Drug-Related Hospitalizations in a Tertiary Care Internal Medicine Service of a Canadian Hospital: A Prospective Study


Study Objectives. To determine the frequency, severity, preventability, and classification of adverse drug events resulting in hospitalization, and to identify any patient, prescriber, drug, and system factors associated with these events.

Design. Prospective, observational study.

Setting. Internal medicine service of a large tertiary care hospital in Canada.

Patients. A total of 565 consecutive adult patients admitted to the hospital during a 12-week period.

Measurements and Main Results. A patient's hospitalization was defined as drug related if it was directly related to one of eight predefined classifications; severity and preventability of the hospitalization were also assessed. Multivariate logistic regression analysis was used to evaluate patient, prescriber, drug, and system factors associated with drug-related hospitalizations. The frequency of drug-related hospitalization was 24.1% (95% confidence interval [CI] 20.6–27.8%), of which 72.1% (95% CI 63.7–79.4%) were deemed preventable. Severity was classified as mild, moderate, severe, and fatal in 8.1% (95% CI 4.1–14.0%), 83.8% (95% CI 76.5–89.6%), 7.4% (95% CI 3.6–13.1%), and 0.7% (95% CI 0.0–4.0%), respectively, of the hospitalizations. The most common classifications of drug-related hospitalization were adverse drug reactions (35.3% [95% CI 27.3–43.9%]), improper drug selection (17.6% [95% CI 11.6–25.1%]), and noncompliance (16.2% [95% CI 10.4–23.5%]). No independent risk factors for drug-related hospitalization were identified with regression modeling.

Conclusion. Approximately 25% of patients in our study were hospitalized for drug-related causes; over 70% of these causes were deemed preventable. Drug-related hospitalization is a significant problem that merits further research and intervention.

Key Words: adverse drug event, ADE, adverse effect, adverse drug reaction, drug-related hospitalization.

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the resulting costs contribute to the overall pressures on our health care system. A probability model estimated that from 1995–2000, costs due to drug-related morbidity and mortality had more than doubled, from $76.6 billion to more than $177.4 billion.5,6

Numerous studies have investigated the problem of drug-related morbidity in ambulatory care, emergency department, and hospitalized patients.72,33 In Canada, however, limited research has been conducted to characterize the impact of drug-related hospitalizations. The 2004 Canadian Adverse Events Study evaluated adverse events in Canadian hospitals, but the study was not designed to evaluate adverse drug events resulting in hospitalization.18 In addition, most research has been retrospective and resulted in inherent methodologic limitations, such as possible underestimation of the problem.

Finally, the definition of an adverse drug event varies significantly among studies, limiting both comparative evaluation and generalizability. In most studies, an adverse drug event has been limited to adverse drug reactions. The World Health Organization (WHO) defines adverse drug reaction as any noxious, unintended, or undesired effect of a drug occurring at dosages administered in humans for prophylaxis, diagnosis, or treatment.34 This definition excludes many other classifications of adverse drug events that may result in hospitalization, such as untreated indication, improper drug selection, subtherapeutic or supratherapeutic dosage, noncompliance, drug interaction, and drug use without an indication.35–38 A more comprehensive, clinically important, and reproducible definition of adverse drug event would result in a more accurate and meaningful characterization of drug-related hospitalization.

In this era of increased attention to improved patient safety coupled with continuing budget restraints, accurate characterization of drug-related hospitalization is an important step toward reducing the potentially significant burden such problems place on our health care system.39 The purpose of this study was to prospectively evaluate the frequency, severity, preventability, and classification of adverse drug events resulting in hospitalization in an internal medicine service of a large tertiary care hospital, and to identify any patient, prescriber, drug, and system factors associated with these events.

