Adverse drug events caused by serious medication administration errors

Abhivyakti Kale, 1,2 Carol A Keohane, 1 Saverio Maviglia, 1,3 Tejal K Gandhi, 1,2,3 Eric G Poon 1,2,3

ABSTRACT

Objective: To determine how often serious or life-threatening medication administration errors with the potential to cause harm (potential adverse drug events (ADEs)) result in actual harm (ADEs) in the hospital setting.

Design: Retrospective chart review of clinical events following observed medication administration errors.

Background: Medication errors are common at the medication administration stage for inpatients. While many errors can cause harm, it is unclear exactly how often.

Methods: In a previous study where 14 041 medication administrations were directly observed, 1271 medication administration errors were discovered, of which 133 had the potential to cause serious or life-threatening harm and were considered serious or life-threatening potential ADEs. As a follow-up, clinical reviewers conducted detailed chart review of serious or life-threatening potential ADEs to determine if they caused an ADE. Reviewers assessed severity of the ADE and attribution to the error.

Results: Ten (7.5% (95% CI 6.98 to 8.01)) actual ADEs resulted from the 133 serious and life-threatening potential ADEs, of which 6 resulted in significant, three in serious, and one life threatening injury. Therefore 4 (3% (95% CI 2.12 to 3.6)) of serious or life-threatening potential ADEs led to serious or life-threatening ADEs. Half of the ADEs were caused by dosage or monitoring errors for anti-hypertensives.

Conclusions: Unintercepted potential ADEs at the medication administration stage can cause serious patient harm. At hospitals where 6 million doses are administered per year, about 4000 preventable ADEs would be attributable to medication administration errors annually.

INTRODUCTION

Adverse drug events (ADEs) are injuries that result from medication use. Incidence rates of ADEs vary from two per 100 admissions to seven per 100 admissions among the hospitals that have conducted ADE studies.1-4 Some ADEs are preventable, while others are not (figure 1). Preventable ADEs are a leading cause of injury in the USA.5 A study done by Bates et al found that 20% of ADEs were associated with medication errors and are by definition preventable.6 Medication errors can occur at any stage of the medication process: drug ordering, transcribing, dispensing, administering or monitoring.6 Errors at the medication administration stage, while accounting for 26% of overall serious medication errors, occur in large numbers.7 One study found that 11.5% of the doses administered had an administration error, and 3.1% of the administrations had errors that could potentially harm patients.8 Another study performed in 36 hospitals showed that 19% of medication administrations contained an error and have found that 7% of administration errors have the potential to cause patient harm and were considered potential ADEs.9 These numbers are significant because medication administration errors are seldom intercepted by nurses or anyone else.10,11 Because so many medication doses are administered, the potential for harm cannot be underestimated; for example, a 300-bed facility (that administers 3000 doses per day) may experience 40 potential ADEs per day,9 while that number at a 735-bed tertiary academic medical centre (that administers 16 200 doses per day) is estimated at 98 per day.

ADEs manifest in a number of ways, ranging from mild allergic reactions to anaphylaxis or even death.1 3 4 11-13 One study estimated that the increased risk of death for a patient who experiences an ADE is nearly twice that of a patient who does not.5
Another study estimated that 9.7% of ADEs caused permanent disability. A study examining the cost implications of ADEs, conducted at two teaching hospitals, found that almost 2% of admissions experienced a preventable ADE, resulting in average increased hospital costs of $4700 per admission.

While the incidence of potential ADEs due to medication administration errors has been well characterised, it is not clear what proportion of these serious errors lead to actual patient harm. Understanding the relationship between potential ADEs and ADEs due to medication administration errors is important, as it will help clarify the clinical and financial impact of medication administration errors. This information will also inform policy makers, hospital administrators and payors who must target patient safety concerns with the largest risk and prioritise a large number of potential patient safety interventions. Therefore, we undertook a study to evaluate the relationship between potential ADEs due to medication administration errors and actual ADEs.

METHODS

Definitions

A medication error is defined as an error anywhere in the process of ordering, delivering or administering a drug. Medication administration errors, a subset of medication errors, are acts of omission or commission committed when medication doses are due for administration to the patient. Subtypes of medication administration errors appear in box 1.

ADEs are injuries that result from medication use. Potential ADEs are medication errors that have the potential to harm the patient. Potential ADEs that cause actual patient harm are considered preventable ADEs (figure 1). The current study uses the same types and definitions of medication errors as previously published studies.

