

Paediatric adverse drug reactions following use of asthma medications in Europe from 2007 to 2011

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Abstract *Background* Information about safety issues from use of asthma medications in children is limited. Spontaneous adverse drug reaction (ADR) reports can provide information about serious and rarely occurring ADRs in children. *Objective* To characterize paediatric ADRs reported for asthma medications licensed for paediatric use. *Setting* Spontaneous ADR reports located in the European ADR database, EudraVigilance. *Method* ADRs reported for asthma medications licensed for paediatric use from 2007 to 2011 were analysed. The included substances were beclometasone, budesonide, fenoterol, fluticasone, formoterol, mometasone, montelukast, salbutamol and terbutaline and the combinations of budesonide/formoterol, fenoterol/ipratropium and fluticasone/salmeterol. *Main outcome measures* Reported ADRs were categorized with respect to distribution on age, sex, type and seriousness of reported ADRs, medications and type of reporter. The unit of analysis was one ADR. *Results* We located 326 spontaneous reports corresponding to 774 ADRs for the inclu-

ded asthma medications. Approximately 85 % of reported ADRs were serious including six fatal cases. In total, 57 % of ADRs were reported for boys. One quarter of all ADRs occurred in children up to 1 year of age. Physicians reported the majority of ADRs. Across medicines, the majority of reported ADRs were of the type “psychiatric disorders” (13 % of total ADRs), followed by “respiratory, thoracic and mediastinal disorders” (10 % of total ADRs) and “skin and subcutaneous disorders” (9 % of total ADRs). The largest number of ADRs was reported for budesonide (21 % of total ADRs), followed by salbutamol (20 % of total ADRs) and fluticasone (19 % of total ADRs). For salbutamol, the largest numbers of serious ADRs were “tachycardia”, “accidental exposure/incorrect dose administered” and “respiratory failure”. *Conclusion* Only a few ADRs from use of asthma medications in children were identified in the EudraVigilance ADR database, but a large majority of these were serious including fatal cases.

Keywords Adverse drug reactions · Asthma · EudraVigilance · Paediatric · Pharmacovigilance · Safety

Lise Aagaard and Ebba Holme have contributed significantly to the manuscript.

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Impacts on practice

- The majority of ADR reports located in the EudraVigilance database was reported for inhaled corticosteroids and beta2-receptor agonists, which also are recommended as first-choice treatment in asthma.
- The large majority of reported ADRs were serious. Many serious cases due to accidental exposure/overdose from use of salbutamol were reported, and thus indicated that patients' uncontrolled asthma lead to overuse of salbutamol.

- Pharmacovigilance databases can be used for the early and constant review of paediatric safety of medicinal products.

Introduction

Respiratory medications are frequently prescribed for children but information about safety issues is scarce [1, 2]. A review of clinical trials on asthma medications in children showed that a large number of trials have been conducted but only few of these studies have reported information about possible ADRs [3]. The reviewed studies primarily reported adverse drug reactions (ADRs) from use of leukotriene receptor antagonists (montelukast and zafirlukast) in 6–11-year-old boys, despite the fact that salbutamol and inhaled corticosteroids (ICS) were used most frequently for paediatric treatment of asthma [3]. The most frequently reported ADRs were exacerbation of asthma, respiratory tract infection, cough, fever and headache, and only few of these were serious [3]. The review also demonstrated that the published clinical trials did not offer information about new, unexpected or rarely occurring ADRs [3]. A study analysing ADRs reported to the Dutch national ADR database for ICS in 89 children below 18 years found that the majority of reported ADRs were psychiatric symptoms (21 % of total children) [4]. Another study, also based on ADR reports submitted to the Dutch database, found a possible relation between use of inhaled steroids in children and the risk of developing “hypertrichosis” [5]. Spontaneous ADR reports may contain information about previously unknown, rarely occurring and serious ADRs that are not detected during the development process before marketing, and are therefore of value in paediatric ADR signal detection [6, 7]. In the European Union, Member States are mandatorily reporting national ADR data to the EU ADR database, EudraVigilance (EV). Since 2012, researchers have been allowed to obtain data from EV and this has opened for cross-national analyses based on a standardized reporting format [8]. Previously, a study analysing paediatric consumer ADR reports located in the EV database has been published [9]. Since the use of asthma medications in children is widespread, particularly in the younger age groups, and that poor evidence of ADRs is present in the clinical trials [10], more studies of spontaneous ADRs located in EV for this age group should be conducted.

Aim of the study

To characterize paediatric ADRs reported for asthma medications in Europe from 2007 to 2011 and located in the EV database.

