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Evidence of harm from off-label or unlicensed medicines in children
EMEA

Executive Summary

This document has been prepared by the EMEA on the basis of limited available evidence, following a request from the European Commission. It focuses on evidence of harm from off label or unlicensed medicines in children from both a review of literature and a search of the EMEA Eudravigilance database.

Very few publications specifically address the issue of off label and/or unlicensed medicines.
Underreporting is the case for paediatric adverse drug reactions (ADR's) as for adults, but may be even more common for unlicensed, off-label medicines. In contrast to spontaneous reporting, prospective monitoring of ADR's indicates higher incidence and in particular shows up to double incidence when including both clinical and laboratory parameters detection.
In a large specific study of children admitted to a paediatric hospital, ADR's were associated with 112 (3.9%) of the 2881 licensed drug prescriptions and 95 (6%) of the 1574 unlicensed or off-label drug prescriptions (35% of all prescriptions). In another large prospective study of community paediatricians, off-label drug use was significantly associated with adverse drug reactions (relative risk 3.44; 95% CI 1.26, 9.38).
The profile of ADR's in children is dominated by anti-infective, anti-asthmatic, and gastrointestinal adverse reactions, which may only reflect the most common diseases observed in children, but central nervous system adverse reactions are equally common. Reporting from various sources provides different profiles of ADR's and for example, parents seem more aware of central nervous system effects. In all cases the publications did not address long-term consequences of medicines' use.
The use of off -label and unlicensed medicines also implies that there were no proper labelling and dosing recommendations. As a consequence, medications errors including dosing errors, more common in children than in adults, should be taken into consideration as additional evidence of harm. This holds true for extemporaneous preparations, which have to be prepared to remedy the lack of appropriate paediatric formulations.

Within the limitations of of spontaneous reporting and a pilot database at EMEA, since December 2001, 820 suspected serious ADR's have been reported in children receiving a medicinal product centrally authorised in an unlabelled use, 130 of these ADR's being reported as fatal.
The seriousness of the concern warrants better scientific evaluation of the use of unlicensed or off label medicines in children and further analysis of the specificity of paediatric ADR's.

In any case, these data show that serious ADR's are indeed reported with off label and unlicensed use and evidence supports the conclusion that to off label and unlicensed use of medicines in children does lead to increased incidence and seriousness of ADR's.

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Introduction

This document has been prepared by the EMEA on the basis of limited available evidence, following the request from the European Commission. It focuses on evidence of harm from off label or unlicensed medicines in children. However by definition this use is outside the legal framework and proper data are lacking.

The report includes in its first part a review of the literature: Medline search using the words: "pharmacovigilance, child, drug, adverse drug reaction, unlicensed, off label" and then selecting the articles of interest. This was confronted with references provided by industry (Aventis Pharma) on this topic, using similar sources [Medline (1995-2004) and Excerpta Medica (1995-2004)]. The second part of the report includes the data obtained by querying the database of adverse drug reactions (ADR's).

Review of literature

Spontaneous reporting

It appears that the reporting rate for unlicensed medicines is lower than for licensed ones. In addition, it is impossible to detect the biases introduced by selective reporting and underreporting and the way this affects the conclusions.

A pilot scheme in the United Kingdom doubled the rate of reporting of paediatric adverse drug reactions (ADR's) by using systematic reminders of targeted prescribers (Clarkson, 2001).

Schirm (2004) published a case control study showing that the proportion of off label prescriptions (outside hospital) was similar for medicines producing ADR's and those not producing ADR's in a general paediatric population.

A Swedish study (Ufer 2004) looked specifically at off-label use of medicines in children (in 2000) through retrospective analysis of spontaneous reporting. 112 patient-linked reports corresponding to 158 ADR's were identified. 31% of ADR's were serious. Antiasthmatic medicines were most frequently suspected as a cause of almost every third adverse reaction. The average proportion of off-label medicines prescribing amounted to 42.4%. It was more frequently associated with serious than non-serious ADR's and mostly due to a non-approved age or dose.

Spontaneous reporting is well known to underestimate the true incidence and severity of adverse drug reactions and provide a biased version of the true safety profile. Despite these biases, there is evidence of harm from off label medicines used in children from spontaneous reporting.

Prospective monitoring of ADR's

Prospective studies do not share reporting biases, but nearly all of the published studies were conducted in hospitalised patients, therefore providing a limited picture of the situation.

