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Rates of Spontaneous Reports of Adverse Drug Reactions for Drugs Reported in Children

A Cross-Sectional Study with Data from the Swedish Adverse Drug Reaction Database and the Swedish Prescribed Drug Register

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Abstract

Background: Knowledge of drug safety is limited in the paediatric population, especially for drugs not used as labelled. Spontaneous reporting of adverse drug reactions (ADRs) may be an important source for increased knowledge, but the extent of the overall rate of reporting in children is not known.

Objective: The main objective of the study was to determine the extent of the spontaneous reporting of ADRs in children with a focus on drugs not used as labelled; this involved investigations of reporting rates of individual case safety reports (ICSRs) per 1000 treated individuals for drugs reported in children, to compare these between drugs labelled and not labelled for use in children, and to compare the rates for children with those of adults.

Methods: ICSRs (extracted from the Swedish ADR database) and number of treated individuals (extracted from the Swedish Prescribed Drug Register) were analysed for a 2-year period (2006–7). For drugs with one or more ICSR regarding children, rates of ICSRs per 1000 treated individuals were determined and compared between children (<18 years of age) and adults (≥18 years of age). Reported drugs for which >10% of the volume was sold over-the-counter or for in-hospital use were excluded. The overall reporting ratio of aggregated ICSRs per 1000 treated individuals was calculated between drugs not labelled and drugs labelled for use in children, separately for children and adults. The overall reporting ratio was also calculated between children and adults, separately for drugs labelled and drugs not labelled for use in children.

Results: A total of 255 (children) and 1402 (adults) ICSRs concerning 94 drugs were included in the analysis. Seventy-four (29%) and 711 (51%) ICSRs in children and adults, respectively, were registered as serious ($p < 0.00001$, two-sided test of proportions). For drugs reported in three or more ICSRs regarding children, the rates of ICSRs per 1000 treated individuals varied between (range) 0.01–6.45 (children) and 0.01–6.39 (adults). For 17 of the

drugs (18%) the rates of ICSRs per treated individual were significantly higher for children than for adults, and for 2 of the drugs (2%) the result was the opposite. The overall comparison of aggregated ICSRs per 1000 treated children revealed a higher reporting rate for drugs not labelled than for drugs labelled for children: rate ratio 3.44 (95% CI 2.67, 4.43); $p < 0.00001$. The corresponding result for adults was 1.52 (95% CI 1.37, 1.68); $p < 0.00001$. The overall reporting rate of aggregated ICSRs per 1000 treated individuals was higher in children than adults for drugs not labelled for children: rate ratio 2.01 (95% CI 1.61, 2.51); $p < 0.00001$.

Conclusions: The results of the present study indicate that the extent of the reporting of ADRs is greater for drugs not labelled for children than for drugs labelled for children. For these drugs, the extent of the reporting is greater for children than for adults. Thus, healthcare personnel willingly report ADRs in children, especially ADRs for drugs used outside the terms of the product licence. The finding is reassuring since there are few other sources for knowledge of paediatric drug safety. Important limitations of the study are (i) only a few ICSRs were registered for most drugs, thus giving each ICSR a strong impact on the rates for individual drugs; and (ii) the results of the present study apply only to the drugs included in the analysis.

Background

A large variety of drugs are used in children.[1] However, drug use may result in adverse drug reactions (ADRs), which are a major problem as they may result in a child suffering, hospitalization, and even in the death of a child.[2-7] A weighing of risks and benefits is therefore essential before and during drug treatment of a child, and such a reflection requires data on paediatric drug safety. For drugs labelled for children (as for drugs labelled for adults), common ADRs but not rare ADRs can be expected to have been identified during clinical trials. Knowledge of drug safety is more limited for drugs that have not been evaluated in paediatric clinical trials, but are prescribed off-label, i.e. used outside the terms of the product licence.[1,8-10] Thus, increased knowledge on paediatric drug safety in clinical practice is warranted. Spontaneous reporting of ADRs has been shown to be an important method of increasing such knowledge[11] and the method could be considered particularly important in children since drugs are not routinely tested in the paediatric population. However, to the best of our knowledge, the extent of the overall rate of spontaneous reporting of ADRs in children has not previously been evaluated.

In Sweden, physicians, dentists and nurses are obliged to report (i) serious ADRs; (ii) ADRs not mentioned in the summary of product characteristics (SPC); (iii) ADRs related to the use of new drugs (≤2 years on the market) except those labelled as common in the SPC; and (iv) ADRs that appear to be increasing in incidence.[12] All individual case safety reports (ICSRs) are reviewed and classified by experts at the six regional pharmacovigilance centres according to the recommendations of the WHO Collaborating Centre for International Drug Monitoring, for aspects such as the preferred term for the ADR and the seriousness of the ADR, before being entered in the SWEdish Drug Information System (SWEDIS).[13] A serious ADR is defined as any untoward medical occurrence that, at any dose (i) results in death; (ii) requires inpatient hospitalization or prolongation of existing hospitalization; (iii) results in persistent or significant disability/incapacity; or (iv) is life-threatening. The ADR can also be registered as serious if assessed as an important medical

event, according to instructions for SWEDIS. In addition, the causality between the suspected drug/s and the reaction/s is assessed as certain, probable, possible, unlikely, unclassified or unclassifiable.

