ARTICLE

Incidence and Impact of Adverse Drug Events in Pediatric Inpatients

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Objectives: To determine the incidence and causes of adverse drug events (ADEs) and potential ADEs in hospitalized children, and to examine the consequences of these events.

Design: Prospective review of medical records and staff interviews were performed. The ADEs were defined as injuries from medications or lack of an intended medication, and potential ADEs, as errors with the potential to result in injury.

Setting: A general pediatric unit and a pediatric intensive care unit in a metropolitan medical center.

Patients: A total of 1197 consecutive patient admissions were studied from September 15, 2000, to May 10, 2001. The admissions represented a total of 922 patients and 10 164 patient-days.

Results: The ADEs (6/100 admissions, 7.5/1000 patient-days) and potential ADEs (8/100 admissions, 9.3/1000 patient-days) were common in hospitalized children. Demographic variables associated with the occurrence of these events were the length of hospital stay, case-mix index, and amount of medication exposure. After adjusting for length of stay, medication exposure continued to have a significant influence on ADEs and potential ADEs. For ADEs, 18 (24%) were judged to be serious or life threatening. Most ADEs were not associated with major or permanent disability. Patients with both ADEs and potential ADEs were less likely to be routinely discharged and more likely to be discharged with home health care or to another institution, suggesting that patient disposition was not related to the adverse event.

Conclusions: Both ADEs and potential ADEs are common among hospitalized children with greater disease burden and medication exposure. These findings suggest that these events were a consequence, rather than a cause, of more severe illness.

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ADVERSE DRUG events (ADEs) are injuries from medications or from the lack of an intended medication.[1] It has been demonstrated that ADEs contribute to morbidity and mortality among hospitalized patients.[2-5] To date, almost all investigations of ADEs have been performed in adult populations. There is recent evidence that potential ADEs may be more common in pediatrics, suggesting that the epidemiologic characteristics of medication errors may be different between children and adults.[6]

There is reason to believe that hospitalized children may be a population at increased risk for ADEs. As a group, they represent patients with significant developmental variability in whom a broad range of pathologic conditions necessitate extensive medication exposure. Information regarding the most common types of ADEs in children would aid in the development of computerized knowledge-based warning systems and/or in the enhancement of existing systems that could prevent adverse outcomes. A computerized ADE alert system has been used to prevent injury in the adult population.[7]

The goals of this study were to determine the incidence and the most common causes of actual and potential ADEs in the pediatric inpatient population, and the consequences associated with these events.

METHODS

An ADE was defined as an event resulting in an injury from a medication or lack of an intended medication.[1] A potential ADE was defined as an error that had the potential to result in a significant injury. Potential ADEs included errors detected before drug administration as well as errors that did not produce significant adverse consequences. Errors that

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were identified and corrected before the medication was entered onto the medication administration record were excluded.

Data on ADEs and potential ADEs were collected from the pediatric intensive care unit (PICU) and the general pediatric unit of a large metropolitan tertiary care center. The PICU and the general pediatric unit consisted of 20 and 30 beds, respectively. The PICU is a multidisciplinary unit that functions as a major referral center for a large health care network and a major cancer center, and provides medical and surgical intensive care to all pediatric patients, including infants. Both units had computerized medical records in place for various aspects of documentation. Only the PICU used a computerized medication administration record. On both units, physician orders were faxed to the satellite pharmacy and a daily supply of medications was delivered with the use of a unit dose dispensing system.

A clinical pharmacist served as the primary reviewer and visited the 2 units on each weekday during a 7-month period (from September 15, 2000, through May 10, 2001). The reviewer searched each medical record for evidence of ADEs and potential ADEs by reviewing physician and nursing notes, pharmacy records, medication administration records, and laboratory data. Actual medication orders were not reviewed. To uncover additional information, nursing, medical, and pharmacy personnel were interviewed when questions arose during the medical record review. Nursing and pharmacy supervisory personnel were also interviewed on a weekly basis to obtain reports of any additional adverse events.

