ORIGINAL RESEARCH ARTICLE

Drug Saf 2010; 33 (4): 327-339
0114-5916/10/0004-0327/$49.95/0

Adverse Drug Reactions in the Paediatric Population in Denmark

A Retrospective Analysis of Reports Made to the Danish Medicines Agency from 1998 to 2007

Lise Aagaard,[1,2] *Camilla Blicher Weber*[1] and *Ebba Holme Hansen*[1,2]

1 Department of Pharmacology and Pharmacotherapy, Section for Social Pharmacy, Faculty of Pharmaceutical Sciences, University of Copenhagen, Copenhagen, Denmark
2 FKL-Research Centre for Quality in Medicine Use, Copenhagen, Denmark

Abstract

Background: The potential risk of adverse drug reactions (ADRs) in the paediatric population has become a public health concern and regulatory agencies in Europe and the US have acknowledged that there is a need for more research in this area. Spontaneous reporting systems can provide important new information about ADRs.

Objective: To characterize ADRs in children reported in Denmark over a period of one decade.

Methods: We analysed ADRs reported to the Danish Medicines Agency from 1998 to 2007 for individuals aged from birth to 17 years. Data were analysed with respect to time, age and sex, category of ADR (System Organ Class [SOC]), seriousness, suspected medicines (level 2 of the Anatomical Therapeutic Chemical [ATC] Classification System) and type of reporter.

Results: 2437 ADR reports corresponding to 4500 ADRs were analysed. On average, 234 ADR reports were submitted annually, corresponding to approximately two ADRs per report. From 2003 to 2005, an increasing number of ADRs submitted per report were observed, but after 2005 the reporting rate decreased. One-half of ADRs were reported for infants from birth to 2 years of age. Similar total numbers of ADRs were reported for boys and girls. The majority of ADRs reported were from the following SOCs: general disorders and administration site conditions (31%), skin and subcutaneous tissue disorders (18%) and nervous system disorders (15%). Reports encompassed medicines from ATC group J: vaccines and anti-infectives for systemic use (65%); and ATC group N: nervous system (17%). On average, 42% of ADRs were classified as serious. ATC group N had the highest proportion of ADRs that were classified as serious. Although physicians reported approximately 90% of the ADRs, a relatively large proportion of serious ADRs were reported by other sources.

Conclusion: In Denmark, the ADR reporting rate in the paediatric population has declined since 2005. The majority of ADRs reported in young children were reported for vaccines and anti-infectives, but also a high number of serious ADRs were reported for medicines from ATC group N. The Danish Medicines Agency should monitor prescribing patterns more tightly to identify potential risks in the paediatric population in relation to the evolving pattern of medicine use among children.

Background

The potential risk of adverse drug reactions (ADRs) in children has become a public health concern and regulatory agencies in Europe and the US have acknowledged that there is a need for more research in this area.[1-4] Postmarketing surveillance of medicine safety is important because the randomized controlled clinical trials (RCCTs) used in the clinical development process have limited capacity to detect serious, rare and unexpected ADRs, which are especially problematic in vulnerable populations such as children, who are rarely represented in the RCCT.[5,6] Therefore, it is important to survey the paediatric population as the safety of many medicine regimens prescribed for children is not well documented.[7,8] In a meta-analysis of 17 prospective studies conducted in the US and Europe and published from 1973 to 2000, the overall incidence of ADRs in children was estimated to be 9.5%, with serious reactions accounting for 12% of the total number of ADRs.[9] In the literature, we identified five studies on ADRs in children reported to national databases in the Netherlands, Spain, the US, Sweden and Canada.[10-14] These studies report ADRs in children from different settings, time periods, patient populations of different sizes and age groups, and different type of reporters. Although there were wide variations in the incidence of ADRs between studies, the studies found ADRs to be most commonly reported in children from birth to 5 years of age and youth from 13 to 17 years of age.[10,12,13] Serious ADRs comprised between 15% and 60% of all reported ADRs in these studies.[11-14] The majority of reported ADRs were from the system organ classes (SOCs) 'psychiatric and nervous system disorders' as well as 'skin disorders'. ADRs were most commonly reported for vaccines, anti-infectives, analgesics and psychotropic medicines.[10-14] The need for more thorough analysis of ADRs in children is compelling as medicine utilization patterns among children have changed since the beginning of the 1990s, for example due to the launch of new types of medicines, especially within the therapeutic classes of antipsychotics, antidepressants and antiepileptic medicines.[15,16]

The objective of this study was to analyse ADRs in children reported to the Danish Medicines Agency over one decade. We analysed data with respect to time, age and sex, category and seriousness of ADRs, suspected medicines and type of reporter.

Methods

Setting

During the study period the total Danish population included approximately 5.5 million inhabitants and 20% of these were aged from birth to 17 years. The Danish ADR reporting system was established by law in 1968 and reporting of ADRs are mandatory for physicians, dentists, veterinarians and pharmaceutical companies, and voluntary for consumers and other healthcare professionals.[17] The reporting system receives approximately 2000 ADR reports annually, corresponding to a reporting rate of close to 400 ADR reports per million inhabitants. The Danish ADR database contains

all spontaneous ADR reports in Denmark, including those reported directly to the pharmaceutical companies. An ADR report is defined by the following four criteria, which must be included in all reports: (i) information about the patient; (ii) the suspected medicines(s); (iii) the presumed ADR(s); and (iv) information about the person making the report. An ADR report may contain one or more ADRs. Adverse reactions due to unauthorized use are also classified as ADRs and are included in the database.

