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Frequency and Preventability of Adverse Drug Reactions in Paediatric Patients

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Abstract

Purpose: To evaluate the frequency, severity and preventability of adverse drug reactions (ADRs) in paediatric patients during the 6-year period from 1 January 1994 to 31 December 1999.

Methods: Data on patient demographics, documented allergies, suspected drug, American Hospital Formulary Service drug classification and dosage regimen were collected retrospectively from ADRs reported to a hospital surveillance programme. ADRs were categorised by severity, preventability and causality. Analysis was conducted by Chi-square and Wilcoxon rank sum (Mann-Whitney) tests.

Results: During the 6-year period, 565 ADRs were reported at a rate of 0.85 ADRs per 100 admissions. The mean patient age was 9.6 years. No history of allergies was documented in 87.4% of the cases, although 2.8% of patients had a documented allergy to the suspected medication. Opioids (narcotics) [n = 65, 11.5%], anticonvulsants (n = 67, 11.9%) and antibiotics (n = 149, 26.4%) were the most frequently implicated drug classes. Over 50% of the reported ADRs resulted in treatment intervention and/or temporary patient harm and of these, 73% required drug therapy. Causality was classified as 'definite' (44.1%), 'probable' (49.9%) or 'possible' (6.0%). Of the reported ADRs, 20.7% were preventable.

Conclusions: ADRs resulted in treatment intervention or temporary patient discomfort in >50% of patients. The incidence of preventable ADRs is similar to that found in adult literature. No single drug caused >5% of reported ADRs. Opioids, anticonvulsants and antibiotics were the most common drug classes associated with ADRs. Thus, strategies targeting these drug classes and interventions during the medication ordering and administration processes may reduce the number of ADRs and possibly the associated costs. Even though preventable ADRs may not be entirely eliminated, the goal should be to increase ADR awareness and encourage early detection and intervention to minimise patient discomfort.

Background

Adverse drug reactions (ADRs) are events related to a medication that are noxious, unintended and occur at normal doses used in humans for prophylaxis, diagnosis or therapy, or through inadvertent administration of toxic doses. Medical errors, including ADRs, are the eighth leading cause of mor-

bidity and mortality in the US.[1] Unfortunately, estimates of drug-related hospital admissions vary widely from 0.2% to 27.3%.[1,2] Epidemiological studies indicate that adverse drug events may occur in 1.5–35% of hospitalised patients.[3,4] In a study involving 30 000 hospitalised patients, 3.7% had a documented and clinically important adverse medical event of which 19% involved an ADR.[5] The true incidence of ADRs is controversial; however, extrapolated data indicate that up to 180 000 deaths and over one million injuries occur annually as a result of ADRs.[4,6]

The cost to society due to these ADRs has been estimated to be in the range of $US76–177 billion each year among adults.[2,7] Costs to treat other diseases such as obesity ($US45.8 billion), all diabetes-related care ($US45.2 billion) and cardiovascular disease ($US117–154 billion) are far less than the costs associated with ADRs.[2,4] Public attention has recently been heightened due to the Institute of Medicine's priority to identify and prevent ADRs. In 1999, the Committee on the Quality of Health Care in America issued its recommendations to Congress to reduce the number of adverse events in medicine.[8] Their goal was to reduce errors in medicine by 50% in 5 years. To do so, they recommended that Congress create a Center for Patient Safety within the Agency for Health Care Policy and Research to set national goals for patient safety, track progress in meeting these goals and develop knowledge and understanding of errors through an intensive research programme. They also recommended voluntary reporting of ADRs based on a non-punitive system and a greater focus by health organisations and professionals on patient safety. In addition, they recommended implementation of systems that address areas where errors occur. The impact of their recommendations was realised with the passage of a US Senate Bill requiring pharmaceutical companies to provide ADR information to consumers and with the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) requiring hospitals to report all adverse drug events resulting in death.[9] These measures were implemented in an attempt to resolve the serious consequences of this medical challenge.

