explore reporting patterns of adverse reactions in children.

Objective: The first aim of this study was to characterize and contrast child reports against adult reports in an overall drug and adverse reaction review. The second aim was to highlight increases in reporting of specific adverse reactions during recent years subdivided by age group.

Study Design: This was an exploratory study of internationally compiled individual case safety reports (ICSRs).

Setting: Reports were extracted from the WHO global ICSR database, VigiBase, up until 5 February 2010. The reports in VigiBase originate from 97 countries and the likelihood that a medicine caused the adverse effect may vary from case to case. Suspected duplicate and vaccine reports were excluded from the analysis, as were reports with age not specified. The Medical Dictionary for Regulatory Activities (MedDRA®) and the WHO Anatomical Therapeutic Chemical (ATC) classification were used to group adverse reactions and drugs.

Patients: In the general review, reports from 1968 to 5 February 2010 were divided into child (aged 0–17 years) and adult (≥18 years) age groups. To highlight increases in reporting rates of specific adverse reactions during recent years, reports from 2005 to February 2010 were compared with reports from 1995 to 1999. The ten adverse reactions with the greatest difference in the proportion of reports between the two time periods were reviewed. In the latter analysis, the reports were subdivided into age groups: neonates ≤27 days; infants 28 days–23 months; children 2–11 years; and adolescents 12–17 years.

Results: A total of 3 472 183 reports were included in the study, of which 7.7% (268 145) were reports for children (0–17 years). Fifty-three percent of the

child reports were for males, whilst 39% of reports in the adult group were for males. The proportion of reports involving children among Asian reports was 14% and was 15% among reports from Africa and Latin America, including the Caribbean. Among reports from North America, Oceania and Europe, 7% of the reports involved children. For the ATC drug classification groups, the largest difference in percentage units between the child and adult groups was seen for the anti-infective (33 vs 15%), respiratory (11 vs 5%) and dermatological (12 vs 7%) drug groups. Skin reactions were most commonly reported for the children; these were recorded in 35% of all reports for children and 23% of all reports for adults. Medication error-related terms in the younger age groups were reported with an increased frequency during recent years. This was particularly noticeable for the infants aged 28 days–23 months, recorded with accidental overdose and drug toxicity. Reactions reported in suspected connection to medicines used for attention-deficit hyperactivity disorders (ADHD) completely dominated the 2- to 11-year age group and were also common for the adolescents. This study presents variations in the reporting pattern in different age groups in VigiBase which, in some cases, could be due to susceptibilities to specific drug-related problems in certain age groups. Other likely explanations might be common drug usage and childhood diseases in these age groups.

Conclusions: Reports in VigiBase received internationally for more than 40 years reflect real concerns for children taking medicines. The study highlights adverse reactions with an increased reporting during recent years, particularly those connected to the introduction of ADHD medicines in the child population. To enhance patient safety, medication errors indicating administration and dosing difficulties of drugs, especially in the younger age groups, require further attention.

Background

The WHO recently initiated a campaign to increase the awareness of the specific needs of children worldwide with regard to medicines.[1,2] Regulatory authorities have introduced guidelines and regulations concerning the development of medicines for use in the pediatric population;[3-5] however, many medicines are used outside their product licence (i.e. off-label) in children[6,7] despite the lack of clinical studies that support their efficacy and safety in this specific population. In such circumstances, age-specific dose guidelines and adverse reaction profiles are often not available to the prescriber.[8] For this reason, compilations of suspected adverse drug reaction (ADR) reports in children constitute a valuable source of safety information.

International collections of ADR reports could be particularly important when evaluating drug safety problems in children, since nationally compiled data for this population could be limited. Reports for children with rare diseases, or relating to drugs not commonly used for these age groups, result in low reporting rates. In addition, the problem that suspected ADRs are generally underreported further reduces the number of reports submitted.[9] With only a few reports available when investigating a drug safety issue at a national level, decision making becomes difficult

and international collaboration crucial. This was already evident in the 1960s after the thalidomide crisis.[10] A more recent example is a study on neonatal withdrawal syndrome associated with SSRIs based on international ADR data.[11] At the start of this study there were 66 cases from nine countries, of which six of the countries had only received one or two cases each. With so few reports, this problem might not have been recognized and therefore evaluated early on in the individual countries.

Studies reviewing spontaneously reported ADR information in children have mostly been published using national data.[12-19] However, one recent study evaluated international ADR data on children but focused on reports with ADRs resulting in fatal outcome.[20] This specific study included vaccine reports in the analysis, which constituted a large proportion of the dataset on children for the time period studied.

As a first step towards implementing routine screening of safety issues specifically related to children in the database of the WHO Collaborating Centre for International Drug Monitoring in Uppsala, Sweden, i.e. the Uppsala Monitoring Centre (UMC), this study was performed to explore the non-vaccine reporting patterns. The aim of the study was to characterize and contrast international ADR reports in children against reports for adults. In addition, a review of ADRs reported during recent years was performed to highlight increases in reporting rates of specific adverse reactions in different age groups.