Data Extraction

The ADRs are assessed by the Danish Medicines Agency and categorized in the ADR database by degree of seriousness according to the CIOMS criteria.[18] ADR reports are classified by criteria of seriousness by trained staff at the Danish Medicines Agency. The Danish reporting system has been described elsewhere in more detail.[19] Data were placed at the disposal of this study in anonymous form with encrypted identification of the medicine user. Data were extracted from the ADR database on Microsoft® Excel files using the following criteria: Anatomical Therapeutic Chemical (ATC) code of medications, registered tradename and active substance of the medicines, ADRs coded according to Medical Dictionary for Regulatory Activities[20] terminology at SOC level, degree of seriousness, age of patient and type of reporter. For the purposes of this study, in order to present the large amount of data in a comprehensive way, the medicines about which the ADRs are reported are presented at ATC level 2. The material comprised all ADR reports on children from birth to 17 years of age reported to the Danish Medicines Agency from 1998 to 2007. The unit of analysis was one ADR.

The Danish ADR database defines five categories of people who may submit data to the database. This study applies the following official designation for the category of people submitting reports:

- lawyer: patient injury insurers and/or law firms;
- pharmacist: community or hospital pharmacists;
- physician: general practitioners, physicians and dentists;
- other healthcare professionals: nurses, pharmaceutical companies, and social and healthcare assistants;
- consumers: patients, patients' relatives, other members of the public.

Because consumers have had the opportunity to report ADRs in Denmark since 2003, results in this category only cover data from the last 5 years of the study period.

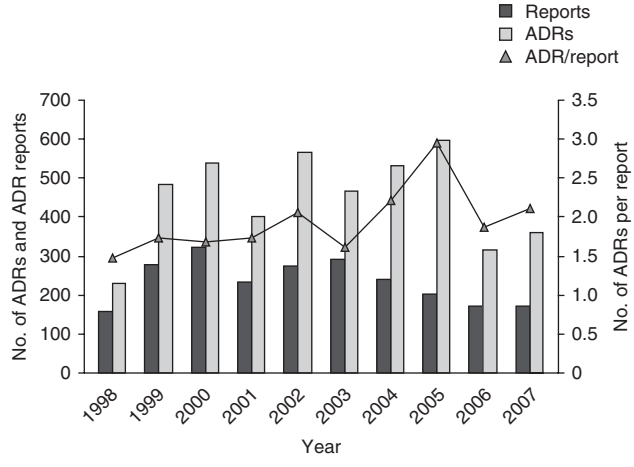

Fig. 1. No. of adverse drug reaction (ADR) reports and ADRs reported annually (1998–2007).

Results

A total of 2437 ADR reports corresponding to 4500 ADRs were reported for individuals from birth to 17 years of age during the study period. The number of ADR reports per year is illustrated in figure 1. On average, 234 ADR reports (range 157–322) were submitted per year, corresponding to approximately two ADRs per report. From 2003 to 2005, an increasing number of ADRs submitted per report were observed, but after 2005 the reporting rate decreased.

Adverse Drug Reactions (ADRs) by Age and Sex

Figure 2 shows the distribution of reported ADRs by age of the child and number of serious ADRs. In total, 51% of all ADRs were reported for girls and 49% for boys. Fifty-two percent of ADRs were reported for infants from birth to 2 years of age with almost the same number of ADRs reported for boys and girls. More ADRs were reported for boys than girls among the 5- to 12-year age group, but for teenagers (13–17 years of age) the majority of ADRs were reported for girls.

ADRs by Category and Seriousness

Table I provides an overview of the reported ADRs classified by SOC and distributed by age group and number of serious ADRs. Total numbers of reported ADRs are shown for all SOCs and age groups. ADRs were most commonly reported in the following SOCs: 'general disorders and administration site conditions' (31%), 'skin and subcutaneous tissue disorders' (18%) and 'nervous system disorders' (15%). Forty-two percent of all ADRs were classified as serious and 28 of these cases were reported deaths. Table II displays further characteristics of these cases. The largest number of serious ADRs was reported for the SOC 'nervous system disorders' (24%) followed by the SOCs 'general disorders and administration site conditions' (16%) and 'skin and subcutaneous tissue disorders' (11%). The distribution of serious and non-serious ADRs by SOCs varied widely, from 97% in 'congenital, familial and genetic disorders' to 11% in 'skin and subcutaneous tissue disorders'. The distribution between serious and non-serious ADRs within SOCs varied with the age of the children. More than half of the ADRs reported for children up to 2 years of age were in the SOCs 'general disorders and administration site conditions' and 'psychiatric disorders', and only 15–20% of these ADRs were serious. Serious ADRs encompassed a wide range of reactions, e.g. convulsion, feeding disorder neonatal, apnoea, ventricular septal defects, cardiac defects, premature labour and neonatal symptoms reported for medicines from ATC group N

