Incidence of Adverse Drug Events and Potential Adverse Drug Events

Implications for Prevention

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Objectives.—To assess incidence and preventability of adverse drug events (ADEs) and potential ADEs. To analyze preventable events to develop prevention strategies.

Design.—Prospective cohort study.

Participants.—All 4031 adult admissions to a stratified random sample of 11 medical and surgical units in two tertiary care hospitals over a 6-month period. Units included two medical and three surgical intensive care units and four medical and two surgical general care units.

Main Outcome Measures.—Adverse drug events and potential ADEs.

Methods.—Incidents were detected by stimulated self-report by nurses and pharmacists and by daily review of all charts by nurse investigators. Incidents were subsequently classified by two independent reviewers as to whether they represented ADEs or potential ADEs and as to severity and preventability.

Results.—Over 6 months, 247 ADEs and 194 potential ADEs were identified. Extrapolated event rates were 6.5 ADEs and 5.5 potential ADEs per 100 nonobstetrical admissions, for mean numbers per hospital per year of approximately 1900 ADEs and 1600 potential ADEs. Of all ADEs, 1% were fatal (none preventable), 12% life-threatening, 30% serious, and 57% significant. Twenty-eight percent were judged preventable. Of the life-threatening and serious ADEs, 42% were preventable, compared with 18% of significant ADEs. Errors resulting in preventable ADEs occurred most often at the stages of ordering (56%) and administration (34%); transcription (6%) and dispensing errors (4%) were less common. Errors were much more likely to be intercepted if the error occurred earlier in the process: 48% at the ordering stage vs 0% at the administration stage.

Conclusion.—Adverse drug events were common and often preventable; serious ADEs were more likely to be preventable. Most resulted from errors at the ordering stage, but many also occurred at the administration stage. Prevention strategies should target both stages of the drug delivery process.

(*JAMA*. 1995;274:29-34)

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Presented in part at the Society of General Internal Medicine annual meeting, April 30, 1994, Washington, DC.

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IN THE Medical Practice Study (MPS), almost 4% of patients hospitalized in New York State in 1984 suffered an adverse event, defined as an injury due to medical treatment.[1] If the numbers from New York are extrapolated to the country as a whole, over a million patients are injured in hospitals each year, and approximately 180 000 die annually as a result of these injuries. Therefore, the iatrogenic injury rate dwarfs the annual automobile accident mortality of 45 000 and accounts for more deaths than all other accidents combined.[2] However, little attention has been focused on understanding causes of iatrogenic injuries or on developing methods to prevent them. In part, this is because medical injuries seem to have few common causes, but it also reflects the general lack of awareness of the problem. A critical question is how many of these medical injuries are preventable. In the MPS, 69% of adverse events were judged by physician reviewers to be due, at least in part, to an error in management; presumably most of these adverse events are preventable.[3]

See also pp 35 and 75.

The leading cause of medical injury in the MPS was use of drugs, accounting for 19.4% of these injuries.[4] Other studies, most of which used the adverse drug reaction (ADR) as the outcome, have also shown that injuries due to drugs are common in hospitalized patients,[5-15] although the true incidence is controversial and varied widely (1.5% to 35%) depending on the rigor with which the events were sought.[16]

While the ADR is often used as the outcome in studies of injuries caused by medications, its definition by the World Health Organization (WHO) is an effect that is "noxious and unintended, and which occurs at doses used in man for prophylaxis, diagnosis or therapy."[17] This includes only appropriate use of drugs, when in fact most preventable drug-related injuries suffered by patients occur as a result of errors in their use.[5] For these reasons, we prefer the term adverse drug event (ADE), defined as an injury resulting from medical intervention related to a drug, because it is more comprehensive and clinically significant than the ADR. For example, oversedation and aspiration pneumonia resulting from a 10-fold overdose of a drug would not be considered an ADR according to the WHO definition, but would be an ADE. Few data are available about what

percentage of ADEs are potentially preventable,[18] and what strategies may be used to prevent them.[19,20]

Traditional medical quality assessment of ADEs has focused on identifying and castigating providers who make many errors—the "bad apple" approach.[21] The total quality improvement perspective, on the other hand, assumes that most providers are doing the best they can in the current system and that major improvements in system performance require redesign of systems rather than pushing people harder within the current system. Better systems should promote fewer errors and include effective mechanisms for catching those that do occur.