Demographic data were collected on all patients within the units, including data on case-mix index (CMI), an index reflecting case severity and resource utilization. All data were entered into a handheld, computerized data entry unit (Palm Pilot; Palm, Inc, Milpitas, Calif) and transferred to a computerized database (Microsoft Excel; Microsoft, Corp, Redmond, Wash) with the use of Pendragon Forms software (Pendragon Software Corporation, Libertyville, Ill) as previously described.[8] When an ADE or potential ADE was identified, additional information was collected. This included drug and drug class associated with the event, severity of the event, whether a medication error occurred, type of error and proximal cause, and the attributed system failure that led to the error. The severity of the event was assigned according to a previously published scale as significant, serious, or life threatening, on the basis of the potential or actual consequences relating to such factors as dose, route, and choice of medication.[9,10]

For all ADEs and potential ADEs, disability or potential disability was graded by means of a standard disability scale[11] and a judgment regarding preventability was made. Since judgment regarding errors can be complicated, a standard confidence scale (1, little or no evidence; 6, virtually certain evidence) was used to rate the likelihood that the ADE was the result of a medication error.[11] The type of error recorded included the following categories: underdose, overdose, wrong drug choice, error in frequency, error in timing, excessive infusion rate, lack of premedication, wrong route, drug interaction, and dispensing error. A proximal cause and likely systems failure that contributed to the error were assigned by the primary reviewer (M.T.H.) using previously published definitions.[12]

Each event identified by the primary reviewer was further examined independently by 3 validators, consisting of 2 pediatric residents (A.A., M.G.) and a pediatric clinical pharmacist (E.M.-R.). Events were reviewed for actual occurrence, preventability, type of error, and the severity and disability ratings. Agreement or disagreement with the primary reviewer was rated by means of the same 6-point confidence scale used for the analysis of medication errors. When all of the validators disagreed with the primary reviewer, the event was excluded. When validators could not reach agreement through this review process, a meeting was held to achieve consensus. Once complete data were obtained for all patients entered into the database, all patient identifiers were removed. Approval from the institutional review board was obtained before the study was initiated.

Table 1. Data and Patient Characteristics*

Characteristic	ADE (n = 76)	Potential ADE (n = 94)	No ADE (n = 1025)
No./100 admissions	6	8	. . .
No./1000 patient-days	7.5	9.3	. . .
Age, mean (SD), y	8.4 (6.5)	7.5 (6.7)	6.1 (5.8)
Sex, No. (%)			
M	43 (56.6)	50 (53.2)	566 (55.1)
F	33 (43.4)	44 (46.8)	461 (44.9)
Length of stay, mean (SD), d	21.7 (18.6)	20.8 (18.1)	6.4 (9.5)†
No. of medications, mean (SD)	10.0 (5.6)	10.4 (4.5)	5.2 (3.9)†
Case-mix index, mean (SD)	5.2 (5.3)	6.5 (6.7)	2.4 (4.3)†
Nursing unit, No. (%)			
Pediatric intensive care unit	41 (7.9)	63 (12.2)‡	413 (40)
General pediatric unit	35 (5.1)	31 (4.6)	614 (60)

Abbreviation: ADE, adverse drug event.
*The "potential ADE" group refers to errors detected before drug administration and errors that the patient received but that did not result in any significant adverse consequences.
†$P<.001$ vs ADE and potential ADE.
‡$P<.001$ vs general pediatric unit.

Rates of adverse events according to ADE group (ie, ADEs, potential ADEs, and no ADEs) were compared by nursing unit and disposition by means of χ^2 tests. Analysis of variance with post hoc Scheffé tests was used to compare the CMI, the number of medications, and the duration of hospitalization among ADE groups. For this analysis, the ADE group designation was the independent variable and the CMI, number of medications, and hospital days were dependent variables. Patients were divided into 16 groups, using 4 levels of CMI and 4 levels of medication usage, on the basis of quartiles of the frequency distributions of these variables. Poisson regression analysis was used to determine the impact of CMI and the number of medications on adverse event incidence, using hospital stay as the exposure variable and ADEs or potential ADEs as dependent variables. The incident rate ratios of ADEs and potential ADEs were calculated for each group. Relative risk ratios and 95% confidence intervals were calculated to compare the ADE groups by the 5 most common drug classes prescribed. The statistical package used was NCSS (Number Cruncher Statistical System, Kaysville, Utah). For all statistical tests, significance was $\alpha \leq .05$.