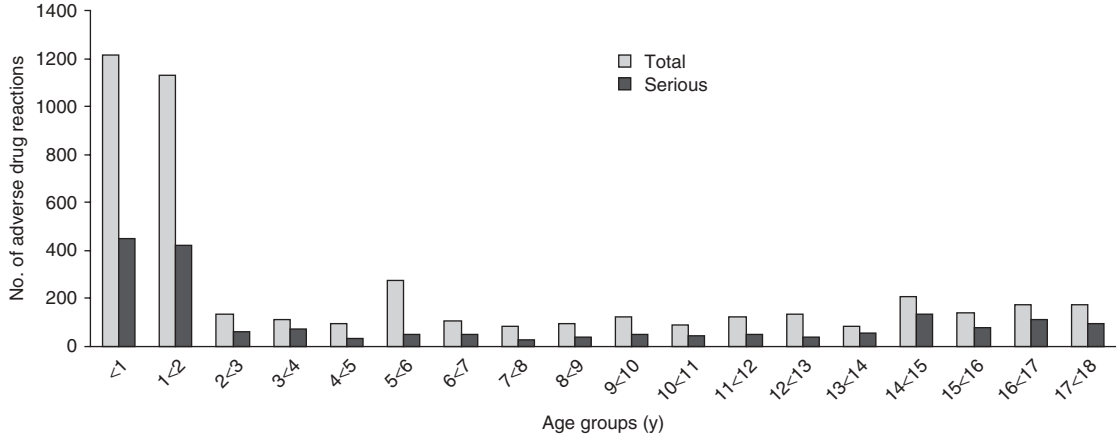

Fig. 2. Adverse drug reactions (ADRs) by age group and number of serious ADRs (1998–2007).

Table I. Adverse drug reactions (ADRs) distributed by System Organ Class (SOC) and age group (no. of serious ADRs in parentheses)

SOC	Age group [y]				
	<1	1 < 2	2–10	11–17	Total
General disorders and administration site conditions	509 (124)	430 (86)	354 (56)	104 (35)	1397 (301)
Skin and subcutaneous tissue disorders	161 (27)	293 (74)	189 (53)	160 (52)	803 (206)
Nervous system disorders	151 (97)	224 (182)	123 (74)	172 (101)	670 (454)
Psychiatric disorders	126 (20)	23 (7)	94 (51)	108 (71)	351 (149)
Gastrointestinal disorders	50 (16)	32 (8)	100 (44)	89 (49)	271 (117)
Respiratory, thoracic and mediastinal disorders	31 (26)	15 (3)	27 (17)	76 (54)	149 (100)
Infections and infestations	26 (12)	39 (12)	23 (12)	13 (7)	101 (43)
Investigations	10 (5)	6 (5)	23 (16)	61 (42)	100 (68)
Musculoskeletal and connective tissue disorders	18 (16)	15 (10)	25 (16)	29 (16)	87 (58)
Immune system disorders	3 (3)	1 (1)	31 (18)	46 (34)	81 (56)
Blood and lymphatic system disorders	9 (8)	23 (14)	13 (12)	27 (19)	72 (53)
Cardiac disorders	19 (16)	5 (2)	15 (7)	28 (21)	67 (46)
Eye disorders	10 (4)	6 (2)	17 (8)	29 (15)	62 (29)
Vascular disorders	17 (8)	3 (2)	16 (6)	17 (16)	53 (32)
Metabolism and nutrition disorders	13 (9)	5 (4)	11 (7)	11 (8)	40 (28)
Injury, poisoning and procedural complications	17 (16)	3 (3)	11 (11)	2 (2)	33 (32)
Congenital, familial and genetic disorders	27 (26)	2 (2)	1 (1)	0	30 (29)
Reproductive system and breast disorders	3 (1)	0	9 (2)	16 (1)	28 (4)
Hepatobiliary disorders	3 (3)	4 (3)	7 (6)	12 (5)	26 (17)
Renal and urinary disorders	3 (3)	0	13 (7)	8 (4)	24 (14)
Ear and labyrinth disorders	3 (3)	2 (2)	6 (3)	9 (5)	20 (13)
Neoplasm benign, malignant and unspecified	0	0	6 (4)	5 (5)	11 (9)
Pregnancy, puerperium and perinatal conditions	8 (8)	0	0	2 (1)	10 (9)
Endocrine disorders	0	0	2 (2)	6 (2)	8 (4)
Surgical and medical procedures	0	0	0	6 (3)	6 (3)
Total	**1217 (451)**	**1131 (422)**	**1116 (433)**	**1036 (568)**	**4500 (1874)**

(nervous system disorders). For vaccines, the majority of serious ADRs were pyrexia, febrile convulsion, injection site reaction, thrombocytopenia, gait disturbance, rash and autism. For antibacterials the majority of reported ADRs were skin reactions such as rash, urticaria, erythema multiforme and hyperhidrosis, and gastrointestinal disorders such as oesophageal ulcer haemorrhage, abdominal pain upper and vomiting.