- The incidence of adverse drug reactions (ADR's) to unlicensed and off-label drugs used in paediatric inpatients was specifically determined in a prospective surveillance on five different paediatric wards in a United Kingdom regional children's hospital for 13 weeks (Turner 1999). In total, 4455 courses of drugs were administered to 936 patients in 1046 admissions. In 507 (48%) of the 1046 admissions, patients received one or more unlicensed or off-label drugs. ADR's occurred in 116 (11%) of the 1046 patient admissions. ADR's were associated with 112 (3.9%) of

the 2881 licensed drug prescriptions and 95 (6%) of the 1574 unlicensed or off-label drug prescriptions. Gill prospective study (1995) of ADR's in critically ill children showed that one third of ADR's were involved off-label drug use. It can be concluded from these studies that ADR's are a significant problem following unlicensed or off-label drug prescriptions.

- Adverse drug reactions in paediatric outpatients were studied in a prospective pharmacovigilance survey of drug prescribed by office-based paediatricians (Horen 2002). The study involved a sample of 1419 children under 16 years old. Forty-two percent of patients were exposed to at least one off-label prescription. The incidence of adverse drug reactions was 1.41% (95% CI 0.79, 2.11). Off-label drug use was significantly associated with adverse drug reactions (relative risk 3.44; 95% CI 1.26, 9.38), particularly when it was due to a different indication from that defined in the Summary of Product Characteristics (relative risk 4.42; 95% CI 1.60, 12.25).

Even when the following prospective studies do not specify whether off label medicines were used, it has been largely demonstrated that more than half of prescriptions in children are using off label or unlicensed medicines.

- A Norwegian study (Buajordet, 2002) showed that prospective intensive monitoring of adverse drug reactions in children leads to a much higher incidence. In 579 children hospitalised in a paediatric ward, 28% experienced adverse drug events (ADE's); 7% at the time of admission, 18% during hospitalization and 9% after discharge. ADE's occurred in all children treated for cancer, 19% treated with anti-infective medicines, 15% treated with antiasthmatics and 10% treated with medicines affecting the nervous system. The most frequent events were gastrointestinal, central nervous system (CNS) and skin reactions, and 19% were considered as serious.
In this study, most ADE's were found by screening patient records, where physicians mostly described adverse drug events requiring interventions and nurses described less serious events. Parents reported 14% of the events, of which a majority were CNS reactions. A conclusion can be that CNS reactions may be more common than expected and observations by parents are important when investigating such reactions in children.
The same Norwegian study (Buajordet, 2002) showed that ADE's caused 6% of the admissions, 44% required interventions and in 19% the reactions were serious reactions. This study did not make the distinction between off label and licensed medicines.

- A prospective study (González-Martin, 1998) determined the frequency and the characteristics of ADR's in 219 hospitalised pediatric patients, using an intensive and prospective medicines surveillance method. The frequency of ADR's in these patients was 13.7%. According to causality, 54.2% of the ADR's were regarded as probable, and 32.2% as possible. The majority of the ADR's were moderate (51.2%), 27.9% were severe. The length of the stay in the hospital and the total number of medicines given to the patients influenced significantly the frequency of ADR's. Finally, 93% of the ADR's were dose-dependent.

- A study (Weiss-Jutta 2001) was performed to detect ADR's in children in a ward using a computerized monitoring system. An 8-month prospective study was conducted at a 10-bed pediatric isolation ward. Charts were reviewed once weekly by a pharmacoepidemiological team. Clinical signs as well as laboratory changes were documented and assessed. Algorithms were used to assess the probability and severity of each detected event. All 214 patients admitted were enrolled in the study. A total of 68 ADR's were detected in 46 of 214 patients (22%) by the team. Thirty-four ADR's (50%) were detected by the staff physician, and 27 (40%) were detected primarily by analyzing laboratory parameters. Antibiotics-associated ADR's (50%) predominated, followed by glucocorticoids (16%), tuberculostatic (4%), and immunosuppressive

agents (4%). In 5 cases, an ADR was responsible for the prolongation of hospital stay, and in 4 children, the ADR was responsible for hospitalization. The detection rate of ADR's would almost be doubled by a computerized monitoring system analyzing laboratory data.

Underreporting of ADR's is the case for children as for adults but seems more common for unlicensed, off label medicines. Prospective safety monitoring shows up to double incidence when including both clinical and laboratory parameters detection. Reporting from various sources provides different profile of ADR's and parents seem more aware of CNS effects.
The profile of ADR's in children is dominated by anti-infective, anti-asthmatic, and gastrointestinal adverse reactions, which may only reflect the most common diseases observed in children, but CNS adverse reactions are equally common. In the latest studies the drugs most frequently suspected of causing ADR are antibiotics, respiratory medications, and vaccines, which might be partly due to the fact that antibiotics and vaccines are the most widely used drugs in children (Morales-Olivas-F-J, 2000).
In all cases these publications only referred to short term consequences whilts it has been published that long term adverse drug reactions may occur and are even more difficult to measure (see for example, effects of phenobarbital on cognition, Farwell 1990). Sometimes serious ADR's can be discovered much later even after the drug has even received approval (Ladewski LA, 2003).

