Evaluation of Trigger Tool Methodology Related to Adverse Drug Events in Hospitalized Patients

By Sara Kolc Brown*, PharmD, Jacob Peterson†, PharmD, Shayne Harris Schiedel‡, PharmD, MBA & Kari Vavra Janes§, PharmD, BCPS

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*Corresponding author
†Meijer Pharmacy
‡Spectrum Health, Ferris State University
§Spectrum Health, Ferris State University

At the time of the project, Dr. Brown, Dr. Peterson, and Dr. Schiedel were PharmD students at the Ferris State University College of Pharmacy in Big Rapids, Michigan.

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The use of trigger tool methodology was useful for identifying ADEs related to hypoglycemia with insulin and naloxone administration.

Introduction

The Institute for Healthcare Improvement (IHI) defines patient harm as “unintended physical injury associated with medical care that requires additional monitoring, treatment, or hospitalization, or that results in death.” Adverse drug events (ADEs) are the most common source of patient injury and have been estimated to affect 19% of inpatients in Western countries. An ADE is defined as an injury resulting from medical intervention related to a drug. This includes medication errors, adverse drug reactions, allergic reactions, and overdoses. To reduce patient harm and improve patient care, the Institute for Healthcare Improvement (IHI) Global Trigger Tool, the information gathered could be used by the institution to help establish new policies and procedures to prevent these events from occurring in the future.

Summary: The positive predictive value (PPV) for elevated INR was 35% (confidence interval [CI] 21–53%), hypoglycemia was 70.4% (CI 62–78%), and 53% for naloxone administration (CI 45–60%). Drug interactions were the most common factor that may have contributed to an elevated INR, with a mean INR of 7.9. Basal insulin monotherapy, recent diet changes, decreases in renal function, and discontinuation/tapering of corticosteroids were all observed to be contributing factors to hypoglycemia events. The mean trigger glucose level was 42.98 mg/dL. Dose range order sets, high morphine milligram equivalents (MME), and decreased renal function may have contributed to naloxone administration. Polypharmacy was attributed to some of these adverse events, with the average inpatient MME of 100.5 mg.

Conclusion: The use of trigger tool methodology was useful for identifying ADEs related to hypoglycemia with insulin, moderately useful for naloxone administration, and least successful for elevated INR with warfarin. The ADEs that were identified revealed a wide variety of contributing factors that can be used as areas of interest when creating new policies and procedures to reduce ADEs in the future.

Keywords: global, trigger, tool, naloxone, INR, hypoglycemia

Abstract

Purpose: To determine why an inpatient has had one of the following occurrences in the electronic health record due to an adverse drug event (ADE): international normalized ratio (INR) > 6, plasma blood glucose ≤ 50 mg/dL, or naloxone administration use. Utilizing the Institute for Healthcare Improvement (IHI) Global Trigger Tool, the information gathered will be used to determine how to prevent these events from occurring in the future.

Introduction

The objective of this quality-improvement project was to determine why an inpatient has had one of the following adverse event triggers: an INR > 6, a plasma glucose ≤ 50 mg/dL, or naloxone administration. The data from this project could be used by the institution to help establish new policies and procedures to prevent these events from occurring in the future.

Methods

This project retrospectively reviewed adverse event triggers for patients with an INR > 6, a plasma glucose ≤ 50 mg/dL, or naloxone administration at all of the institution’s inpatient adult facilities. An institutional review board (IRB) protocol was submitted; however, it was deemed a quality-improvement project and exempt from IRB approval. A quality reports dashboard was utilized to capture trigger events. For each trigger, the dashboard reported the time and date of the event, the location, the patient identification number, and the lab value (for INR and blood glucose) or naloxone administration. The electronic health record (Cerner) was then reviewed for each trigger event to determine eligibility. Trigger events starting January 1, 2017, were reviewed by three fourth-year student pharmacists, and data was collected on the initial BB application to the identified intervention related to the reversal agent(s); patient status (e.g., symptoms, severity, respiratory rate, and oxygen saturation for the naloxone trigger); and opioid naïve status and home opioid regimen (for the naloxone trigger). Finally, data pertaining to risk factors that may have contributed to the trigger event was collected (e.g., interacting medications, diet changes, inappropriate dosing for age or weight, etc.).