Methods

Study Design and Setting

This prospective, observational study was conducted at the internal medicine units of Vancouver General Hospital, a 700-bed tertiary referral center and the major teaching hospital affiliated with the University of British Columbia. The internal medicine service has approximately 2500 admissions/year. Care is provided by attending internists certified by the Royal College of Physicians and Surgeons of Canada and an associated team of medical residents and students. Patients admitted to this service are medically managed for diverse conditions, including but not limited to cardiovascular disease, diabetes mellitus, pneumonia, gastrointestinal hemorrhage, liver and renal failure, hematologic abnormalities, complex skin and soft tissue infections, and various comorbidities complicated by psychiatric or behavioral challenges related to substance abuse. The study was conducted by the Clinical Service Unit Pharmaceutical Sciences at Vancouver General Hospital. Ethics approval was obtained from the research ethics boards of both the University of British Columbia and the Vancouver Coastal Health Research Institute.

Patient Selection

Consecutive adult patients admitted to the internal medicine units during a predefined 12-week period from January 10–April 4, 2005, were enrolled into the study. Data regarding patients
who were admitted more than once during the study period were entered as discrete hospitalizations. Patients were included if they were admitted under the internal medicine service to one of six predefined hospital units. Acute medical care was provided in four of these units for patients younger than 75 years and in two units for patients aged 75 years or older. Patients were excluded if they were admitted to a non–internal medicine unit, transferred from another hospital for specialized care, or transferred from a non–internal medicine service.

Data Collection

Patients were enrolled by one of 10 residency-trained clinical pharmacists specializing in adult acute care medicine and participating in activities of a multidisciplinary patient care team. Each pharmacist was trained in the practice of pharmaceutical care and in the application of the Hepler and Strand classification of drug-related problems. In addition, each pharmacist received training before the study began and participated in a 3-week pilot study period to ensure proper use of the data collection tool and application of the study definitions.

A daily admission census list generated by a computerized patient care information system was used to identify all patients admitted to the hospital. The enrolling clinical pharmacist obtained a bedside history from each patient to determine the chief complaint, history of the present illness, medical and drug history, compliance with drug therapy, and allergy status. For patients unable to provide their medical or drug history due to acute illness, language barrier, or other issues, information was obtained by chart review or proxy. When necessary, ancillary information was obtained from family members, the family physician, specialists, and the community pharmacy. PharmaNet, a secured provincial computer network that links all pharmacies in British Columbia and provides information concerning patient-specific prescription drugs dispensed in community pharmacies, was used when necessary to verify drugs prescribed. Information regarding physical examinations conducted by the attending internist or internal medicine resident was reviewed when necessary, as were results of laboratory and diagnostics tests. Clinical care was not altered as a result of this study.

Personal digital assistant (PDA) database development software (Pendragon Forms 3.2; Pendragon Software Corp., Libertyville, IL) was used to develop a multitable relational database for point-of-care data entry. A Tungsten E PDA (Palm, Inc., Sunnyvale, CA) was used for data entry. Access to data on the PDA was secured with both password access control and 128-bit data-encryption algorithms using PDA Defense Pro software (Asyncrony Solutions, St. Louis, MO). Data were transferred daily from the PDA to a secured personal computer. Information transfer involved importing data from the PDA to a desktop relational database program (Access; Microsoft Corp., Redmond, WA). The data were then queried with the desktop database software and exported to statistical analysis software for analysis.

Outcomes and Definitions

Primary outcomes of the study were the frequency, severity, preventability, and classification of drug-related hospitalizations. A hospitalization was defined as drug related if it was directly related to one of eight predefined classifications: adverse drug reaction, drug interaction, improper drug selection, untreated indication, subtherapeutic dosage, supratherapeutic dosage, noncompliance, and drug use without indication. Adverse drug events unrelated to a patient’s chief complaint were not considered as the cause of hospitalization.

We used the WHO’s definition of adverse drug reaction and included all reactions to drugs administered at appropriate dosages, as well as those associated with abnormal drug concentrations or laboratory values. All other terms were defined using the Hepler and Strand classification system.

- Improper drug selection: any noxious, unintended, or undesired effect due to the use of a drug not optimal in the treatment of a confirmed indication.
- Noncompliance: any noxious, unintended, or undesired effect caused by failure to receive a drug. This definition included both patient and physician noncompliance.
- Supratherapeutic dosage: any noxious, unintended, or undesired effect caused by excessive drug dosage or duration for a given indication or patient.
- Subtherapeutic dosage: any noxious, unintended, or undesired effect caused by failure to receive sufficient drug dosage or duration for a given indication or patient.
• Untreated indication: any noxious, unintended, or undesired effect resulting from the failure to treat a known indication.
• Drug interaction: any noxious, unintended, or undesired effect caused by the coadministration of two or more drugs.
• Drug use without an indication: any noxious, unintended, or undesired effect caused by the use of a drug for which there is no clear indication.

