Adverse drug reactions in childhood: a review of prospective studies and safety alerts

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CRD summary
This review concluded that adverse drug reactions among children and adolescents were most commonly reported in hospitalised children and those who received unlicensed and off-label drugs. The reliability of these conclusions is unclear given potential for missing data, a lack of any assessment of study quality and poor reporting of review methods.

Authors' objectives
To determine the incidence of adverse drug reactions in children and adolescents. Incidence of safety alerts issued by international drug regulatory agencies was also investigated.

Searching
MEDLINE and EMBASE were searched for studies published between January 2001 and December 2007. Search terms were reported. Reference lists of retrieved studies were examined for further studies. Websites of international drug regulatory agencies were searched for safety alerts from 2001 to 2007 (further details reported in the review).

Study selection
Prospective studies that reported sufficient data to calculate incidence of adverse drug reactions in unselected populations of children and adolescents were eligible for inclusion in the review. Studies were excluded if they assessed adverse drug events defined as "any injury resulting from medical interventions related to a drug", including complications that resulted from medication errors and adverse drug reactions where no error occurred.

Most included studies focused on hospitalised children and adverse drug reactions that resulted in hospital admissions; others included adverse drug reactions during out-patient treatments. Incidence of adverse drug reactions ranged from 1.5% to 19.9% among hospitalised children. Age of children ranged from 0 to 18 years. The most commonly affected systems were the gastrointestinal system and skin. The most common therapeutic classes of interventions were central nervous system drugs and anti-infective agents. A quarter of the studies were conducted in France and a quarter in Germany. Study duration ranged from 0.25 to 11 months; most studies were carried out over a five- or six-month period.

The authors stated neither how papers were selected for review nor how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors stated neither how data were extracted for the review nor how many reviewers performed data extraction. Percentage adverse drug reaction incidences with 95% confidence intervals (CIs) were extracted or calculated according to body system and therapeutic class (such as antibiotics, vaccines, and hormones).

Methods of synthesis
Data were grouped according to type of participants, body system and intervention type (such as drug type). Pooled percentage incidences with 95% CIs were calculated using a random-effects model with studies weighted by sample size.

Results of the review
Eight prospective studies (n=at least 6,756) were included in the review. Pooled incidence of adverse drug reactions was 10.9% (95% CI 4.8 to 17.0; six studies) for hospitalised children, 1.8% (95% CI 0.4 to 3.2; four studies) for adverse drug reactions that led to hospitalisation and 1.0% (95% CI 0.3 to 1.7; two
studies) for out-patient children. Rate of hospitalisation due to adverse drug reactions ranged between 0.6% to 6% and incidence in out-patient children ranged from 0.7% and 11%. Of the five studies that reported severity of adverse drug reactions, two reported no severe reactions and three included between 2% and 30% of severe adverse drug reactions. Risk of adverse drug reactions was 3.6 times higher in those children who received off-label drugs in hospital and double in children under out-patient care. Three studies reported the specific intervention associated with adverse drug reactions. The drugs most commonly associated with adverse drug reactions were oxacillin, vancomycin and amoxiclavulanic acid.

Authors’ conclusions
Drug reactions in children and adolescents adverse were most commonly reported in hospitalised children and those who received unlicensed and off-label drugs. The most commonly involved organ systems were the skin and gastrointestinal system. The most commonly associated drugs were antibiotics.

CRD commentary
The review answered a clear review question using broad criteria for study design, intervention and population. A limited number of resources were searched for studies over a period of only six years; therefore, some relevant data may have been missed. It appeared that no language restrictions were used, which minimised the risk of language bias. Some unpublished data may have been missed. The risk of reviewer error and bias was unclear as the authors did not report their methods. The reliability of the data was also unclear as the authors did not assess methodological quality of the included studies. Study data were grouped to take into account some differences in the study populations and interventions. However, the reliability of the authors’ conclusions is unclear given the potential for missing data, lack of any assessment of study quality and poor reporting of review methods.

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Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that further research in the form of prospective multinational studies was required to investigate incidence of adverse drug reactions. Further initiatives aimed at updating knowledge through clinical trials were required.

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