Results

Elevated INR

A total of 77 positive triggers were identified for INR > 6 (Figure 1). Of these, 37 met inclusion criteria and 13 met screening criteria for classification as adverse drug events. The PPV was calculated to be 35% (CI 21–53%). Patients were initially included for chart review if they had an INR > 6 triggers and were receiving warfarin therapy. If the INR > 6 was present on admission, patients were excluded. The 24 patients that did not meet screening criteria included those for whom no reversal agent was given (n=9), warfarin reversal was used for procedure (n=2), a laboratory error occurred (n=5), no bleeding occurred (n=8). Patients were considered to have experienced an ADE if the elevated INR was associated with the anticoagulant, if there was a clinical intervention, and if there was evidence of bleeding. For the 13
ADEs, 61.5% (n=8) of patients were female, the mean age was 70.3 years, and 61.5% (n=8) of patients had been on warfarin at home versus newly starting it in the hospital. Atrial fibrillation was the most common reason for therapy (n=7), followed by cardiac thrombosis (n=4), venous thromboembolism (n=3), and aortic stenosis (n=1). Two patients had more than one indication noted. The mean INR was 7.9. Patients often had more than one INR > 6, but the first triggering INR was used to determine the mean. The most common reversal agent was vitamin K 5 mg by mouth (16 doses) followed by vitamin K 2.5 mg by mouth (3 doses), fresh frozen plasma (FFP) (3 doses), and vitamin K 5 mg subcutaneously (2 doses). Patients often received more than one dose of vitamin K. Factors contributing to INR > 6 included liver dysfunction (n=3), drug interactions (n=6), nutrition changes (n=1), and inappropriate dosing/titration (n=3). Two patients had more than one contributing factor and another two did not have any identifiable factors. Interacting medications of note included piperacillin/tazobactam, azithromycin, fluconazole, hydrocortisone, ceftizime, and metronidazole.

**Hypoglycemia**

A total of 148 positive triggers were identified for plasma glucose ≤ 50 mg/dL. Of these, 142 met inclusion criteria and 100 met screening criteria for classification as adverse drug events. Of the 6 patients excluded, 5 had hypoglycemia upon admission and 1 patient was pregnant. For events that did not meet screening criteria, the top reasons for the event being screened out as an ADE were no intervention given for hypoglycemia (n=19), plasma glucose > 50 mg/dL upon recheck (n=13), and the patient having no recent exposure to hypoglycemia agents that could have led to the hypoglycemia (n=10). The PPV was calculated to be 70.4% (CI 62–78%). Figure 2 outlines the chart review process for the hypoglycemia trigger. For the 100 ADEs, 43% (n=43) of patients were female, the mean age was 63.97 years, and 88% (n=88) of patients had diabetes mellitus. Decreased renal function was common with 30% (n=30) and 27% (n=27) of patients having a creatinine clearance < 30 mL/min or 31–60 mL/min, respectively. Insulin glargine alone (n=49, 49%) and insulin glargine/insulin lispro (n=30, 30%) were the most common insulin regimens associated with hypoglycemia. Insulin lispro alone, insulin glargine (IV continuous or IV push), and other subcutaneous agents were less commonly involved. The mean trigger glucose level was 42.98 mg/dL. Patients often had more than one glucose level ≤ 50 mg/dL, but the first triggering glucose was used to determine the mean. The most common reversal agent was dextrose 50% (50 events) followed by oral glucose tablets (32 events), food/sugary beverage (10 events), and a combination of interventions (8 events). Factors contributing to plasma glucose ≤ 50 mg/dL included diet changes (n=15) and co-administration of dysglycemic agents (n=20). Contributing factors could not be identified for all patients. Diet changes incorporated patients with nothing by mouth (NPO) orders, decreased appetite, or diet reinitiation without adjusting the home insulin dose. The most common dysglycemic agents were corticosteroids, which were either discontinued or tapered without sufficient insulin dose adjustment in 15% of events (n=15).