Evidence for the need for dosing and interaction labelling

In addition to the well-established differences between children and adult metabolism of medicines, the need for clear labelling in respect of dosing and interactions (which is missing in off label medicines) is highlighted by the following studies.

- The FDA (Cote, 2000) requested a case report analysis of ADR's from medicines used in children for sedation. 118 case reports to the Food and Drug Administration, the US Pharmacopoeia, and the results of a survey of pediatric specialists were used. Outcome measures were death, permanent neurologic injury, prolonged hospitalization without injury, and no harm. 95 incidents fulfilled study criteria and all 4 reviewers agreed on causation; 60 resulted in death or permanent neurologic injury. Negative outcomes (death and permanent neurologic injury) were often associated with medicines overdose (n = 28). Some medicines overdoses were attributable to prescription/transcription errors. Negative outcomes were also associated with medicines combinations and interactions. The use of 3 or more sedating medications compared with 1 or 2 medications was strongly associated with adverse outcomes (18/20 vs 7/70). Negative outcomes were also associated with medicines administered by non-medically trained personnel and medicines administered at home. Deaths and injuries after discharge from medical supervision were associated with the use of medications with long half-lives.

- In another study (Cowley 2001) aimed at medication errors, pediatric patients were involved in 333 (9%) of 3818 error records submitted to the MER Program and in 1969 (5%) of 43,287 records submitted to the MedMARx database. In the MER Program, 104 (31%) of the 333 errors were cited as harmful or fatal, and 102 (5%) of the 1969 errors submitted to MedMARx were cited as harmful. Improper dose/quantity was the most frequently reported type of pediatric error among the 337 types of errors identified in the MER Program (157 (47%)); of the 2003 types of errors identified in Med MARx, the most frequently reported types were omission (543 (27%)) and improper dose/quantity (494 (25%)). The products involved most often (eg, intravenous fluids, including both premixed and extemporaneously compounded preparations) were similar in the 2 programs.

The use of off -label and unlicensed medicines implies that there is no proper labelling and dosing recommendations. As a consequence, this leads to medications errors including dosing errors, which are a major concern in children, and should be treated as additional evidence of harm.

Reports from the EMEA Eudravigilance database

Based on reports received in the EudraVigilance System from 1 December 2001 to 29 March 2004, 820 suspected serious adverse drug reactions (ADR's) have been reported worldwide in children receiving a centrally authorised product in an unlabelled use (in the European Union). Among them 130 were reported as fatal and 361 as having either induced a hospitalisation or prolonged it.

It should be noted that these reports concern suspected ADR's and that a definite relationship with the use of the medicinal products has not been established. It should also be emphasized that the numbers provided are underestimates of the real extent of the problem due to the widely recognised spontaneous underreporting of ADR's.

The age of the patients was unavailable for this analysis in a third of the reports (20,803 out of 60,956)[•]. It is probable that some these reports concern children, but this uncertainty largely undermines the accuracy of our estimation that can only be considered as an absolute minimum. No information can be given about the respective frequency of occurrence of ADR's in the paediatric population: although the number of reports for children (820) could seem very low as compared to those received for adults (39,333), since there is no information about the respective numbers of children and adults exposed to the medicinal products during this period, any comparison is meaningless.

The profile of paediatric ADR's differs from the adult one: the congenital anomalies are of course almost exclusively reported in children; in addition, neuro-psychiatric reactions seems more frequently reported in children than in adults (26% vs 14% of all reports).

In conclusion, and within the limitations detailed above, since December 2001, 820 suspected serious ADR's have been reported in children receiving a medicinal product centrally authorised in an unlabelled use, 130 of them being reported as fatal.
The seriousness of the concern justifies better scientific evaluation of the use of medicines in children and further analysis of the specificity of paediatric ADR's. It is possible that a complete scientific evaluation of these unlabelled paediatric indications could prevent some of these reactions (i.e. in avoiding an unappropriate dosage or in detecting earlier some specific ADR's or risk factors). It would at least ensure that, when the paediatric benefit-risk balance is considered favourable, the benefit to be gained by the treatment would justify the risks taken.

The EMEA will continue working on this topic and further refine queries when the database is fully developed.

[•] These data were extracted from a pilot version of the data warehouse in which the age of the patient can only be obtained from one field. In the future version, a more appropriate algorithm taking into account other fields present in the report will be implemented and a more precise estimate could then be provided.

Conclusions

The level of evidence published on the harm from off label and unlicensed medicines use in children is scarce. There is however sufficient evidence that harm actually occurs and is under-reported. This supports measures to improve information on medicines used in children. This also supports setting up prospective monitoring of ADR's in children, including for children in the community, in order to obtain an objective picture of the risks and benefits of paediatric medicines.