ADRs by Therapeutic Groups

Table III displays the number of reported ADRs by therapeutic group (ATC level 2), age group and number of serious ADRs. Of the reported ADRs, 65% concerned anti-infectives and vaccines (ATC group J), 17% concerned medicines for nervous system disorders (ATC group N) and 3% concerned medicines belonging to ATC group V01 (allergens). A large proportion of the ADRs reported in infants (birth to 2 years of age) involved vaccines (ATC J07). Although serious ADRs were primarily reported in the same therapeutic groups as the majority of reports, the share of serious reports varied between therapeutic groups, e.g. 57% for anti-infectives for systemic use (ATC J), 19% for nervous system medications (ATC N) and 2% for respiratory medications (ATC R). The distribution between serious and non-serious ADRs within ATC groups and SOCs also varied with the age of the children. For immune sera and immunoglobulins (ATC group J06) and vaccines (ATC group J07), the majority of ADRs were reported for infants from

Table II. Reported adverse drug reactions (ADRs) in children leading to death (1998–2007)

Case	Year of report	ATC	Medicine(s)	ADR(s) reported	Sex	Age (y)
1	1998	N03AG01	Valproic acid	Cerebrovascular disorder	Male	1
		N03AX09	Lamotrigine	Hepatic function abnormal		
				Purpura		
2	1998	N03AX09	Lamotrigine	Hepatitis	Female	17
3	1998	G03AA09	Desogestrel/estrogen	Pulmonary embolism	Female	17
4	1999	L01BA01	Methotrexate	Guillain-Barré syndrome	Male	11
5	2000	H01AC01	Somatropin	Acute leukaemia	Male	14
6	2000	N01AF01	Methohexital	Shock	Female	1
7	2000	NA	Insulin-like growth factor 1	Sudden death	Male	0
8	2000	N03AX	Felbamate	Sudden death	Female	17
9	2002	G03AA12	Drospirenon/ethinylestradiol	Pulmonary embolism	Female	17
10	2002	J07AG01	Ditekipol/Act-Hib vaccine	Sudden infant death syndrome	Male	0
11	2003	G03AA10	Norgestimate/ethinylestradiol	Brain stem thrombosis	Female	17
12	2003	A07EC02	Mesalazine	Disseminated intravascular coagulation	Male	16
			Budesonide			
			Azathioprine			
13	2003	J07BD52	MMR vaccine	Hydrocephalus	Female	12
14	2003	C02KX01	Bosentan	Right ventricular failure	Male	12
15	2003	L01XE02	Gefitinib	Toxic epidermal necrolysis	Male	15
16	2005	A10AE04	Insulin glargine	Blood glucose increased	Male	17
17	2005	H02AB04	Methylprednisolone	Bradycardia	Female	15
				Cardiac arrest		
				Bronchospasm		
18	2005	D10BA01	Isotretinoin	Cardiac failure	Female	15
19	2005	J01CA02	Pivampicillin	Carnitine decreased	Female	14
20	2005	A10AE04	Insulin glargine	Vomiting	Male	17
21	2005	J01CA02	Pivampicillin	Vomiting	Female	14
				Carnitine decreased		
				Fatigue		
				Restlessness		
22	2005	J01CA02	Pivampicillin	Vomiting	Female	14
23	2006	N06AB03	Fluoxetine	Persistent fetal circulation	Female	0
24	2006	G03AA09	Ethinylestradiol/desogestrel	Pulmonary embolism	Female	17
25	2006	B03AC02	Iron	Stillbirth	Male	0
26	2007	N06AB04	Citalopram	Chorioamnionitis	Female	0
27	2007	C01EB16	Ibuprofen	Necrotizing colitis	Male	0
28	2007	C01EB16	Ibuprofen	Necrotizing colitis	Male	0
				Sepsis neonatal		

ATC = Anatomical Therapeutic Chemical; **MMR** = measles, mumps and rubella; **NA** = not available.

birth to 2 years of age, but only 30–35% of these ADRs were serious. A larger proportion of serious ADRs (75–80%) was reported for children from 11 to 17 years of age. The opposite phenomenon was observed in ATC group N (nervous system).

ADRs by Type of Reporter and Seriousness

The distribution of ADRs by seriousness and type of reporter is displayed in table IV. Physicians reported the majority of ADRs (89%),

Table III. Adverse drug reactions (ADRs) distributed by therapeutic group, age group (no. of serious ADRs in parentheses)

ATC group	Age group (y)				
	<1	1 < 2	2–10	11–17	Total
Alimentary tract and metabolism (A)					
A01 Stomatological preparations	0	0	0	2	2
A02 Drugs for acid-related disorders	1 (1)	0	9 (6)	1	11 (7)
A03 Drugs for functional gastrointestinal disorders	0	0	2 (2)	14 (6)	16 (8)
A04 Antiemetics and anti-nauseants	6 (6)	0	0	0	6 (6)
A05 Bile and liver therapy	1 (1)	0	0	0	1 (1)
A06 Laxatives	0	3	6	0	9
A07 Anti-diarrheals	0	0	4 (1)	16 (11)	20 (12)
A08 Anti-obesity preparations	1	0	0	9 (9)	10 (9)
A10 Drugs used in diabetes	1	0	7 (4)	14 (11)	22 (15)
A16 Other alimentary tract and metabolism products	0	0	1	8 (8)	9 (8)
Total A	**10 (8)**	**3**	**29 (13)**	**64 (45)**	**106 (66)**
Blood and blood forming organs (B)					
B01 Antithrombotic agents	0	0	0	3	3
B03 Anti-anaemic preparations	1 (1)	0	0	0	1 (1)
B06 Other haematological agents	0	0	0	1 (1)	1 (1)
Total B	**1 (1)**	**0**	**0**	**4 (1)**	**5 (2)**
Cardiovascular system (C)					
C01 Cardiac therapy	5 (5)	0	1	0	6 (5)
C02 Antihypertensives	2 (2)	2 (2)	0	3 (3)	7 (7)
C03 Diuretics	1	0	0	0	1
C05 Vasoprotectives	0	0	1 (1)	0	1 (1)
C07 β-blocking agents	0	1 (1)	0	6	7 (1)
C08 Calcium channel blockers	3	0	0	0	3
C09 Agents acting on the renin-angiotensin system	3 (2)	0	0	3	6 (2)
C10 Lipid-modifying agents	2	0	0	0	2
Total C	**16 (9)**	**3 (3)**	**2 (1)**	**12 (3)**	**33 (16)**
Dermatological (D)					
D01 Antifungal for dermatological use	0	0	1	1 (1)	2 (1)
D06 Dermatological antibiotics and chemotherapeutics	0	0	2	1	3