Another issue is that ADEs are costly: one study estimated that additional costs associated with an ADE for hospitalized patients were about $2000,[22] not including malpractice costs or the cost of injury to the patient. Drug injuries frequently result in malpractice claims and accounted for the highest total expenditure of any type of procedure-related injury in a large study of closed claims.[23] To justify quality improvement efforts, their economic impact must be considered; injuries due to drugs may represent an area in which efforts to improve the quality of care may be cost-neutral or even reduce costs.

Most previous studies of adverse occurrences due to drugs have not evaluated their preventability, have not explicitly taken a systems approach, and many (such as the MPS) have used a retrospective design,[1] which severely limits the ability to obtain detailed information about individual events. In addition, most have not evaluated potential ADEs, or near misses, although systems failures associated with these events may be similar to those that result in ADEs. Because our eventual aim was to design strategies to prevent ADEs, we undertook a prospective study with these goals: (1) to evaluate the incidence and preventability of ADEs and potential ADEs; (2) to categorize them by drug class and type of unit in which they occurred; (3) to classify the preventable events according to the stage of the process at which the error occurred; and (4) to classify errors by stage.

METHODS

Patient Population

Subjects included all adults at two large tertiary care hospitals, Brigham and Women's Hospital (726 beds) and Massachusetts General Hospital (846 beds), admitted to any of 11 units over a 6-month period from February through July 1993, with the exception that at one hospital, patients from two surgical intensive care units (ICUs) were studied for the first 3 months of the study, and then patients from a medical ICU were studied for the final 3 months. This exception was made because we wanted information about both medical and surgical ICUs from that hospital. We previously found[18] that ADEs were more common on ICUs vs general care units and that obstetric units had almost no ADEs. To identify as many events as possible for designing prevention strategies, we oversampled ICUs and omitted obstetric units. Overall, there were 61 adult, nonobstetric units between the two hospitals. These units were stratified according to hospital, whether medical or surgical, and whether intensive or general care, and then study units were selected randomly from all units within a stratum using a random number generator. The study units included five ICUs (three surgical and two medical), and six general care units (four medical and two surgical). The primary unit of evaluation was the patient-day, although we also recorded the number of admissions.

This study was approved by the institutional review boards of both hospitals and the Harvard School of Public Health. Because of potential liability concerns, details of individual cases are not provided, and results are blinded by institution. The major risk to patients was from continuing hazardous treatment; investigators and review boards agreed that if patterns of care that could be harmful to a patient or future patients were detected that the information would be brought immediately to caregivers and appropriate authorities for correction.

Case Finding and Definitions

We used three mechanisms for identifying incidents: (1) nurses and pharmacists were asked to report incidents to nurse investigators; (2) a nurse investigator visited each unit at least twice daily on weekdays and solicited information from nurses, pharmacists, and clerical personnel concerning all actual or potential drug-related incidents; and (3) the nurse investigator reviewed all charts at least daily on weekdays.

The primary outcome of the study was the ADE. An example would be a patient with first-degree atrioventricular block who received a β-blocker and developed complete heart block requiring temporary pacing. We also identified potential ADEs, defined as incidents with potential for injury related to a drug. An example is a patient who received penicillin despite a known allergy to penicillin, but did not react. Included in this category were drug errors that were intercepted before the order was actually carried out. Incidents were excluded if an error was made but was judged to have minimal potential for injury (for example, a patient receiving a maintenance dose of carbamazepine with no recent seizures who missed one dose), as were incidents in which an injury occurred that was not clearly drug-related. We chose to include potential ADEs as an outcome because our goal is to reduce the number and severity of drug-related injuries. Based on our pilot study,[18] our hypothesis was that the causes of many potential ADEs are similar to the causes of actual adverse events.

