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Cutaneous adverse drug reactions reported in children: a national register-based study

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Abstract

Background: Cutaneous adverse drug reactions (CADRs) are the most common type of adverse drug reactions (ADRs) reported in the paediatric population, but they are rarely considered serious, despite that serious cases have been reported.

Objective: To characterise CADRs reported to the Danish national ADR database from 1998 to 2007.

Methods: We included reports submitted for children less than 18 years of age and extracted information about ADRs involving skin and subcutaneous disorders. ADRs were classified according to type, medications, seriousness, and age and gender of child. The unit of analysis was one ADR.

Results: We analysed 2437 reports corresponding to 4500 ADRs, and 674 of these ADRs reported information about CADRs. One quarter (N = 174) of all CADRs were serious including two fatal cases. More than half of CADRs were reported in children less than two years of age, and there was an equal distribution of number of reports for the two genders. The majority of CADRs were reported for anti-infectives for systemic use (66% of total CADRs), followed by nervous system medications (16% of total CADRs) and dermatologic agents (10 % of total CADRs). The largest number of reported CADRs was labelled with the term 'rash'. Serious cases such as erythema/erythema multiforme and urticaria were reported.

Conclusions: One-fifth of all ADRs reported over a decade were cutaneous, and one-third of them serious.

Prescribers should be aware of the risk of the occurrence of dermatological ADRs in children from medications for systemic use as well as dermatological agents.

Cutaneous adverse drug reactions (CADRs) are the most common type of adverse drug reactions (ADRs) reported in the paediatric population, and CADRs may lead to frequent clinical visits or discontinuation of therapy.¹⁻² Analysis of ADR reports submitted to the WHO ADR Vigibase showed that CADRs were recorded in 35% of all ADR reports for children, and the majority of reactions were reported for anti-infectives for systemic use, nervous system medications and dermatological agents.³ Analysis of spontaneous reports submitted in Italy showed that 45% of all reported ADRs were cutaneous and the majority associated with use of antimicrobials and analgesics.⁴ Reports submitted in Canada from 2005 to 2008 showed that CADRs constituted 16% of all ADRs reported in children, 66% of them serious, and the majority reported for antimicrobials and antiepileptics.⁵ However, more studies on CADRs are needed as medicine use patterns vary across countries and knowledge of CADRs in children is scarce.

Databases have been established to characterize the epidemiology of CADRs, i.e. the European Registry of Severe Cutaneous ADRs to drugs and biological samples (RegiSCAR).⁶ National ADR databases store data on ADRs reported for medicines after marketing, which makes them obvious sources for conducting such analyses.¹ A previous study showed that CADRs constituted approximately 20% of all ADRs in Danish children from the ages of 0 to 17 reported to the Danish National Board of Health (NBH) from 1998 to 2007.⁷ The objective of the present study was to characterise these ADRs with respect to type and seriousness, suspected medications and age and gender of the children. We included ADRs involving the system organ class “skin and subcutaneous disorders”, cf. the MedDRA terminology.⁸ Suspected medicines were classified according to the Anatomical Therapeutic Chemical [ATC] classification system.⁹ The unit of analysis was one ADR. ADR reports were assessed by staff at the Danish NBH and categorised in the ADR database by degree of seriousness and type of ADR. Seriousness of reported ADRs was classified according to international criteria.¹⁰ ADRs were classified serious if they lead to death, were life-threatening, required hospitalisation or prolongation of existing hospitalisation, resulting in persistent or significant disability/incapacity, a congenital anomaly/birth defect and other medically important conditions.¹⁰

Data were placed at the disposal of this study in anonymous form with encrypted personal identification. We included 2437 reports corresponding to 4500 ADRs and 15% of these ADRs were cutaneous. Twenty-five percent of CADRs were serious, including two fatal cases: *toxic epidermal necrolysis* reported for gefitinib (Iressa®) in a 15-year-old boy and *vasculitis purpura* reported for valproic acid (Deprakine®) and lamotrigine (Lamictal®) in a one-year-old boy. The majority of CADRs (56% of all ADRs) was reported in children below 2 years of age, however the

largest share of serious CADR_s (range 40 to 50%) was reported in 14- to 17-year-olds. Half of ADR_s were reported in boys, with the gender distribution varying by age group. More CADR_s were reported for girls than boys in the youngest age groups (below age three) and the oldest (ages 16 to 17). Table 1 displays the distribution of CADR_s by therapeutic group and seriousness. Two third of CADR_s were reported for anti-infectives for systemic use, particularly vaccines followed by nervous system medications (16% of total) and allergens (5% of total). Physicians were responsible for more than 90% of the ADR reports. For vaccines the majority of ADR_s was labelled with the term “rash”, but also many serious cases of erythema and urticaria were reported. The reporting patterns for CADR_s in Danish children were in line with international studies with respect to number and seriousness of ADR_s, age group and suspected medications.³⁻⁵ The number of CADR_s reported for anti-infectives and analgesics in Denmark was relatively low compared to other countries, and we have no explanation of this.³⁻⁵ The strength of our study is that the material consisted of all reported ADR_s in one country over a decade. The study design and results are based on spontaneous reports. A major limitation is that we do not know the causality of these CADR_s, and this should be borne in mind when interpreting the data. Additionally many CADR_s occurring in children might not be drug related but caused by skin manifestations of the underlying infection.¹¹ Further, a recent study has shown that clinical assessments often overestimate the role of drug allergies in CADR_s.¹²

