ADRIC: Adverse Drug Reactions In Children – a programme of research using mixed methods

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Scientific summary

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Scientific summary

Background

Drug safety is an important issue in all medical disciplines but in paediatrics this is compounded by the fact that medicines are often not tested in children, and therefore at the time of licensing there is no indication for use in children. This leads to off-label and/or unlicensed (OLUL) prescribing, estimated to occur in 25% of paediatric inpatient prescriptions. It is clear that extrapolation of efficacy, dosing regimens and adverse drug reactions (ADRs) from adult data to children is inappropriate owing to size differences, developmental changes in physiology and drug handling. Taken together with the fact that the pattern of diseases in children is different from that in adults, this puts them at high risk of serious and unpredictable ADRs. Much of the work to identify and address these problems was led from Liverpool, and this programme of research was conceived to address important gaps in the evidence.

Most studies to date have focused on individual aspects of ADRs, for example ADRs causing hospital admission, ADRs occurring within small, specialised units, etc. However, no previous programme of work has looked at the whole spectrum from when and where ADRs are occurring to developing solutions to reduce the burden of ADRs. Our research planned to focus on this spectrum and the clinical studies were conducted in the largest children's hospital in Europe, with between 12,000 and 13,000 admissions per annum. During the course of the programme, we found that none of the commonly used tools to assess causality and avoidability of ADRs was sufficiently reliable to be used in these studies. This led us to develop and validate new assessment tools (see objectives 4 and 5, below). We also wished to assess the impact of ADRs on families to identify any unmet communication needs. Because of the scale of the communication problems that we identified, the final objective of the programme was to develop strategies to improve communication between clinicians and families about ADRs.

Objectives

1. To determine the incidence of ADRs that were associated with admission to hospital in children; describe their causality, severity, avoidability and nature; and identify which children were particularly at risk of this complication.
2. To determine the incidence of ADRs that occurred in children in hospital; characterise them in terms of type, drug aetiology, causality and severity; and identify risk factors for the occurrence of ADRs in hospitalised children.
3. To conduct a systematic review of observational studies of ADRs in children in three settings: causing admission to hospital; occurring during hospital stay; and occurring in the community. We were particularly interested in understanding how these ADRs might be better detected, assessed and avoided.
4. To develop and validate a new ADR causality assessment tool (CAT) that would be easy to use and reliable.
5. To develop and validate a new ADR avoidability assessment tool (AAT) that would be generalisable and applicable to a variety of settings.
6. To identify any unmet information and communication needs described by families following a suspected ADR in a child.
7. To develop a strategy to support communication between families and clinicians by identifying any barriers to effective communication with families from the perspective of clinicians following a suspected ADR, and to develop information leaflets about ADRs for parents, children and young people to support their communication with clinicians.

Methods

All clinical studies were conducted in Alder Hey Children's NHS Foundation Trust (Alder Hey), a large children's hospital, with an accident and emergency department, providing local and specialist regional and national paediatric care in the north-west of England. Participants were aged between 0 and 16 years 11 months. Study 1 was a prospective observational study of all acute paediatric admissions, over a 1-year period, of all children who had taken any form of medication during the previous 2 weeks. The outcome measure was a suspected ADR. Study 2 was a prospective cohort study of children admitted over 48 hours; patients were not observed while admitted to the paediatric intensive care unit (PICU), the transitional care unit (TCU), theatre, recovery or the department of radiology. A nested case–control study within the cohort examined the impact of OLUL drug use on ADR risk.

The systematic review was conducted by searching 19 electronic databases using a comprehensive search strategy. The primary outcome was any clinical event described as an ADR to one or more drugs. Additional information relating to the ADR was collected: associated drug classification; clinical presentation; associated risk factors; methods used for assessing causality, severity and avoidability.