The overall aim of the present study was to investigate the extent of the spontaneous reporting of ADRs in children with a focus on drugs not used as labelled. More specifically, we wanted to investigate the reporting rates of ICSRs per 1000 treated individuals for drugs reported as suspected to have caused an ADR in children, to compare the reporting rates between drugs labelled and not labelled for children, and to compare the reporting rates for children with those of adults.

Methods

All ICSRs registered between 1 January 2006 and 31 December 2007 with a relationship assessed as possible, probable or certain between the suspected drug(s) and the reaction(s) were extracted from SWEDIS. Forty-nine ICSRs were excluded since the age of the reported individual was missing or not reported. ICSRs concerning drugs reported at least once in children (<18 years of age) were included in the analyses. ICSRs with vaccines as the only suspected drug were excluded, as were ICSRs in which infants experienced ADRs after their mother's intake of a drug during pregnancy, and ICSRs regarding biological agents mainly used to treat rheumatoid arthritis.[14] The latter drugs are monitored in a special quality register that does not include children, and from that register ICSRs are generated and registered in SWEDIS (suspected biologicals in these ICSRs: etanercept, infliximab, adalimumab, anakinra).

The number of treated individuals can be obtained from the Swedish Prescribed Drug Register (SPDR) for drugs prescribed to a specific individual irrespective of their being prescribed in hospital or in primary care, but not for drugs sold over-the-counter (OTC) or for use during in-hospital care. To establish the proportion of drugs sold by prescription, data on sold volumes of drugs (defined daily doses [DDDs][15] or costs for drugs where DDD is not established) including sales classification (by prescription, for in-hospital use and OTC) were extracted from a national aggregated sales register. Events, defined as a unique combination of an adverse reaction and a drug, for drugs where >10% of the volume was sold for use during in-hospital care and/or OTC were excluded from the study since the number of treated individuals would be underestimated in the SPDR (151 events for 51 substances, see figure 1).

Chlorhexidine	Sulfamethoxazole and trimethoprim	Lidocaine + prilocaine
Ranitidine	Ciprofloxacin	Morphine
Omeprazole	Linezolid	Oxycodone
Dicycloverine	Fluconazole	Paracetamol
Macrogol combinations	Voriconazole	Prochlorperazine
Nystatin	Caspofungin	Quetiapine
Ferrous sulphate	Pyrazinamide	Chloral hydrate
Clonidine	Ganciclovir	Midazolam
Lidocaine	Immunoglubulins for intravascular adm.	Metronidazole
Silver nitrate	Temozolomide	Malathion
Estriol	Methotrexate	Nasal budesonide
Betamethasone	Cytarabine	Omalizumab
Cloxacillin	Rituximab	Meclozine
Piperacillin and enzyme inhibitor	Diclofenac	Cetirizine
Ceftriaxone	Ibuprofen	Loratadine
Meropenem	Propofol	Allergen extracts
Trimethoprim	Levobupivacaine	Tuberculin

Fig. 1. Reported drugs where >10% of the volume was sold for use during in-hospital care and/or over-the-counter. **adm** = administration.

All ICSRs were classified according to the age of the reported individual (children: newborn [0–1 month], infant [1–23 months], preschool child [2–5 years], child [6–12 years], adolescent [13–17 years]; adults: adolescent [18 years], young adult [19–24 years], adult [25–44 years], middle-aged [45–64 years], aged [65–79 years], aged 80 or over [≥80 years]). Moreover, all reactions were categorized according to the System Organ Class (SOC) of the preferred term in the SWEDIS Adverse Reaction Terminology (ART). These SOCs correspond to the SOCs of the WHO-ART, but not to the SOCs of the Medical Dictionary for Regulatory Activites (MedDRA®).

All 'suspected' drugs in the included ICSRs were categorized on the basis of their being labelled for use in children or not in the Swedish SPC in September 2008. Thus, drugs labelled for use at any age <18 years were categorized as *labelled*, whereas drugs not labelled for use at any age <18 years were categorized as *not labelled*. Unlicensed drugs, prescribed on a compassionate named-patient basis after permission from the Medical Products Agency, were all categorized as *not labelled* since no Swedish SPCs were available for these drugs.

The number of children (<18 years of age) and adults (≥18 years of age), respectively, who were dispensed each drug reported as 'suspected' in the included ICSRs (aggregated on the substance level of the Anatomical Therapeutic Chemical [ATC] classification system [ATC code, seven positions][15]) between 1 January 2006 and 31 December 2007 was obtained from the SPDR. Moreover, the total aggregated number of children and adults who were dispensed any of the drugs reported as 'suspected' in the included ICSRs were extracted, separately for drugs labelled and drugs not labelled for use in children.

The study was approved by the regional ethics committee.