Methods

VigiBase

This was an exploratory study using the WHO global individual case safety report (ICSR) database, VigiBase.[21] As of 5 February 2010, VigiBase, contained almost 5 million reports from 97 national pharmacovigilance centres. Each report includes records such as age, sex, drug(s) [assigned as suspected, interacting or concomitant by the reporter], adverse reaction(s) and additional information relevant for the case. The reported drugs and ADRs are allocated codes according to hierarchical structures of the WHO Drug Dictionary Enhanced,[21] WHO Adverse Reaction Terminology (WHO-ART) and Medical Dictionary for Regulatory Activities (MedDRA®).[22] The information in VigiBase is heterogeneous, i.e. originates from multiple sources (different countries and type of reporters), and the amount of information given, as well as the likelihood that a medicine caused the ADR, may vary from case to case.

Reports Excluded

Suspected duplicate reports were excluded from this study. An automated duplication detection tool was used to screen for possible duplicates, according to previously described algorithms.[23] Duplication of reports can occur in large compilations of data when reports of the same event are sent from more than one source. In each group of suspected duplicate reports, the reports with the least information were excluded. It should be noted that all duplicate reports will not be captured by this algorithm, particularly if the reports contain very limited data.

Reports on vaccines, and reports without information on age were also excluded. The proportion of vaccine reports in VigiBase at the time of this study was 46% of the reports concerning the 0–17 years age group. Due to this dominance and the fact that a review of vaccine reports in VigiBase has already been published,[24] these reports were excluded from this analysis (defined as reports with at least one drug from the WHO Anatomical Therapeutic Chemical [ATC][25] classification group J07).

Age Categories

The age categories denoted 'child reports' include all reports in the 0–17 years age group, while 'adults' includes all reports involving ages 18 years and above. When subdividing the child reports, the age categories were based on the International Conference on Harmonisation (ICH) guideline on Clinical Investigation of Medicinal Products in the Paediatric Population:[26] neonates ≤27 days; infants 28 days–23 months; children 2–11 years; adolescents 12–17 years.

Scope of Study

The first aim of the study was to characterize and contrast child reports (0–17 years) against adult reports (age ≥18 years). The overall review comprises reports from 1968 to 5 February 2010 and displays the number or proportion of reports for the child and adult groups:

1. over time;
2. by sex;
3. by type of reporter;
4. by country of origin and geographical region;
5. by drug and ADR groups: (i) ATC classification group for drugs that were reported as suspected or interacting, given with first-level ATC classification (anatomical main group); and (ii) System Organ Classes (SOCs) according to MedDRA® (version 12.1).

Note that one report can be counted in more than one ATC or SOC group because more than one suspected substance or ADR can be reported in a single report, and single substances can belong to several ATC groups.

The second aim of the study was to highlight increases in reporting rates of specific adverse reactions during recent years in each child age group. For this purpose, two 5-year periods were compared where reports entered in VigiBase from 2005 to 5 February 2010 were compared with reports received between 1995 and 1999. A percentage was calculated based on the number of reports with a MedDRA® preferred term (PT) in the specific age group, and time period divided by the total number of reports in the age group and time period. The difference in percentage units between the two time periods was calculated and the ten MedDRA® PTs with the greatest difference were reviewed. Between 1995 and 1999, MedDRA® was not available and WHO-ART was solely used in VigiBase, hence MedDRA® terms without a corresponding term in WHO-ART during this earlier time period were excluded from the top listing in our analysis. A further analysis was made by investigating which drug classes (ATC classification; fourth level, chemical subgroup) were reported most commonly for the ten adverse reactions with a recent increase in reporting per age group.

Results

Overall Characterization of VigiBase Reports

Number of Reports by Age Group

On 5 February 2010, VigiBase contained 4 978 565 ICSRs. After exclusion of suspected duplicate reports (n = 52 581), reports including vaccines (n = 358 632) and reports without age specified (n = 1 095 169), a total of 3 472 183 reports remained and were used in this analysis, of which 7.7% (268 145) were reports for children. The number of reports by age group in this subset is given in table I.

Reporting Over Time

The number and proportion of reports entered in VigiBase over 10-year periods from 1968 up to February 2010 are given for children and adults separately in table II. Reports concerning children and adults have corresponding increases in proportion of reports over time. More than half of the reports had been entered in VigiBase during the most recent decade.

Sex

In the reports where sex was known, 53% of the child reports concerned males, whilst in the adult group 39% concerned males. The proportion of males in each age group was 55% for the 0–27 days age group, 56% for the 28 days–23 months and 2–11 years age groups, whilst the proportion of males in the 12–17 years age group was 46%.

Table I. Number and proportion of reports by age group[a]

Age group	Number of reports	Total reports (%)
0–27 days	6 142	0.18
28 days–23 months	38 205	1.1
2–11 years	124 321	3.6
12–17 years	99 477	2.9
≥18 years	3 204 038	92

a Proportion is based on the number of reports in the age group/total number of reports in VigiBase (total number of reports = 3 472 183). Note the exclusion of vaccine, and duplicate and non-specified age reports in these counts.

Table II. Number and proportion of reports by decade and age group[a]

Years entered in VigiBase	Ages 0–17 years [no. of reports (%)]	Ages ≥18 years [no. of reports (%)]
1968–79	11 519 (4.3)	128 541 (4.0)
1980–9	33 481 (12)	398 705 (12)
1990–9	72 192 (27)	837 279 (26)
2000–10[b]	150 953 (56)	1 839 513 (57)

a Proportion is based on the number of reports in the time period and age group/total number of reports for the age group in VigiBase (child = 268 145, adults = 3 204 038). Note the exclusion of vaccine, and duplicate and non-specified age reports in these counts.

b Including reports up to 5 February 2010.