Medication administration errors studied

In a previously published study, the rate of errors related to transcribing orders and administering medications was determined in 35 adult medical, surgical and intensive care units in a 735-bed tertiary academic medical centre. In the study year, physicians (or physician extenders) wrote approximately 1.7 million medication orders and nurses administered approximately 5.9 million doses of medications. A unit dose system and automated medication dispensing cabinets were used when the medication administration observations were made. Approximately half of the observations were made before the deployment of bedside bar code medication verification. Two main outcomes for administration errors were separately defined: errors in timing (involving administrations that were early or late by more than 1 h) and errors unrelated to timing. Overall, 14,041 medication administrations were observed by a team of five trained nurses, and administration errors were determined by reconciling the observed administrations against the physician orders. Each administration error was further adjudicated independently by two members of a multidisciplinary panel consisting of physicians, nurses and pharmacists to confirm the presence of an error and the potential for that error to lead to patient harm. Any disagreements between the two panel members concerning the presence of an error or the severity of potential harm were resolved by consensus. The study identified 1271 timing and non-timing medication administration errors. Of these, 133 administration errors were judged to have the potential to cause serious or life-threatening patient harm and were considered serious and life-threatening potential ADEs, respectively. Some patients had more than one error, but mostly these were one error per patient.

Determination of ADEs

We conducted a structured chart review on this closed cohort to determine the proportion of these serious and life-threatening potential ADEs that led to ADEs. We reviewed details of each potential ADE identified in the
ADEs


Severity of harm was defined based on previous studies including the drug involved, the type of error and error description. Using standard medical reference texts, we then prospectively identified possible ADEs that might result from the potential ADEs. For example, we identified possible ventricular arrhythmias and poorly controlled tachycardia as possible ADEs in a patient who received half of the prescribed dose of the antiarrhythmic Mexiletine (mexiletine hydrochloride) orally. As another example, we anticipated increased chances of bleeding, easy bruising, petechial formations or frank bleeds in a patient who received heparin dose intravenously instead of subcutaneously. This list of possible ADEs as well as the anticipated time-frame for the occurrence of the ADEs following the index potential ADE was identified before the charts were reviewed. Severity of harm was defined based on previous studies as shown in box 2 with examples.

We then performed a detailed chart review to look for ADEs within the a priori defined time-frame following the index potential ADE. The duration of follow-up of each patient depended on both the nature of the potential ADE and the patient’s hospital stay. If the chart review revealed a possible ADE, that event was further classified as a candidate adverse event. Two clinical reviewers then each reviewed candidate adverse events independently to (A) confirm the presence of an ADE; (B) determine severity of the ADE; and (C) determine (on a 5-point Likert scale) whether the ADE was directly attributable to the potential ADE. Both the presence and severity of the ADE were evaluated using previously established criteria (reference available upon request). The Likert scale for attributability was dichotomised with candidate ADEs that were judged to be ‘very likely’ and ‘more likely than not’ to be caused by the potential ADE considered attributable to the potential ADE. The reviewers had perfect inter-rater agreement about the presence of an ADE and attribution to error. The agreement regarding the severity of ADEs was moderate with a Cohen’s κ of 0.571, and subsequent review of materials resulted in total agreement. The level of agreement for adjudications performed for the parent study (such as whether administration errors had the potential to cause patient harm) can be found in the original NEJM study.

RESULTS

Following the review of the 133 serious and life-threatening potential ADEs, we identified 35 candidate adverse events. Of these, 10 (7.5% of serious and life-threatening potential ADEs) were confirmed as ADEs and were directly attributable to the potential ADE (with eight of these ADEs judged to be very likely caused by the administration error and two judged more likely than not). Of the 10 ADEs, six were associated with significant harm, three with serious harm and one with life-threatening harm. Overall, 4 (3% (95% CI 2.12 to 3.6)) of serious and life-threatening potential ADEs led to serious or life-threatening ADEs (tables 1 and 2). The

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**Box 1 Medication administration errors**

<table>
<thead>
<tr>
<th><strong>Timing errors</strong></th>
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<tbody>
<tr>
<td>Early administration</td>
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<tr>
<td>– 1–2 h</td>
</tr>
<tr>
<td>– &gt;2–4 h</td>
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<tr>
<td>– &gt;4 h</td>
</tr>
<tr>
<td>Late administration</td>
</tr>
<tr>
<td>– 1–2 h</td>
</tr>
<tr>
<td>– &gt;2–4 h</td>
</tr>
<tr>
<td>– &gt;4 h</td>
</tr>
<tr>
<td>Non-timing errors</td>
</tr>
<tr>
<td>– Oral versus nasogastric-tube administration</td>
</tr>
<tr>
<td>– Errors in administration documentation</td>
</tr>
<tr>
<td>– Dose error</td>
</tr>
<tr>
<td>– Wrong medication</td>
</tr>
<tr>
<td>– Errors in directions, monitoring or both</td>
</tr>
<tr>
<td>– Administration without order</td>
</tr>
<tr>
<td>– Errors in routes of administration other than oral/ nasogastric tube</td>
</tr>
</tbody>
</table>

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**Box 2 Definition of severity level for adverse drug events (ADEs)**

**Significant ADE** occurs if the event causes symptoms that while harmful to the patient pose little or no threat to the patient’s life function. These ADEs can include elevated or depressed laboratory test levels. Examples of physical symptoms include dizziness, fatigue, constipation, muscle cramps, insomnia, headaches and pedal oedema.