**Naloxone**

A total of 201 positive triggers were identified for naloxone. Of these, 190 met inclusion criteria and 100 met screening criteria for classification as adverse drug events. The 90 patients that did not meet screening criteria were due to a few reasons, such as naloxone was administered, but the patient was never given a narcotic, or naloxone was used as a planned, clinical intervention (e.g., used to wake up a patient following surgery). The PPV was calculated to be 53% (CI 45–60%). Figure 3 outlines the chart review process for the naloxone trigger. For the 100 ADEs, 57% (n=57) of patients were female, the mean age was 64.5 years, and 49% (n=49) patients were opioid naive prior to hospitalization. Chronic health conditions of note included renal dysfunction (CrCl < 50 mL/min) in 30 patients (30%) and liver dysfunction in 3 patients (3%), respiratory disease in 41 patients (41%), heart disease in 44 patients (44%), and pain in 63 patients (63%). The mean home morphine milligram equivalents (MME) in a 24-hour period was 56.1 mg (range 0-564 mg) with 47 patients (47%) receiving 0 mg. The mean inpatient MME in a 24-hour period was 100.5 mg (range 0-683 mg) with 60 patients (60%) receiving ≥ 50 mg. The mean difference between home and inpatient MME was 44.3 mg (range 490 to 470 mg) indicating that patients received more MME inpatient than outpatient. The mean naloxone dose was 0.24 mg (range 0.04–2 mg) and the mean number of naloxone doses was 1.6 (range 1–9; one patient received a naloxone infusion). Factors contributing to the need for naloxone administration included concomitant sedatives (n=13), sleep apnea (n=12), concomitant antihistamines (n=5), polypharmacy (n=91), obesity (n=13), coincidental stroke (n=3), and inappropriate dosing for age or weight (n=4). Patients could have more than one contributing factor. A variable (n=22) of other contributing factors were identified such as pneumonia, anemia, chronic obstructive pulmonary disease (COPD), etc.

**Discussion**

A systematic review by Musy et al. evaluated and described 10 studies using trigger methodology. Their review included consideration of INR, hypoglycemia, and naloxone triggers. The observed PPV ranged from 10.8% for INR, 15.8% for hypoglycemia, and 20–91% for naloxone. Musy et al. noted significant variation between the studies.

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**Table 1: Trigger Inclusion and Exclusion Criteria**

<table>
<thead>
<tr>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated INR</td>
<td>INR &gt; 6 present on admission</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Plasma glucose ≤ 50 mg/dL</td>
</tr>
<tr>
<td>Naloxone</td>
<td>Patient received opioid medications (any route)</td>
</tr>
<tr>
<td></td>
<td>Naloxone administration in the emergent department or freestanding/independent surgery centers</td>
</tr>
</tbody>
</table>

**Table 2: Trigger Screening Criteria**

<table>
<thead>
<tr>
<th>Screening Criteria</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated INR</td>
<td>Exclude if INR &gt; 6 or on warfarin or other anticoagulant that has an INR effect</td>
</tr>
<tr>
<td>Clinical intervention?</td>
<td>Patient must have received vitamin K, FFP, or other treatment agent. Holding a dose of warfarin is not considered a clinical intervention. Planned reversal before/after a procedure is not an intervention.</td>
</tr>
<tr>
<td>Bleeding?</td>
<td>Some evidence of bleeding must be present (hemoglobin drop, noticeable/evtch. s)</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Exclude if plasma glucose ≤ 50 mg/dL</td>
</tr>
<tr>
<td>Associated with insulin?</td>
<td>Exclude if patient is not receiving insulin.</td>
</tr>
<tr>
<td>Clinical intervention?</td>
<td>Patient must have received D50W, glucagon, juice, etc. Reducing or holding a dose of insulin is not included as an intervention.</td>
</tr>
<tr>
<td>Legitimate screen?</td>
<td>Exclude if naloxone is not charted as administered.</td>
</tr>
<tr>
<td>Naloxone</td>
<td>Exclude if naloxone is given to rule out symptoms caused by opioids with no response.</td>
</tr>
<tr>
<td>Associated with Barwon?</td>
<td>Exclude if an opioid is administered and no clinical intervention.</td>
</tr>
<tr>
<td>Clinical intervention?</td>
<td>Planned reversal, such as naloxone reversal following a procedure, is not a clinical intervention.</td>
</tr>
<tr>
<td>Overdose?</td>
<td>Reversing or holding a dose of opioid is not a clinical intervention. Planned reversal, such as naloxone reversal following a procedure, is also not a clinical intervention.</td>
</tr>
</tbody>
</table>

*The original screening criteria only specified a hemoglobin drop; however, the criteria was later revised to a hemoglobin drop ≥ 2 g/dL, as this is more clinically significant.*
Figure 1: Chart review process for INR > 6 trigger

77 patients
- Exclusion criteria details:
  - Not receiving warfarin: 27
  - INR > 6 on admission: 6
  - IRB date/location conflict: 2

17 patients
- Screening criteria exclusion details:
  - No reversal agent: 9
  - Warfarin reversal for procedures: 2
  - Lab error: 5
  - No bleeding: 8
- PPV 35% (CI 21-53%)
  - Using any hypoglycemic trigger for the screening criteria, there would have been 21 ADEs but reviewing clinically significant drop of ≤ 2 mg/dL omitted 8 patients