Type of Reporter

Reports were issued by physicians in 55% of the reports concerning children and 49% of the reports concerning adults. The distribution of reporter types for reports involving children and adults is given in table III.

Reporting from Country and Geographical Regions

Countries contributing the most child reports in VigiBase were the US (39% of the total number of VigiBase child reports), UK (8%) and Thailand (8%). The top contributing countries among the adults were the US (41%), UK (12%) and Germany (6%). The proportion of reports for children in relation to the overall reporting for each geographical region in VigiBase was 14% among the Asian reports, and 15% among the reports from Africa and Latin America, including the Caribbean, whilst in North America, Oceania and Europe, 7% of the reports were for children.

Reports of Drugs by Anatomical Therapeutic Chemical Classification

The proportions of reports by first-level ATC classification (anatomical main group) in the child and adult groups are displayed in figure 1. The ATC groups are sorted in descending order by the number of reports in the child group. For the children, the most frequently reported drugs belonged to the 'Antiinfectives for systemic use' (33%) and 'Nervous system' (28%) ATC groups. The most reported substances in these ATC groups were amoxicillin and atomoxetine (a centrally acting sympathomimetic agent used for the control of attention-deficit hyperactivity disorders [ADHD]). In the adult group, the most frequently reported drugs belonged to the 'Nervous system' and 'Cardiovascular system' ATC groups. The child group had a higher proportion of reports than the adult group for seven of the ATC groups where the highest difference in percentage units was found in the anti-infective (33 vs 15%), respiratory (11 vs 5%), dermatological (12 vs 7%) and nervous system (28 vs 25%) ATC groups.

Table III. Number and proportion of reports by type of reporter and age group[a]

Type of reporter	Ages 0–17 years [no. of reports (%)]	Ages ≥18 years [no. of reports (%)]
Physician	146 971 (55)	1 570 931 (49)
Other[b]	59 355 (22)	676 531 (21)
Unspecified	33 173 (12)	520 661 (16)
Consumer/non-health professional	11 426 (4.3)	206 886 (6.5)
Other health professional	8 772 (3.3)	97 952 (3.1)
Pharmacist	6 710 (2.5)	106 562 (3.3)
Literature	1 471 (0.55)	9 811 (0.31)
Lawyer	267 (0.10)	14 704 (0.46)

a Proportion is based on the number of reporter types in age group/total number of reports for the age group in VigiBase (child = 268 145, adults = 3 204 038). Note the exclusion of vaccine, and duplicate and non-specified age reports in these counts.

b These have been reported according to an older report format and can include consumer reports and various types of other health professionals (specified as 'not physician or dentist') and manufacturer reports.