**Serious ADE** occurs if the event causes persistent alteration of life function. Serious ADEs can also include elevated or depressed lab values that require medical intervention, especially if they suggest organ system dysfunction. Examples of physical symptoms include a two-unit gastrointestinal bleed, a symptom requiring hospitalisation, an altered mental status/ excessive sedation, or allergic reaction—shaking chills/ fever or symptomatic hypoglycaemia.

**Life-threatening ADE** occurs if the event causes symptoms or changes that if not treated, would put the patient at risk of death. Life-threatening ADEs include laboratory values that are either elevated or depressed to the point that a critical physiological function is at risk of failure. Examples of physical symptoms: patient transferred to intensive care unit due to respiratory failure, cardiac arrest or anaphylaxis.
ADEs were distributed equally in the medical and surgical units (four ADEs each) and two occurred in the intensive care unit. Details of these 10 ADEs can be found in table 3.

Around 50% of the drugs implicated in causing patient harm were antihypertensives, followed by insulin, heparin, Ativan (lorazepam) and Solu-Medrol (methylprednisolone sodium succinate). The top three error categories of potential ADEs were dosage errors, administration documentation errors, and monitoring and direction errors. These were also the top causes of ADEs. The event associated with life-threatening patient harm was caused by Solu-Medrol that was given on the wrong day postoperatively to a kidney transplant patient, contributing to organ rejection. An example of a serious ADE was when insulin was given without checking existing blood glucose levels, resulting in dangerously low sugar levels classified as a serious ADE (table 3).

**DISCUSSION**

The rate of serious and life-threatening potential ADEs resulting in actual patient harm or ADEs (known as the actualisation rate in previous studies) stands at 7.5% (95% CI 6.98 to 8.01). In addition, 3% (95% CI 2.12 to 3.6) of serious and life-threatening potential ADEs led to serious or life-threatening ADEs. Given previous estimates of serious or life-threatening potential ADE(s) of 1.33 per 100 medication doses administered, we estimate that in the study hospital where 6 million doses are administered per year, more than 4200 preventable ADEs attributable to medication administration errors occur annually. There are several studies that attempt to calculate the cost of an ADE, with the cost ranging from $4700 to $8700 per ADE depending on the considerations and methodology used to make these estimations. Given these estimates, the cost of patient harm from medication administration errors could range anywhere between $25 and $33 million in a 700-bed teaching hospital annually.

Medication administration errors warrant attention as they are typically not intercepted; 84% of these errors go unintercepted according to a study by Leape et al. Medication administration is carried out by nurses, who are mostly alone at the time of medication administration. Nurses at the point-of-care also face a variety of cognitive and system challenges as they complete many medication-related and non-medication-related tasks in a compressed time window. Hospital workflow and process studies have shown that nurses are likely to get distracted and/or interrupted several times in the course of performing their duties, which include administering medications. For instance, a study that measured workflow interruptions showed a nurse interrupted 17 times during one medication pass. The likelihood of an error rises with increasing complexity of the work environment and with building work pressure. Nursing human factors studies have suggested that a high nursing workload leads to medication errors. While interventions like no interruptions during medication passes, quiet medication prep rooms or two-nurse medication administration can work to improve human level performance, well-targeted system improvements and safety technology implemented at the point-of-care may reduce errors, protect the healthcare worker and patient from harm, and save costs to the system.

Our study has significant implications on the information technology improvement opportunities. A
### Table 3  Details of actual ADEs that resulted from potential ADEs