Statistics

Statistical analyses were conducted using SPSS 12.0.1 for Windows (IBM Corporation, Armonk, NY, USA) and Stata 11 (Stata Corporation, College Station, TX, USA). Differences in proportions were assessed by using the two-sided test of proportions. Rates of ICSRs per 1000 treated individuals (children and adults, separately) were determined for the suspected drugs in the included ICSRs. Ratios (95% confidence interval [CI]) between the rates of ICSRs per 1000 treated individuals in children and adults were calculated. Because of small numbers in the numerators, statistical significance was assessed using the Fisher's exact test, which is appropriate since all ICSRs in SWEDIS are scrutinized to avoid duplicates. The overall reporting rate ratio of aggregated ICSRs per 1000 treated individuals was calculated between drugs not labelled and drugs labelled for use in children, separately for children and adults. The overall reporting rate ratio of aggregated ICSRs per 1000 treated individuals was also calculated between children and adults, separately for drugs labelled and drugs not labelled for use in children. A p-value of <0.05 was considered significant.

Results

A flowchart and characteristics of the ICSRs analyzed in the present study are presented in figure 2. A total of 255 (children: median [interquartile range] age 13 [9–16] years, 49% female) and 1402 (adults: age 54 [35–72] years, 64% female) ICSRs concerning 94 drugs were included in the analysis. Seventy-four (29%) and 711 (51%) ICSRs, respectively, were registered as serious ($p < 0.00001$, two-sided test of proportions). In children, the most common adverse reaction was in the SOC 'Psychiatric disorder' (24% of the events), whereas 'Skin disorder' was the most common SOC reported in adults (16% of the events). In children, 156 (61%), 38 (15%), 49 (19%) and 12 (5%) ICSRs were reported by in-hospital physicians, general practitioners (GPs), specialists in outpatient clinics, and others, respectively. The corresponding figures for adults were 871 (62%), 387 (28%), 98 (7%) and 46 (3%).

An overall comparison of aggregated ICSRs per 1000 treated children revealed a higher reporting rate for drugs not labelled than for drugs labelled for use in children: 0.62 versus 0.18, rate ratio 3.44 (95% CI 2.67, 4.43), $p < 0.00001$. The