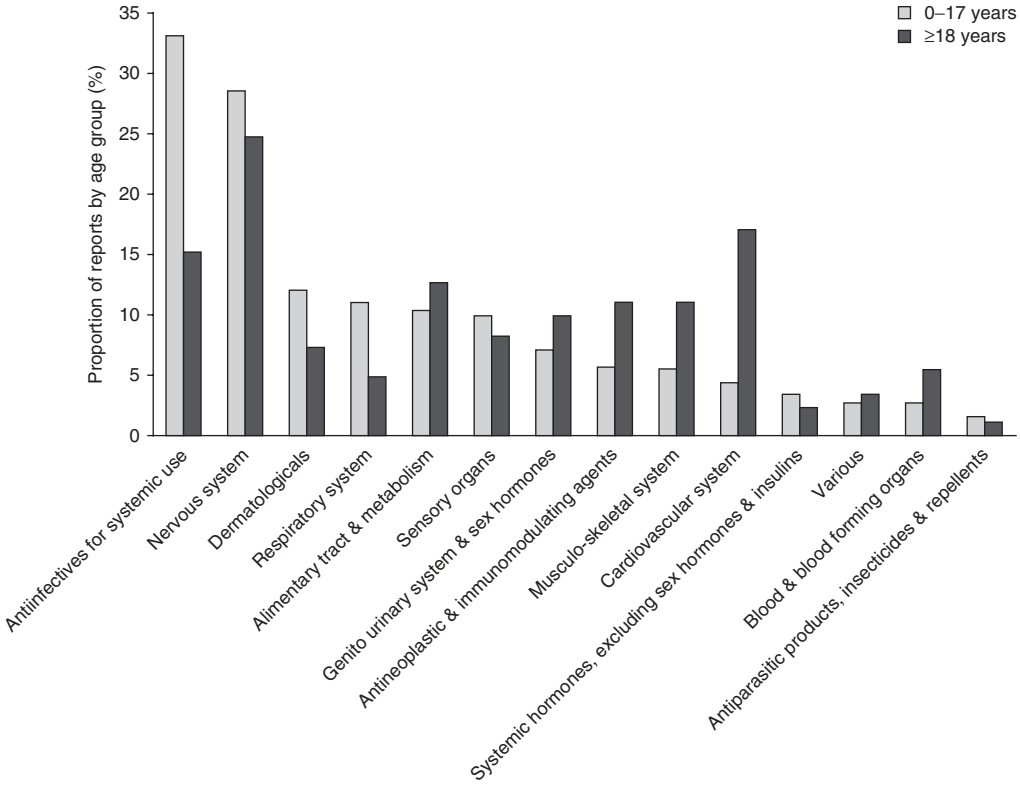

Fig. 1. Proportion of reports by drug group (Anatomical Therapeutic Chemical [ATC] classification, anatomical main group) in child and adult groups. One report can be counted in more than one ATC group (one report can list more than one drug and one drug can belong to more than one ATC group). Proportion given is based on the number of reports with the specific ATC group/total number of reports for the age group (child = 268 145, adults = 3 204 038). The figure is sorted in descending order of the proportion for the child group.

Reports of Adverse Reactions by System Organ Class

The proportion of reports in the different MedDRA® SOCs for the child and adult groups are displayed in figure 2. The SOCs are sorted in descending order by the number of reports in the child group. 'Skin and subcutaneous tissue disorders' were most commonly reported for children, followed by the 'General disorders and administration site conditions' and 'Nervous system disorders' SOCs. For the adults, the highest proportion of reports was found for the same top five SOCs as for the children. The child group had a greater proportion of reports than adults (more than one percentage unit) only for reactions belonging to the 'Skin and subcutaneous tissue disorders' SOC, which were recorded on 35% of all reports for children and 23% of all reports for adults. It should be noted that congenital disorders are not completely accounted for in this study since 51% of the reports referring to congenital disorders did not have an age registered and were consequently excluded from the analysis.

Adverse Reactions with a Recent Increase in Reporting

Between 2005 and 5 February 2010, 91 861 reports for the 0–17 years age group were entered in VigiBase. The number of reports in each child sub-age group for this period was as follows: neonates ≤27 days = 3189 reports, infants 28 days–23 months = 12 901 reports, children 2–11 years = 41 476 reports and adolescents 12–17 years = 34 295 reports. The top reported reactions for the children

during recent years were rash, urticaria, vomiting, pruritus, pyrexia, rash maculopapular, nausea, drug ineffective, rash erythematous and headache.

Table IV lists the ten adverse reactions with the greatest increase in reporting during recent years (2005–February 2010) compared with an earlier time period (1995–9) per age group. The three most commonly reported drug classes (ATC 4th level, chemical subgroup) for each term are also displayed. The table shows the number and proportion of reported MedDRA® PTs for each age group during recent years and is sorted according to the greatest difference in percentage units compared with the corresponding percentage at the earlier time period (1995–9). The MedDRA® terms without a relevant corresponding WHO-ART term during 1995–9 were excluded (more detail is provided in the last paragraph of this section).

Neonates (0–27 Days)

For the neonates, neutropenia, anaemia, increased blood lactic acid, hypertriglyceridaemia and macrocytic anaemia were mainly reported with antiretrovirals. No such dominance of drug classes was seen for the other reported reactions in this age group. Premature baby and neonatal disorder were reported in suspected connection to SSRIs. Various drug classes were reported with medication error: most frequently with heparin. Neonatal feeding disorder was most commonly reported with benzodiazepine derivatives,

