Prescribing of medicines in the Danish paediatric population outwith the licensed age group: characteristics of adverse drug reactions

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Off-label use of medicine in children is common, as few medications are licensed for use in this population.
- There is concern about off-label use of medicines in children due to lack of knowledge about safety beyond the indication area described in the official product information documented in the licensing material.

WHAT THIS STUDY ADDS

- One-fifth of all ADRs reported over a decade in Danish children were associated with off-label prescribing of medicines.
- Serious ADRs from off-label prescribing primarily appeared in therapeutic groups: allergens, dermatologicals and sex hormones.
- Until more clinical studies are conducted in children, prescribers and carers must be aware of the risk of potentially serious ADRs from off-label prescribing, and the safety of off-label prescribing in the paediatric population should be closely monitored.

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Keywords

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AIM

To identify adverse drug reactions (ADRs) associated with off-label prescribing of medicines in a paediatric population.

METHODS

We analysed spontaneous ADR reports for children from ages 0 to 17 years submitted to the Danish national ADR database from 1998 to 2007. We defined off-label prescribing as prescriptions outside the licensed age group. Off-label ADRs were categorized by therapeutic group, age of child, type and severity. The unit of analysis was one ADR.

RESULTS

We analysed 4388 ADRs for children reported in the national database. Approximately 17% of reported ADRs were associated with off-label use, 60% of them serious. More than one half of off-label ADRs were reported in adolescents. Serious ADRs due to off-label prescribing are more likely to be reported for hormonal contraceptives (ATC group G), anti-acne preparations (ATC group D) and allergens (ATC group V).

CONCLUSION

One-fifth of all ADRs reported over a decade in Danish children was associated with off-label prescribing, and serious ADRs due to off-label prescribing were primarily present in three therapeutic groups: sex hormones, dermatologicals and allergens. There is a need for more research into the prescribing of these medicines in the teenage population, as well as tighter reporting and monitoring of ADRs for medicines prescribed off-label in the paediatric population.

Introduction

Many medicines used in the paediatric population are prescribed without license (unlicensed) or in disagreement with the product license (off-label). Off-label prescription includes prescribing outside the recommended dosage, indication, route of administration or age of patient [1–3]. Lack of knowledge about possible adverse drug reactions (ADRs) [4, 5] makes off-label use of medicine in the paediatric population a concern. The extent of off-label prescribing in the paediatric population has been assessed in different settings, e.g. neonatal intensive care units, paediatric hospital wards and in the community (general practice) [1, 2, 4]. The overall off-label prescription rates ranged between 25% and 60% across populations and were highest in children under 2 years of age and in adolescents (11–17-year-olds) [6, 7]. Off-label prescription also varied with respect to dosage, indication, route of administration and therapeutic group [1–3]. Analgesics (paracetamol, ketoprofen, thiopental, fentanyl), bronchodilators (budesonide and salbutamol) and psychotropic drugs were among those medicines most frequently prescribed off-label across countries [7–10]. Very few studies have examined the contribution of medicines used in children in an off-label or unlicensed manner to ADR occurrence [7]. The few studies providing information on the subject refer to a variety of settings, time periods and types of patient populations. Across studies, anticonvulsants, antibiotics, rhinologics, antitussives and gastrointestinal medicines were the therapeutic groups with the highest proportions of ADRs related to off-label prescribing, and 50% of ADRs reported for these therapeutic groups were serious [11–19]. The regulatory authorities in the USA and Europe as well as the World Health Organization (WHO) have acknowledged that information about the efficacy and safety of medicines in children must be increased. Several regulatory initiatives have been launched to stimulate studies in children, such as providing extended patent periods for new medicines and opportunities for paediatric studies of already-marketed medicines [20–22]. The lack of sufficient knowledge of ADRs at the point of licensing new medicines makes spontaneous ADR reporting an important source of information about medicine safety [23]. As clinical trials in the paediatric population are scarce, clinicians and health authorities have to rely on spontaneous reports as the major source of information about previously unknown ADRs [24]. The objective of this study was to identify ADRs associated with off-label prescribing by age in a paediatric population.