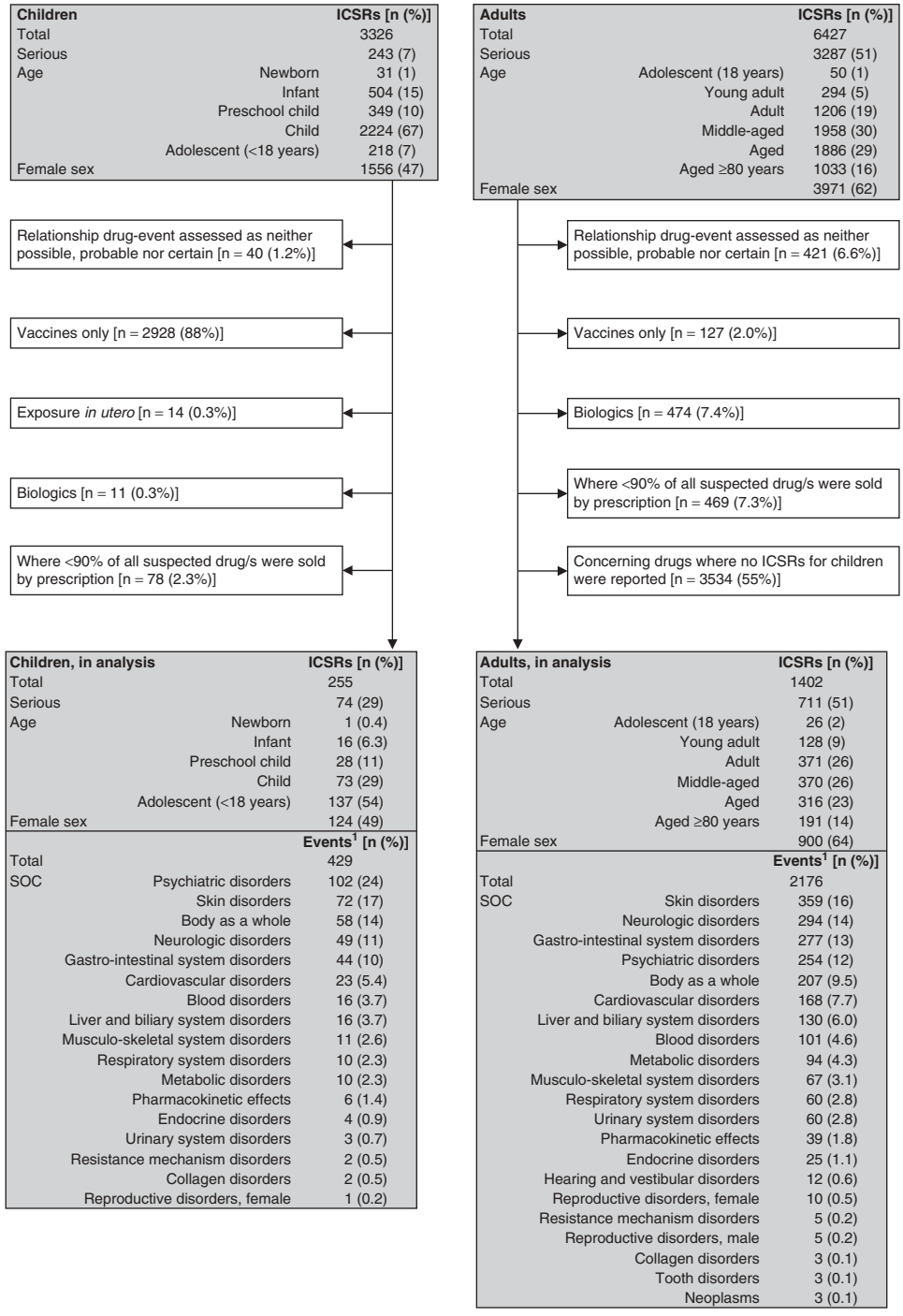

Fig. 2. Flowchart and characteristics of individual case safety reports (ICSRs) included in the present study. The events are classified according to System Organ Class (SOC). **1** An event is defined as a unique combination of an adverse drug reaction and a drug.

corresponding figures for adults were 0.31 versus 0.20, rate ratio 1.52 (95% CI 1.37, 1.68), $p < 0.00001$.

For 70 of the drugs (74%), one or two ICSRs involving children were reported (see figure 3).

For the remaining 24 drugs reported in three or more ICSRs involving children (26%), the rates of ICSRs per 1000 treated individuals varied between (range) 0.01–6.45 (children) and 0.01–6.39 (adults), as presented in table I. All ICSRs assessed as serious concerning these drugs are presented in table II. Eighty-four of 255 (33%) ICSRs in children concerned four substances: 47 (18%), 22 (8.6%) and 15 (5.9%) ICSRs concerned methylphenidate and/or atomoxetine (drugs for attention-deficit hyperactivity disorder [ADHD]), montelukast and isotretinoin, respectively.

For 17 of the drugs (18%), the reporting rates of ICSRs per treated individual were significantly higher for children than for adults (metformin, propranolol, sotalol, ezetimibe, isotretinoin, sildenafil, prednisolone, doxycycline, thalidomide, dixyrazine, diazepam, zopiclone, mirtazapine, formoterol, salmeterol and other drugs for obstructive airway, budesonide and montelukast), 9 of which (53%) were not labelled for use in children. For two of the drugs (2%) the result was the opposite (flucloxacillin and phenoxymethylpenicillin) [table I], both of which were labelled for use in children.

The overall reporting rates of aggregated ICSRs per 1000 treated individuals were also compared between children and adults, separately for drugs labelled and drugs not labelled for use in children. This comparison revealed higher rates in children compared with adults concerning drugs not labelled for use in children [0.62 (children) vs 0.31 (adults), rate ratio 2.01 (95% CI 1.61, 2.51), $p < 0.00001$], but not drugs labelled for use in children [0.18 (children) vs 0.20 (adults), rate ratio 0.89 (95% CI 0.75, 1.04), $p = 0.15$].

Discussion

The key finding of the present study is that healthcare personnel willingly report ADRs in children, especially for drugs used outside the terms of the product licence. For children, the overall reporting rate was more than three times as high for drugs not used as labelled compared with drugs labelled for use in children, although

2 ICSRs	1 ICSR	
Sulfasalazine	Hyoscyamine	Mercaptopurine
Mesalazine	Scopolamine	Imatinib
Insulin detemir	Sibutramine	Celecoxib
Propranolol	Metformin	Etoricoxib
Levonorgestrel and estrogen	Coagulation factor VIII	Baclofen
Etonogestrel	Von Willebrand factor and coagulation factor VIII	Sumatriptan
Amoxicillin	Disopyramide	Zolmitriptan
Flucloxacillin	Sotalol	Topiramate
Thalidomide	Ezetimibe	Dixyrazine
Naproxen	Terbinafine	Lithium
Codeine combinations	Adapalene	Risperidone
Valproic acid	Clindamycin	Propiomazine
Olanzapine	Tacrolimus	Citalopram
Aripiprazole	Vaginal ring with progestogen and estrogen	Reboxetine
Diazepam	Norethisterone and estrogen	Amfetamine
Hydroxyzine	Drospirenone and estrogen	Proguanil combinations
Zopiclone	Desogestrel	Mometasone
Fluoxetine	Tolterodine	Phenylpropanolamine
Mefloquine	Sildenafil	Salbutamol
Formoterol	Somatropin	Expectorants combinations
Opium derivatives and expectorants	Lymecycline	Mucolytics combinations
Desloratadine	Cefadroxil	Clemastine
	Norfloxacin	Deferiprone
	Nitrofurantoin	Diazoxide

Fig. 3. Drugs for which one or two individual case safety reports (ICSRs) were reported.