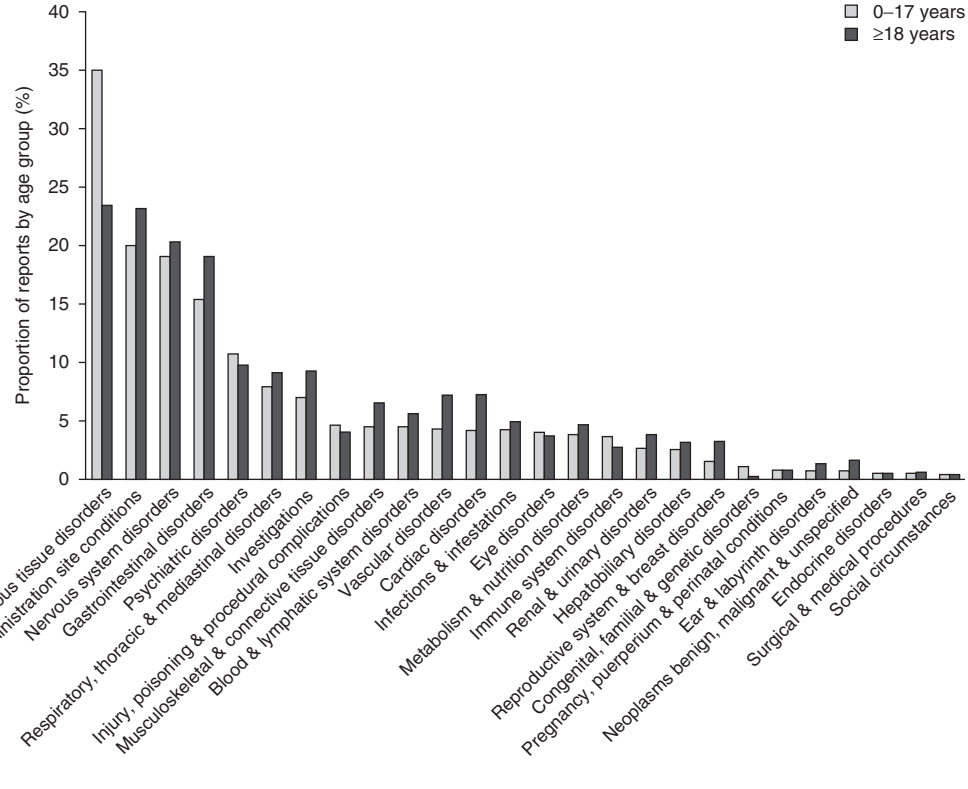

Fig. 2. Proportion of reports by Medical Dictionary for Regulatory Activities (MedDRA®) System Organ Class (SOC) in child and adult groups. One report can be counted in more than one SOC (one report can list more than one adverse reaction). Proportion is based on the number of reports with the specific SOC/total number of reports for the age group (child = 268 145, adults = 3 204 038). The figure is sorted in descending order of the proportion for the child group.

Table IV. Medical Dictionary for Regulatory Activities (MedDRA®) preferred terms (PT) with an increase in reporting during the time period 2005–February 2010 by each age group, and the three most frequently reported Anatomical Therapeutic Chemical (ATC) groups for each PT. Within each age group, the PTs are listed according to the greatest difference in percentage units between the time periods 2005–February 2010 and 1995–9

MedDRA® PT	No. of reports 2005–10[a,b] [n (%)]	Difference in percentage units compared with 1995–9[c] (%)	Three most frequently reported ATC groups by PT (percentage of no. of reports for PT in specific age group)[d]
0–27 days age group			
Premature baby	302 (9.47)	+9.14	SSRI (11); NRTI (10); PI (9)
Neutropenia	173 (5.42)	+4.77	NRTI (88); NNRTI (25); PI (21)
Neonatal disorder	121 (3.79)	+3.79	SSRI (14); other cardiac preparations (7); other antidepressants (5)/insulins and analogues for injection, intermediate-acting (5)/other respiratory system products (5)
Anaemia	143 (4.48)	+3.34	NRTI (77); NNRTI (20); PI (15)
Blood lactic acid increased	97 (3.04)	+2.23	NRTI (98); NNRTI (29); PI (25)
Fetal growth retardation	57 (1.79)	+1.79	β-blocking agents, selective (25); glucocorticoids (14); corticosteroids acting locally (14)/SSRIs (14)
Medication error	55 (1.72)	+1.72	Heparin group (20); other ophthalmologicals (20); heparins or heparinoids for topical use (18)
Hypertriglyceridaemia	54 (1.69)	+1.69	NRTI (96); PI (48); NNRTI (39)
Feeding disorder neonatal	111 (3.48)	+1.69	Benzodiazepine derivatives (21); non-selective monoamine reuptake inhibitors (14); other antiepileptics (14)
Anaemia macrocytic	53 (1.66)	+1.66	NRTI (98); non-NRTI (25); PI (17)
28 days–23 months age group			
Erythema	374 (2.90)	+2.23	Penicillins with extended spectrum (13); antibiotics (11); β-lactamase-sensitive penicillins (9)
Pruritus	605 (4.69)	+2.17	Penicillins with extended spectrum (27); antibiotics (12); combinations sulfonamides and trimethoprim, including derivatives (11)
Irritability	239 (1.85)	+1.65	H_2-receptor antagonists (7); specific immunoglobulins (6); propulsives (5)
Medication error	291 (2.26)	+1.50	H_2-receptor antagonists (16); piperazine derivatives (5); anilides (5)
Drug ineffective	207 (1.60)	+1.46	H_2-receptor antagonists (17); proton pump inhibitors (9); specific immunoglobulins (8)
Accidental overdose	164 (1.27)	+1.21	Anilides (7); natural opium alkaloids (7); H_2-receptor antagonists (7)
Drug toxicity	155 (1.20)	+1.12	Opium alkaloids and derivatives (21); anilides (19); aminoalkyl ethers (19)
Lethargy	143 (1.11)	+1.01	Natural opium alkaloids (13); opioid anaesthetics (9); phenylpiperidine derivatives (9)
Eyelid oedema	123 (0.95)	+0.85	Penicillins with extended spectrum (21); antibiotics (13); propionic acid derivatives (9)/combinations sulfonamides and trimethoprim, including derivatives (9)
Respiratory arrest	107 (0.83)	+0.67	Natural opium alkaloids (20); specific immunoglobulins (14); drugs used in opioid dependence (13)
2–11 years age group			
Drug ineffective	1450 (3.50)	+3.40	Centrally acting sympathomimetics (45); other antiepileptics (5); corticosteroids (4)