RESULTS

A total of 1197 patient admissions were evaluated. These admissions represented a total of 922 patients and a cumulative hospital stay of 10 164 patient days. Patient demographics and the occurrence rates of ADEs and potential ADEs are presented in **Table 1**. Children with ADEs or potential ADEs did not differ significantly from those without events with regard to age, sex, or diagnosis related group category. Infants in either unit did not experience a disproportionate number of these events, accounting for 25.4% of the total sample and representing 25.3% (n=43) of all events (19.7% of ADEs [n=15] and 29.8% of potential ADEs [n=28]). Hospital stay, medi-

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Table 2. ADEs and Potential ADEs According to CMI and Medication Usage Strata*

ADE Data by CMI Level	No. of Different Medications 0-3	4-5	6-8	>8
≤0.67				
No. of hospitalizations	111	127	37	16
ADEs	0	1	0	2
Potential ADEs	2	1	3	3
Hospital days	311	388	170	50
ADE rate/1000 d	0	2.6	0	40.0
Potential ADE rate/1000 d	6.4	2.6	17.6	60.0
0.68-1.15				
No. of hospitalizations	85	109	61	36
ADEs	0	7	2	4
Potential ADEs	0	1	2	4
Hospital days	297	503	311	295
ADE rate/1000 d	0	2.0	6.4	13.6
Potential ADE rate/1000 d	0	13.9	6.4	13.6
1.16-2.85				
No. of hospitalizations	32	130	63	71
ADEs	0	8	2	9
Potential ADEs	1	5	3	9
Hospital days	152	840	383	834
ADE rate/1000 d	0	8.3	5.2	10.8
Potential ADE rate/1000 d	6.6	6.0	7.8	10.8
>2.85				
No. of hospitalizations	25	61	65	141
ADEs	2	4	6	26
Potential ADEs	0	4	7	45
Hospital days	233	789	988	3108
ADE rate/1000 d	8.6	5.1	6.0	8.4
Potential ADE rate/1000 d	0	5.1	7.0	14.5

Abbreviations: ADE, adverse drug event; CMI, case-mix index.
*The "potential ADEs" category represents errors detected before drug administration and errors that the patient received but that did not result in any significant adverse consequences.

Table 3. Incidence Rate Ratios From Poisson Analysis, Including Length of Stay as Exposure Variable*

	Group	Incidence Rate Ratios	95% Confidence Interval
ADE results			
CMI effect (reference, ≤0.67)	0.68-1.15	2.83	0.67-8.43
	1.16-2.85	1.74	0.50-6.06
	>2.85	1.46	0.43-4.90
Medications effect (reference, ≤3)	4-5	3.67	0.84-15.91
	6-8	2.67	0.58-12.40
	>8	4.93	1.15-21.20
Potential ADE results			
CMI effect (reference, ≤0.67)	0.68-1.15	0.36	0.13-0.98
	1.16-2.85	0.46	0.20-1.08
	>2.85	0.48	0.22-1.05
Medications effect (reference, ≤3)	4-5	1.68	0.45-5.99
	6-8	3.20	0.90-11.40
	>8	6.02	1.76-20.61

Abbreviations: ADE, adverse drug event; CMI, case-mix index.
*The "potential ADE" category represents errors detected before drug administration and errors that the patient received but that did not result in any significant adverse consequences.

cation exposure, and CMI values were greater for children with either ADEs or potential ADEs. Potential ADEs were more likely to occur within the PICU.

Rates of ADEs and potential ADEs within each strata of CMI and medication use are displayed in **Table 2**. After adjustment for the duration of hospitalization, the number of medications had a significant influence on the rates of ADEs or potential ADEs, although CMI did not. The incident rate ratios from this analysis are provided in **Table 3**. The influence of medications was significant only at the highest quartile of exposure for both ADEs and potential ADEs.

The distribution of the severity ratings for ADEs showed that 58 ADEs (76%) were classified as significant, 10 (13%) as serious, and 8 (11%) as life threatening. For potential ADEs, 89 (95%) were rated as significant, 5 (5%) as serious, and none as life threatening. Disability ratings illustrate that most of the outcomes were not significant or permanent (**Table 4**). However, 20 events (11.8%) did result or have the potential to result in a major temporary disability.

Forty-four drug classes and subclasses were represented by these events. Antibiotics were most frequently associated with events in the PICU (41.3% of all events [n=43]), while opiates were most commonly implicated in the general pediatric unit (33.3% of all events [n=22]). For the 5 most commonly prescribed drug classes, drug exposure was greater for ADEs and/or potential ADEs when compared with children with no ADEs (**Table 5**). Drug exposure for children

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Table 4. ADE Disability Ratings by Type of ADE and Hospital Care Unit*

Disability Rating	Type of ADE, No. (%)		Hospital Care Unit, No. (%)	
	ADE	Potential ADE	PICU	General Pediatric Unit
Emotional	21 (27.6)	7 (7.4)	9 (8.7)	19 (28.8)
Insignificant	13 (17.1)	77 (81.9)	61 (58.7)	29 (43.9)
Minor temporary	21 (27.6)	7 (7.4)	17 (16.3)	11 (16.7)
Major temporary	17 (22.4)	3 (3.2)	15 (14.4)	5 (7.6)
Minor permanent	1 (1.3)	0	0	1 (1.5)
Significant permanent	2 (2.6)	0	1 (1.0)	1 (1.5)
Major permanent	1 (1.3)	0	1 (1.0)	0
Total	**76 (100.0)**	**94 (100.0)**	**104 (100.0)**	**66 (100.0)**

Abbreviations: ADE, adverse drug event; PICU, pediatric intensive care unit.
*The "potential ADE" group represents errors detected before drug administration and errors that the patient received but that did not result in any significant adverse consequences.