Although substantial research has been conducted in adult patients, little has been done in the paediatric population in the US with regard to the incidence of ADRs, drugs most frequently associated with ADRs, preventability of ADRs and the incremental hospital costs in patients who experience ADRs versus those who do not.[10] We hypothesised the following regarding ADRs in our paediatric population: (i) ADRs occur at a significant rate in paediatric patients and the rate is similar to that found in the adult population; (ii) ADRs are associated with an increased length of stay and thus higher costs; and (iii) many ADRs are preventable. The objectives for this study were to: (i) evaluate the incidence of reported ADRs at a paediatric hospital; (ii) categorise the ADR by associated drug class; (iii) evaluate the severity of the ADRs; (iv) determine the type of adverse reaction and the body systems affected by the ADR; and (v) assess the preventability of ADRs in paediatric patients. This study was approved by the Human Subjects Committee at the Children's Hospital, Columbus, Ohio, USA.

Methods

This retrospective study was conducted using data from a 313-bed paediatric, tertiary care hospital in the Midwest US collected over a 6-year period from 1 January 1994 until 31 December 1999. For the purpose of this study, an ADR was defined as any event related to a medication that was noxious, unintended and occurred at doses used in humans for prophylaxis, diagnosis or therapy, or through inadvertent administration of toxic doses. ADR detection and reporting is part of standard hospital operation and reporting procedures that are consistent across the organisation. ADRs were identified through the following mechanisms: (i) a written voluntary ADR report from a health professional; (ii) a report from the medical records department upon discharge coding; (iii) communication from the quality improvement staff including physicians, nurses, and pharmacists; and (iv) daily review of medication ordered and dispensed by the hospital pharmacy. Data from ADRs reported by more than one health professional were combined, improving reporting of the events. Medication orders involving drugs with a narrow therapeutic index or commonly used to treat patients with an ADR were screened for possible ADRs. Therefore, all medication orders for

digoxin, antihistamines, ciclosporin, epinephrine (adrenaline) auto-injector, corticosteroids (injectable and topical), atropine, benzatropine, dextrose 50%, naloxone, phenytoin (stat doses only), phytomenadione (phytonadione, vitamin K), protamine sulfate, flumazenil and digoxin immune Fab were reviewed.

After potential ADR cases were identified, medical records were reviewed and persons directly involved with the care of the patient at the time of the ADR were then interviewed to determine if an ADR had occurred. Demographic data including age, gender, race and method of hospital payment were documented. Dates of admission, discharge and the date when an ADR was first observed were collected. In addition, the primary physician, the location of the patient and the medical team caring for the patient at the time of the ADR were documented. The medications taken prior to hospital admission, documented allergies, number of concurrent medications and the number of co-morbidities at the time of the ADR were recorded. The suspected drug involved, American Hospital Formulary Service classification,[11] dose, frequency, route, rate and duration of administration prior to the occurrence of an ADR were noted. The times when the suspected medication was last administered prior to the ADR and when it was discontinued were also documented.

To determine the crude incidence of ADRs at this institution, hospital admission census data were collected from 1 January 1994 until 31 December 1999. The crude incidence was calculated by dividing the number of ADRs by the total number of hospital admissions during the study period. The incidence was calculated per 100 hospital admissions detected by the ADR monitoring process of the hospital. National ADR rates were obtained by multiplying our rate of ADRs by the national number of admissions to paediatric acute care hospitals during the study period.[12-17] In order to estimate a national incidence in paediatric hospitals, it was assumed that patients across the nation received similar levels of care and paediatric hospitals had similar patient populations.

Drug treatment (drug, dose, route, frequency and duration) was documented for each medication given to the patient to alleviate the signs and symptoms associated with the adverse event. Any tests or procedures performed to evaluate or treat the patient due to the ADR, such as laboratory tests, ECG monitoring and radiological studies were also recorded. Many ADRs resulted in clinic visits, admission to the emergency department (ED), intensive care unit (ICU) or hospital. If a patient was admitted to the ICU due to an ADR, only those days attributable to the ADR were considered in calculating the length of stay in the ICU related to an ADR.

