Incidence of adverse drug reactions in paediatric in/out-patients: a systematic review and meta-analysis of prospective studies

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Authors' objectives
To explore the usefulness of data derived from observational studies on adverse drug reactions, in defining and preventing the risk of pharmacological interventions in children in different health care settings.

Searching
MEDLINE was searched from January 1966 to May 2000, and EMBASE from January 1988 to May 2000. The search terms used were: 'adverse drug reaction reporting system', 'drug therapy/adverse effects' or 'pharmaceutical preparations/adverse effects', and 'child' or 'child-pre-school', and 'prospective studies'. Additional studies were identified by examining the reference lists of the retrieved papers, and of published reviews found by a manual search of various journals. Studies published in any language were considered.

Study selection
Study designs of evaluations included in the review
Prospective studies. No further inclusion criteria were specified.

Specific interventions included in the review
Studies were included if they were of adverse drug reactions (ADRs). The specific drugs investigated were not reported.

Participants included in the review
Hospitalised children, children from out-patient departments, and children admitted to hospital because of an adverse drug reaction. To be included in the review, the study population had to have not been selected on account of particular conditions or drug exposure.

Outcomes assessed in the review
The studies had to report sufficient information to enable the calculation of the incidence of ADRs. Studies in which prospective monitoring was used to identify ADRs were eligible for inclusion. The proportion of children who developed ADRs was the outcome of interest.

How were decisions on the relevance of primary studies made?
All studies that met the defined criteria were included in the review. The authors do not report how many of the reviewers were involved in this process.

Assessment of study quality
The authors state that data were extracted on the quality criteria. However, no further details of the criteria were provided. Two researchers reviewed each study independently using a standard form. Data on the methodology, outcome and quality criteria were extracted.

Data extraction
Data were extracted independently by two researchers using a standard form, which recorded the incidence of ADRs in children. The proportion of children who developed an ADR was also extracted. The classification of the ADR in terms of severity and potential was also taken into account; severe ADRs were defined as those which were fatal or life threatening. Other data extracted included the year of publication, the country in which the study was conducted, and the duration of the data collection period.
Methods of synthesis
How were the studies combined?
A random-effects model was used to pool the incidence of ADRs and the 95% confidence interval (CI).

How were differences between studies investigated?
A meta-regression was performed using the mean number of drugs per child as the covariate, and the incidence of ADR as the outcome variable. The authors noted that this covariate was used as it was the only available data reported in most studies in the hospital setting. Data were pooled separately for hospitalised children, for children admitted to the hospital due to ADRs, and for general paediatric out-patients.

Results of the review
Seventeen prospective studies were included.

The ADR incidence in hospitalised children (9 studies) ranged from 4.4 to 16.8%; the pooled weighted average was 9.5 (95% CI: 6.8, 12.3). The rate of severe ADRs ranged from 7 to 20% among the studies, and the weighted proportion was 12.3% (95% CI: 8.4, 16.2). The meta-regression yielded a between-study variable reduction of 0.52 and a regression coefficient of 0.017. The authors noted that this finding showed that 50% of the variability in ADR might be explained by the different prescription rates in the various studies.

The incidence of ADRs leading to hospital admission (5 studies) ranged from 0.6 to 4.1%; the pooled weighted average was 2.1% (95% CI: 1.0, 3.8). The weighted average of severe drug reactions in this category was 39.3% (95% CI: 30.7, 47.9).

In out-patient children (3 studies) the incidence of ADRs ranged from 0.7 to 2.7%; the pooled weighted average was 1.46% (95% CI: 0.7, 3.0). The study results also showed a linear trend in the ADR in relation to the children's age (from younger to older: chi-squared for linear trend 40.2; p<0.001).

Authors’ conclusions
The authors state that the results showed that ADRS in children were a significant public health issue. There appears to be a lack of complete and accurate reports of prescriptions and clinical information from studies, making it difficult for health practitioners to implement evidence-based preventive strategies. Further methodologically-sound drug surveillance studies are necessary for the effective promotion of safer drug use in children.

CRD commentary
This was a useful review, highlighting an important area. A clear review question was addressed by the stated inclusion criteria. The literature search was relatively comprehensive, although the authors freely acknowledged that they did not address the grey literature due to resource constraints and feasibility. Details were given of some aspects of the review methodology, such as the number of reviewers who extracted the data. Greater detail on the validity assessment would have been useful, since this process is of particular importance in observational studies.

The method of analysis was appropriate for the data available and collected by the researchers. However, no formal test for heterogeneity was performed. The authors state that a random-effects model was used to account for heterogeneity, which was inappropriate; the pooled estimate should therefore be interpreted with caution. The authors acknowledged the limitations of their study. In addition, it was notable that they raised the issue of importance of the contextual nature of the current studies under review, and the difficulty in attempting to generalise from these studies.

The authors’ conclusions appear to follow from the results presented, but should be interpreted with caution given the limitations mentioned.

Implications of the review for practice and research
Practice: This study highlights the need to develop greater awareness of issues such as poly-pharmacy in children, and
the need to incorporate audits of prescription reporting and clinical information in relation to the incidence of ADRs in children. In addition, the authors note that the factors which predispose children to ADRs can be enhanced by age-related differences in physiological function, difference in disease patterns, and smaller size. The authors noted that the findings of the reviewed studies were of children in teaching hospitals, and therefore, cannot be generalised to other populations of children.

Research: Further research studies are required in this area.

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