To discover the causes of preventable events, the involved persons were interviewed, and the results of the investigation were analyzed by a multidisciplinary team of physicians, pharmacists, nurses, and systems analysts (see accompanying article by Leape et al[24]).

Classification of Incidents

All incidents were evaluated independently by two physician reviewers, who classified them according to the following criteria: whether or not an ADE or potential ADE was present, severity, preventability, and if an error was present, the type of error and the stage in the process at which the error occurred. Reviewers were asked to consider ADEs as preventable if they were due to an error or were preventable by any means currently available. In the long term it is likely that many ADEs currently judged nonpreventable may become preventable with new approaches. Categories of preventability were as follows: definitely preventable, probably preventable, probably not preventable, and definitely not preventable[25]; results were collapsed into preventable and not preventable in the analyses. Categories of severity were fatal, life-threatening, serious, and significant.[26] The stages of process considered were: ordering (essentially all by physicians), transcribing (performed by a secretary or nurse depending on the unit and time of day), dispensing (by pharmacy), and administration (by nursing). When there were disagreements that affected classification of an event (eg, one reviewer scored it as preventable, but the other did not) or about presence of an event, severity, or preventability, reviewers met and reached consensus. If consensus could not be reached, a third reviewer evaluated the incident.

Analysis

Interrater reliabilities for key judgments were calculated using percentage of agreement and the κ statistic. The percentage of agreement and the mean κ scores between reviewers at the two hospitals (Table 1) were better for judgments regarding presence of an ADE (κ = 0.98 and 0.81) and preventability (κ = 0.92)

Table 1.—Interrater Agreement on Incident Type, Preventability, and Severity of Adverse Drug Events (ADEs)

Judgment	Agreement, %*	κ
ADE vs potential ADE or exclude	98.5	0.98
Exclude vs ADE or potential ADE	92.5	0.81
Preventable vs not preventable	96	0.92
Life-threatening vs serious or significant	85	0.37
Significant vs serious or life-threatening	66	0.32

*Mean between raters at the two hospitals.

Table 2.—Numbers and Crude and Adjusted Rates of Adverse Drug Events (ADEs) and Potential ADEs

	No. (%)	Crude Rate per 1000 Patient-Days (95% CI)*	Crude Rate per 100 Admissions (95% CI)	Adjusted Rate per 100 Admissions*	Annual Hospital-Wide No.†
ADEs	247 (100)	11.5 (10.1-13.0)	6.1 (5.4-6.9)	6.5	1923
Preventable ADEs	70 (28)	3.2 (2.5-4.0)	1.7 (1.3-2.1)	1.8	538
Nonpreventable ADEs	177 (72)	8.3 (7.1-9.5)	4.4 (3.8-5.0)	4.7	1385
Potential ADEs	194 (100)	9.1 (7.8-10.3)	4.8 (4.2-5.5)	5.5	1643
Nonintercepted potential ADEs	111 (57)	5.2 (4.2-6.1)	2.7 (2.2-3.3)	3.1	937
Intercepted potential ADEs	83 (43)	3.9 (3.0-4.7)	2.1 (1.6-2.5)	2.4	706

*Crude rates are those actually observed in the study. Adjusted rates are hospital-wide rates, after adjusting for the sampling scheme, which did not equally represent all unit types (see "Methods" section). CI indicates confidence interval.
†Mean number per hospital per year.