Two independent reviewers (study authors with at least 4 years of experience in the field after postdoctoral training) classified ADRs according to probability, severity, reaction class and body system(s) most affected. The probability that an ADR had occurred was based on the scoring system of Naranjo et al.[18] Based on this system, an ADR was classified as 'definite', 'probable', 'possible', or 'unlikely'. Categories of ADR severity were based on the level of care required by the patient with an ADR. These severity categories included: (i) increased patient monitoring, no patient harm; (ii) treatment intervention, temporary patient harm; (iii) initial/prolonged hospitalisation, temporary patient harm; (iv) permanent patient harm; (v) near patient death (including anaphylaxis, cardiac or respiratory arrest); and (vi) patient death. Adverse drug reaction classifications included: (i) drug interaction; (ii) exaggeration of effect; (iii) intentional and unintentional overdosage (including prescribing errors); and (iv) unexpected effect (including type A and type B hypersensitivity reactions). ADRs classified as overdosage included intentional and unintentional ingestion by patients often resulting in hospital admission. All ADRs were further categorised as preventable or non-preventable ADRs. The body system(s) affected by the ADR included allergic, cardiac, dermatological, endocrine, gastrointestinal, haematological, hepatic, neurological, ophthalmic, renal, reproductive and respiratory. More than one body system could be noted as being affected by an ADR.

Two independent reviewers, blinded to treating physician when reviewing the cases, considered the preventability of ADRs. Preventability of an ADR was based on previously published criteria.[19] An affirmative answer to any of the following questions indicated that the ADR may have been preventable:

- Was the drug involved in the ADR not considered appropriate for the patient's clinical condition based on published guidelines, clinical studies, abstracts, case reports and case series?
- Was the dose, route and frequency of administration not appropriate for the patient's age, weight or disease state, based on published literature (e.g. Pediatric Dosage Handbook, Harriet Lane Handbook)?
- Was required therapeutic drug monitoring or other laboratory test not performed?
- Was there a history of allergy or previous reactions to the drug?
- Was a drug interaction involved in the reaction?
- Was the serum drug concentration above the therapeutic range documented in adults?
- Was poor compliance involved in the reaction?

Statistical Analyses

The Chi-square test was utilised to evaluate differences between categorical variables such as gender and race, and the Wilcoxon rank sum (Mann-Whitney) test was used to determine differences between continuous variables. Kappa tests were utilised to assess the inter-rater reliability between reviewers for the severity, causality, preventability and reaction classification. When too few subjects were available to report a Kappa test, we use the symbol NR. For tests involving ordered categories, association was evaluated with the non-parametric Kendall's tau-b. For all statistical tests, differences were considered significant if the p-value was <0.05.

Results

Incidence data

Between 1 January 1994 and 31 December 1999, 65 864 patients were admitted to the paediatric hospital. A total of 565 ADRs were reported during this period by the ADR reporting system, at a rate of 0.85 ADRs per 100 admissions. Clinical pharmacists reported 69.1%, staff pharmacists 0.9%, pharmacy residents/students 4.6%, nurses 6.9% and physicians 5.3% of the 565 ADRs. Medical records documented 8.0% of the events and other sources reported 5.2% of ADRs. The mean age of the patients was 9.6 years (SD = 7.6 years) [table I]. 230 of the 565 patients (40.7%) were admitted directly to hospital due to an ADR and the geometric mean length of stay for these patients was 2.28 days (95% CI 1.05, 10.7 days).

Most hospitalised patients who experienced an ADR were located in the haematology/oncology, pulmonary or infectious disease units (59.8%). Patients experienced an ADR after a mean of 3.1 days in the hospital (SD = 6.1 days). Eighty-seven percent of patients had no documented drug allergies. However, 2.8% of patients had a documented allergy to the suspected medication. 166 suspected drugs were associated with all ADRs (table II). Morphine was the most common medication associated with an ADR followed by vancomycin, carbamazepine, ceftazidime and phenytoin. In 53.6% of the cases, the causative drug had been administered intravenously.