A new ADR CAT, the Liverpool Causality Assessment Tool (LCAT), and a new AAT were developed by the 'Adverse Drug Reactions In Children' (ADRIC) programme group to address the limitations of the widely used Naranjo CAT and the Hallas scale, respectively. The LCAT was compared with the Naranjo CAT in 80 cases from a prospective observational study and 37 published ADR case reports (819 causality assessments in total). The AAT development occurred in two phases: first defining the tool, modifying the tool and refining the tool, by a multidisciplinary team, and, second, the independent assessment of 50 ADR cases from study 2 by six different reviewers and a comparison of the results. Following the completion of phase 2, it was decided that further testing was needed and that perhaps the best way to assess avoidability is in a group setting. Agreement in phase 2 ranged from poor to good; possible reasons for this may be attributable to lack of experience in certain specialty areas or a possible training effect. The next step in the development process will be to carry out group assessments of additional cases and look for an improvement in the results. For both CAT and AAT, we assessed utilisation of categories, measure of disagreements and inter-rater reliability (IRR).

We conducted semistructured qualitative interviews with 20 children and young people, and the parents of 44 children and young people who had experienced a suspected ADR. Interviews were conducted face to face or by telephone; most were audio-recorded and transcribed. To develop a communication strategy about ADRs between clinicians and families, we conducted semistructured qualitative interviews with 42 clinicians about their experiences of ADRs in children. Face-to-face interviews were audio-recorded and transcribed. The parental leaflet on ADRs was developed based on feedback from a range of stakeholders, including parents and clinicians. The usefulness of the leaflet was further examined by conducting structured interviews with 17 clinicians after they had used the leaflet during routine parent–clinician discussions about suspected ADRs. Analysis of these parts of the programme was informed by the principles of the constant comparative method.

Findings

In study 1, 240 out of 8345 admissions in 178 out of 6821 patients admitted acutely to a paediatric hospital were thought to be related to an ADR, giving an estimated incidence of 2.9% [95% confidence interval (CI) 2.5% to 3.3%], with the reaction directly causing, or contributing to the cause of, admission in 97.1% of cases. No deaths were attributable to an ADR. Of the reactions, 22.1% (95% CI 17% to 28%) were either definitely or possibly avoidable. Prescriptions originating in the community accounted for 44 out of 249 (17.7%) ADRs, the remainder originating from hospital. Of 16,551 prescription medicine courses, 11,511 (69.5%) were authorised, 4080 (24.7%) were off-label and 960 (5.8%) were unlicensed. Treatment for malignancies resulted in 120 out of 249 (48.2%) reactions. The drugs most commonly implicated in

causing admissions were cytotoxic agents, corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), vaccines and immunosuppressant drugs. OLUL medicines were more likely to be implicated in an ADR than authorised medicines [relative risk (RR) 1.67, 95% CI 1.38 to 2.02; $p < 0.001$]. When medicines used to treat oncology patients were excluded, OLUL medicines were not more likely to be implicated in an ADR than authorised medicines (RR 1.03, 95% CI 0.72 to 1.48; $p = 0.830$). The most common reactions were neutropenia, immunosuppression and thrombocytopenia.

In study 2, over the 1-year period, 5118 children were admitted to hospital for > 48 hours. Of all children, 17.7% experienced at least one ADR. Opiate analgesic drugs and drugs used in general anaesthesia (GA) accounted for > 50% of all drugs implicated in ADRs. A total of 0.9% of ADRs caused permanent harm or required admission to a higher level of care. The hazard of an ADR for children after GA is more than six times that in children who had not received a GA [hazard ratio (HR) 6.38, 95% CI 5.30 to 7.68]. Other factors increasing the risk of an ADR were increasing age (HR 1.06 for each year, 95% CI 1.04 to 1.07), increasing number of drugs (HR 1.25 for each additional drug, 95% CI 1.22 to 1.28) and oncological treatment (HR 1.89, 95% CI 1.36 to 2.63). Our nested case–control study included 1388 patients. The odds ratio of an OLUL drug being implicated in an ADR compared with an authorised drug was 2.25 (95% CI 1.95 to 2.59; $p < 0.001$). Risk factors identified were exposure to a GA, age, oncology treatment and number of medicines.