Continued next page

Table IV. Contd

MedDRA® PT	No. of reports 2005–10[a,b] [n (%)]	Difference in percentage units compared with 1995–9[c] (%)	Three most frequently reported ATC groups by PT (percentage of no. of reports for PT in specific age group)[d]
Erythema	880 (2.12)	+1.58	Penicillins with extended spectrum (7); antibiotics (7); macrolides (5)
Decreased appetite	934 (2.25)	+1.44	Centrally acting sympathomimetics (69); other antiepileptics (3); leukotriene receptor antagonists (2)
Psychomotor hyperactivity	625 (1.51)	+1.36	Centrally acting sympathomimetics (51); corticosteroids (6); glucocorticoids (6)
Abdominal pain upper	547 (1.32)	+1.24	Centrally acting sympathomimetics (52); leukotriene receptor antagonists (8); macrolides (4)
Aggression	1059 (2.55)	+1.14	Centrally acting sympathomimetics (46); leukotriene receptor antagonists (17); SSRIs (5)
Somnolence	1158 (2.79)	+1.11	Centrally acting sympathomimetics (35); carboxamide derivatives (5); other antipsychotics (4)
Crying	555 (1.34)	+1.05	Centrally acting sympathomimetics (49); leukotriene receptor antagonists (18); corticosteroids (3)
Suicidal ideation	444 (1.07)	+1.04	Centrally acting sympathomimetics (45); leukotriene receptor antagonists (31); SSRIs (12)
Medication error	577 (1.39)	+1.00	Centrally acting sympathomimetics (12); other antiepileptics (5); other antipsychotics (4)
12–17 years age group			
Drug ineffective	999 (2.91)	+2.85	Centrally acting sympathomimetics (26); SSRIs (8); other antiepileptics (6)
Suicidal ideation	718 (2.09)	+1.97	Centrally acting sympathomimetics (25); SSRIs (24); retinoids for treatment of acne (19)
Suicide attempt	659 (1.92)	+1.63	SSRIs (31); centrally acting sympathomimetics (14); anilides (9)
Completed suicide	442 (1.29)	+1.27	SSRIs (33); other antidepressants (15); anilides (11)
Depression	862 (2.51)	+1.19	Retinoids for treatment of acne (30); retinoids for topical use in acne (26); centrally acting sympathomimetics (18)
Erythema	544 (1.59)	+1.18	Penicillins with extended spectrum (5); antibiotics (4); propionic acid derivatives (4)/glycopeptide antibacterials (4)
Nausea	1651 (4.81)	+1.13	Centrally acting sympathomimetics (12); neuraminidase inhibitors (9); progestogens and estrogens, fixed combinations (6)
Intentional overdose	385 (1.12)	+1.08	SSRIs (17); anilides (16); other antidepressants (11)
Loss of consciousness	388 (1.13)	+1.07	Centrally acting sympathomimetics (20); SSRIs (8); natural opium alkaloids (7)
Feeling abnormal	375 (1.09)	+1.03	Centrally acting sympathomimetics (41); SSRIs (9); other antidepressants (6)

a Number and proportion of reports = the number of reports with the MedDRA® PT in the specified age group during 2005–February 2010, with the proportion of the total number of reports for the specified age group and time period.

b Including reports up to 5 February 2010.

c The table is sorted according to the greatest difference in percentage units for the MedDRA® PTs and specified age group comparing the time periods 2005–February 2010 with 1995–9.

d The three most frequently reported drugs grouped by ATC 4th level for the MedDRA® PT and specified age group during 2005–February 2010. The proportion given after each ATC is based on the number of reports within the ATC divided by the total number of reports for the MedDRA® PT and specified age group during 2005–February 2010. A '/' between ATC groups indicates that each ATC has the same number of reports; such instances are limited to the third most frequent ATC. The percentages for the ATC do not add up because one report can include more than one suspected drug and one single substance can belong to more than one ATC group.

NNRTI = non-NRTI; **NRTI** = nucleoside reverse transcriptase inhibitors; **PI** = protease inhibitors.

antidepressants and antiepileptics, while fetal growth retardation was most commonly reported with selective β-blocking agents and glucocorticoids. It should be noted that many of the reports in this age group concern reactions resulting from *in utero* exposure.

Infants (28 Days–23 Months)

For the infants, erythema, pruritus and eyelid oedema were most commonly reported with penicillins. The other terms were associated with a more varied pattern of reported drugs and therefore an account follows for only some of the top reported drug classes for each term. Irritability, medication error and drug ineffective were reported with histamine H_2-receptor antagonists (ranitidine) and drug toxicity was reported with cough suppressants (dextromethorphan) and anilides (paracetamol [acetaminophen] and paracetamol combinations). Accidental overdose was reported with paracetamol, ranitidine and natural opium alkaloids (oxycodone, morphine), the latter also being the top reported drug group for lethargy and respiratory arrest reports. Respiratory arrest was also reported with specific immunoglobulins (pavilizumab is used for respiratory syncytial virus infections).

Children (2–11 Years)

For the 2- to 11-year age group, all reactions except erythema were reported most frequently with centrally acting sympathomimetic agents (used for ADHD). A total of 14% of all reports in this age group and time period (2005–February 2010) were reported with ADHD medicines. The ADHD medicines with decreased appetite were reported 22-fold more than the second most reported drug class for this term, and drug ineffective, psychomotor hyperactivity, somnolence and upper abdominal pain were reported between 10- and 7-fold more than the next drug class. In addition to ADHD medicines, aggression, crying and suicidal ideation were reported with leukotriene receptor antagonists (montelukast) and medication error was reported with antiepileptics. Erythema was reported with penicillins.