Clinical pharmacists had access to two comprehensive clinical information software resources that were installed on the study’s PDAs (Lexi-Drugs and Lexi-Interact for Palm OS; Lexi-Comp, Inc., Hudson, OH). These resources provided access to drug information and drug interaction analysis at the point of care. In addition, literature evaluation was used if questions remained regarding drug-related issues. MEDLINE was searched using generic drug names and patient complaints or laboratory test abnormalities.

Severity of hospitalization was defined as mild (laboratory abnormalities or symptoms not requiring treatment), moderate (laboratory abnormalities or symptoms requiring treatment or resulting in nonpermanent disability), severe (life threatening or resulting in permanent disability), or fatal. 31–43

Drug-related hospitalizations were defined as preventable if treatment was inconsistent with current knowledge of ideal medical practice. This included inappropriate drug, dosage, or route of administration relative to the patient’s clinical condition, age, weight, and renal function; known drug allergy or previous reaction to drug; known drug interaction; noncompliance; laboratory monitoring not performed; and prescribing, dispensing, or administration errors. 2, 13, 17, 41, 42

Cases identified as questionable for likelihood of drug-related association, severity, or preventability were independently adjudicated by three external reviewers (two pharmacists and one internist) using an explicit predefined approach. The presence or absence of a causal relationship between the drug administered and the reason for hospitalization, severity, and preventability were established by consensus.

Secondary outcomes of the study were patient, prescriber, drug, and system factors associated with hospitalization. Patient factors assessed were age, sex, and renal function; prescriber factors were use of a regular family physician and the numbers of prescribers; drug factors were the number of prescription drugs prescribed, number of over-the-counter (OTC) drugs taken, and use of complementary and alternative medicine (CAM); and system factors were the use of more than one pharmacy and the use of compliance aids (e.g., blister pack, dosette, alarm, calendar, caregiver).

Statistical Analysis

Primary outcomes were reported as proportions, presented as percentages with 95% confidence intervals (CIs). Secondary analysis of factors associated with drug-related hospitalization was

![Figure 1. Patient flow diagram. *Due to lack of space in the internal medicine service, patients were admitted to other services, which were not covered by the internal medicine clinical pharmacists.*]
performed by fitting a logistic regression model (SPSS, version 6.1; SPSS Inc., Chicago, IL). To avoid overfitting, covariates for this model were selected and defined a priori, with appropriate thresholds of cases and outcomes of interest for each covariate.

Results

The patient flow diagram (Figure 1) illustrates the breakdown of the study patients. During the 12-week study period, 739 patients were admitted to the internal medicine service at Vancouver General Hospital; 134 (18.1%) of these patients met some exclusion criteria, and 40 (5.4%) were missed (i.e., admitted or discharged over a weekend or without study data). Thus, 565 patients were included in our final analysis. Mean ± SD age of the study population was 69.3 ± 18.8 years, and 286 (50.6%) were women (Table 1).

Drug-related hospitalizations occurred in 136 (24.1% [95% CI 20.6–27.8%]), of which 98 (72.1% [95% CI 63.7–79.4%]) were deemed preventable. Severity was classified as mild, moderate, severe, and fatal in 11 (8.1% [95% CI 4.1–14.0%]), 114 (83.8% [95% CI 76.5–89.6%]), 10 (7.4% [95% CI 3.6–13.1%]) and one (0.7% [95% CI 0.0–4.0%]), respectively, of drug-related hospitalizations. Adverse drug reactions, improper drug selection, and noncompliance were the most common classifications of drug-related hospitalization (Table 2); examples are provided in Table 3.