Table I. Rates of individual case safety reports (ICSRs) per 1000 treated individuals in children and adults, and rate ratios (95% CI) between children and adults, for all drugs with three or more ICSRs in children, and all other drugs with a statistically significant difference between the rates in children and adults

ATC[15]	Substance	Labelled for children	<18 y		≥18 y		<18 y vs ≥18 y	
			ICSRs (n)	ICSRs per 1000 treated individuals	ICSRs (n)	ICSRs per 1000 treated individuals	rate ratio (95% CI)	p-value
Three or more ICSRs in children								
N06BA04	Methylphenidate	Y	31	2.44	22	3.00	0.81 (0.47, 1.40)	0.48
R03DC03	Montelukast	Y	22	1.29	13	0.42	3.11 (1.57, 6.18)	0.001
N06BA09	Atomoxetine	Y	17	6.45	9	6.39	1.01 (0.45, 2.26)	1.00
D10BA01	Isotretinoin	N	15	4.57	15	1.84	2.48 (1.21, 5.07)	0.014
G03AA07	Levonorgestrel and estrogen	N	9	0.18	20	0.17	1.05 (0.48, 2.30)	1.00
N03AX09	Lamotrigine	Y	9	2.21	52	2.04	1.08 (0.53, 2.19)	0.85
R03BA02	Budesonide	Y	9	0.091	3	0.012	7.44 (2.01, 27.5)	0.001
J01AA02	Doxycycline	Y	7	0.36	27	0.041	8.89 (3.87, 20.4)	≤0.0001
J01FA01	Erythromycin	Y	6	0.079	10	0.080	0.99 (0.36, 2.72)	1.00
R05DA20	Opium alkaloids and derivatives, combinations	Y	6	0.082	1	0.017	4.90 (0.59, 40.7)	0.14
N06AB06	Sertraline	Y	5	0.78	88	0.48	1.63 (0.66, 4.00)	0.25
J01CR02	Amoxicillin and enzyme inhibitor	Y	4	0.070	8	0.16	0.43 (0.13, 1.43)	0.25
N03AF01	Carbamazepine	Y	4	2.17	54	1.11	1.95 (0.71, 5.39)	0.16
N05CH01	Melatonin	N	4	1.23	1	0.62	1.97 (0.22, 17.6)	1.00
R03AK06	Salmeterol and other drugs for obstructive airway	Y	4	0.38	5	0.074	5.11 (1.37, 19.0)	0.024
G03AA11	Norgestimate and estrogen	N	3	0.29	6	0.17	1.67 (0.42, 6.66)	0.44
G03AA13	Norelgestromin and estrogen	N	3	2.28	7	0.81	2.82 (0.73, 10.9)	0.14
H01BA02	Desmopressin	Y	3	0.22	8	0.79	0.27 (0.07, 1.03)	0.062
H02AB06	Prednisolone	N	3	0.57	36	0.15	3.92 (1.21, 12.7)	0.047
J01CE02	Phenoxymethylpenicillin	Y	3	0.006	22	0.019	0.30 (0.09, 1.01)	0.049
L04AX01	Azathioprine	N	3	3.24	18	1.06	3.05 (0.90, 10.3)	0.092
N02AX02	Tramadol	Y	3	0.66	99	0.19	3.54 (1.12, 11.2)	0.056
N06AX11	Mirtazapine	N	3	3.35	63	0.45	7.38 (2.32, 23.5)	0.009
R03AK07	Formoterol and other drugs for obstructive airway	Y	3	0.15	6	0.039	3.93 (0.98, 15.7)	0.072
Fewer than three ICSRs in children and $p < 0.05$								
C07AA05	Propranolol	Y	2	1.41	9	0.10	13.5 (2.92, 62.5)	0.013

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Table I. Contd

ATC[15]	Substance	Labelled for children	<18 y		≥18 y		<18 y vs ≥18 y	
			ICSRs (n)	ICSRs per 1000 treated individuals	ICSRs (n)	ICSRs per 1000 treated individuals	rate ratio (95% CI)	p-value
C10AX09	Ezetimibe	Y	1	37.0	19	0.76	48.6 (6.75, 351)	0.021
J01CF05	Flucloxacillin	Y	2	0.020	41	0.096	0.21 (0.05, 0.87)	0.017
N05BA01	Diazepam	Y	2	0.26	6	0.037	7.06 (1.42, 34.9)	0.047
R03AC13	Formoterol	Y	2	0.26	1	0.014	18.9 (1.72, 209)	0.025
A10BA02	Metformin	N	1	7.09	54	0.27	26.5 (3.69, 190)	0.038
C07AA07	Sotalol	N	1	9.35	15	0.43	21.8 (2.90, 163)	0.048
G04BE03	Sildenafil	N	1	30.3	5	0.060	502 (60, 4182)	0.002
L04AX02	Thalidomide	N	2	666	9	46.4	14.4 (5.16, 40.0)	0.008
N05AB01	Dixyrazine	N	1	7.63	1	0.051	149 (9.34, 2363)	0.013
N05CF01	Zopiclone	N	2	1.53	17	0.040	38.36 (8.87, 166)	0.001

ATC = Anatomical Therapeutic Chemical classification; **N** = no; **Y** = yes.

the rates of ICSRs per 1000 treated individuals varied greatly between drugs. This is reassuring since there are few other sources for knowledge of paediatric drug safety. All ICSRs registered in SWEDIS are also registered in the international WHO ADR database (VigiBase), and thus they add important data for pharmacovigilance in children worldwide.