Severity

The ADRs led to 'increased patient monitoring with no patient harm' in 4.1% of the cases and to 'treatment intervention with temporary patient harm' in 52.9% of the cases (reviewer agreement kappa = 0.737, 0.947, respectively). Adverse drug events caused 'initial/prolonged hospitalisation with temporary patient harm' in 37.5%, 'treatment intervention with permanent patient harm' in 0.7%, 'near death' in 3.7%, and 'death' in 1.1% of the cases (reviewer agreement kappa = 0.917, NR, 0.793, NR, respectively).

Causality

Anticonvulsants, opioids (narcotics) and antibiotics were most commonly associated with an ADR and most of the anticonvulsant ADRs were considered 'definite' ADRs (table III). The probability that an ADR had occurred was 'definite' in 44.1% of the reported ADRs; 49.9% were 'probable'; and 6.0% were 'possible' (reviewer agreement kappa = 0.844, 0.816, 0.794, respectively). Most ADRs determined as 'definite' or 'probable' required treatment intervention or prolonged hospital stay.

Table I. Adverse drug reaction reports by age and seriousness of event[a]

Age	Increased monitoring, no patient harm (n = 23) [no. (%)]	Treatment intervention/ temporary harm (n = 299) [no. (%)]	Initial/prolonged hospitalisation (n = 212) [no. (%)]	Permanent patient harm (n = 4) [no. (%)]	Near death (n = 21) [no. (%)]	Death (n = 6) [no. (%)]
0–6mo	1 (4.3)	26 (8.7)	13 (6.1)	0	4 (19.0)	0
>6–12mo	1 (4.3)	12 (4.0)	9 (4.2)	1 (25.0)	1 (4.8)	0
>12–23mo	1 (4.3)	21 (7.0)	12 (5.7)	1 (25.0)	0	1 (16.7)
>23mo–6y	6 (26.1)	48 (16.1)	61 (28.8)	0	3 (14.3)	4 (66.7)
>6–10y	3 (13.0)	45 (15.1)	43 (20.3)	0	3 (14.3)	0
>10–17y	8 (34.8)	91 (30.4)	47 (22.2)	0	6 (28.6)	0
>17y	3 (13.0)	56 (18.7)	27 (12.7)	2 (50.0)	4 (19.0)	1 (16.7)

a Percent may not add up to 100% due to rounding.

mo = months; **y** = years.

Treatment intervention

Treatment intervention involving a medication was required in 72.9% of the ADRs to alleviate signs and/or symptoms of an ADR. The most common route of administration for medications used to treat the ADR was intravenous (55.7%) and oral (42.4%). Intramuscular, rectal, inhalation, topical and subcutaneous routes were also utilised to treat patients experiencing an ADR. Most patients with an ADR required treatment with at least one medication (72.9%) and the most common agents used were histamine H_1 receptor antagonists (antihistamines) [37.8%], followed by electrolyte replacement (6%) and cardiac medications (5%). Eighteen percent of patients with a reported ADR required at least two different medications to treat their symptoms and 4.1% required at least three medications to alleviate their symptoms. In addition, ancillary treatment in the form of laboratory tests was required in 34.5%, noninvasive monitoring (e.g. ECG or radiograph) was required in 7.6%, invasive monitoring (e.g. intubation) in 3.0% and a specialist was consulted in 0.5% of patients experiencing an ADR. No drug treatment or ancillary treatment was required in 54.2% of the patients with ADRs.

Reaction classification

According to reaction class, the ADR was unexpected in 65.0%, involved a drug overdose in 18.2%, and was an exaggerated effect in 15.6% of the ADRs. Only 1.9% of these cases involved a drug interaction. There was no disagreement between judges in evaluating the reaction classifications (reviewer agreement kappa = 1). Body systems most commonly affected included dermatological 33.8%, immune 21.9%, neurological 22.1% and cardiac 12.2%.