Table 5. Relationships Among Common Drug Classes and ADEs, Potential ADEs, and No ADEs*

Drug Class	ADE vs No ADE	ADE vs Potential ADE	Potential ADE vs No ADE
Adrenals (corticosteroids)			
%†	31.6 vs 24.7	31.6 vs 35.1	35.1 vs 24.7
RR	1.37 (P=.18)	0.91 (P=.63)	1.57 (P=.03)
95% CI	0.83-2.27	0.48-1.74	1.01-2.46
Antibiotics			
%	76.3 vs 65.3	76.3 vs 79.8	79.8 vs 65.3
RR	1.66 (P=.05)	0.90 (P=.59)	1.99 (P<.01)
95% CI	0.98-2.86	0.43-1.86	1.18-3.35
Antineoplastics			
%	13.2 vs 4.6	13.2 vs 6.4	6.4 vs 4.6
RR	2.78 (P<.01)	1.46 (P=.13)	1.37 (P=.43)
95% CI	1.34-5.74	0.50-4.21	0.57-3.30
Cardiac drugs			
%	36.8 vs 13.1	36.8 vs 41.5	41.5 vs 13.1
RR	3.38 (P<.01)	0.89 (P=.54)	3.88 (P<.01)
95% CI	2.05-5.58	0.48-01.67	2.48-6.07
Opiates			
%	67.1 vs 33.1	67.1 vs 59.6	59.6 vs 33.1
RR	3.72 (P<.01)	1.20 (P=.31)	2.70 (P<.01)
95% CI	2.26-6.11	0.84-2.26	1.75-4.16

Abbreviations: ADE, adverse drug event; CI, confidence interval; RR, relative risk.
*For RR, values greater than 1.0, with 95% CIs that exclude 1.0, indicate that significantly more patients in the first group listed were prescribed the drug.
†Percentages of patients who were prescribed the class of drugs during their hospitalization.

Table 6. Patient Disposition by Type of ADE*

Type of Discharge†	No. (%)		
	ADE (n = 76)	Potential ADE (n = 94)	No ADE (n = 1025)
Routine	50 (65.6)	55 (58.5)	875 (85.4)‡
Home health care	7 (9.4)	15 (14.6)	41 (4.0)‡
Other institution	14 (18.8)	20 (20.7)	72 (7.0)‡
Deceased	4 (4.7)	1 (1.2)	10 (1.0)

Abbreviation: ADE, adverse drug event.
*The "potential ADE" group refers to errors detected before drug administration and errors that the patient received but that did not result in any significant adverse consequences.
†Routine means discharge to home; other institution represents other hospital or extended care facility.
‡P<.001 vs ADE and potential ADE.

with ADEs and potential ADEs was similar among these drug classes. There were no differences in the occurrence of serious or life-threatening events among the various drug classes, although this analysis was limited by the small number of events for most of the drug classes.

Of the ADEs, 46 (61%) were judged to be preventable, as were all potential ADEs. Overall, 78 (75%) of the events in the PICU and 47 (71%) in the general pediatric unit were judged to be preventable. Preventable ADEs were adjusted for length of stay and the average medication exposure within specific units. This calculation included all preventable events per 1000 patient-days, divided by the mean number of medications within the specific unit. After this adjustment, the number of preventable events was nearly identical, with rates of 1.99 for the PICU and 2.1 for the general pediatric unit.

The most common error types were underdose (n=25 [63%]), wrong drug choice (n=7 [18%]), and overdose (n=3 [8%]) for ADEs, and dispensing error (n=39 [42%]), underdose (n=27 [29%]), and overdose (n=12 [13%]) for potential ADEs. Opiate analgesics and antibiotics were most frequently implicated in underdose situations. Most dispensing errors were due to medication order tracking, particularly related to discontinuation orders within the PICU. Common systems failures were lack of dose and frequency standardization (n=23 [58%]), procedure standardization (n=9 [23%]), and drug knowledge dissemination (n=2 [5%]) for ADEs, and medication order tracking (n=35 [37%]), dose and frequency standardization (n=13 [14%]), dose or identity checking (n=12 [13%]), and drug knowledge dissemination (n=9 [10%]) for potential ADEs.