Adolescents (12–17 Years)

For this age group, ADHD medicines were also reported with adverse reactions such as drug ineffective, nausea, loss of consciousness and feeling abnormal. Suicidal ideation was reported with ADHD medicines as well as with SSRIs and retinoids used for acne. Suicide attempt, completed suicide and intentional overdose were mostly reported with SSRIs but also with paracetamol (including combinations). Depression was reported mostly with retinoids for the treatment of acne, and erythema was reported most commonly with penicillins.

Excluded Terms

In table IV, some MedDRA® PTs are not shown among the top recently reported adverse reactions because they were not available in WHO-ART during the reference period. Most of these terms were considered unspecific as ADR terms. The following terms were excluded for the 0–27 days age group: 'drug exposure during pregnancy', 'caesarean section' and 'maternal drugs affecting the fetus'; for the 28 days to 23 months age group: 'accidental exposure', 'overdose', 'accidental drug intake by child', 'drug exposure during pregnancy', 'respiratory syncytial virus infection', 'product quality issue' and 'oxygen saturation decreased'; for the 2–11 years age group: 'overdose' and 'product quality issue'; and for the 12–17 years age group: 'overdose'. 'Abnormal behaviour', mostly reported with ADHD medicines, was also listed among the top recently reported reactions for the 2–11 years age group (n = 1120) and 12–17 years age group (n = 533), but was not included since no relevant match to this term was available during the reference period.

Discussion

This exploratory analysis identified a range of characteristic reporting patterns for children. A much larger proportion of the reports for children involved skin reactions compared with the reports for adults. Reports concerning children were proportionally higher for Latin American, African and Asian reports compared with those

from North America, Europe and Oceania. A higher proportion of reports involving males were found for reports in children compared with reports concerning adults. Medication error-related terms were reported with an increased frequency during recent years in the younger age groups. An increase of adverse reactions indicating dosing difficulties was seen, particularly in the 1–23 months age group. Adverse reactions reported in suspected connection with ADHD medicines completely dominated the 2–11 years age group and was also commonly reported for the adolescents.

Skin reactions in children were reported more frequently than in adults, which could be due to a number of underlying causes. Skin physiology is different in children compared with adults,[27] possibly leading to a predisposition to skin reactions. Allergic reactions to antibiotics are likely to be detected at a young age and antibiotics are thereafter avoided. Indeed, an additional analysis showed that only 7% of the reports concerning adults with a drug from the 'Antiinfectives for systemic use' ATC group listed a skin reaction, while the corresponding proportion for children was 19%.

The countries that contributed the most reports involving children (and those involving adults) to VigiBase in this study have been members of the WHO drug monitoring programme for a long time, i.e. the US, UK and Germany since 1968, and Thailand, which was the first Asian country to join, since 1984. The length of membership is probably the most plausible explanation for the higher number of reports from these countries. The higher proportion of reports involving children originating from Latin America, Africa and Asia compared with the overall reporting in these regions was not anticipated, but may be due to the younger population age structures in these regions.[28] The reasons for the higher proportions of reports involving children in these regions need to be investigated.

The higher reporting for boys among the children compared with the adults has been noted in previous studies based on similar data.[13,15,29,30] No definite explanation for this difference has been identified. In our study, 53% of all reports involving children were for boys, with an even greater proportion in the younger age groups. Part of the explanation might be that certain childhood diseases are more prevalent in boys, e.g. ADHD and asthma.[31] This might explain the higher proportion of boys among the 2–11 years age group, but not the higher proportion of boys for the <2 years age groups, when these diagnoses do not apply. It is unclear whether boys more commonly have health problems severe enough to require medication, or are more likely to receive medical treatment or to cause an ADR report to be sent. Alternatively, the younger male population could be physiologically more sensitive to experiencing ADRs. For adults, there is a consistent dominance of reports concerning females of around 60%, as shown in a recent review of the sex distribution in VigiBase.[29] The female dominance seen in that study, starting from age 15 years, could be a result of the adverse reactions reported when initiating the use of oral contraceptives. However, the consistent female dominance for all ages above 15 years, seen across all years of the WHO drug monitoring programme (since 1968), in the majority of reporting countries, SOCs and ATC groups,[29] suggests that the higher proportion of reports for adult females is unlikely to be explained solely by the use of oral contraceptives.

Antiinfectives and respiratory tract medicines made up a greater proportion of reports for children than for adults, which is likely to reflect the fact that infections and asthma are common childhood diseases.[31] Indeed, drug utilization studies of children in Europe,[32] the US[33] and Canada[34] show that the most commonly prescribed drugs are antibiotics and respiratory medicines.

There was considerable variation between age groups in the types of reactions more commonly reported over the past 5 years compared with the reference period 10 years earlier. Among the neonates, five reactions were mostly reported with antiretrovirals, of which many reports originated from one country's systematic follow-up. As a consequence, there was an overrepresentation of reactions specific for antiretrovirals and neonates in this study. The neonate group showed

a great variation in the type of drugs used by the mothers, as indicated by the reported terms 'premature baby', 'neonatal disorder' and 'fetal growth retardation'.