Methods

Design

We conducted a retrospective analysis of all spontaneous ADR reports for 0–17-year-old children from 1998 to 2007.

Data were obtained from the national Danish ADR database and placed at the disposal of this study in anonymous form with encrypted person identification. The unit of analysis was one ADR. Data on labelling status were obtained from the official summary of product characteristics (SPC) for each of the reported medicines. The website of the Danish Medicines Agency (DKMA) provided access to SPC information. In this study, medicine use was defined as off-label if medicines were prescribed for children below the recommended age group listed in the SPC. ADRs reported for children due to the mothers' use of medicine during pregnancy and/or the lactation period were excluded in the specific analyses. The excluded ADR reports related to the mothers' medicine use during pregnancy or lactation covered 114 ADRs, many of them serious. The off-label ADRs were analysed as number of ADRs distributed by therapeutic group, age of the child, type and seriousness of ADRs.

Setting

The reporting of ADRs has been obligatory in Denmark since 1 May 1968 [25]. Initially, only physicians were covered by the obligation; however, in 1972, dentists were also required to report ADRs. Since 1995, drug manufacturers have been obliged to keep registers of suspected and demonstrated ADRs and to make these available to the authorities [25]. Since July 2003, consumers have been able to report ADRs directly to the authorities. The Danish reporting system has been described in details elsewhere [25]. The Danish ADR system contains all spontaneous 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 ADR terms. After receiving the ADR reports, professional staff at the DKMA code and categorize the ADRs by degree of seriousness and type of reaction according to the Medical Dictionary for Regulatory Activities (MedDRA) terminology [26]. ADR reports are forwarded electronically to the respective pharmaceutical companies which periodically assess the ADR reports received. The results of their assessments are reported to the DKMA via periodic safety update reports (PSURs) [25].

Adverse drug reaction (ADR)

An ADR is defined as 'any noxious and unintended response to medicines that occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease' [27].

Criteria for seriousness

Seriousness of reported ADRs was classified according to the criteria defined in Volume 9 of the rules governing medicinal products in the European Union [27]. Here

serious ADRs are divided into the following categories: fatal, life-threatening, requiring hospitalization or prolongation of existing hospitalization, resulting in persistent or significant disability/incapacity in the reporter's opinion, in a congenital anomaly/birth defect and other medically important conditions [27]. Other reported ADRs are classified as non-serious.

Anatomical therapeutic chemical (ATC) classification groups

The ATC system classifies medicinal products according to the primary constituent, organ or system on which they act and their chemical, pharmacological and therapeutic properties. Medicines are divided into 14 main groups (first level), with one pharmacological/therapeutic subgroup (second level) [28]. The third and fourth levels are chemical/pharmacological/therapeutic subgroups and the fifth level is the chemical substance. The extract from the ADR database only provides information according to the trade name of those medicinal products that have been reported as causing ADRs [28]. Therefore, it was necessary to translate manually trade names into generic names at ATC level 5 in the DKMA's medicines register, and then run the generic form of the medicine name against the ADRs reported.

Results

From 1998 to 2007 a total of 4388 ADRs were reported for children aged 0–17 years, and 17% of these ADRs were for medicines prescribed off-label (age of the child).

ADRs by age

Table 1 shows the distribution of ADRs reported from off-label prescribing by age group, therapeutic group (ATC level 2) and seriousness. The largest share of ADRs associated with off-label prescribing was reported for nervous system medications (ATC group N) (25%), followed by medicines from ATC group V (various) (18%) and hormonal contraceptives (ATC group G) (13%). Two-thirds of off-label ADRs were reported in young people from 11–17 years of age. Less than 10% of off-label ADRs were reported in children less than 2 years of age. In children up to 2 years of age, more than half of the ADRs were reported for antiemetics (ATC group A04) and anti-epileptics (ATC group N03), and approximately 20% for antineoplastic and immunomodulating agents, especially medicines for endocrine therapy (ATC group L02). In children up to 10 years of age, approximately one-half of off-label ADRs were reported for psychotropic medicines and allergens (ATC group V01). In adolescents, more than one-half of off-label ADRs were reported for hormonal contraceptives, anti-acne preparations and allergens (ATC group V01). In both younger children and adolescents, a considerable number of ADRs were reported for anti-inflammatory agents, e.g. ibuprofen.