Preventability

Overall, there were 117 preventable ADRs (20.7%) and 448 non-preventable ADRs (79.3%) [reviewer agreement kappa = 0.620]. Four (3.4%) preventable ADRs led to increased patient monitoring with no patient harm compared with 19 patients (4.2%) with non-preventable ADRs. Preventable ADRs were associated with increased monitoring and treatment intervention with temporary patient

Table II. Adverse drug reaction reports classified by drug class and seriousness of event[a]

American Hospital Formulary Service drug classification	Increased monitoring, no patient harm (n = 23 [4.1%]) [no. (%)]	Treatment intervention/ temporary harm (n = 299 [52.9%]) [no. (%)]	Initial/prolonged hospitalisation (n = 212 [37.5%]) [no. (%)]	Permanent patient harm (n = 4 [0.7%]) [no. (%)]	Near death (n = 21 [3.7%]) [no. (%)]	Death (n = 6 [1.1%]) [no. (%)]
Analgesic, narcotic	7 (30.4)	51 (17.1)	3 (1.4)	0	4 (19.0)	0
Antiarrhythmic	0	4 (1.3)	4 (1.9)	0	0	1 (16.7)
Antibiotic, aminoglycoside	0	11 (3.7)	1 (0.5)	1 (25.0)	0	0
Antibiotic, cephalosporin	1 (4.3)	33 (11.0)	6 (2.8)	0	3 (14.3)	1 (16.7)
Antibiotic, miscellaneous	0	40 (13.4)	6 (2.8)	0	1 (4.8)	0
Antibiotic, penicillin	0	18 (6.0)	12 (5.7)	1 (25.0)	1 (4.8)	1 (16.7)
Antibiotic, sulfonamide	0	3 (1.0)	9 (4.2)	0	0	0
Anticoagulant	1 (4.3)	1 (0.3)	5 (2.4)	0	0	0
Anticonvulsant	1 (4.3)	10 (3.3)	52 (24.5)	1 (25.0)	1 (4.8)	2 (33.3)
Antidepressant	0	2 (0.7)	7 (3.3)	0	0	0
Antiemetic	0	5 (1.7)	5 (2.4)	0	0	0
Antifungal	0	12 (4.0)	2 (0.9)	0	0	0
Antihypertensive	0	1 (0.3)	7 (3.3)	0	0	0
Antineoplastic	3 (13.0)	19 (6.4)	29 (13.7)	0	0	0
Cardiac glycoside	0	6 (2.0)	3 (1.4)	0	1 (4.8)	0
Corticosteroid	4 (17.3)	14 (4.7)	7 (3.3)	0	1 (4.8)	0
Immune globulin	0	14 (4.7)	4 (1.9)	0	0	0
Respiratory smooth muscle relaxant	2 (8.7)	2 (0.7)	2 (0.9)	0	0	1 (16.7)
Other	4 (17.3)	53 (17.7)	48 (22.6)	1 (25.0)	9 (42.9)	0

a Percent may not add up to 100% due to rounding.