The reporting rate was higher for children than adults for many individual drugs. Furthermore, the overall reporting rate for drugs not labelled for children was higher for children than adults. One explanation for the higher reporting rates in children compared with adults may be that children are more closely monitored by parents and healthcare personnel. Moreover, the latter may be more attentive to adverse effects for drugs not labelled for use in children.

The findings of high reporting rates for drugs not labelled for children, and for children compared with adults, do not necessarily indicate an increased risk of ADRs since reporting biases exist, including underreporting of ADRs,[16] the degree of which may differ between drugs and patient groups, e.g. children and adults. However, previous findings suggest an increased risk of ADRs for drugs used off-label,[9,17] although factors associated with the patient rather than the drug may be of importance.[18] The present results indicate that the drugs *per se* may differ between those labelled and those not labelled for use in children, since the reporting rate for drugs not labelled for children was also higher for adults.

Regarding reporting of ADRs associated with drugs used off-label, the majority of paediatricians are concerned about safety when prescribing these drugs, although only a few actually have observed ADRs when treating children with unlabelled drugs.[19] On the other hand, a minority of GPs admit concerns about safety when prescribing drugs off-label to children.[20] Indeed, in our material, a smaller proportion of ICSRs regarding children were reported by GPs (15%) compared with ICSRs regarding adults (28%).

Interestingly, 24% of the events in children concerned psychiatric disorders, compared with 12% in adults. The high proportion of psychiatric disorders is in contrast to recent results from the

Table II. Description of all serious individual case safety reports (ICSRs) for drugs reported three or more times

Suspected drug(s)	Age (y)	Sex	Daily dose	Treatment duration	Pos dechallenge	Pos rechallenge	ADR diagnosis	Time to ADR onset	E/U	Serious classification	Outcome	Concomitant medication
Amoxicillin + enzyme inhibitor	1	M	7.5 mL	10 d	Pos	No rechallenge	Thrombocytopenia	15 d	E	HC	RWS	NK
Azathioprine	17	M	250 mg	3.5 mo	Pos	No rechallenge	Pancytopenia	3.5 mo	E	HC	NYR	Mesalazine
Budesonide + formoterol	6	M	NR	NW	NW	NW	Weight decrease Mycosis	1 mo	U E	HC	RWS	Sodium cromoglycate
Phenoxymethylpenicillin			NR	10 d	NR	NR	Oesophagitis		U			
Carbamazepine	12	F	400 mg	Many y	NR	NR	Osteoporosis	NR	E	HC	NYR	No
Carbamazepine	16	M	1.3 g	4.5 mo	NA	NA	Pulmonary embolism	4.5 mo	E	HC	Death	No
Carbamazepine	2	F	113 mg	12 d	Pos	No rechallenge	Erythema multiforme	12 d	E	HC	RWS	No
Desmopressin	7	F	20 μg	3 d	Pos	NR	Hyponatraemia Seizures	3 d	E U	HC	RWS	No
Diclofenac Tramadol Mirtazapine	16	F	Intoxication	NA	NA	No rechallenge	Haemorrhage	NA	E	IME	RWS	Sertraline
Diphenhydramine Ephedrine + ethylmorphine	3	F	1 mL 2 mL	2 d	Pos	NR	Hallucination	3 doses	U E	HC	NK	NK
Doxycycline	13	F	100 mg	8 d	Pos	Pos	Anaphylactic reaction	7 d	E	HC	RWS	No
Ephedrine + ethylmorphine	1	F	6 mL	5 d	NR	NR	Lethargy	5 d	E	HC	RWS	Hydrocortisone + oxytetracycline + polymyxin
Ephedrine + ethylmorphine	3	M	5 mL	3 wk	Pos	NR	Hallucination	3 wk	E	HC	NYR	NK
Ephedrine + ethylmorphine	3	M	Intoxication	1 dose	NR	NR	Fatigue Nausea	1 dose	E	IME	RWS	No
Erythromycin	1	M	NR	NR	NR	NR	Abdominal pain	NR	E	HC	RWS	NK