Table 3.—Adverse Drug Event (ADE) Rate by Unit Type*

Unit Type	Patient-Days, No.	ADE Rate per 1000 Patient-Days (95% CI)	Mean (SD) No. of Drugs Used†	ADE Rate per 1000 Patient-Days per Drug Used‡
Medical ICUs	2439	19.4 (14.0-24.9)	15.3 (4.9)	15.3
Surgical ICUs	3135	10.5 (6.9-14.0)	14.5 (4.5)	8.7
Medical general care units	11 499	10.6 (8.7-12.4)	9.8 (4.1)	12.9
Surgical general care units	4339	8.9 (6.1-11.7)	8.4 (4.5)	12.7

*ICU indicates intensive care unit, and CI, confidence interval.
†Mean number of drugs ordered for patients within 24 hours of the adverse drug event (includes as-needed drugs).
‡Rates are adjusted by multiplying them by the unit-specific mean number of drugs and then dividing by overall mean number of drugs.

than for judgments regarding severity (κ = 0.32 and 0.37). All "wrong choice" errors—ordering errors in which the reviewers felt an inappropriate judgment was made regarding a medication selection or dose given the clinical circumstances—were blindly reviewed by two additional reviewers along with an assortment of other cases; the additional reviewers agreed with the initial reviewers in all but one of these instances.

Crude rates of events were calculated by unit type (medical vs surgical) and level of care (intensive vs general) within the hospitals, and these rates were then used to extrapolate to hospital-wide annual rates. To perform the extrapolations, we first obtained hospital-wide census data for all units in the hospitals; obstetric and pediatric admissions were excluded. The observed rate for each unit type within the hospital was applied to all the units of that type. To determine a hypothetical hospital's annual average number of events, we took the mean between the two hospitals. The extrapolations make the following assumptions: (1) that units studied are representative of other units included in the same category; (2) that the rate during the 6-month study period was representative of the rate during the remainder of the year; (3) because no surgical general care unit was studied at one of the hospitals, that the rate of events on surgical general care units was equal to that of surgical general care units at the other hospital, after adjusting for hospital effect (this assumes that hospital effect was multiplicative across units); and (4) that the percentage preventable for ADEs and the percentage intercepted for potential ADEs were constant across unit types. Because more drugs are used in ICUs and on medical than surgical services, we also calculated rates that were adjusted for the number of drugs given within 24 hours of the event.

Comparisons between categorical variables were made using the χ^2 test, all with 1 *df* unless noted otherwise, and two-sided trend tests for trend for comparison were used for variables with multiple ordered categories. Analyses were performed using SAS[27] except for trend tests, which were performed using StatXact.[28]

RESULTS

During the study period, there were 214 486 patient-days in the two hospitals combined in adult, nonobstetric units, and 21 412 patient-days on the study units, so that 10% of all patient-days fell within the study sample. These 21 412 patient-days included 4031 admissions to study units. We found 247 ADEs, of which 70 (28%) were preventable, and 194 potential ADEs, of which 83 (43%) were intercepted before the drug was given (Table 2). Thus, the crude rates of ADEs were 11.5 per 1000 patient-days and 6.1 per 100 admissions. When these figures were extrapolated to determine hospital-wide rates, the results were approximately 3800 ADEs between the hospitals, or an average of 1900 ADEs per hospital per year. The adjusted rates per 100 admissions were 6.5 for ADEs and 5.5 for potential ADEs. Also, in every 100 admissions there were 7.3 preventable occurrences (preventable ADEs and potential ADEs combined).

The rate of ADEs was highest in medical ICUs (19.4 per 1000 patient-days), and relatively similar among surgical ICUs, and medical and surgical general care units (8.9 to 10.6 per 1000 patient-days, Table 3). Because the number of drugs used differed substantially by unit type, we also adjusted these figures for the number of drugs ordered within 24 hours by unit. After this adjustment, the rate was still highest in the medical ICUs (15.3 per 1000 patient-days), but was now lowest in surgical ICUs.

Three patients suffered a fatal ADE during the study (Table 4), representing 1% of all ADEs: none was preventable. An example is a patient who died of Stevens-Johnson syndrome secondary to a chemotherapeutic agent. However, of life-threatening and serious ADEs, 42% were preventable, vs 18% of the significant ADEs. Overall, more severe ADEs were more often preventable ($P<.001$, trend test, 2 *df*). Many of the significant nonpreventable ADEs were allergic reactions such as rashes. The potential ADEs were similar to the preventable ADEs in severity.