Table III. Adverse drug reactions by drug class and probability

American Hospital Formulary Service drug classification	Definite (n = 249 [44.1%]) [no. (%)]	Probable (n = 282 [49.9%]) [no. (%)]	Possible (n = 34 [6.0%]) [no. (%)]
Analgesic, narcotic	23 (9.2)	39 (13.8)	3 (8.8)
Antiarrhythmic	4 (1.6)	5 (1.8)	0
Antibiotic, aminoglycoside	6 (2.4)	7 (2.5)	0
Antibiotic, cephalosporin	18 (7.2)	25 (8.9)	1 (2.9)
Antibiotic, miscellaneous	21 (8.4)	21 (7.4)	5 (14.7)
Antibiotic, penicillin	14 (5.6)	15 (5.3)	4 (11.8)
Antibiotic, sulfonamide	5 (2.0)	6 (2.1)	1 (2.9)
Anticoagulant	5 (2.0)	1 (0.4)	1 (2.9)
Anticonvulsant	42 (16.9)	23 (8.2)	2 (5.9)
Antidepressant	3 (1.2)	5 (1.8)	1 (2.9)
Antiemetic	3 (1.2)	7 (2.5)	0
Antifungal	4 (1.6)	9 (3.2)	1 (2.9)
Antihypertensive	3 (1.2)	4 (1.4)	1 (2.9)
Antineoplastic	21 (8.4)	27 (9.6)	3 (8.8)
Cardiac glycoside	6 (2.4)	3 (1.1)	1 (2.9)
Corticosteroid	10 (4.0)	14 (5.0)	2 (5.9)
Immune globulin	10 (4.0)	8 (2.8)	0
Respiratory smooth muscle relaxant	4 (1.6)	3 (1.1)	0
Other	47 (18.9)	60 (21.3)	8 (23.5)

harm in 46 patients (39.3%), which was significantly less than the 276 patients (61.6%) requiring increased monitoring or treatment intervention with temporary patient harm in patients with non-preventable ADRs ($p < 0.001$). Hospitalisation or worse occurred in 71 patients (60.7%) with preventable ADRs and 171 patients (38.2%) with non-preventable ADRs ($p < 0.001$). There were no differences between these two groups for patients with permanent harm or death. Anticonvulsants, opioids and antibiotics were the class of medications most commonly associated with a preventable ADR (table IV).

The number of ADRs identified varied between sites: the ED (n = 116), ICU (n = 46), clinic (n = 17) or during initial hospitalisation (n = 211). The remaining 175 ADRs were identified throughout the hospital; haematology/oncology, infectious disease, general paediatrics, cardiology, pulmonology and neurology. Two percent of the preventable ADRs were associated with a clinic visit and were not significantly different from the 3.4% of the patients with non-preventable ADRs. Significantly more patients with preventable ADRs (n = 48, 41.0%) were admitted to the ED compared with patients with non-preventable ADRs (n = 68, 15.2%, $p < 0.001$). Significantly more patients with preventable ADRs (n = 23, 19.7%) were admitted to the ICU compared with patients with non-preventable ADRs (n = 23, 5.1%, $p < 0.001$). Preventable ADR cases were approximately 2.7 times more likely to present in the ED and 3.9 times more likely to present in the ICU than non-preventable cases ($p < 0.001$ and $p < 0.001$, respectively).

Discussion

In this study, we sought to determine the incidence of ADRs per 100 admissions detected by the ADR monitoring process of the hospital. The incidence was 0.85 ADRs per 100 admissions which is much lower than the incidence reported in a matched case control study[20] or an intensive multicentre prospective study.[4] Very few patients only requiring increased monitoring were reported, suggesting that the lower number may be due to underreporting. The variability may be explained by the differences in study design and hospital programmes implemented at the time of these studies. In the case control ADR study, a hospital-wide surveillance programme for detecting and characterising ADRs had been established for 1 year prior to the study.[20] In this hospital, such a system was absent so many ADRs may not have been reported. Many

Table IV. Adverse drug reaction (ADR) by drug class and preventability[a]