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Table II. Contd

Suspected drug(s)	Age (y)	Sex	Daily dose	Treatment duration	Pos dechallenge	Pos rechallenge	ADR diagnosis	Time to ADR onset	E/U	Serious classification	Outcome	Concomitant medication
Erythromycin	16	F	NR	2 d	NR	NR	Abdominal pain	2 d	E	HC	NK	Ranitidine
Fluticasone + salmeterol	4	M	Daily	1 y	Pos	No rechallenge	Adrenal cortical insufficiency	1 y	E/U[a]	HC	RWS	NK
Montelukast				2 y 4 mo			Hypoglycaemia Depressed mood	2 y 5 mo	U U		RWS NYR	
Isotretinoin	14	F	NR	5 d	Pos	NR	Elevated transaminases Nausea Vomiting Dizziness Headache	5 d	E E E U E	HC	RWS	No
Isotretinoin	16	M	50 mg	1 mo	NR	NR	Suicide attempt	1 mo	E	HC	RWS	No
Isotretinoin	16	M	40 mg	8 mo	NR	NR	Thoughts of suicide	NR	E	IME	NK	NK
Isotretinoin	16	F	NR	4 mo	Pos	NR	Myoclonus	4 mo	E	HC	RWS	No
Isotretinoin	17	M	60 mg	6 mo	Neg	NR	Elevated transaminases Elevated AP/GGT Colitis/proctitis Ulcer	6 mo	E	HC	NYR	No
Lamotrigine	16	F	25 mg	12 d	Pos	NR	Fever Erythematous rash	10 d	E	HC	RWS NK	No
Lamotrigine	17	F	50 mg	2.5 wk	NR	NR	Maculopapular rash	2.5 wk	E	HC	NYR	Terbutaline Budesonide
Lamotrigine	6	M	25 mg	12 d	Pos	No rechallenge	Rash Elevated temperature	12 d	E	HC	RWS	No
Levonorgestrel + estrogen	15	F	Daily	1 y	NR	NR	Cerebral infarction	1 y	E	HC	NYR	No
Levonorgestrel + estrogen	15	F	Daily	2 mo	NR	NR	Venous leg thrombosis	2 mo	E	HC	NYR	No
Levonorgestrel + estrogen	15	F	Daily	2.5 mo	NR	NR	Cerebral vein thrombosis	2.5 mo	E	IC	NYR	No

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Table II. Contd

Suspected drug(s)	Age (y)	Sex	Daily dose	Treatment duration	Pos dechallenge	Pos rechallenge	ADR diagnosis	Time to ADR onset	E/U	Serious classification	Outcome	Concomitant medication
Levonorgestrel + estrogen	16	F	Daily	2 mo	Neg	No rechallenge	Pulmonary embolism	2 mo	E	HC	NK	No
Levonorgestrel + estrogen	16	F	Daily	3 wk	NR	NR	Venous leg thrombosis	3 wk	E	IME	RWS	No
Levonorgestrel + estrogen	17	F	Daily	2 y	NA	NA	Pulmonary embolism	2 y	E	IME	Death	NK
Levonorgestrel + estrogen	17	F	Daily	2 wk	NR	No rechallenge	Subclavicular thrombosis	2 wk	E	HC	RWS	Tramadol
Methylphenidate	13	M	20 mg	7 wk	Pos	No rechallenge	Thoughts of suicide	7 wk	E	IME	RWS	No
Methylphenidate	17	M	36 mg	3 y 4 mo	NR	No rechallenge	Generalized seizures	1.5 y	E	HC	NK	NK
Mirtazapine	17	M	30 mg	2.5 wk	Pos	NR	Aggressiveness	2.5 wk	U	HC	NK	NK
Montelukast	3	M	NR	3 y	Pos	NR	Fatigue Vomiting Dyspepsia	1 y	E	IME	RWS	Fluticasone + salmeterol Cetirizine
Montelukast	4	M	4 mg	7 mo	Pos	NR	Thirst Polyuria	7 mo	E U	HC	RWS	Budesonide Salbutamol
Norelgestromin + estrogen	15	F	NR	2 mo	Pos	No rechallenge	Venous leg thrombosis	2 mo	E	HC	NYR	NK
Prednisolone	12	M	75 mg	3 mo	NR	NR	Oedema Myalgia Osteonecrosis	2 mo 2 mo 6 mo	E	IME	NYR	No
Prednisolone	14	F	20 mg	2 y	NR	NR	Osteonecrosis	2 y	E	HC	NYR	Azathioprine Levothyroxine
Sertraline	17	M	1 g	1 dose	Pos	No rechallenge	Intoxication	1 dose	E	IC	RWS	NK
Tramadol	16	M	50 mg	1 dose	Pos	No rechallenge	Convulsions	1 dose	E	HC	RWS	No

a E for fluticazone + salmeterol, and U for montelukast.

ADR = adverse drug reaction; **AP** = alkaline phosphatase; **E** = expected (mentioned in the SPC); **F** = female; **GGT** = gamma-glutamyl transpeptidase; **HC** = hospital care; **IC** = intensive care; **IME** = important medical event; **M** = male; **NA** = not applicable; **Neg** = negative; **NK** = not known; **NR** = not registered; **NW** = not withdrawn; **NYR** = not yet recovered (at reporting date); **Pos** = positive; **RWS** = recovered without sequelae; **SPC** = summary of product characteristics; **U** = unexpected (not mentioned in the SPC).