Overall, a total of 167 drugs were implicated in the 136 drug-related hospitalizations. In 105 (77.2%) of these 136 hospitalizations, a single drug was associated with hospitalization, whereas in 31 hospitalizations (22.8%), several drugs were implicated. The most common drug classes associated with drug-related hospitalization were cardiovascular agents (27.5%), antibiotics (23.4%), nonsteroidal antiinflammatory drugs (13.2%), central nervous system agents (7.8%), anticoagulants (5.4%), and hypoglycemic agents (4.8%). The most common agents associated with drug-related hospitalizations were aspirin (14.0%), furosemide (7.4%), ciprofloxacin (7.4%), warfarin (6.6%), ramipril (6.6%), and spironolactone (5.9%).

Results of the multivariate logistic regression analysis (Table 4) indicate that the occurrence of drug-related hospitalization was independent of age, sex, number of prescription drugs prescribed, number of OTC drugs taken, use of complementary and alternative medicine, impaired renal function, use of a compliance aid, use of more than one pharmacy, use of a regular family physician, and use of more than one prescriber.

Discussion

Our study found that over a 12-week period involving 565 admissions to internal medicine units at a large Canadian teaching hospital, 24.1% of hospitalizations were drug related; 72.1% of the 136 were deemed preventable. Although 83.8% patient outcomes associated with drug-related hospitalization were moderate in severity, 7.4%) were considered severe, and 0.7% resulted in death.

The frequency of drug-related hospitalizations in our study is similar to that of adverse drug events reported in studies conducted in the emergency department and ambulatory care settings; however, it is higher than reported in studies evaluating drug-related hospitalizations.
This may be explained by a number of factors. First, the prospective design of our study allowed us to obtain complete medical and drug histories and ensure that all information required to accurately classify the events was gathered. Second, we used experienced clinical pharmacists trained in recognition and resolution of drug-related problems. Physician recognition of adverse drug events has been estimated at 50%36; however, detailed histories of drug therapy obtained by pharmacists may improve detection of drug-related hospitalization and prevent interrupted or inappropriate drug therapy during the hospital stay.40, 41 Finally, use of the Hepler and Strand comprehensive classification system likely maximized the probability that all possible drug-related causes of hospitalization were identified.35–37

The classification and specific drug therapy associated with hospitalizations in our study are consistent with those in previous reports. Adverse drug reaction, improper drug selection, and noncompliance were the most common classifications of drug-related hospitalization in our study population. Adverse drug reaction and noncompliance have been consistently cited as the primary reasons for drug-related morbidity, regardless of study setting. Previous reports also have determined that cardiovascular agents, antibiotics, nonsteroidal antiinflammatory drugs, central nervous system agents, anticoagulants, and hypoglycemic agents account for 60–70% of adverse drug events.19, 20

Various patient traits associated with drug-related hospitalization have been reported; however, specific risk factors continue to be inconsistently identified. Although a trend toward increased risk of drug-related hospital-
ization was observed in patients not using a drug compliance aid and those using more than one community pharmacy, our study did not identify any factors with a statistically significant association with drug-related hospitalization. Whether this was due to our small sample size is unclear; however, despite the lack of any specific patient, prescriber, drug, or system characteristics associated with drug-related hospitalization in our study, several factors merit close monitoring of patients. Advanced age, female sex, impaired renal function, numerous comorbidities, and the number of concomitant drugs administered have been risk factors for drug-related problems.\[45, 48, 49\]

Avoiding therapeutic duplications, discontinuing unnecessary drugs, monitoring for renal function, anticipating drug interactions, individualizing dosage, and optimizing overall drug therapy are all strategies that may prevent drug-related hospitalization. Improvements in seamless care for patients transitioning from acute to ambulatory care—including formal admission and discharge communication among the hospital, family physician, and community pharmacist; periodic monitoring of symptoms and laboratory values; proper drug counseling; and regular review of prescriptions—may also minimize drug-related hospitalization.\[41\]

Hospital and community pharmacists can evaluate and reinforce compliance with drug therapy by determining how patients have been taking and tolerating their drug, and by ensuring that patients refill their prescriptions at appropriate intervals. Pharmacists can also provide instructional material and support group links, dispense convenient dosage schedules and drug packages, and provide patients with reminder calendars.\[30, 31\] Patients should be encouraged to use only one community pharmacy and to discuss any OTC and CAM products with a physician or pharmacist to limit potential interactions. The availability of PharmaNet in British Columbia allows pharmacists to review all prescriptions filled at pharmacies throughout the province. Nevertheless, maintaining a complete patient profile that includes OTC and CAM products can further enable better patient monitoring and prevent drug-related hospitalization.\[36\]