<table>
<thead>
<tr>
<th>Error description</th>
<th>Error category</th>
<th>Severity of potential ADE</th>
<th>ADE description</th>
<th>ADE severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ativan (lorazepam) 1 mg PO Q4H PRN anxiety. Drug was administered dose 3 h early and not documented</td>
<td>Documentation error</td>
<td>Serious</td>
<td>Two doses of Ativan given closely together resulted in increased somnolence, longer duration and deeper sleep on the following 2–3 days</td>
<td>Serious ADE</td>
</tr>
<tr>
<td>Atenolol 50 mg PO in AM. Hold if SBP &lt; 90 or HR &lt; 60. HR at the time of administration was 56, vital signs not checked</td>
<td>Direction/monitoring error</td>
<td>Serious</td>
<td>The heart rate dropped subsequent to medication error. Heart rate and blood pressure dropped further to about HR 55–98 and BP 90/64–100/60. Patient uncomfortable. Mild T wave changes on EKG</td>
<td>Serious ADE</td>
</tr>
<tr>
<td>Lopressor (metoprolol) 5 mg IV q6 h. Hold if: SBP &lt; 100, HR &lt; 60. Observer recorded vitals at HR 50. HR below hold parameters</td>
<td>Direction/monitoring error</td>
<td>Serious</td>
<td>Heart rate dropped a day after the medication error to HR 47–64.</td>
<td>Significant ADE</td>
</tr>
<tr>
<td>Solu-Medrol (methylprednisolone sodium succinate) 60 mg IV BID × 2. Medication was administered 2 days after surgery.</td>
<td>Transcription error and medication given on wrong day</td>
<td>Fatal or life-threatening</td>
<td>Patient was s/p renal transplant. This error led to acute tubular renal injury and graft rejection</td>
<td>Life-threatening ADE</td>
</tr>
<tr>
<td>Heparin ordered 5000 units SC. Observer recorded dose administered as IV</td>
<td>Wrong route error</td>
<td>Serious</td>
<td>Heparin given by the wrong route is known to increase bleeding and bruising tendency. Patient had conjunctival haemorrhages which did not exist before the IV administration of heparin</td>
<td>Significant ADE</td>
</tr>
<tr>
<td>Lopressor (metoprolol) 6.26 mg PO. Hold if SBP &lt; 100. Dose administered at 08:15 h when the observer recorded BP 92/46 and HR 86</td>
<td>Direction/monitoring error</td>
<td>Serious</td>
<td>Blood pressure dropped to BP 77/37–110/46</td>
<td>Significant ADE</td>
</tr>
<tr>
<td>Advair (fluticasone and salmeterol) diskus 250/50 × 1 puff inhalation BID. Was transcribed at QID and patient received 4 doses</td>
<td>Transcription error</td>
<td>Serious</td>
<td>BP 106/58, HR 70s; patient complained of coughing and heart pounding. 27 beats NSVT on the monitor of unclear aetiology</td>
<td>Significant ADE</td>
</tr>
<tr>
<td>Novolog (insulin aspart) 6 units SC prebreakfast. Hold if BS &lt; 70. Drug dose given when blood sugar was 29</td>
<td>Dosage error</td>
<td>Fatal or life-threatening</td>
<td>Sharp fall in blood sugar. BS 32, compensated by administration of D50. Serious ADE bordering on life-threatening</td>
<td>Serious ADE</td>
</tr>
<tr>
<td>Captopril 6.25 mg PO TID. Observer observed 12.5 mg administered documented as 6.25</td>
<td>Dosage error</td>
<td>Serious</td>
<td>BP dropped after observed error. BP dropped after observed error to BP 90–120/50–70</td>
<td>Significant ADE</td>
</tr>
<tr>
<td>Lopressor (metoprolol) 5 mg PO. Observer saw 2.5 mg administered, vital signs within range and dose was not documented</td>
<td>Dosage error</td>
<td>Serious</td>
<td>Half the prescribed dose of Lopressor was given resulting in rise of SBP from 108 to 140 consistently for 2 days after the error</td>
<td>Significant ADE</td>
</tr>
</tbody>
</table>

ADE, adverse drug event; AM, BID, twice daily; BP, blood pressure; BS, blood sugar; EKG, electrocardiogram; HR, heart rate; IV, intravenously; NSVT, non-sustained ventricular tachycardia; PO, orally; PRN, ‘take as needed’; QID, four times a day; s/p, special procedure; SBP, systolic blood pressure; SC, subcutaneously; TID, three times a day.
Previous study demonstrated that bar code medication verification technology reduced the rate of non-timing potential ADEs by 50.8%. Our findings suggest that ADEs are associated with a small number of drug classes and, therefore, computerized warnings during administration of high-risk drug classes such as insulin, opiates, potassium chloride and anticoagulants may be of value. This strategy is supported by Leape who previously pointed out that improved dissemination and display of drug and patient data should make errors in the use of drugs less likely. Other promising interventions that have been studied in this area include the use of Radio Frequency Identification (RFID). High reliability technologies are effective at reducing error rates although they are expensive to acquire and deploy; given the costs of ADEs, the investments seem well worthwhile.

Our study should be considered in light of its limitations. Although chart reviews detect more errors than incident reports, retrospective medical chart reviews may not completely detect all clinical events or capture all the relevant details. This could lead to an underestimation of harm resulting from medication administration errors. This is especially true with regard to patients’ self-reported symptoms secondary to the medication errors, as they may not be recorded consistently in the medical record. Another limitation is that we followed precede second author—data analysis second reviewer, k analysis, result interpretation, manuscript review and edits. SM: third author—data analysis review, statistical analysis support, gave technical and conceptual advice, manuscript review and edits. TG: fourth author—jointly conceived the study with EP, gave conceptual advice, data analysis review, advice on results presentation, manuscript review and edits.

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