Danish ADR database where 7.8% of the events in children during a 10-year period concerned this SOC.[21] The divergent findings may be explained by the exclusion of, for example, vaccine reports in the present study. Moreover, our results are driven by reactions from drugs for ADHD (methylphenidate and atomoxetine) in addition to montelukast and isotretinoin, both of which are associated with psychiatric events.[22-25] These drugs were suspected in one-third of all ICSRs in children.

The proportion of ICSRs classified as serious was low in children compared with adults, both before and after the exclusion of ICSRs (7% vs 51% when all ICSRs concerning drugs reported in children were included, and 29% vs 51% when only ICSRs analysed in the present study were included [see figure 2]). In the publication by Aagaard et al.,[21] 42% of the ADRs were classified as serious; however, the latter study does not supply data on the proportion of ICSRs classified as serious, which may differ since one ICSR can contain several ADRs. Doctors judge seriousness and unexpectedness of an ADR as important factors when making their decision to report the ADR.[26] Reactions in children may be considered more severe and unexpected, and thus be reported more often, although they may not formally be serious according to the definition of seriousness. This may be one explanation for the low proportion of serious ICSRs in the present study. Indeed, the results support the idea that clinicians may be more likely to submit ICSRs regarding children than adults.

To the best of our knowledge, no overall data concerning rates of ICSRs per treated individual have been published before. The importance of considering prescribing practice when interpreting ADR reporting data has been emphasized previously as nearly half of the variation in reporting rates could be explained by differences in prescribing.[27] However, the choice of an appropriate denominator when evaluating pharmacovigilance data is difficult.[28] Number of dispensed DDDs is one example of a denominator that has been used for assessing spontaneous reporting rates, but this denominator is inappropriate, especially in children, since the prescribed daily dose varies largely between ages. Furthermore, this makes comparisons between children and adults impossible, and thus the present study may be the first to compare reporting rates between children and adults.

Analyses of ICSRs and data-mining techniques can reveal ADR signals, which are defined as reported information on a possible causal relationship between an adverse event and a drug, the relationship being unknown or incompletely documented previously.[29] Many signal detection methods used today, e.g. Bayesian Confidence Propagation Neural Network[30] and Proportional Reporting Ratio,[31] give information only on disproportional reporting within databases of spontaneously reported ADRs. The method used in the present study, rates of ICSRs per 1000 treated individuals and ratios between different populations (e.g. children and adults), includes information of additional value for pharmacovigilance and signal detection, i.e. a well defined and informative denominator: the number of treated individuals.

Drugs for which numerous ICSRs have been reported in children, and where the reporting rates are significantly higher in children than adults, could be worth attention, i.e. may represent ADR signals. Montelukast, which was reported in 22 ICSRs, has previously been associated with psychiatric ADRs in children.[22] More data on ADRs in children for this substance would be of value. In addition, isotretinoin may be worth further investigation. As regards budesonide and doxycycline, on the other hand, the higher reporting rate in children compared with adults may not be surprising since these drugs are known for causing ADRs in children. Indeed, the high reporting rates for anti-asthmatic drugs, which, in addition to montelukast and budesonide mentioned previously, also include salmeterol and formoterol, could well be expected since children with this chronic disease may be closely monitored by doctors and parents.

Valuable information for signal detection in children can also be derived from case-by-case evaluation of paediatric ICSRs, and, in particular, serious ADRs may be worth extra attention. In the present study, two serious ICSRs for substances reported three or more times resulted in the death

of a child. These ICSRs concerned carbamazepine and levonorgestrel + estrogen, respectively.

The present study has several limitations. First, only few ICSRs regarding children were registered for most drugs, thus giving each ICSR a strong impact on the rates. Indeed, the highest rates of ICSRs per treated child were derived from small numbers in the denominator rather than numerous ICSRs. For thalidomide, for example, only three children were treated during the study period, for two of whom ADRs were reported. Second, the results of the present study apply only to the included drugs, i.e. no conclusions can be drawn concerning drugs for which >10% of the volume is sold OTC and/or for in-hospital use, and for drugs that have not been reported as suspected in ICSRs involving children. Third, children aged 0–17 years are a heterogeneous group. The potential for ADRs can, for example, be expected to be greater in infants who have immature detoxification mechanisms. Indeed, children between 0 and 4 years of age were recently reported to have the highest incidence of adverse drug event (ADE)-related visits to outpatient clinics and emergency departments among children.[32] ADEs include all reactions during drug therapy, but in contrast to ADRs they do not necessarily have a causal relationship with the treatment.[13] Fourth, the rates of ICSRs per 1000 treated individuals may be underestimated since data on the number of treated individuals originate from dispensings rather than drug intake, i.e. the number of individuals actually exposed to the drugs may be lower. In addition, our way of defining drugs as not labelled for use in children may have influenced the results.

Conclusion and Implications

The results of the present study are reassuring since they indicate that the extent of the ADR reporting in children is greater for drugs where knowledge is most limited, i.e. for drugs not used as labelled. The method presented in this study, i.e. reporting rates of ICSRs per treated individual, may be valuable in future pharmacovigilance work, e.g. to identify ADR signals, as it allows for comparisons between drugs and between populations.

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