American Hospital Formulary Service drug classification	No. of ADRs (n = 565) [no. (%)]	Preventable ADRs (n = 117 [20.7%]) [no. (%)]	Non-preventable ADRs (n = 448 [79.3%]) [no. (%)]
Analgesic, narcotic	65 (11.5)	7 (6.0)	58 (12.9)
Antiarrhythmic	9 (1.6)	3 (2.6)	6 (1.3)
Antibiotic, aminoglycoside	13 (2.3)	8 (6.8)	5 (1.1)
Antibiotic, cephalosporin	44 (7.8)	7 (6.0)	37 (8.3)
Antibiotic, miscellaneous	47 (8.3)	0	47 (10.5)
Antibiotic, penicillin	33 (5.8)	7 (6.0)	26 (5.8)
Antibiotic, sulfonamide	12 (2.1)	1 (0.9)	11 (2.5)
Anticoagulant	7 (1.2)	3 (2.6)	4 (0.9)
Anticonvulsant	67 (11.9)	30 (25.6)	37 (8.3)
Antidepressant	9 (1.6)	2 (1.7)	7 (1.6)
Antiemetic	10 (1.8)	2 (1.7)	8 (1.8)
Antifungal	14 (2.5)	2 (1.7)	12 (2.7)
Antihypertensive	8 (1.4)	2 (1.7)	6 (1.3)
Antineoplastic	51 (9.0)	1 (0.9)	50 (11.1)
Cardiac glycoside	10 (1.8)	5 (4.3)	5 (1.1)
Corticosteroid	26 (4.6)	2 (1.7)	24 (5.4)
Immune globulin	18 (3.2)	0	18 (4.0)
Respiratory smooth muscle relaxant	7 (1.2)	6 (5.1)	1 (0.2)
Other	115 (20.4)	29 (24.8)	86 (19.2)

a Percent may not add up to 100% due to rounding.

ADRs were reported by pharmacists and few by physicians or nurses. Based on this study, the extrapolated national number of ADRs for the 6-year period, based on 1 969 886 paediatric admissions over the study period, was 16 941 ADRs over 6 years or an average of 2824 ADRs per year in paediatric hospitals in the US.[12-17] This extrapolated incidence may be an underestimation, as many ADRs may be unreported.

In our study, a significant number of ADRs were identified in the ED or prior to being seen in our hospital. The number of ADRs identified in the ED or just prior to admission that resulted in hospitalisation was greater than that found in adult patients.[21-23] This may be explained by the unique characteristics associated with the drug therapy in children compared with the adult population. Children are at a greater risk for ADRs due to their inability to evaluate and express clinical responses to medications, lack of clinical trials for medications used in children, lack of paediatric dosage forms and no standard compounding approaches, unique disease states, and reliance on parents or guardians to measure, administer, store and purchase medications.[10] Our incidence was higher than the incidence reported in a paediatric study, which only reviewed ADR admissions.[24]

The data in adults found that 5–60% of the ADR admissions were avoidable.[25] In our study, 20.7% of the ADRs were preventable. In order to decrease ADR-related admissions, development of improved systems from drug selection to administering and monitoring, improving patient compliance, communication between drug prescribers in hospitals and community, communication between community pharmacists and prescribers, and early recognition of therapeutic drug failure by parents should be emphasised. Finally, provision of accurate dosage spoons or marked oral syringes with the exact volume of medication for the parent to administer has been effective in reducing adverse drug events.[26]

The majority of patients experiencing an ADR were located on non-ICUs such as infectious disease and haematology/oncology units and had an ADR after a mean of 3.1 days in the hospital. This is in contrast to results from a prospective study in paediatric patients, which had fewer admissions to the paediatric ICU, but over two-thirds of the ADRs occurred in paediatric ICU patients.[27] This can be explained by the number and complexity of medica-

tions received, which is greater than in other units. Our results may not agree with those found in their study due to differences in scope and identification of ADRs in the two studies.

A large number of medications were implicated to cause ADRs in this study. However, opioids, antibiotics and anticonvulsants were the most problematic. Because the probability of an ADR was rated 'definite' in a high percentage of each of these medication classes, systems to target these drugs to reduce the number of ADRs need to be developed. This premise is supported by results from the multicentre Pediatric Pharmacy Advocacy Group (PPAG) study in which antibiotics, opioids, anticonvulsants and antineoplastics were the most common causes of ADRs in paediatric patients.[10] Additionally, the resultant severity of the ADRs and the association with certain drug classes support the development of a monitoring system to target high-risk medications. In our study, over 50% of those requiring initial/prolonged hospitalisation and over 60% of those requiring treatment were receiving opioid analgesics, antibiotics or anticonvulsants. The greater use of antibiotics, opioids and anticonvulsants may also contribute to the greater frequencies of adverse events noted.