To facilitate comparisons with other studies, we also determined the number of ADEs that met the MPS definition of an adverse event, which required both injury and either measurable disability at discharge or increased length of stay due to the event. Of the 247 ADEs, 19 (7.7%) met this definition, of which seven (37%) were preventable. Many serious and life-threatening ADEs did not result in clearly defined disability at discharge or delay in discharge; for example, in the case of a patient who received too much sedation and required intubation and transfer to the ICU, but the event did not clearly prolong hospitalization.

Drugs and ADEs and Potential ADEs

The 247 ADEs were associated with 101 different drugs. Morphine sulfate accounted for 23 (9%) of all ADEs, meperidine for 13 (5%), and oxycodone for

11 (4%); no other individual drug was associated with more than 10 ADEs. Correspondingly, for all ADEs (Table 5), analgesics was the drug class most often associated with ADEs (30%), followed closely by antibiotics (24%).

Analgesics was also the leading drug class associated with preventable ADEs, with sedatives (10%) representing the next highest category. However, antibiotics caused only 9% of preventable ADEs vs 30% of nonpreventable ADEs ($P<.005$). Central nervous system depressants, including sedatives and antipsychotics in particular, were associated with preventable ADEs more often than nonpreventable ADEs. Combined, analgesics, sedatives, and antipsychotics accounted for 46% of preventable ADEs. Overmedication accounted for eight of 20 ADEs due to analgesics, while undermedication accounted for six of 20. In nine of the 20 ADEs due to analgesics, misuse or malfunction of infusion pumps or devices (involving either epidural catheters or patient-controlled analgesia) was involved. Concurrent use of multiple psychoactive drugs (including opiates, benzodiazapines, tricyclics, and antipsychotics) was the rule: the 20 patients with analgesic-related preventable ADEs had orders for an average of two other psychoactive drugs (range, zero to five). Use of diabetes medications caused four preventable ADEs; all were instances in which the patient had NPO (nothing by mouth) orders, but their insulin dose was not reduced and they suffered significant reactions.

Drug classes associated with potential ADEs were somewhat different (Table 5), most notably in that concentrated electrolyte solutions (primarily potassium chloride, $P<.001$), anticoagulants ($P<.03$), and cardiovascular drugs ($P<.009$) were more often associated with potential ADEs, while centrally acting agents—primarily analgesics ($P<.001$), but also sedatives ($P=.006$)—were less often associated with potential ADEs. Five of 20 potential ADEs associated with anticoagulants were instances in which heparin infusions were turned off (eg, to perform a phlebotomy) during an important period such as immediately after coronary angioplasty, but were inadvertently not restarted.

Preventable Events by Stage

Among preventable events (264 preventable ADEs and potential ADEs), the primary error occurred in the ordering stage in 49%; only 11% occurred in the transcription, and 14% in the dispensing stage, and 26% occurred in the administration stage (Table 6). Errors were much more likely to be intercepted if they occurred early in the process ($P<.001$, trend test): 62 (48%) of 128 ordering errors were intercepted, 23% of transcription, and 37% of dispensing errors, but 0% of the administration errors.

Among ordering errors, wrong dose was the most common, followed by wrong choice, known allergy, wrong frequency, and drug-drug interaction. Wrong choice errors were cases in which reviewing physicians attributed the ADE or potential ADE to an error in judgment in choosing a medication, eg, giving heparin to a patient with occult gastrointestinal bleeding, or giving amitriptyline to an elderly patient (amitriptyline is strongly anticholinergic and more appropriate alternatives exist). The most common transcription errors were wrong frequency and missed dose, while the most common dispensing errors were wrong time, wrong drug, and wrong dose. Among administration errors, wrong dose, wrong technique, wrong drug, missed dose, and wrong time of administration were most frequent.