Continued next page

Table III. Contd

ATC group	Age group (y)				
	<1	1 < 2	2–10	11–17	Total
D10 Anti-acne preparations	1	0	0	63 (29)	64 (29)
D11 Other dermatological preparations	1 (1)	2 (1)	4 (1)	1	8 (3)
Total D	**2 (1)**	**2 (1)**	**7 (1)**	**66 (30)**	**77 (33)**
Genitourinary system and sex hormones (G)					
G03 Sex hormones and modulators of the genital system	1	0	0	100 (76)	101 (76)
Total G	**1**	**0**	**0**	**100 (76)**	**101 (76)**
Systemic hormonal preparations (H)					
H01 Pituitary and hypothalamic hormones	1 (1)	0	27 (16)	8 (5)	36 (22)
H02 Corticosteroids for systemic use	0	0	5 (5)	4 (3)	9 (8)
H03 Thyroid therapy	1 (1)	0	0	4	5 (1)
Total H	**2 (2)**	**0**	**32 (21)**	**16 (8)**	**50 (31)**
Anti-infectives for systemic use (J)					
J01 Antibacterials for systemic use	10 (7)	7 (2)	38 (25)	57 (35)	112 (69)
J02 Antimycotics for systemic use	1	0	5 (3)	8 (3)	14 (6)
J05 Antivirals for systemic use	8 (8)	1	8 (6)	2 (2)	19 (16)
J06 Immune sera and immunoglobulins	1 (1)	2 (2)	21 (20)	8 (8)	32 (31)
J07 Vaccines	1035 (310)	1065 (384)	485 (153)	167 (96)	2752 (943)
Total J	**1055 (326)**	**1075 (388)**	**557 (207)**	**242 (144)**	**2929 (1065)**
Antineoplastic and immunomodulating agents (L)					
L01 Antineoplastic agents	0	0	13 (13)	5 (4)	18 (17)
L02 Endocrine therapy	2	0	22 (4)	3	27 (4)
L03 Immunostimulants	2 (2)	1	7 (7)	6 (6)	16 (15)
L04 Immunosuppressants	0	0	4 (4)	21 (18)	25 (22)
Total L	**4 (2)**	**1**	**46 (28)**	**35 (28)**	**86 (58)**
Musculoskeletal system (M)					
M01 Anti-inflammatory and rheumatic products	5 (4)	2	13 (9)	20 (16)	40 (29)
M03 Muscle relaxants	1 (1)	0	10 (5)	6 (4)	17 (10)
Total M	**6 (5)**	**2**	**23 (14)**	**26 (20)**	**57 (39)**
Nervous system (N)					
N01 Anaesthetics	2 (1)	7 (2)	46 (6)	51 (10)	106 (19)
N02 Analgesics	3 (3)	2 (2)	18 (7)	9 (3)	32 (15)

Continued next page

Table III. Contd

ATC group	Age group (y)				
	<1	1 < 2	2–10	11–17	Total
N03 Antiepileptics	24 (17)	10 (10)	78 (33)	69 (22)	181 (82)
N04 Antiparkinson drugs	0	0	0	1 (1)	1 (1)
N05 Psycholeptics	17 (17)	5 (5)	12 (5)	83 (37)	117 (64)
N06 Psychoanaleptics	53 (52)	5 (5)	123 (48)	131 (72)	312 (177)
N07 Other nervous system drugs	0	0	0	1	1
Total N	**99 (90)**	**29 (24)**	**277 (99)**	**345 (145)**	**750 (358)**
Antiparasitic (P)					
P01 Antiprotozoals	2	0	25 (15)	9 (4)	36 (19)
P02 Anthelmintics	2 (2)	0	5 (2)	1 (1)	8 (5)
P03 Ectoparasiticides	0	0	2	5	7
Total P	**4 (2)**	**0**	**32 (17)**	**15 (5)**	**51 (24)**
Respiratory system (R)					
R01 Nasal preparations	0	0	0	2 (1)	2 (1)
R02 Throat preparations	0	0	2	0	2
R03 Drugs for obstructive airway diseases	1	14 (5)	39 (10)	22 (11)	76 (26)
R05 Cough and cold preparations	0	0	3	1 (1)	4 (1)
R06 Antihistamines for systemic use	5 (5)	1	12 (3)	4	22 (8)
Total R	**6 (5)**	**15 (5)**	**56 (13)**	**29 (13)**	**106 (36)**
Sensory organs (S)					
S01 Ophthalmologicals	1	0	2	0	3
S02 Otologicals	0	0	2	0	2
Total S	**1**	**0**	**4**	**0**	**5**
Various (V)					
V01 Allergens	7	0	45 (16)	81 (50)	133 (66)
V03 All other therapeutic products	0	1 (1)	2 (2)	0	3 (3)
V04 Diagnostic agents	2	0	0	1	3
V08 Contrast media	1	0	1 (1)	0	2 (1)
V09 Diagnostic radiopharmaceuticals	0	0	3	0	3
Total V	**10**	**1 (1)**	**51 (19)**	**82 (50)**	**144 (70)**
Total all therapeutic group	**1217 (451)**	**1131 (422)**	**1116 (433)**	**1036 (568)**	**4500 (1874)**