The classification of causality of ADRs in our study was similar to those in a computerised surveillance study of ADRs in adults.[21] Both studies utilised Naranjo scoring criteria to determine causality. Our causality estimates differed substantially from those found in the PPAG study,[10] which did not utilise the Naranjo scoring system to determine causality, but instead used a modified version of Karch's criteria, which is less stringent and thus may have under-reported 'definite' and 'probable' ADRs.[28] Patients in our study were more likely to require prolonged hospitalisation if an ADR was classed as 'definite'.

Our preventable ADRs rate (20.7%) was lower than that found in a prospective multicenter ADR study in adults (28%) and was consistent with the prospective study of medication errors and ADRs in paediatric inpatients (19%).[29] However, our rate was significantly greater than that in the PPAG study, which found only 8% of reported ADRs preventable.[10] It should be noted that their method used to define preventable ADRs was not reported and the study intent was to review ADRs. In addition, 42% of ADRs in their study were characterised as unknown with regard to preventability suggesting that no defined criteria were utilised to determine preventability. Through implementation of strategies to reduce these errors, costs related to ADRs may be reduced and patient care improved in the future. Our data are in agreement with both paediatric and adult studies and will provide necessary information to make system changes and possibly decrease the number of ADRs.[24,30,31]

The available data support considering implementation of computer based prescribing systems.[4-6,21,24,32-36] In a two-phase study, computerised order entry was evaluated for efficacy in preventing serious ADRs.[35] In the first phase, standard order entry was used and the incidence of ADRs was followed for 6 months. In the second phase, computerised physician order entry and a system including distribution of a recommended dilution chart, standardised labels, and a pharmacist rounding with the medical team were implemented for a 9-month period. The incidence of ADRs and preventable ADRs was compared between the two phases. The rate of non-intercepted ADRs fell by 55% and preventable ADRs by 17% in the second phase compared with the first phase. Using the second phase interventions, the incidence of drug ordering mistakes decreased by 19% and the number of transcription errors fell by 84%. Thus, if computer systems were utilised in paediatric hospitals and these systems were linked to drug information databases using national consensus prescribing guidelines, the ADR incidence may be reduced.[29,33] However, cost versus benefit must be considered. Implementation of an electronic chart may also reduce the number of ordering errors due to lack of knowledge regarding a patient's concurrent medications and allergy history. At the national level, there appears to be limited utilisation of these systems.

The implementation of a non-punitive system may increase the number of reported ADRs and thus, awareness of potential system problems. The ongoing surveillance system at our institution is a relatively good measure of both type and relative frequency of ADR occurrence within the institution, and demonstrates the effectiveness of an institution in gathering information with relatively limited re-

sources. In addition, our results indicate that the majority of ADRs occur with three different medication classes. Targeting of these medication classes and use of a team approach that includes a physician, pharmacist and nurse may help eliminate a considerable number of ADRs.[36] In an attempt to reduce ADRs, the hospital has employed a medication safety pharmacist.

This study had a few limitations. First, it was a single centre study and extrapolation to other paediatric hospitals may be difficult unless a similar patient population exists. In addition, important details may have been missed regarding the ADRs because severity, causality and preventability required implicit judgement due to the reliance on medical record documentation, laboratory data and caregiver information about the ADR, that was not within a 24-hour time frame. ADR rates detected were based on the collection system used in our hospital. Finally, events that were not recorded, reported or detected through daily review of medication orders filled by the pharmacy were not identified.

Conclusion

ADRs were reported at a rate of 0.85 ADRs per 100 admissions. Anticonvulsants, opioids and antibiotics were most commonly associated with ADRs. ADRs resulted in treatment intervention or temporary patient harm in >50% of paediatric patients. ADRs may be prevented by implementing strategies to target certain drug classes. Although all ADRs may not be eliminated, the goal should be to increase ADR awareness to minimise their occurrences in paediatric patients. Institutions can gather less complete but equally representative and useful information utilising the relatively limited resources available.

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