13 ADEs
- PPV 35% (CI 21-53%)

INR: international normalized ratio; IRB: institutional review board; ADEs: adverse drug events; PPV: positive predictive value; CI: confidence interval

Figure 2: Chart review process for plasma glucose ≤ 50 mg/dL trigger

148 total patients
- Exclusion criteria details:
  - Pregnancy: 1
  - Hypoglycemia on admission: 5
  - Screen: 3
- Screening criteria exclusion details:
  - Not a legitimate screen: 13
  - Not related to insulin: 10
  - No intervention: 19
- PPV 70.4% (CI 62-78%)

142 patients
- IRB date/location conflict: 5
- PPV 70.4% (CI 62-78%)
- No related documentation

100 ADEs
- IRB date/location conflict: 5
- PPV 70.4% (CI 62-78%)

ADEs: adverse drug events; PPV: positive predictive value; CI: confidence interval

Figure 3: Chart review process for naloxone trigger

201 total patients
- Exclusion criteria details:
  - Free-standing/independent emergency surgery center: 2
  - Outpatient: 2
  - Pregnancy: 2
  - Emergency department: 1
  - IRB date/location conflict: 5
  - Screen: 3
- Screening criteria exclusion details:
  - Not a legitimate screen: 3
  - No oversedation with a narcotic: 53
  - No clinical intervention: 18
  - Not associated with oversedation: 11
- PPV 53% (CI 45-60%)
  - *113 total trigger events but duplicates were only counted once

190 patients
- IRB date/location conflict: 5

100 ADEs
- PPV 53% (CI 45-60%)

IRB: institutional review board; ADEs: adverse drug events; PPV: positive predictive value; CI: confidence interval

in terms of PPV despite the use of similar triggers and trigger definitions, reviewers, methods, and reporting. With our project, we focused on adult patients over the course of a seven-month period, and the other studies looked at adults or children over shorter or longer periods. For INR, some of the studies used INR > 4 as the trigger. For hypoglycemia, some of the studies used the same glucose level ≤ 50 mg/dL trigger, while others had a different glucose threshold and/or used IV glucose bolus administration as the trigger. For naloxone, all of the studies used naloxone administration as the trigger, but some added additional specifications (e.g., opioid order, respiratory depression, etc.). Our project was done retrospectively while some studies were evaluated in real-time shortly thereafter instead of months later. Some studies had ADEs verified by an expert (e.g., endocrinologist, anesthesiologist, etc.) which was not done in our project. Although our quality-improvement project found comparable PPVs to other studies, it is difficult to make conclusions about our findings relative to other studies given the aforementioned variables.

Elevated INR
Drug interactions were the most common factor that may have contributed to an elevated INR. Some of these patients were already taking warfarin when an interacting medication was started, while others were started on warfarin while taking an interacting medication. In both cases, the warfarin dose was not adjusted accordingly.

This institution does not currently have an insulin dosing adjustment protocol beyond initial dosing recommendations, but rather adjustments are provider specific. Dosing algorithms and alerts for renal dysfunction, basal insulin monotherapy, and high insulin doses could be considered. Limiting high-dose insulin orders to endocrinology staff and/or a protocol to taper supplemental insulin along with the corticosteroid taper might be useful as well. Although there is not one evidence-based method for solving hypoglycemia related to diet changes within health systems, improving communication and documentation could prevent hypoglycemia events. Education, improved documentation of the times and plans for meals and insulin coverage in the electronic health record, and increased communication could decrease hypoglycemia in these situations. Lastly, compliance requiring one specific location for hypoglycemia reversal could improve documentation related to trigger events for quality improvement purposes and improve the PPV of the trigger tool.

Naloxone
Dose range order sets, high MME, and decreased renal function may have contributed to naloxone administration. At the time of this project, the order sets within Cerner® included dose ranges (e.g., hydrocodone/acetaminophen 5/325 mg 1-2 tablets by mouth every four hours. Start with one tablet and if pain not controlled, may increase to two tablets). The higher end of the range was commonly given before trialing the lower end of the range. Despite the average MME being 56.1 mg outpatient, inpatients were receiving almost double that amount, with an average of 100.5 mg. Although most opioids do not have to be renally adjusted, if a patient is not clearing the drug, the metabolites are building up and can cause an adverse event. This project had 87 patients (87%) that were greater than or equal to 50 years old.
Additionally, naloxone indication documentation was an issue encountered during this project, leading many patients to be excluded.