Our purpose was to analyse information on CADR_s in children reported to a national database, not to calculate the incidence of CADR_s in the paediatric population. Such calculations are not feasible in material based on spontaneous reports, as the system does not monitor individual patients and is dependent on the willingness to report.¹³ Despite the limitations of this study, we believe that it adds to the knowledge base about the occurrence and characteristics of CADR_s from medicine use in children. Prescribers should be aware of the risk of the occurrence of dermatological ADR_s in children from medications for systemic use as well as dermatological agents.

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Conflict of interest statement

We have no conflicts of interest to declare.

Contributors

L Aagaard and EH Hansen designed the study, analysed the data and wrote the first version of the manuscript. L Aagaard did the sampling. Both authors saw and approved the final version of the manuscript.

Ethical approval

According to Danish law, no ethical approval is required for this register study with encrypted person information.

References

1. Aagaard L, Christensen A, Hansen EH. Information about adverse drug reactions reported in children: a qualitative review of empirical studies. *Br J Clin Pharmacol* 2010;**70**:481-91.
2. Segal AR, Doherty KM, Leggott J, Zlotof B. Cutaneous reactions to drugs in children. *Pediatrics* 2007;**120**:e1082-e96.
3. Star K, Noren NG, Edwards IR. Suspected adverse drug reactions reported for children worldwide: an exploratory study using VigiBase. *Drug Saf* 2011;**34**:415-28.
4. Naldi L, Conforti A, Venegoni M, Troncon MG, Caputi A, Ghiotto E, Cocci A, Moretti U, Velo G, Leone R. Cutaneous reactions to drugs. An analysis of spontaneous reports in four Italian regions. *Br J Clin Pharmacol* 1999;**48**:839-46.
5. Castro-Pastrana LI, Ghannadan R, Rieder MJ, Dahlke E, Hayden M, Carleton B. Cutaneous adverse drug reactions in children: an analysis of reports from the Canadian Pharmacogenomics Network for Drug Safety (CPNDS). *J Popul Ther Clin Pharmacol*. 2011;**18**:e106-e20.
6. Sekula P, Liss Y, Davidovici B, Dunant A, Roujeau JC, Kardaun S, Naldi L, Schumacher M, Mockenhaupt M. Evaluation of SCORTEN on a cohort of patients with Stevens-Johnson syndrome and toxic epidermal necrolysis included in the RegiSCAR study. *J Burn Care Res* 2011;**32**:237-45.

7. Aagaard L, Weber CB, Hansen EH. Adverse drug reactions in the paediatric population in Denmark: a retrospective analysis of reports made to the Danish Medicines Agency from 1998 to 2007. *Drug Saf* 2010; **33**:327-39.
8. MedDRA – the Medical Dictionary for Regulatory Activities; the MSSO-Maintenance and Support Services Organization [online]. Available from URL: <http://www.meddramsso.com/> [Password required]
9. WHO Collaborating Centre for Drug Statistics Methodology. ATC classification index with DDDs, 2008. Oslo: WHO Collaborating Centre for Drug Statistics Methodology, 2011.
10. Volume 9 Pharmacovigilance: Medicinal products for human use and veterinary products: Available at: (<http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/homev9.htm>) [Accessed November 30, 2011].
11. Gomes RE, Fonseca J, Araujo L, Demoly P. Drug allergy claims in children: from self-reporting to confirmed diagnosis. *Clin Exp Allergy* 2008;**38**:191-8.
12. Heinzerling LM, Tomsitz D, Anliker MD. Is drug allergy less prevalent than previously assumed? A 5-year analysis. *Br J Dermatol* 2012;**166**:107-14.
13. Lopez-Gonzalez E, Herdeiro MT, Figueiras A. Determinants of under-reporting of adverse drug reactions: a systematic review. *Drug Saf* 2009;**32**:19-31.