Methods

Design

We retrospectively reviewed ADR reports submitted to the EV database. The reported ADRs were analysed with respect to type and seriousness of reported ADRs, age and sex of the child as well as type of reporter. The unit of analysis was one ADR.

Included asthma medications

ADR reports submitted to the EV database for the following asthma medications licensed for paediatric use were included in this study. Approved paediatric indication age (year) was listed for the included substances in parenthesis. The asthma medications were: *beclometasone* (≥ 5), *budesonide* (≥ 0), *fenoterol* (≥ 0), *fluticasone* (≥ 1), *formoterol* (≥ 5), *mometasone* (≥ 12 months), *montelukast* (≥ 15), *salmeterol* (≥ 4), *salbutamol* (≥ 18 months), and *terbutaline* (≥ 3); and the combination products *budesonide/formoterol* (≥ 12 years), *fenoterol/ipratropium* (≥ 6) and *fluticasone/salmeterol* (≥ 4).

EudraVigilance

EV is the central database of suspected ADRs reported post-marketing for all medicinal products authorized in the European Economic Area (EEA) [11]. ADRs are reported electronically to EV by regulatory agencies and pharmaceutical companies, and these reporting obligations are mandatory for the national regulatory agencies and the pharmaceutical companies. EV is not accessible to the general public, and therefore the European Medicines Agency (EMA) was approached to grant data access. ADR information was placed at the disposal of this study in anonymous form with encrypted identification of the medicine user. Data comprised all ADRs in children below 18 years and reported for asthma medications occurring from 2007 to 2011 and located in EV by 14 March 2012. Data were extracted from the EV database using the following criteria: patient's sex and age, medicines (active substance), type and seriousness of the reported ADRs. ADR data were then delivered to us by EMA in large Excel files. In STATA[®] (statistical software package), the Excel files were merged into one major file. The file was searched for duplicates by report number. Duplicates primarily derived from double entries by regulatory agencies and pharmaceutical companies. The data analysis, including coding of reports, was conducted in an Access database. We included ADRs for medicines that were listed as suspected by the reporter, that is, the reporter suspected this medicine and not other concomitant medications to have

caused the ADR. The data files did not contain information about causality because not all EU countries are routinely doing causality assessment of reported ADRs. According to EU regulation (EC) 1049/2001 [12], the protection of privacy and integrity of individuals must be maintained and to comply with this legislation, information about country of reporter is not available to the researchers [12]. Each ADR report may include one or more suspected ADR as well as one or more medicinal product(s). EMA forwarded the ADR data divided into three age groups: below <1 year, 1–9 years and 10–17 years. The reported ADRs were coded according to type and seriousness by academic staff in the national regulatory agencies. Type of reported ADRs were classified according to the Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) on system organ class level and preferred term [13].

Criteria of seriousness

Seriousness of reported ADRs was classified according to the international acknowledged ICH E2A criteria [14]. 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 a congenital anomaly/birth defect and other medically important conditions. All other ADRs are classified as non-serious [14]. The scientific staff working in the different national regulatory agencies made the seriousness evaluations, and these evaluations were forwarded to us together with the copies of the ADR reports.

Ethical approval

According to Danish law, no ethical approval was required for this study.

Results

From 2007 to 2011, a total of 326 ADR reports corresponding to 724 ADRs were reported and submitted to the EV database for the examined asthma medications (Table 1). Totally, 59 % of ADRs were reported for boys and 41 % for girls. Physicians reported the majority of ADRs (range 59–100 % of total ADRs). One quarter (25 %) of total ADRs occurred in children below 1 year of age. The number of ADRs varied widely across substances, age groups and with respect to type of reporter. The largest share of ADRs was reported for salbutamol (21 % of total ADRs) followed by budesonide (13 % of ADRs) and fluticasone/salmeterol (13 % of total ADRs). Approximately 85 % of reported