This institution currently does not have any type of pain protocol or stewardship program in place. Adjustments to current practice to address the above contributing factors could include requiring documentation that the patient has tried lower dose ranges before increasing the dose, adding a calculation system for MME into the electronic health record, and/or creating a renal dose adjustment policy for opioids. The indication for naloxone administration should be charted along with the time of administration. The institution is currently working on a variety of projects and policies to prevent ADEs. There is an ongoing audit with the medication history team to help assess gaps, monthly naloxone use data is being followed by the Pharmacy and Therapeutics Committee, and a pain stewardship program was planned to be piloted in April 2018.

Strengths and Limitations

The data collected during this quality-improvement project was from 2017 and very relevant to the patient population we aim to serve today. Data was collected by three fourth-year student pharmacists, with one being responsible for each of the trigger medication categories, to reduce variances in charting and review overall consistency. Additionally, a screening tool was utilized for each of the triggers to assist the students in determining if an ADE truly occurred. Using a screening tool ensured that ADEs were determined objectively. Collecting data from all of the institution’s inpatient facilities allowed for a wide range of contributing factors to be observed, since data was collected from small and large facilities.

There were many limitations that may have affected the results of this quality improvement project. Due to the data being collected directly from patient charts, the results of this project were dependent on documentation by staff. Data collected for trigger events took place months after the event occurred and prospective data collection would have allowed for input from frontline staff involved with the event. A tool was utilized to screen for data to be collected for 100 events for each trigger, but due to the sample size of elevated INR triggers, there may be contributing factors that were not found during this project. Lastly, this quality-improvement project did not look at a comparator group, so sensitivity and specificity were unable to be calculated to further validate the use of these triggers.

Conclusion

The use of trigger tool methodology was useful for identifying ADEs related to hypoglycemia with insulin, moderately useful for naloxone administration, and least successful for elevated INR with warfarin. Other types of tripping methodology may be beneficial to review in regards to ADEs, perhaps in the emergency department or related to mental health. The ADEs that were identified revealed a wide variety of contributing factors that can be used as areas of interest when creating new policies to reduce ADEs in the future.

References


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Sara Kolc Brown (Sara.Brown@meijer.com) graduated with her Doctor of Pharmacy from the Ferris State University College of Pharmacy in 2018. She completed a postgraduate, community-based pharmacy practice residency with Meijer Pharmacy and Wayne State University in Detroit, Michigan, in 2019. Brown plans to practice as staff pharmacist with Meijer Outpatient Pharmacy located inside of Spectrum Health Butterworth Hospital in Grand Rapids, Michigan. She is an active member of the Wayne County Pharmacists Association (WCPA), Michigan Pharmacists Association (MPA), MPA Political Action Council Board, American Pharmacists Association, and the Lambda Kappa Sigma (LKS) professional women’s pharmacy fraternity. She serves on the board for WCPA, which is currently the president of the LKS Alpha Iota alumni chapter, and is on various national LKS committees.

Jacob Peterson (Jacob.Peterson@spectrumphealth.org) is a graduate of the Ferris State University College of Pharmacy class of 2018 and recently completed a postgraduate pharmacy practice residency at Spectrum Health. Currently he is a clinical pharmacist at Spectrum Health HealthWest with particular interest in the geriatric population with adult acute care service lines, including general medicine, intensive care, and cardiology, at Butterworth Hospital and the Fred and Lena Meijer Heart Center. Peterson is also a member of the American Society of Health-System Pharmacists and the Western Michigan Society of Health-System Pharmacists.

Shayne Harris Schiedel has been involved in community pharmacy for 10 years. She dual-enrolled at Ferris State University in order to complete her PharmD and a Master of Business Administration in 2018. Schiedel was an active member of the National Community Pharmacists Association and served as secretary of her chapter while in school. She began her pharmacist career as a relief and staff pharmacist with Meijer Pharmacy immediately upon graduation. Currently she is in a management role as pharmacy team leader with Meijer Pharmacy in Three Rivers, Michigan.

Kari Vavna Janes is an associate professor of pharmacy practice at Ferris State University and practices in adult general medicine at Spectrum Health Grand Rapids. She has held this position for nine years. Janes has completed a pharmacy practice residency and is board certified in pharmacotherapy. Additionally, she has served on numerous local, regional, and state professional organizations. She has an interest in internal medicine, health-system pharmacy, and academia.

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