Limitations

Our study has several limitations. First, although we used the Hepler and Strand classification of drug-related problems to define drug-related hospitalization, we could not assess causality in a reliable and valid manner. The Naranjo probability scale\[52\] has been used to estimate causality for adverse drug reactions, but no validated instrument is available for the other seven classifications of drug-related problems we used. Thus, we relied on the clinical experience and judgment of the clinical pharmacist for classifying drug-related hospitalizations.

Second, because 10 clinical pharmacists participated in data collection throughout the study, variability among raters may have affected the assignment of an event into the appropriate classification, as well as the assessment of

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients with Drug-Related Hospitalizations (n=136)</th>
<th>Patients without Drug-Related Hospitalizations (n=429)</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>Mean ± SD 67.9 ± 19.5</td>
<td>69.8 ± 18.6</td>
<td>0.26</td>
</tr>
<tr>
<td>Prescription drugs (no.)</td>
<td>Mean ± SD 6.0 ± 3.3</td>
<td>4.9 ± 3.4</td>
<td>0.22</td>
</tr>
<tr>
<td>OTC drugs (no.)</td>
<td>Mean ± SD 1.6 ± 1.7</td>
<td>1.7 ± 1.8</td>
<td>0.82</td>
</tr>
<tr>
<td>Total drugs (no.)</td>
<td>Mean ± SD 7.5 ± 4.0</td>
<td>7.0 ± 11.2</td>
<td>0.85</td>
</tr>
<tr>
<td>Female sex</td>
<td>No. (%) 58 (42.6)</td>
<td>229 (53.4)</td>
<td>0.14</td>
</tr>
<tr>
<td>Use of CAM</td>
<td>No. (%) 20 (14.7)</td>
<td>66 (15.4)</td>
<td>0.89</td>
</tr>
<tr>
<td>Clcr &lt; 50 ml/min</td>
<td>No. (%) 68 (50.0)</td>
<td>185 (43.1)</td>
<td>0.44</td>
</tr>
<tr>
<td>Use of compliance aid</td>
<td>No. (%) 54 (39.7)</td>
<td>198 (46.2)</td>
<td>0.14</td>
</tr>
<tr>
<td>Use of more than one pharmacy</td>
<td>No. (%) 29 (21.3)</td>
<td>44 (10.3)</td>
<td>0.15</td>
</tr>
<tr>
<td>Regular family physician</td>
<td>No. (%) 129 (94.9)</td>
<td>407 (94.9)</td>
<td>0.46</td>
</tr>
<tr>
<td>More than one physician</td>
<td>No. (%) 80 (58.8)</td>
<td>210 (49.0)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

OTC = over the counter; CAM = complementary and alternative medicine; Clcr = creatinine clearance.
severity and preventability. This was not evaluated. We attempted to minimize such variability by providing the pharmacists with pre-study training regarding the application of study definitions and a 3-week pilot study. We encouraged the pharmacists to consult one another about questionable cases as needed, and we convened an independent adjudication committee when difficult cases could not be resolved.

Finally, because our study involved patients admitted to an internal medicine service, generalizability of the results to other services may be limited. Further research is warranted to determine the most commonly implicated drugs and risk factors associated with drug-related hospitalizations in other hospitalized populations, patients living in the community, and nursing home residents.

Conclusion

Drug-related hospitalization is a significant problem. Increased awareness and enhanced collaborative efforts among patients, physicians, pharmacists, and caregivers within the community and hospital have the potential to minimize the impact of this problem. Recognition of patient, prescriber, drug, and system factors, as well as appropriate therapeutic modifications, should be pursued. Further research is necessary to implement and evaluate strategies aimed at reducing drug-related hospitalizations.

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References


"DRUG-RELATED HOSPITALIZATION" Samoy et al 1585