ADRs were serious including 6 fatal cases. For budesonide, one fatal case of sudden death presumably due to “disseminated intravascular coagulation” was reported in a boy of unknown age. For the combination product fluticasone and salmeterol, two fatal cases were reported, the first one due to severe diarrhoea occurring in a 7-year-old boy, and the second case of wheezing and asthma occurring in an 11-year-old-child (unknown sex). For montelukast, two fatal cases were found in EV. The first case reported due to “drug toxicity” occurred in a girl (unknown age). The second case reported the ADRs “premature baby” and “polyhydramnios” in a girl due to her mother’s use of montelukast during pregnancy. For salbutamol, one fatal case due to “respiratory failure”, “cardiac failure” and “acute pulmonary oedema” was reported in a 20-month-old boy. Table 2 displays the distribution of ADRs by type and asthma medications. Across medications, the majority of reported ADRs were of the type “psychiatric disorders” (13 % of total ADRs), followed by “respiratory, thoracic and mediastinal disorders” (10 % of total ADRs) and “skin and subcutaneous disorders” (9 % of total ADRs). The largest share of serious ADRs was reported for formoterol, the combination product fluticasone/salmeterol and salbutamol. Table 3 displays the most commonly occurring reported ADRs for these medications. For salbutamol, the largest number of serious ADRs was “tachycardia” ($n = 19$), “accidental exposure/incorrect dose administered” ($n = 18$) and “respiratory failure” ($n = 12$). For formoterol and fluticasone/salmeterol, the largest numbers of serious ADRs were “asthma/bronchospasm”, “adrenal insufficiency/suppression” and “tachycardia”. For budesonide the largest number of reported ADRs were “aggression” ($n = 5$) and “respiratory failure” ($n = 5$).

Discussion

This is the first study analysing ADR reports located in the EV database reported for asthma medications licensed for paediatric use. A low number of ADR reports were located, however, the majority of these were serious. More than one half of ADRs were reported for boys, and physicians reported the majority of ADRs. The largest numbers of reported ADRs were of the type “psychiatric disorders” and “respiratory, thoracic and mediastinal disorders”. The majority of ADRs reported for asthma medications were ICS and beta2-receptor agonists, products that are recommended as first-line standard asthma treatment in children [15].

ADRs by type and seriousness

In spite of findings in clinical studies, reporting ADRs for asthma medications in pediatric treatment to be non-

Table 1 Distribution of cases and adverse drug reactions (ADRs) for asthma medications by medication, seriousness, age and sex of the child, and type of reporter, located in the EudraVigilance database, 2007–2011

Medications	Cases (% of total)	ADRs (% of total)	Serious ADRs (% of total)	Male ADRs (% of total)	Age groups (% of total)				Reporter (% of total)				
					Age groups (% of total)				Reporter (% of total)				
					0–6 months	7–12 months	>1–9 years	>9–18 years	Physician	Pharmacist	OHCP	Consumer	NA
Total (N)	326	724	614	427	165	26	265	318	662	29	22	42	19
Beclometasone	7	5	3	5	21	6	33	38	100	0	0	0	0
Budesonide	17	13	10	22	16	1	70	13	59	13	2	27	0
Budesonide/ formoterol	2	2	3	3	0	0	0	100	88	12	0	0	0
Fenoterol	3	2	3	3	94	0	6	0	77	0	0	13	0
Fenoterol, ipratropium	1	2	2	2	91	0	9	0	36	0	27	0	36
Fluticasone	17	11	12	9	19	1	42	37	100	0	0	0	0
Fluticasone/ salmoterol	23	13	16	10	9	0	41	51	100	0	0	0	0
Formoterol	<1	10	14	6	22	0	11	67	88	6	6	0	0
Mometasone	5	4	3	4	33	0	48	19	78	7	0	15	0
Montelukast	16	10	9	12	0	0	0	100	100	0	0	0	0
Salmeterol	2	3	2	3	37	0	32	32	99	0	0	1	0
Salbutamol	6	21	23	19	19	13	44	24	100	0	0	0	0
Terbutaline	<1	5	6	2	59	3	12	26	74	26	0	0	0
OHCP Other health care professional, NA not available													

Table 2 Distribution of the number of paediatric adverse reactions (ADRs) reported for asthma medications to EudraVigilance by system organ classes and seriousness (in parenthesis), from 2007 to 2011