ADRs by therapeutic group and severity

Table 2 displays the distribution of off-label ADRs by therapeutic group (ATC level 1) and seriousness. Sixty percent of ADRs reported for medicines prescribed off-label were serious and, in contrast, 35% of ADRs reported for labelled medicine use were serious. The largest number of paediatric ADRs, both serious and non-serious, were reported for 'anti-infectives for systemic use' (ATC group J) and anti-parasitic medicine (ATC group P), but almost all of these were found in labelled prescriptions. The share of off-label ADRs within therapeutic groups ranged from 1–100%. The therapeutic groups: ATC group S (sensory organs), ATC group G (genito-urinary system and sex hormones) and ATC group V01 (allergens) were the therapeutic groups with the highest occurrence of off-label ADRs (range 92–100%). The largest number of serious off-label ADRs were reported for nervous system medications (ATC group N), followed by sex hormones (ATC group G) and for allergens (ATC group V01). For allergens, a large number of *anaphylactic shock* and other *allergic reactions* were reported. For serious ADRs, the share of off-label ADRs within therapeutic groups ranged from 0–76%. The therapeutic groups ATC group V01 (allergens), ATC group G (genito-urinary system and sex hormones) and ATC group D (dermatological) were three therapeutic groups with the highest share of serious off-label ADRs (range 40–76%). For non-serious ADRs, the share of off-label ADRs within therapeutic groups ranged from 28 to 100%. In the following therapeutic groups no serious off-label ADRs were reported: anti-parasitic products (ATC group P) and sensory organs (ATC group S). Table 3 displays the characteristics of the 13 fatal cases reported in relation to off-label use during the 10 years under study. Four of these fatal cases, pulmonary *embolism* and *thrombosis*, were reported for hormonal contraceptives in 17-year-old girls. Necrotizing colitis was reported in two male infants, possibly related to ibuprofen use to treat *patent ductus arteriosus*.

Discussion

This is the first study from a national ADR database that has examined the contribution of off-label prescribing by age in the paediatric population to ADR occurrence. The study shows that off-label prescribing is associated with a large number of serious ADRs including fatal cases, and more than half of off-label ADRs were reported in adolescents. Psychotropic medicines, hormonal contraceptives and allergens were the therapeutic groups with the highest occurrence of ADRs for medicines prescribed off-label.

Off-label-related ADRs by age and severity

In this study, more than half of the ADRs related to off-label prescribing were reported in adolescents, which is in line

Table 1

Distribution of reported ADRs (*n*) for off-label prescriptions by age group, therapeutic group and seriousness (numbers of serious ADRs in parentheses)