Patients with both ADEs and potential ADEs were less likely to be routinely discharged than children with no ADE, suggesting that disposition was unrelated to the ADE (**Table 6**). There was no significant difference in the mortality among children with ADEs or potential ADEs and those with no ADE.

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What This Study Adds

The incidence and types of ADEs are currently established in the adult inpatient population but are not well characterized among children and adolescents. The few studies of ADEs in children have not examined the consequences of these events.

This study provides further documentation that ADEs are common events among hospitalized children, especially for those with greater disease burden and medication exposure. However, the findings from this study demonstrate that ADEs did not directly contribute to adverse outcomes in children. The implications of these findings are that ADEs in this patient population are not necessarily a risk for extended hospital stay and excess resource utilization, but rather that they may be a marker for children with greater disease burden.

COMMENT

The results of this study suggest that ADEs are common in the pediatric inpatient population. These events were more likely to occur among children with longer stay and greater medication exposure. Patients with ADEs and potential ADEs were both less likely to be routinely discharged and more likely to be transferred to another institution and/or a home health care agency than were children with no ADEs. It appears that children who developed or had the potential to develop these events represented more complicated cases in terms of severity of illness, especially related to medication exposure. An ADE may be a consequence of disease severity among hospitalized patients, rather than a significant factor that directly contributes to patient morbidity.

Both ADEs and potential ADEs occurred across many different diagnostic categories and were associated with exposure to a wide range of medications. Opiates and antibiotics accounted for more adverse events than any other drug classes. These were also the 2 most commonly prescribed drug classes in these children. Previous studies also document that these 2 drug classes accounted for most ADEs among hospitalized adult patients.[3,13,14]

The occurrence rate of events in the present study is similar to the reported rate of ADEs in the adult population.[3,13,15] There has been 1 published study concerning ADEs in pediatric patients.[6] Unlike the present investigation, this previous study also included a neonatal intensive care unit. Although the ADE frequency per 100 admissions was lower than in the present study (2.3 vs 6.0), the reported rate per 1000 patient-days was similar (6.6 vs 7.5). Because of the longer duration of data collection in the present trial (10 164 vs 3932 patient-days), it is likely that a greater percentage of the data reflects the entire length of stay; thus, the rates per 100 admissions and per 1000 patient-days are similar. The greater rate of potential ADEs in the previous trial (10 of 100 admissions or 29 of 1000 patient-days) likely reflects the methodology whereby each order was screened as a potential ADE source.

In the present study, 18 (24%) of the ADEs were associated with serious or life-threatening complications. The 1 previous study in pediatric patients also reported high rates of serious (35%, n=9) and life-threatening (8%, n=2) adverse events, although this was based on a small number of events (n=26).[6] Debate continues regarding the actual extent to which ADEs contribute to patient morbidity and mortality in the adult population.[16,17] In the present study, it was not apparent that these events were an important cause of adverse outcomes in the pediatric population. This finding is not meant to imply a lack of importance of system modifications to prevent these events.

When examined in terms of specific events, 2 types of errors more frequently led to ADEs and potential ADEs. Regarding ADEs, the most frequent error was an inadequate dose of an opioid analgesic for a patient with postoperative pain. This was often ascribed to a systems problem concerning drug knowledge dissemination. This finding is consistent with results of other studies documenting undertreatment of pain in pediatric patients.[18,19] The most frequent potential ADE was the result of a failure to acknowledge or process antibiotic discontinuation orders. Regardless of where the error occurred, this likely represents a breakdown in a manual ordering system. Although it was evident that new orders were prioritized and promptly addressed, discontinuation orders did not receive the same attention.

The methodology used in this study (as with all ADE studies and reporting systems) may have missed some ADEs and potential ADEs. These results may thus underestimate the true rate in this patient population. Frontline operators may have been reluctant to report ADEs that resulted from medication errors. Medication errors, especially those involving medication administration, may have occurred that went undetected in the medical record review.

This study demonstrates that ADEs and potential ADEs are common in hospitalized children. In particular, children with more complicated medical conditions requiring a greater number of medications and a longer hospital stay were at greater risk for these events. Adverse drug events in children may not necessarily result in increased length of stay, but rather seem more likely to occur in patients with increased medication exposure and extended hospital stay.

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