System organ class (SOC)	Beclometasone	Budesonide	Budesonide formoterol	Fenoterol	Fenoterol ipratropium	Fluticasone	Fluticasone salmeterol	Formoterol	Mometasone	Montelukast	Salmeterol	Salbutamol	Terbutaline	Total
Blood and lymphatic system disorders	0	1 (1)	0	0	0	4 (4)	1 (1)	2 (2)	0	5 (5)	1 (1)	3 (3)	0	17 (17)
Cardiac disorders	1 (1)	0	1 (1)	0	0	2 (2)	7 (7)	7 (7)	0	2 (2)	2 (2)	28 (27)	4 (4)	54 (53)
Congenital, familial and genetic disorders	4 (4)	1 (1)	0	2 (2)	5 (5)	5 (5)	1 (1)	5 (5)	0	0	3 (3)	4 (4)	1 (1)	31 (31)
Ear and labyrinth disorders	0	0	0	0	0	0	1 (1)	0	0	0	0	0	0	1 (1)
Endocrine disorders	0	1 (1)	0	0	0	4 (4)	6 (6)	0	0	0	1 (1)	0	0	12 (12)
Eye disorders	1 (1)	1 (1)	0	1 (1)	0	5 (5)	2 (2)	4 (4)	0	0	0	1 (1)	1 (1)	16 (16)
Gastrointestinal disorders	7 (4)	12 (12)	0	0	3 (3)	0	12 (11)	6 (6)	2 (2)	2 (1)	2 (2)	4 (4)	1 (1)	51 (48)
General disorders	2 (2)	8 (6)	3 (3)	2 (2)	0	5 (5)	12 (12)	11 (10)	0	5 (3)	1 (1)	8 (8)	5 (5)	62 (57)
Hepatobiliary disorders	0	0	0	1 (1)	0	0	0	0	0	1 (1)	0	1 (1)	0	3 (3)
Immune system disorders	1 (1)	0	0	0	0	2 (2)	0	0	0	0	0	1 (1)	0	4 (4)
Infections and infestations	0	1 (1)	1 (1)	0	0	0	1 (1)	0	2 (2)	0	0	4 (4)	1 (1)	10 (10)
Injury and poisoning	0	0	0	0	0	2 (2)	4 (4)	1 (1)	4 (4)	1 (1)	0	24 (24)	2 (2)	38 (38)
Investigations	0	1 (1)	0	0	0	2 (2)	2 (2)	1 (1)	0	4 (3)	0	5 (5)	1 (1)	16 (15)
Metabolism and nutrition disorders	0	0	0	1 (1)	0	2 (2)	2 (2)	1 (1)	0	2 (2)	0	11 (11)	2 (2)	21 (21)
Musculoskeletal disorders	0	2 (2)	1 (1)	1 (1)	0	1 (1)	9 (7)	0	0	3 (1)	1 (0)	4 (3)	3 (3)	25 (19)
Neoplasms benign, malignant	0	0	0	0	1 (1)	5 (3)	1 (1)	0	0	0	0	0	0	7 (5)
Nervous system disorders	2 (0)	7 (6)	5 (5)	4 (4)	1 (0)	0	9 (8)	7 (6)	2 (2)	6 (3)	4 (2)	10 (9)	5 (5)	62 (50)
Pregnancy and perinatal conditions	1 (1)	1 (1)	0	4 (4)	0	1 (1)	0	2 (2)	0	0	1 (1)	1 (1)	0	11 (11)
Psychiatric disorders	3 (0)	24 (15)	0	0	0	16 (13)	10	5 (5)	3 (3)	31 (20)	1 (1)	7 (6)	2 (2)	102 (65)
Renal and urinary disorders	2 (2)	0	0	0	0	0	0	0	0	0	1 (0)	1 (1)	0	4 (3)
Reproductive system and breast disorders	0	1 (1)	0	0	0	0	0	1 (0)	0	2 (2)	0	0	0	4 (3)
Respiratory disorders	2 (1)	15 (10)	4 (4)	0	1 (1)	6 (6)	7 (7)	14 (14)	4 (4)	2 (1)	1 (1)	16 (15)	2 (2)	74 (66)
Skin and subcutaneous disorders	7 (1)	14 (4)	1 (1)	0	0	0	5 (3)	4 (3)	10 (7)	8 (7)	0	14 (8)	4 (4)	67 (38)
Social circumstances	0	0	0	0	0	16 (15)	0	0	0	0	0	0	0	16 (15)
Surgical and medical procedures	0	2 (2)	0	1 (0)	0	0	1 (1)	0	0	0	0	1 (1)	0	5 (4)
Vascular disorders	0	0	0	0	0	0	0	2 (2)	0	2 (2)	0	7 (7)	0	11 (11)
Total (N)	33 (18)	92 (65)	16 (16)	17 (16)	11 (10)	78 (72)	93 (77)	73 (69)	27 (24)	76 (54)	19 (15)	155 (144)	34 (34)	724 (614)

Table 3 Characteristics and distribution of serious ADRs reported for salbutamol, fluticasone/salmeterol, formoterol and budesonide ($n \geq 2$) in European children, 2007–2011