ATC = Anatomical Therapeutic Chemical.

Table IV. Adverse drug reactions (ADRs) distributed by type of reporter and criteria of seriousness

Type of reporter	Total ADRs [n (%)]	Serious ADRs [n (%)]	Non-serious ADRs [n (%)]
Physicians	4015 (89)	1532 (38)	2483 (62)
Pharmacists	3 (0)	0 (0)	3 (0)
Other healthcare professional	319 (7)	234 (73)	85 (27)
Lawyer	2 (0)	2 (100)	0 (0)
Consumer[a]	161 (4)	106 (66)	55 (34)
Total	**4500 (100)**	**1874 (42)**	**2626 (58)**

a Data only reported 2003–2007.

followed by other healthcare professionals (7%) and consumers (4%). Lawyers and pharmacists reported very few ADRs, and the reports from pharmacists were all non-serious. Both ADRs reported by lawyers were serious. Other healthcare professionals and consumers were more likely to report serious ADRs than physicians.

Discussion

The study showed a decline in the number of ADR reports in the paediatric population in Denmark over one decade. ADRs were mainly reported in infants (birth to 2 years of age and in adolescents from 11 to 17 years of age. ADRs were primarily from the SOC general disorders and administration site conditions, as well as skin and nervous system disorders. Two-thirds of ADRs were reported for anti-infectives and vaccines, followed by medicines from ATC group N. Differences in seriousness of ADRs between age groups and therapeutic groups were detected. The majority of ADRs in children are reported by physicians but a larger share of serious ADRs was reported by other sources.

Number of Reports

The detected ADR reporting rate for the paediatric population is low in Denmark compared with other EU countries, although it is comparatively high for adults.[21] In 2004, reporting rates of ADRs for children were estimated as being 30 reports/million capita in Denmark, and 400, 330 and 250 reports/million capita in Sweden, France and the Czech Republic, respectively.[21] The number of ADR reports for the paediatric population decreased in Denmark from 2004 to 2007 despite the fact that the number of eligible reporters increased during the same time period.[17] In contrast, the number of ADR reports involving adults increased in the same period in Denmark, and we had expected an increase in ADR reports for children. The data does not offer a ready explanation for the decrease, nor for the relatively low reporting rate for children in Denmark. The findings point to a need for further extrapolation of this issue, not least in view of calls from the EU and WHO to expand the examination of medicines safety in children. Since 2003, consumers have been allowed to report ADRs in Denmark [22] and the extent to which consumer reports will increase the number or quality of ADR cases and thus increase the data in the system is an interesting question that cannot yet be answered. From a public health perspective, the declining reporting rate is worrying as this indicates decreasing awareness or inherent lack of vigilance among reporters in monitoring drug safety.

Age and Sex of the Paediatric Population

In this study, more than 50% of the ADRs were reported for infants (birth to 2 years of age). Similar findings were observed in other studies.[10-14] This could be due to parents' close attention to symptoms in young children, particularly in connection with vaccinations; however, a large number of ADRs reported in this age group may also be due to the mother's intake of medicine during pregnancy, especially psychotropic medicines. This is an important issue regarding children's health risks that has been

neglected in the ADR literature. In empirical studies, relatively higher shares of ADRs were reported in children up to 5 years of age and in 11- to 17-year-olds.[10,11,14] In this study, equal shares of ADRs were reported for girls and boys. In the literature, approximately 55% of ADRs were reported for boys and 45% for girls; in Denmark, more ADRs were reported for boys than girls in the 5- to 12-year-old age group.[10-14]

System Organ Class and Anatomical Therapeutic Classification

The reports of ADRs for the SOCs 'nervous system disorders', 'psychiatric disorders', 'skin and subcutaneous disorders' and 'gastrointestinal disorders', were consistent with reports in other empirical studies,[10-14] but higher shares of ADRs from the SOC 'general disorders and administration site conditions' and lower shares of ADRs from the SOC 'skin and subcutaneous disorders' were reported in this study. Among infants and children aged 2–10 years a high number of ADRs were reported for methylphenidate and atomoxetine (both in ATC group N). This finding is probably due to the rapid increase in the prescribing of these medications to adolescents too, in which case one would expect an increase in this age group too.[23] The high number of ADR reports involving psychotropic medicines could also partly be attributed to the regulatory warnings on antidepressants and attention-deficit hyperactivity disorder treatments.[24-26] In 2005, the US FDA and European Medicines Agency recommended that antidepressants not be prescribed for children less than 18 years of age. In 2009, the European Medicines Agency recommended that all patients receiving stimulants should be screened to see if they have any problems with their blood pressure or heart rate during treatment; blood pressure, heart rate, height and weight should also be monitored regularly.[27]

Because of national immunization programmes and a high incidence of infectious disease among children up to 2 years of age, the prevalence rate for the use of anti-infective medicines (ATC J) was as high as 48%, and a high number of ADRs reported for these medicines are expected in this study.[28] We found a higher share of ADRs reported for ATC group J (65%) than in the literature (40%).[11,13] The large number of ADR reports on vaccines and anti-infectives among young children is a concern for immunization coverage.