For the 1–23 months age group, several of the terms more commonly reported recently concerned drug administration and dosing difficulties, such as medication error, drug ineffective, accidental overdose and drug toxicity. Accidental overdose was reported for both over-the-counter medicines such as paracetamol, and prescription medicines such as morphine and ranitidine, suggesting administration errors made by health professionals, parents or even the child. In this instance, the pharmacovigilance reporting system is used to communicate concerns regarding medication errors. Medication error and substandard and counterfeit medicines are a concern in resource-poor countries where self-medication and unsupervised medication use are more common than in resource-rich countries and monitoring systems are generally lacking. The World Alliance for Patient Safety in collaboration with the UMC has started a pilot project with 11 countries to define how spontaneous reporting systems can be optimized for collection and detection of ADRs related to medication errors.[35] The Moroccan Pharmacovigilance Centre (the pilot project coordinator) conducted a study on medication errors and concluded that the reporting format needs to be adjusted to make it possible to fully capture medication errors.[36] One possible explanation for the increased reporting of medication errors in recent years might be the increased attention stimulated by the US-based Institute of Medicine's 1999 report ''To err is human: building a safer health system''.[37] Another reason for the increased reporting of these terms could be the greater availability of such terms in MedDRA®.

Furthermore, respiratory arrest was more commonly reported during recent years than in the reference period for the 1–23 months age group. The top reported substances for these terms were oxycodone, morphine and palivizumab, the latter being fairly new on the market and most likely closely monitored, leading to higher reporting rates.[38] Palivizumab is used to prevent respiratory syncytial virus infections in premature babies with bronchopulmonary dysplasia or significant congenital heart disease. These reports could be confounded by the underlying diseases of these babies and a more in-depth investigation of the cases is needed before any conclusions can be made.

Reactions for the 2–11 years age group reviewed in this study were strongly influenced by ADHD medicines. Atomoxetine, which was one of the top reported ADHD medicines, is a newly marketed drug for children, therefore the high number of reports is most likely connected with the intense monitoring that newly marketed drugs undergo.[38] Somnolence and psychomotor hyperactivity reported with these ADHD medicines could be signs of overdose,[39] suggesting difficulties in dosing with these children.

For the adolescents, the greatest increase in recent years was for suicide-related terms, in particular with psychotropic medicines. In 2004 the US and European regulators issued public warnings regarding a possible causal association between SSRIs and suicide in teenagers.[40,41] Thus, there is a clear publicity bias for SSRI and suicide during the time period studied. Suicide events, including intentional overdose were also reported with paracetamol, and it is likely that teenagers use this drug in a suicide attempt. Subsequently, easy access to potent drugs that can be used in excess for suicide attempts constitute a patient safety issue for teenagers.

One of the terms that had increased reporting during recent years was 'drug ineffective', reported for all child age groups, except the neonates, and most commonly with ranitidine, atomoxetine and methylphenidate. Reports of unexpected lack of effect of a medicine can signify a range of underlying problems such as inappropriate dose or indication, or pharmaceutical defects such as counterfeit drugs.[42] Reports of 'drug ineffective' soon after marketing might also highlight ineffectiveness of a medicine in certain subpopulations. The individual cases need to be further investigated to determine the specific meaning of 'drug ineffective' in the VigiBase reports with ranitidine and ADHD medicines.

The distinct pattern of reactions and drugs reported in each age group of this study highlights

the importance of grouping neonates, infants, children and adolescents separately. While we consider the age groupings used in this overview relevant for the purpose of our study, it may not be optimal for all specific investigations in children. There is no common age group standard within pharmacovigilance, therefore we used the ICH guideline on Clinical Investigation of Medicinal Products in the Paediatric Population.[26] Initially, we considered dividing the 2–11 years age group into pre-school and school-aged children since the drugs used by a 2-year-old would differ considerably from those used by an 11-year-old. Finally, we decided to adhere to the guideline. A positive outcome of using the 0–27 days age group was that we could assign most problems related to *in utero* exposure into one group.

The majority of reports for children in VigiBase originated from North America, Europe and Oceania, particularly the US; hence, the results seen in this study are highly influenced by the reported concerns specific for these countries. The pharmacovigilance reporting system is based on individual case reports with recorded details considered relevant for the specific event. Some of this relevant information will be lost in the overview summary statistics. For example, in our study it was sometimes unclear whether reactions in the neonates resulted from drug exposure directly to the baby or via the mother (*in utero* or breastfeeding).

This study presents the overall reporting of ADRs for children in VigiBase, but does not give the variation of risks for ADRs in different age groups since access to the worldwide frequency of drug use, or general occurrence of adverse reactions in the specific age groups, is not easily available. It should therefore be considered that commonly reported drugs highlighted in this study might not necessarily be burdened with more ADRs than other drugs but can be signs of common usage in the age group, such as for antibiotics. The medicines might also be assigned intensive monitoring, especially if they are new drugs or drugs newly indicated for children, resulting in a higher reporting rate. A larger number of adverse reactions in a specific age group could also reflect specific susceptibilities for certain diseases in that age group. As with all spontaneous reporting systems, reports in VigiBase are subject to possible reporting biases, duplication of reports, confounding issues and heterogeneity over time and across regions. As a consequence, these summary statistics must be interpreted with caution.

Conclusions

Reports in VigiBase, received internationally for more than 40 years, demonstrate real concerns for children taking medicines. The study highlights adverse reactions showing an increased reporting during recent years, particularly those connected to the introduction of ADHD medicines in the child population. To enhance patient safety, medication errors indicating administration and dosing difficulties with drugs, especially in the younger age groups, require further attention.

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