Adverse drug reaction (s) (listed alphabetically)	Salbutamol	Fluticasone/ salmeterol	Formoterol	Budesonide
Accidental exposure/incorrect dose	18	2	3	0
Adrenal insufficiency/suppression	0	4	4	0
Agitation	3	0	0	2
Aggression	0	0	0	5
Anxiety	0	0	0	2
Benign intracranial hypertension	0	0	2	0
Bradycardia	2	0	0	0
Chemical burn of skin	4	0	0	0
Cough	0	0	0	2
Discomfort	0	2	0	0
Dizziness	0	2	5	0
Drug ineffective	0	0	0	2
Electrocardiogram changed	5	0	0	0
Erythema/erythema multiforme	3	0	0	0
Gastrointestinal pain	0	0	0	2
Growth retardation	0	3	3	2
Hyperglycaemia	3	0	0	0
Hypertension	3	0	0	0
Hypertrophy	0	2	3	0
Hypocalcaemia	6	0	0	0
Hypokalaemic syndrome	2	0	0	0
Mental disorder	0	0	0	2
Mouth haemorrhage	0	0	0	3
Osteoporosis	0	2	2	0
Palpitations	2	0	0	0
Pituitary-dependent Cushing's syndrome	0	2	2	0
Pyrexia	0	0	0	2
Rash	0	0	0	2
Respiratory failure/asthma/bronchospasm	12	7	7	5
Tachycardia	19	3	3	0
Tooth hypoplasia	0	0	0	2
Tremor	4	0	0	0
Vomiting	0	2	2	0

serious, the majority of ADRs located in the EV database were serious. These reports can therefore give researchers and healthcare professionals access to further information about possible ADRs. For salbutamol, fluticasone/salmeterol and formoterol, a number of cases of respiratory disorders (asthma/bronchospasm) were reported, and these cases were expected and can be explained by the mechanism of action of the included substances. However, a high number of psychiatric reports were reported for budesonide and montelukast. The psychiatric ADRs reported for montelukast were nightmare and aggression, which were also previously reported for montelukast [16] and for ICS in the Dutch study [4]. A high number of cardiac disorders, i.e. “tachycardia”, were reported for salbutamol.

According to the official product information for salbutamol, “tachycardia” is a commonly occurring ADR ($\geq 1/100$ to $<1/10$). Hypocalcaemia is also a known ADR reported for salbutamol, however, it was listed in the product information as rarely occurring ($\geq 1/10,000$ to $<1/1,000$). A large number of ADRs were reported in 0–6-month-old children, and only few ADRs were found in 7–12-month-old children. This ADR reporting pattern can probably only partly be explained by use of asthma medications as cough relief in infants, since a large number of reports were found for asthma medications such as beclometasone, the combination of fenoterol/ipratropium and mometasone, all asthma medications which are not licensed and recommended for use in children under

5 years of age. At least some of these ADR reports located in infants may be due to their mothers' use of asthma medications during pregnancy. Due to lack of causality information, we cannot prove this. Unfortunately, we have no information about the period of use in relation to pregnancy and childbirth as we did not have access to original ADR reports. For salbutamol, a large number of cases of accidental use/unintended overdose were reported which may indicate that these patients did not have a controlled asthma leading to an overuse of reliever medications. More information about correct use of asthma medications, including preventive medications must be provided to children and their caretakers in order to minimize serious ADRs due to medication overuse.

ADRs versus medicines use

Despite the large and widespread use of asthma medications in children, only a limited number of ADRs were found in EV [1, 17]. The low number may indicate that the products are rather safe, as only few ADRs have been reported for asthma medications. The many serious cases may also indicate, that healthcare professionals and patients report only unknown and serious events, which is also mandatory for healthcare professionals in many EU Member States. However, it is also well known that a high rate of underreporting is biasing the spontaneous reporting systems, and probably a much higher number of ADRs have occurred in real life [18]. Therefore, we encourage healthcare professionals and consumers/patients to continue reporting ADRs to their national pharmacovigilance databases in order to increase knowledge about ADRs from use of medicine in vulnerable populations, such as children and elderly patients.

Strengths and limitations of this study

The strength of this study is that the material consisted of all paediatric ADR reports located in EV over a 5-year period reported for asthma medications. However, a major limitation is that causality of the reported ADRs is unknown and this has implications for the interpretation of the findings. Additional detailed studies of ADRs reported for asthma medications to various national databases over a longer period of time are recommended, as national prescribing practices may affect the occurrence and characteristics of ADRs from asthma medications in children. Since we only had access to data entered into EV and not the original reports, we were unable to evaluate the validity of the consumer reports and this is a further limitation.

Conclusion

Only a few ADRs from use of asthma medications in children were identified in EV, but a large majority of these were serious and included fatal cases. The findings indicate that ADR reports may be of value in paediatric ADR signal detection, and therefore we encourage healthcare professionals and patients to report ADR data to national pharmacovigilance databases.

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