COMMENT

We found that ADEs were common and that almost a third of ADEs were preventable. Serious and life-threatening ADEs were more likely than significant ADEs to be preventable. For each preventable ADE, there were nearly three times as many potential ADEs, or near misses. Errors resulting in ADEs were most frequent at the ordering stage, and a large group occurred at the administration stage.

We sought to estimate ADE rates in hospitalized patients, using an intensive detection methodology, including both multiple concurrent chart reviews by nurses and self-reporting. We found an adjusted rate of 6.5 ADEs per 100 admissions, similar to a rate of 6.4 per 100 admissions we found in a pilot study.[18] The MPS,[4] a population-based study that sampled patients from all types of acute care hospitals randomly, used one-time retrospective chart review by medical record reviewers to identify events and identified 0.7 ADE per 100 admissions. Classen et al[5] found a rate of 2.0 ADEs per 100 admissions using a computerized detection strategy in one tertiary care hospital. However, these studies used more restrictive definitions of ADEs. The MPS required that the event either prolong hospital stay or result in disability at discharge, and Classen et al included only

Table 4.—Severity of Adverse Drug Events (ADEs) and Potential ADEs

	Category of Severity			
	Fatal, No. (%)	Life-Threatening, No. (%)	Serious, No. (%)	Significant, No. (%)
All ADEs (n=247)	3 (1)	30 (12)	73 (30)	141 (57)
Preventable ADEs	0 (0)	14 (20)	30 (43)	26 (37)
Nonpreventable ADEs	3 (2)	16 (9)	43 (24)	115 (65)
All potential ADEs*	. . .	33 (17)	83 (43)	78 (40)
Nonintercepted potential ADEs	. . .	13 (12)	43 (39)	55 (50)
Intercepted potential ADEs	. . .	20 (24)	40 (48)	23 (28)

*Potential ADEs could not by definition be fatal.

Table 5.—Frequency of Adverse Drug Events (ADEs) by Drug Classes*

Drug Class	ADEs, No. (%) (n=247)	Preventable ADEs, No. (%) (n=70)	Nonpreventable ADEs, No. (%) (n=177)	Potential ADEs, No. (%) (n=194)	Nonintercepted Potential ADEs, No. (%) (n=111)	Intercepted Potential ADEs, No. (%) (n=83)
Analgesics	73 (30)	20 (29)	53 (30)	19 (10)	11 (10)	8 (10)
Antibiotics	59 (24)	6 (9)	53 (30)	46 (24)	29 (26)	17 (20)
Sedatives	20 (8)	7 (10)	13 (7)	4 (2)	2 (2)	2 (2)
Antineoplastic	18 (7)	3 (4)	15 (8)	5 (3)	3 (3)	2 (2)
Cardiovascular	9 (4)	3 (4)	6 (3)	16 (8)	5 (5)	11 (13)
Anticoagulants	8 (3)	3 (4)	5 (3)	19 (10)	15 (14)	4 (5)
Antipsychotics	6 (2)	5 (7)	1 (1)	3 (2)	1 (1)	2 (2)
Diabetes	5 (2)	4 (6)	1 (1)	6 (3)	3 (3)	3 (4)
Electrolytes	3 (1)	3 (4)	0 (0)	27 (14)	10 (9)	17 (20)
Other	46 (19)	16 (23)	30 (17)	49 (25)	32 (29)	17 (20)

*Percentages may not add to 100% because of rounding.

Table 6.—Stages of Primary Errors Associated With Preventable and Potential Adverse Drug Events (ADEs)

	Stage of Event			
	Ordering, No. (%)	Transcription, No. (%)	Dispensing, No. (%)	Administration, No. (%)
Preventable ADEs (n=70)	39 (56)	4 (6)	3 (4)	24 (34)
Intercepted potential ADEs (n=83)	62 (75)	7 (8)	14 (17)	0 (0)
Nonintercepted potential ADEs (n=111)	27 (24)	19 (17)	21 (19)	44 (40)
All above events (n=264)	**128** (49)	**30** (11)	**38** (14)	**68** (26)

"severe" adverse events. Of our patients with an ADE, 8% met the MPS definition of an adverse event, resulting in a rate of 0.5, close to that found in the MPS. Assuming that our "serious" and "life-threatening" categories can be equated with the "severe" category in the study by Classen et al, restricting our analysis to the 43% of events that were serious or life-threatening would result in a rate of 2.8, similar to that found by Classen et al.