One hundred and two studies were included in the systematic review. Seventy-one per cent (72/102) of studies assessed causality and 33% (34/102) performed a severity assessment. Only 19 studies (19%) assessed avoidability. Incidence rates for ADRs causing hospital admission ranged from 0.4% to 10.3% of all children [pooled estimate of 2.9% (95% CI 2.6% to 3.1%)] and from 0.6% to 16.8% of all children exposed to a drug during hospital stay. Anti-infective drugs and antiepileptic drugs were the most frequently reported therapeutic class associated with ADRs in children admitted to hospital (17 studies and 12 studies, respectively) and children in hospital (24 studies and 14 studies, respectively), whereas anti-infective drugs and NSAIDs were frequently reported as associated with ADRs in outpatient children (13 studies and 6 studies, respectively). Fourteen studies reported rates ranging from 7% to 98% of ADRs being either definitely or possibly avoidable.

The LCAT, using 40 cases from an observational study, showed causality categories of 1 unlikely, 62 possible, 92 probable and 125 definite (1, 62, 92, 125) and 'moderate' IRR [kappa (κ) = 0.48] compared with Naranjo (0, 100, 172, 8) with 'moderate' IRR ($\kappa = 0.45$). In a further 40 cases, the LCAT (0, 66, 81, 133) showed 'good' IRR ($\kappa = 0.6$), whereas Naranjo (1, 90, 185, 4) remained 'moderate'.

In the qualitative study to assess the impact on families of their children experiencing an ADR, many parents described being dissatisfied with clinicians' communication about ADRs. In contrast, the accounts of parents of children with cancer emphasised confidence in clinicians' management of ADRs and the way clinicians communicated about medicines. The accounts of children and young people largely reflected parents' accounts. Families were positive about the Yellow Card Scheme and felt recording and reporting ADRs was important. Parents, children and young people linked symptoms to medicines using a similar reasoning as clinicians use to evaluate the possibility of an ADR.

Clinicians reported all of the features of communication about ADRs that parents wanted to see. However, clinicians made active decisions about when and what to communicate to families about suspected ADRs. These decisions mean that communication may not always match families' needs and expectations. Clinicians describe a number of complexities with effective communication, some of which are unique to paediatric settings. The complexities perceived by clinicians may explain, at least in part, the discordance between clinician and family perspectives. Clinicians found the leaflet useful in supporting discussions with parents about a suspected ADR in their child.

Conclusions

1. ADRs in children are an important public health problem. Most of those serious enough to require hospital admission are due to hospital-based prescribing, of which just over one-fifth may be avoidable.
2. ADRs are as common in hospitalised children as in hospitalised adults. A concerning aspect of our findings was that GA agents and opiate analgesic drugs were the most important causes. OLUL drugs are more likely to be implicated in an ADR than authorised drugs. It is important to develop strategies to reduce the burden of ADRs occurring in hospitalised children and these areas merit particular attention.
3. Our systematic review found that although there is extensive literature that investigates ADRs in children, studies are heterogeneous and generally not well reported. Further work is needed to address how ADRs in children may be prevented.
4. The LCAT assigns the full range of causality categories and shows good IRR. Further assessment by different investigators in different settings is needed to fully assess the utility of this tool.
5. The Liverpool ADR AAT showed mixed IRR in the individual assessment phase therefore further testing in a group setting is required to develop and validate the tool.
6. Most parents felt clinicians' communication about ADRs was poor, suggesting that improvements are needed. The accounts of parents of children with cancer indicate that prospective explanation about ADRs can be effective. Convergence between parents and clinicians in their reasoning for linking children's symptoms to medicines could be a starting point for improved communication.
7. The parent leaflet was useful in supporting discussions between parents and clinicians about suspected ADRs. Further strategies to improve communication between families and clinicians should focus on aligning clinicians' decision-making about what and when to communicate with the priorities of families following a suspected ADR.

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