Therapeutic groups (ATC level 1)	Subgroups (ATC level 2)	Age (years)			Total ADRs
		0–2	2–10	11–17	
Alimentary tract and metabolism (A)	Stomatological preparations (A02)	1 (1)	3	5 (5)	9 (6)
	Anti-emetics (A04)	7 (7)	0	0	7 (7)
	Antidiarrheals (A07)	0	2	5 (4)	7 (4)
	Anti-obesity products (A08)	0	0	9 (9)	9 (9)
	Antidiabetic products (A10)	1	7 (4)	6 (4)	14 (8)
	Other alimentary tract products (A16)	0	1	0	1
Total A		9 (8)	13 (4)	25 (22)	47 (34)
Blood and blood forming organs (B)	Antithrombotic agents (B01)	0	0	3	3
	Anti-anemic agents (B03)	0	0	0	0
	Blood substitutes (B05)	0	0	1 (1)	1 (1)
Total B		0	0	4 (1)	4 (1)
Cardiovascular system (C)	Cardiac therapy (C01)	1 (1)	1	0	2 (1)
	Antihypertensives (C02)	0	0	3 (3)	3 (3)
	Vasoprotectives (C05)	0	1 (1)	0	1 (1)
	β-adrenoceptor blocking agents (C07)	0	0	5 (2)	5 (2)
	Renin-angiotensin system (C09)	0	0	3	3
		1 (1)	2 (1)	11 (5)	14 (7)
Total C		1 (1)	2 (1)	11 (5)	14 (7)
Dermatological (D)	Anti-acne preparations (D10)	0	0	63 (29)	63 (29)
	Other dermatologicals (D11)	3 (2)	2 (1)	1	6 (3)
Total D		3 (2)	2 (1)	64 (29)	69 (32)
Genito-urinary system and sex hormones (G)	Sex hormones (G03)	0	0	100 (76)	100 (76)
		0	0	100 (76)	100 (76)
Systemic hormonal preparations (H)	Pituitary and hypothalamic hormones (H01)	0	2 (1)	3	5 (1)
	Corticosteroids (H02)	0	5 (5)	4 (3)	9 (8)
	Thyroid therapy (H03)	0	0	4	4
		0	7 (6)	11 (3)	18 (9)
Total H		0	7 (6)	11 (3)	18 (9)
Anti-infectives for systemic use (J)	Antibacterials (J01)	3 (2)	6 (4)	5 (5)	14 (11)
	Antimycotics (J02)	0	0	4	4
	Antimycobacterials (J04)	0	1 (1)	0	1 (1)
	Antivirals (J05)	0	0	4 (4)	4 (4)
	Vaccines (J07)	0	4 (1)	3	7 (1)
		3 (2)	11 (6)	16 (9)	30 (17)
Total J		3 (2)	11 (6)	16 (9)	30 (17)
Antineoplastic and immunomodulating agents (L)	Antineoplastic agents (L01)	0	9 (9)	3 (2)	12 (11)
	Endocrine therapy (L02)	0	22 (4)	3	25 (4)
	Immunostimulants (L03)	1 (1)	7 (7)	5 (5)	13 (13)
	Immunosuppressants (L04)	0	6 (6)	4 (3)	10 (9)
		1 (1)	44 (26)	15 (10)	60 (37)
Total L		1 (1)	44 (26)	15 (10)	60 (37)
Musculoskeletal system (M)	Anti-inflammatory agents (M01)	3	21 (14)	21 (18)	45 (32)
		3	21 (14)	21 (18)	45 (32)
Nervous system (N)	Anaesthetics (N01)	4 (3)	10 (4)	8 (7)	22 (14)
	Analgesics (N02)	0	8 (8)	1 (1)	9 (9)
	Anti-epileptics (N03)	21 (17)	24 (14)	0	45 (31)
	Anti-parkinson medicine (N04)	0	0	1 (1)	1 (1)
	Psycholeptics (N05)	1 (1)	7 (4)	62 (30)	70 (35)
	Psycho-analeptics (N06)	0	11 (2)	32 (16)	43 (18)
	Other nervous medications (N07)	0	0	1	1
		26 (21)	60 (32)	105 (55)	191 (108)
		26 (21)	60 (32)	105 (55)	191 (108)
Total N		26 (21)	60 (32)	105 (55)	191 (108)
Antiparasitic (P)	Antiprotozoals (P01)	0	2	0	2
Total P		0	2	0	2
Respiratory system (R)	Nasal preparations (R01)	0	0	1	1
	Throat preparations (R02)	0	2	0	2
	Obstructive airway diseases (R03)	6	9 (6)	11 (7)	26 (13)
	Cough and cold preparations (R05)	0	2	0	2
	Antihistamines (R06)	1 (1)	8 (3)	0	9 (4)
		7 (1)	21 (9)	12 (7)	40 (17)
Total R		7 (1)	21 (9)	12 (7)	40 (17)
Sensory organs (S)	Ophthalmologicals (S01)	1	2	0	3
	Otologicals (S02)	0	2	0	2
Total S		1	4	0	5
Various (V)	Allergens (V01)	0	45 (26)	79 (49)	124 (75)
	Other therapeutic products (V03)	1 (1)	2 (2)	0	3 (3)
	Diagnostic agents (V04)	0	0	3 (2)	3 (2)
	Radiopharmaceuticals (V09)	0	3	0	3
Total V		1 (1)	50 (28)	82 (51)	133 (80)
Total ADRs medicines prescribed off-label		55 (37)	237 (127)	466 (286)	758 (450)
Total ADRs licensed medicines		2219 (736)	841 (306)	570 (282)	3630 (1324)