Unlike most other studies of adverse occurrences due to drugs, this study emphasized preventable ADEs and potential ADEs. We found that 42% of serious and life-threatening ADEs were preventable; in the MPS, this figure was 45%.[3] Preventable ADEs have received relatively little attention, in part because hospitals are only required to report ADRs to the Food and Drug Administration (FDA), while ADEs due to errors are supposed to be collected by incident report systems. However, these systems are often ineffective for a variety of reasons,[29,30] including that they are often cumbersome and are sometimes used punitively. The FDA has as part of its mission the identification of new ADRs, which is appropriate, because only a large database would have sufficient power to identify rare adverse reactions; moreover, this approach has resulted in success stories such as associating aplastic anemia and chloramphenicol.[7] The new MEDWATCH program[31] promises to be even more effective than previous efforts. However, MEDWATCH does not target ADEs that are associated with errors. The net result is that the problem of preventable ADEs has been given short shrift despite its importance. Hospitals and other groups such as managed care organizations must take the lead in this area.

With respect to identification of which drugs caused the events, perhaps the most important finding was that no single drug accounted for more than 9%. Thus, interventions for preventing ADEs must target many drugs to have a major impact on the overall number of ADEs. The drug classes most often associated with preventable ADEs were those that depress the central nervous system, primarily analgesics, but also sedatives and antipsychotics. Use of these agents is often discretionary,[32] and in this study inappropriately high initial doses were often chosen. Occasionally, a medical disorder such as hypoxemia was not recognized and was treated with sedation, with predictable adverse consequences.

Data on the stage at which errors occur are critical for structuring prevention efforts. Most studies of errors in medication use included errors from only one stage.[26,33,34] Our data show that preventive efforts must be directed at both ordering and administration stages.

In terms of prevention, another important finding was that leading types of ordering errors—wrong dose, known allergy, wrong frequency, and drug-drug interactions—are potentially preventable by computerized order checking. While computerized systems that perform many of these checks are commercially available,[35] the efficacy of a comprehensive system for reducing the rate of ADEs has yet to be proved.[36]

Many errors also occurred in the administration stage. The most frequent categories of errors were wrong dose and wrong technique. Many of the mistakes involved use of nonstandard doses or unusual administration frequencies. In one hospital, nurses prepare a substantial number of intravenous (IV) drugs for use. However, since they are under time pressure and prepare such solutions much less frequently than pharmacists in the "IV room," not surprisingly they make many more mistakes. Some hospitals have all IV packages prepared by the pharmacy, and others have standardized the dosing for many medications, so, for example, only two concentrations of dopamine are used. Another issue stems from variation in physical setup and drug delivery process from unit to unit, eg, the medication administration record is in different locations in different units. This variation makes it difficult for providers who work on multiple units to perform efficiently and sets them up to make errors. These problems are familiar in the context of the managerial paradigm known as "total quality management," which is based on the premise that centralization, standardization, and simplification in processes can reduce variation and help provide more consistent results, with fewer defects.[37]

Policy Implications

Our data on ADE rates confirm that ADEs are a major cause of injury in hospitalized patients. Serious ADEs were particularly likely to be preventable. Also, if ADEs indeed increase patient costs $2000 per ADE as has been reported,[22] the annual cost to a 700-bed hospital is $3.8 million, of which about $1 million is due to events that are preventable today. These figures do not include the costs of injuries to patients, which are clearly substantial, or malpractice costs. In a study by the National Association of Insurance Commissioners, which used data from 1975 through 1978,[23] drug injuries accounted for the largest total awards of any procedure-related claim: $102 million compared with $72 million for anesthetic injuries. Also, medication errors—defined as any error in the process of ordering, dispensing, or administering a drug—were 100 times as frequent as preventable ADEs in a recent study[38]; while most are minor, even those errors carry substantial costs because of the additional work they create for hospital staff.