In spite of the sharp increase in psychotropic drug prescribing in recent years, we found a similar share of ADRs had been reported for psychotropic medicines compared with previous studies (approximately 15%).[10-14] Among adolescents, more ADRs were reported for medicines belonging to ATC group G and ATC group N, i.e. contraceptives and SSRIs, than in children up to 10 years of age, which reflects medicine use among adults. In the literature, ADRs were not reported for contraceptives, which probably is due to the lower age of the studied populations compared with the present study.[10-14] On the contrary, other studies reported a larger share of ADRs for analgesics, antihistamines and antiasthmatic drugs compared with this present study.[10-14] Explanations of these deviations could be due to time differences in studies and differences in licensing status of the medicines (prescription or over-the-counter status) between various countries.

Seriousness of Reported ADRs

Data on the differences in seriousness of ADRs between age groups provides important new information for physicians, who need to be aware of these differences in ADR risks when prescribing medicines for the paediatric population. We found a higher share of serious ADRs in children (42%) than previously reported in Danish adults (25–30%), although the number of serious ADRs in adults has increased since 2000.[17] The shares of serious ADRs in children were in line with results reported in the literature.[10-14]

Who Detects the ADRs?

Although physicians were the primary reporters of ADRs in children, they reported a relatively lower share of serious ADRs than consumers and other healthcare professionals. Pharmacists reported almost no ADRs as expected from previous

analysis of Danish ADR reports.[22] Physicians and consumers reported equal shares of serious ADRs for adults, but other healthcare professionals and pharmacists reported higher shares. Pharmacists have reported more ADRs in the Netherlands and Canada, probably due to their direct contact and dialogue with patients at the pharmacy or in hospital.[10,14,27,29,30] Strategies for encouraging Danish pharmacists to take a more active role in ADR reporting will probably include more teaching in this area during their masters' curriculum. We propose that pharmacists take an active role in reporting ADRs in all countries.

Strengths and Limitations of the Study

The strength of our study is that the material consisted of all reported ADRs in one country over one decade. The purpose was to analyse information reported to the Danish ADR database on ADRs in the paediatric population, and not to calculate the incidence of ADRs in this population as this is not feasible in material based on spontaneous reporting. Spontaneous reporting of ADRs was analysed on ATC level 2, and further analysis of reported ADRs in different therapeutic groups, e.g. ATC J and N, are in progress and will contribute more information on the specific medications causing the ADRs, as well as information about differences in reporting patterns betweens boys and girls or age groups. As consumers and pharmacists contribute a limited number of ADR reports, qualitative studies exploring barriers amongst these groups against reporting of ADRs in children could be conducted.

Conclusions

In Denmark, the ADR reporting rate in the paediatric population has declined since 2005. The majority of ADRs reported in young children are reported for vaccines and anti-infectives, but also a high number of serious ADRs are reported for psychotropic medicines. The Danish Medicines Agency should monitor prescribing patterns more tightly to identify potential risks in the paediatric population in relation to the evolving pattern of medicine use among children.

Acknowledgements

We would like to thank the Danish Medicines Agency for placing data at our disposal.

A supplementary file containing detailed information of all reported ADR cases can be obtained from the authors if wished.

L. Aagaard and E. Holme Hansen designed the study, analysed data and wrote the first version of the study. C. Blicher Weber did the sampling. All authors saw and approved the final version of the study.

No sources of funding were used to assist in the preparation of this study. The authors have no conflicts of interest to declare.