Table 2

Distribution of adverse drug reactions (ADRs) for medicines prescribed off-label by therapeutic group and seriousness

Therapeutic group (ATC level 1)	Total ADRs <i>n</i>	Total ADRs Off-label prescriptions <i>n</i> (%)	Serious ADRs Off-label prescriptions <i>n</i> (%)	Non serious ADRs Off-label prescriptions <i>n</i> (%)
Alimentary tract and metabolism (A)	106	47 (44)	34 (72)	13 (28)
Blood and blood forming organs (B)	5	4 (80)	1 (25)	3 (75)
Cardiovascular system (C)	33	14 (42)	7 (50)	7 (50)
Dermatological (D)	77	69 (90)	32 (46)	37 (54)
Genito-urinary system, sex hormones (G)	101	100 (99)	76 (76)	24 (24)
Systemic hormonal preparations (H)	50	18 (36)	9 (50)	9 (50)
Anti-infectives for systemic use (J)	2927	30 (1)	17 (56)	13 (43)
Antineoplastic, immunomodulating agents (L)	86	60 (70)	37 (62)	23 (38)
Musculoskeletal system (M)	57	45 (79)	32 (71)	13 (29)
Nervous system (N)	750	191 (25)	108 (57)	83 (44)
Antiparasitic (P)	51	2 (4)	0 (0)	2 (100)
Respiratory system (R)	106	40 (38)	17 (43)	23 (58)
Sensory organs (S)	5	5 (100)	0 (0)	5 (100)
Various (V)	144	133 (92)	80 (60)	53 (40)
Total	4386	758 (17)	450 (59)	308 (41)

Table 3

Fatal adverse drug reactions reported for medicines prescribed off-label (age) from 1998 to 2007

Case	ATC	Medicine (s)	ADR(s) reported	Indication for use	Gender	Age (years)
1	A07EC02	Mesalazine	Disseminated intravascular coagulation	Ulcerative enterocolitis	Male	16
2	C01EB16	Ibuprofen	Necrotizing colitis	Patent ductus arteriosus	Male	0
3	C01EB16	Ibuprofen	Necrotizing colitis	Patent ductus arteriosus	Male	0
4	C02KX01	Bosentan	Right ventricular failure	Pulmonary hypertension	Male	12
5	D10BA01	Isotretinoin	Cardiac failure	Acne	Female	15
6	G03AA09	Desogestrel/oestrogen	Pulmonary embolism	Hormonal contraception	Female	17
7	G03AA12	Drospirenon/ethinylestradiol	Pulmonary embolism	Hormonal contraception	Female	17
8	G03AA10	Norgestimat/ethinylestradiol	Brain stem thrombosis	Hormonal contraception	Female	17
9	G03AA09	Ethinylestradiol/desogestrel	Pulmonary embolism	Hormonal contraception	Female	17
10	H02AB04	Methylprednisolone	Bradycardia, cardiac arrest, bronchospasm	Status asthmaticus	Female	15
11	L01BA01	Methotrexate	Guillain-Barre syndrome	NA	Male	11
12	L01XE02	Gefitinib	Toxic epidermal necrolysis	Adrenal carcinoma	Male	15
13	N03AX	Felbamate	Sudden death	NA	Female	17

NA Information not available.

with previous reports in the literature, but higher than for ADRs reported for licensed medicines [11–19]. Only a small number of off-label ADRs were reported in children up to 2 years of age, in contrast to findings in a recent hospital-based monitoring study where a large number of newborns were prescribed medicines off-label [29]. However this study was conducted in a different setting, a neonatal hospital department [29]. The coexistence of ‘patent ductus arteriosus’ and necrotizing colitis in association with ibuprofen treatment is almost certainly more common than the two cases reported here, underpinning the fact that the spontaneous reporting system cannot provide accurate ADR prevalence.