Table 1: Cutaneous adverse drug reactions (CADRs) by therapeutic group (number of serious ADRs in parentheses)

Medicine (s) (ATC level 1, 2 and 5)	Adverse drug reaction (s)	N
Anti-infectives for systemic use (J) – Total		449(101)
Amoxicillin, azithromycin, dicloxacillin, erythromycin, lymecycline, flucloxacillin (J01), sulfamethoxazole, trimethoprim, fluconazole (J02), acyclovir (J05)	Angioedema	2
	Erythema/Erythema multiforme	2(1)
	Lichen planus	1
	Rash	16(3)
	Urticaria	6(2)
	Rash	2
	Urticaria	2(2)
Human immunoglobulin (J06)/Vaccines (J07): Chicken pox, diphtheria, encephalitis, haemophilus influenza, hepatitis A, hepatitis B, human papilloma virus, meningitis, rabies, tetanus, pertussis, polio, pneumococcal bacteria)	Angioedema	12(3)
	Erythema/Erythema multiforme	28(6)
	Livedo reticularis	1
	Petechiae	3(1)
	Rash	308(72)
	Scab	1(1)
	Urticaria	114(21)
Nervous system (N) – Total		106(35)
Articaine, fentanyl, lidocaine, mepivacaine, nitrous oxide, prilocain, propofol, remifentanyl, sevoflurane (N01)	Angioedema	3(1)
	Erythema	1
	Rash	14(1)
	Urticaria	6
Paracetamol, paracetamol/codeine, morphine (N02)	Rash	4(2)
	Toxic epidermal necrolysis	1(1)
	Urticaria	3
Carbamazepine, ethosuximide, lamotrigine, levetiracetam, oxcarbazepine, valproic acid, vigabatrine (N03)	Alopecia	3(2)
	Angioedema	1(1)
	Erythema multiforme	1(1)
	Rash	20(10)
	Stevens-Johnson syndrome	5(4)
	Urticaria	10(5)
Chloralhydrate, midazolam, olanzapine, risperidone, sulpiride (N05)	Angioedema	2(1)
	Rash	8(1)
Atomoxetine, citalopram, methylphenidate, paroxetine, sertraline (N06)	Alopecia	3
	Erythema/Erythema multiforme	4(2)
	Hyperhidrosis	2(1)
	Petechiae	1(1)
	Rash	10(1)
	Urticaria	4
Various (V) – Total		36(14)
Allergens (grass pollen, house dust, betula verrucosa pendula flowers, animals) (V01)	Angioedema	1(1)
	Erythema	1
	Rash	10(6)
	Urticaria	20(8)
Tuberculin (V04)/barium sulphate with suspending agent (V08)	Urticaria	4
Dermatological (D) – Total		14(2)
Terbinafine (D01)/fusidic acid (D06), tea tree oil (D07)	Erythema multiforme	1(1)
	Rash	4

Benzoyl peroxide, clindamycin, isotretionin (D10)	Erythema	2
	Angioedema	2
Verucid, minoxidil (D11)	Rash	5(1)
Respiratory system (R) - Total		14(2)
Salbutamol, terbutaline, formoterol, salmeterol, budesonide, terbutaline, montelukast (R03)	Alopecia areata	1
	Periorbital oedema	1
	Rash	4(2)
	Urticaria	5
Acetylcysteine/cetirizine, fexofenadine (R05/R06)	Urticaria	3
Antiparasitic (P) – Total		13(6)
Metronidazole, atavaquone, proguanil, mefloquine (P01)	Alopecia	1(1)
	Erythema	2(2)
	Petechiae	1(1)
	Rash	4(2)
	Urticaria	1
Mebendazol (P02), Malathion (P03)	Rash	4
Genitourinary system and sex hormones (G) – Total		12(5)
Oral contraceptives (G03)	Erythema nodosum	1(1)
	Rash	8(2)
	Urticaria	3(2)
Antineoplastic and immunomodulating agents (L) - Total		9(3)
Irinotecan (L01)	Nail disorder	1
	Toxic epidermal necrolysis	1(1)
Leuproprolin (L02)	Erythema	1
	Subcutaneous nodule	1
	Urticaria	1
Infliximab, azathioprine (L04)	Erythema nodosum	1(1)
	Rash	2
	Urticaria	1(1)
Alimentary tract metabolism (A) – Total		6(3)
Sodium fluoride (A01)	Angioedema	1
Mineral salts in combination (A06)	Urticaria	1
Sulfasalazine (A07)	Alopecia	1
Insuline (A10), mercaptamine (A16)	Rash	3(3)
Systemic hormonal preparations (H) – Total		7(3)
Somatropin, desmopressin (H01), tetracosactide, thiamazole (H03)	Rash	4(2)
	Urticaria	2(1)
Methylprednisolone (H02)	Angioedema	1
Sensory organs (S) – Total		4
Ofloxacin, fusidic acid (S01), flumetasone (S02)	Urticaria	3
	Rash	1
Musculoskeletal system (M) – Total		3
Ibuprofen, naproxen, dexibufen (M01)	Erythema nodosum	1
	Urticaria	2
Cardiovascular system (C) – Total		1
Propranolol (C07)	Rash	1
Total cutaneous ADRs, all therapeutic groups		674(174)