Given the above, it is clear that errors associated with drug use are costly from a variety of perspectives. Thus, although this remains to be demonstrated, efforts to improve quality by reducing the numbers and consequences of these errors may reduce the costs of care.

Although not all errors can be eliminated, for many categories of errors, the goal should be no errors that reach the patient[21]; eg, we should strive for perfection in preventing patients from receiving drugs to which they have known allergies, in preventing important overdoses, and in preventing one patient from receiving medication intended for another. Computerized approaches are ideal for this because reliability can approach 100%, while methods that rely on human inspection will always miss some errors.

How should a hospital improve the quality of its drug-delivery process? First, an effective mechanism for systematically collecting and feeding back data about ADEs is vital. Although ADR reporting is mandated by the Joint Commission on Accreditation of Healthcare Organizations, most hospitals still use self-reporting, which typically identifies only about 5% of events.[5,9] The case identification strategy used in this study was too expensive to be used except in research. However, computerized detection programs that search for events likely to be associated with an ADE (eg, use of naloxone, an opiate antagonist), supplemented by spontaneous reporting using the computerized information system and a dedicated person or group with responsibility for evaluating these events,[5,39] have been found to represent an effective, relatively inexpensive method for identifying ADEs and will probably be the strategy of the future.[40] Second, the organization must look

for preventable ADEs, and not just ADRs, because the preventable ADEs are more likely to cause serious injuries and represent the area in which improvement is possible. While this may seem obvious, many hospitals, responding to the FDA mandate, have focused on finding ADRs, which are primarily rare and idiosyncratic. Third, systems changes directed at specific parts of the process may be helpful, eg, one systems change that has great potential for preventing ordering errors is computerized order checking. For improving the systems of dispensing and administering medications, quality improvement efforts that focus on the processes involved may be effective.

This study has a number of limitations. It included only two tertiary care hospitals, so results may not be generalizable. The extrapolations are based on the assumptions described in the "Methods" section; most important, that units and patients studied were representative of the remainder of units and patients in the hospitals. Sampling was required because our case identification strategy was too intensive and thus expensive to implement on a larger fraction of units. A bias that may have decreased the number of events identified is a Hawthorne effect, particularly since the units were aware of the study and actively involved in it. Because we needed to interview providers to determine the systems problems responsible for events, we could not blind them to the purpose of the study. Another limitation is that categorization of events required implicit judgments. The percentage agreement and κ between reviewers were good for judgments of presence of an ADE and preventability, but were lower for the judgments regarding severity. Finally, we relied on record review and provider reporting to find events. Thus, events that either were not recorded in the chart[41] or were not reported to us could not be identified. Because of these factors, our rates probably represent lower bounds.

We conclude that ADEs are a major cause of iatrogenic injury, that many are preventable, and that for every preventable ADE there are almost three potential ADEs. Improvement of systems by which drugs are ordered and administered could prevent many of these events and might even reduce costs. Future studies should assess effectiveness and costs of new ways to find and prevent injuries due to drugs.

This study was supported by research grant R01-HS07107-01 from the Agency for Health Care Policy and Research, and a grant from the Risk Management Foundation.

We would like to thank the nurses, pharmacists, physicians, and other personnel on the study units, and George Baker, MD, William Churchill, PharmD, Allan Goldblatt, MD, Sheridan Kassirer, Richard J. Kitz, MD, and Warren Zapol, MD, for their support in carrying out the study. We are especially grateful to Priscilla Dasse and the Risk Management Foundation for the support and encouragement they have given us since the inception of the study.

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Printed and Published in the United States of America