References

1. Le J, Nguyen T, Law AV, et al. Adverse drug reactions among children over a 10-year period. Pediatrics 2006; 118: 555-62
2. Temple ME, Robinson RF, Miller JC, et al. Frequency and preventability of adverse drug reactions in paediatric patients. Drug Saf 2004; 27: 819-29
3. FDA Modernization Act of 1997 [online]. Available from URL: http://www.fda.gov/MedicalDevices/DeviceRegulationandGuidance/Overview/MedicalDeviceProvisionsofFDAModernizationAct/ucm136671.htm [Accessed 2009 Oct 7]
4. Regulation EC No. 1901/2006 of the European Parliament and the Council of 12 December 2006 on Medicinal Products for Paediatric Use and Amending Regulation [online]. Available from URL http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol- 1/reg_2006_1901/reg_2006_1901_en.pdf [Assessed 2009 Oct 7]
5. Hansen EH. Technology assessment in a user perspective: experiences with drug technology. Int J Technol Assess Health Care 1992; 8: 150-65
6. Aagaard L, Soendergaad B, Stenver DI, et al. Knowledge creation about ADRs: turning the perspective from the rearview mirror to the projector? Br J Clin Pharmacol 2008; 65: 364-76
7. Keinonen T, Miettinen P, Saano V, et al. Clinical trials in children and healthy volunteers: quality and characteristics of notifications reviewed by the regulatory agencies in Finland. Paed Perinat Drug Ther 2003; 5: 175-82
8. Sammons HM, Choorara I. Clinical trials of medication in children, 1996-2002. Eur J Clin Pharmacol 2005; 61: 165-7
9. Impicciatore P, Choonara I, Clarkson A, et al. Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies. Br J Clin Pharmacol 2001; 52: 77-83
10. Meyboom RH. Adverse reactions to drugs in children, experiences with "spontaneous monitoring" in the Netherlands. Bratisl Lek Listy 1991; 92: 554-59
11. Morales-Olivas FJ, Martinez-Mir I, Ferrer JM, et al. Adverse drug reactions in children reported by means of the yellow card in Spain. J Clin Epidemiol 2000; 53: 1076-80
12. Moore TJ, Weiss SR, Kaplan S, et al. Reported adverse drug events in infants and children under 2 years of age. Pediatrics 2002; 110: e53

13. Kimland E, Rane A, Ufer M, et al. Paediatric adverse drug reactions reported in Sweden from 1987 to 2001. Pharm Drug Saf 2005; 14: 493-99
14. Carleton BC, Smith MA, Gelin MN, et al. Paediatric adverse drug reaction reporting: understanding and future directions. Can J Clin Pharmacol 2007; 14: e45-57
15. Ackers R, Murray ML, Besag FMC, et al. Prioritizing children's medicines for research: a pharmacoepidemiological study of antiepileptic drugs. Br J Clin Pharmacol 2006; 63: 689-97
16. van de Vrie-Hoekstra NW, de Vries TW, van den Berg PB, et al. Antiepileptic drug utilization in children from 1997-2005: a study from the Netherlands. Eur J Clin Pharmacol 2008; 64: 1013-20
17. Aagaard L, Soendergaard B, Andersen E, et al. Creating knowledge about adverse drug reactions: a critical analysis of the Danish reporting system from 1968 to 2005. Soc Sci Med 2007; 65: 1296-309
18. Roden S. Good case management and reporting practices. In: Mann RD, Andrews EB, editors. CIOMS working groups and their contribution to pharmacovigilance. Chapter V. Middlesex: John Wiley & Sons, Ltd, 2007
19. Aagaard L, Stenver DI, Hansen EH. Structures and processes in spontaneous reporting systems: a comparative study of Australia and Denmark. Pharm World Sci 2008; 30: 563-70
20. Medical Dictionary for Regulatory Activities [online]. Available from URL: http://www.meddramsso.com [Accessed 2008 Aug 20]
21. Fraunhofer Institute for Systems and Innovation Research. Assessment of the European community system of pharmacovigilance, 2004 [online]. Available from URL: http://www.isi.fraunhofer.De/t/projekte/medpharm-e-rt-eurovigilance.htm [Accessed 2009 Dec 31]
22. Aagaard L, Nielsen LH, Hansen EH. Consumer reporting of adverse drug reactions: a retrospective analysis of the Danish adverse drug reaction database from 2004 to 2006. Drug Saf 2009; 32: 1067-74
23. Aagaard L, Thirstrup S, Hansen EH. Opening the white boxes: the licensing documentation of efficacy and safety of psychotropic medicines for children. Pharm Drug Saf 2009; 18: 401-11
24. Cheung A, Sacks D, Dewa CS, et al. Paediatric prescribing practices and the FDA black-box warning on antidepressants. J Dev Behav Pediatr 2008; 29: 213-5
25. European Medicines Agency finalises review of antidepressants in children and adolescents (ref. EMEA/CHMP/128918/2005 corr. London, 25 April 2005 [online]. Available from URL: www.emea.europa.eu/pdfs/human/press/pr/128918 05en.pdf [Accessed 2010 Jan 29]
26. Press release: meeting highlights from the Committee for Medicinal Products for Human Use (ref. EMEA/431407/2007). London, 19 July 2007 [online]. Available from URL: www.emea.europa.eu/pdfs/human/press/pr/43140707en.pdf [Accessed 2010 Jan 29]
27. Sanghera N, Chan PY, Khaki ZF, et al. Interventions of hospital pharmacists in improving drug therapy in children: a systematic literature review. Drug Saf 2006; 29: 1031-47
28. Sturkenboom CJM, Verhamme KMC, Nicolosi A, et al. Drug use in children: cohort study in three European countries. BMJ 2008; 24: 337: a2245
29. de Langen J, van Hunsel F, Passier A, et al. Adverse drug reaction reporting by patients in the Netherlands: three years of experience. Drug Saf 2008; 31: 515-24
30. Schirm E, Tobi H, van Puijenbroek EP, et al. Reported adverse drug reactions and their determinants in Dutch children outside the hospital. Pharm Drug Saf 2004; 13: 159-65

Correspondence: Associate Professor *Lise Aagaard*, Department of Pharmacology and Pharmacotherapy, Section for Social Pharmacy, Faculty of Pharmaceutical Sciences, University of Copenhagen, Copenhagen, Denmark. E-mail: laa@farma.ku.dk