Off-label-related ADRs by therapeutic groups

Few ADRs were related to off-label prescribing for antibiotics and vaccines (ATC group J), as the majority of these products in Denmark are licensed for use in the paediatric population [30]. In contrast, a large number of serious ADRs were reported in both younger children and adolescents for allergens (ATC group V01) prescribed off-label. The high number of reports for allergens could be due to high awareness among physicians and nurses when administering these medications due to the well-known risk of serious ADRs, such as anaphylactic shock and other allergic reactions. Compared with other countries, in Denmark, only a minor number of ADRs were reported for anti-

diabetics and gastrointestinal medicine, antitussives, rhinologics and medicines for obstructive airway diseases [11–19]. The explanation for this remains unclear. For the category of dermatological products, many of the off-label ADRs were reported for Roaccutane®, a product frequently prescribed for acne in teenagers. A large number of serious ADRs such as pulmonary embolism, some cases with fatal outcome, were reported for hormonal contraceptives. In the light of the increasing use of these products among teenagers and girls as young as 10 years old, physicians need to be mindful of the risks of hormonal contraceptives in teenage girls, and give due consideration to alternative methods of contraception.

Implications of off-label prescribing

There are huge gaps in the evidence on the safety of medicines in children, as only few of the medicines prescribed for children to date have been tested in clinical trials and licensed for use in this population [5]. However if a child's serious condition requires treatment and no other alternatives exist, off-label prescribing may be appropriate. This issue is already a concern among health care professionals due to lack of knowledge about long-term safety aspects, and the problems with estimating the correct dosage in children [1–5]. There appears to be a need for studies exploring specific cases of off-label prescribing through questionnaire-based surveys, and scrutiny of case records combined with interviews [31]. The present study showed that off-label prescribing caused a large number of serious ADRs in young children, as well as adolescents. It would be useful to investigate the prescribers' reflections and decision-making and, further, in what fraction of the reported ADRs there was total recovery of the child or recovery with *sequelae* in order to estimate the impact of off-label prescribing on children's health.

Strengths and limitations of this study

Our study material consisted of all spontaneous ADRs reported over a decade in one country. However, a major limitation is that we do not know the causality of these ADRs, which should be borne in mind by anyone interpreting the data. Further, spontaneous reporting systems suffer from different barriers such as incomplete recognition of suspected ADRs and administrative barriers to reporting, which may result in under-reporting of important ADRs. Although ADR reporting is mandatory in Denmark, it is unlikely that the analysed reports provide complete information and therefore, we do not know the actual prevalence of ADRs in the total paediatric population. Data are not available on the prevalence of off-label prescribing in the Danish population and, hence, we could not determine the relative risk of developing ADRs in relation to off-label prescribing. Further, we do not know if some of the ADRs were related to self-medication without involvement of a physician. We restricted our definition of off-label to the children's age, as we did not have data on

indication and dosage schemes. Off-label prevalence would probably be considerably larger if such data were included. Nonetheless, the study provides information about suspected ADRs reported from off-label use, and this information helps broaden the knowledge base about this topic. Our findings may not be generalizable to other populations, due to national differences in medicine use, as well as differences in paediatric licensing status of the medicines.

In conclusion, one-fifth of all ADRs reported over a decade in Danish children were associated with off-label prescribing, 60% of them serious including 13 fatalities. Serious ADRs due to off-label prescribing were primarily present in three therapeutic groups: sex hormones, dermatologicals and allergens. There is a need for more research into the prescribing of these medicines in the teenage population, as well as tighter reporting of ADRs for medicines prescribed off-label in the paediatric population.

Competing Interests

There are no competing interests to declare.

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