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

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Introduction

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

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.

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 miligram 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

Trigger methodology is designed to detect ADEs through a systematic search for “flags” such as the administration of a reversal agent or specific laboratory values. These trigger methods have been found to have higher sensitivity and specificity compared to more conventional methods for detecting ADEs, such as voluntary reporting systems. Although this trigger methodology provides rapid identification of potential ADEs, a disparity in understanding of the causes and trends of ADEs should be examined to prevent future occurrences. Inpatient facilities of the institution currently quantify ADE triggers for elevated INR, hypoglycemia in insulin-receiving patients, and naloxone administration, but have not previously used the trigger tool to identify underlying trends.

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 based on the initial trigger cause of the adverse event or until a trigger event date of August 1, 2017, was reached. Of note, patients with multiple triggers during an admission were only counted as one event. Eligible patients had to have inpatient status. Vulnerable populations, including children (less than 18 years of age), pregnant women, and prisoners, were excluded. These populations were excluded based on the initial trigger application to the institution, and as stated in the Code of Federal Regulations. Additional inclusion and exclusion criteria for each trigger are listed in Table 1.

After determining eligibility for inclusion, each trigger was then assessed using a screening tool. Trigger events had to meet all screening criteria to be considered an adverse drug event. The screening tool criteria was adapted from another institution and modified for this project. Screening criteria for each trigger are listed in Table 2.

Trigger events meeting all inclusion and screening criteria then underwent a full chart review and data collection. Data collected for all triggers included age, sex, reason for hospitalization, creatinine clearance (CrCl), liver function, chronic health conditions, if the patient transferred, whether a code blue was called, and whether a medication error occurred (including type of error and cause). Additional data collection points included the dose, route, and timing of precipitating agent(s) dose and timing of the reversal agent(s), patient status (e.g., symptoms, severity, respiratory rate, and oxygen saturation for the naloxone trigger), and opioid naive 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.).

Data Analysis

Data was deidentified and analyzed in Excel. Descriptive statistics were utilized for baseline characteristics, and a positive predictive value (PPV) was calculated for each trigger using the number of adverse events that met the screening tool criteria divided by the total number of trigger events that met the inclusion criteria.

Results

Elevated INR

A total of 37 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 a trigger 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=3), 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
Table 1: Trigger Inclusion and Exclusion Criteria

| Inclusion Criteria | Exclusion Criteria |
|--------------------|-------------------|
| Elevated INR       | INR > 6           |
| Receiving warfarin anticoagulation therapy | IRN ≥ 6 on admission |
| Hypoglycemia       | Plasma glucose ≤ 50 mg/dL |
| Patients with hypoglycemia present on admission |
| Non-insulin-receiving patients |

| Naloxone           | Patient received opioid medications (any route) |
|--------------------|-----------------------------------------------|
| Naloxone was administered | Naloxone administration in the emergency department or freestanding/independent surgery centers |

Table 2: Trigger Screening Criteria

| Screening Criteria | Notes |
|--------------------|-------|
| Elevated INR       | Exclude if high INR but not on warfarin or other anticoagulant that has an INR effect or with INR with liver disease or malnutrition |
| Clinical intervention? | 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. |
| Bleeding?          | Some evidence of bleeding must be present (hemoglobin drop, nosebleeds, etc.) |
| Legitimate screen? | Exclude if bedside point-of-care glucose is low, but subsequent plasma glucose is > 50 mg/dL. |
| Associated with insulin? | Exclude if patient is not receiving insulin. |
| Clinical intervention? | Patient must have received D50W, glucagon, juice, etc. Reducing or holding a dose of insulin is not included as an intervention. |
| Naloxone            | Exclude if naloxone is not charted as administered. |
| Associated with Barcain? | Exclude if naloxone is given to rule out symptoms caused by other agents with no response. |
| Clinical intervention? | Reducing or holding a dose of naloxone is not a clinical intervention. Planned reversal, such as naloxone reversal following a procedure, is also not a clinical intervention. |
| Overdose?          | Exclude if the patient only experienced nausea or pruritus. Also, exclude if the respiratory symptoms can be attributed to something other than opioids. |

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, cefepime, 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, 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 (eGFR < 60 mL/min/1.73 m²), liver dysfunction (n=1), and aortic stenosis (n=1). Two patients had more than one contributing factor. A variety (n=22) of other contributing factors were identified such as obesity, antipsychotic agents, concomitant antihistamines (n=5), polypharmacy (n=9), obesity (n=1), coincidental stroke (n=3), and inappropriate dosing for age or weight (n=4). Patients could have more than one contributing factor. A variety (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 10.8–100% for INR, 15.8–60% for hypoglycemia, and 20–91% for naloxone. Musy et al. noted significant variation between the studies.
**Figure 1:** Chart review process for INR > 6 trigger

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

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

**Figure 3:** Chart review process for naloxone trigger

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 a warfarin dosing adjustment protocol beyond initial dosing recommendations, but rather adjustments are provider specific. Dosing algorithms and alerts for warfarin are currently being developed. This will hopefully result in more standardized dosing protocols, and decrease the amount of variability in dosing. Additionally, INR monitoring will be followed more closely with this service: therefore, there will be closer review of drug–drug interactions, nutrition concerns, dosing, and liver function assessment.

**Hypoglycemia**

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. Interventions to reverse hypoglycemia, especially sugary liquids or foods, were not documented in one universal location in the electronic health record.

In some instances, the ambiguity of intervention documentation excluded the event from being considered an ADE.

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 insulin are currently being developed. 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 if pain not controlled, may increase to two tablets.

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ADEs. Also, the results of this project may differ from input from frontline staff involved with the triggers to assist the students in determining if trigger medication categories, to reduce variances with one student being responsible for each of the patient population we aim to serve today. Data 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 the study being responsible for each of the trigger medication categories, to reduce variances in review and charting improve overall consistency. Additionally, a screening tool was utilized for each of the triggers to assist the students in determining if an ADE was found. This 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 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. The methodology and screening tool criteria was adapted, perhaps it was too strict, which would have caused some triggers to be excluded when they were in fact ADEs. Also, the results of this project may differ from current trends in ADEs at the institution, with the transfer to a different electronic health record after data collection took place. To collect data for a wide variety of events, the goal was to collect data 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 also proved useful in determining if an ADE was found, with the goal being to collect data for 100 events for each trigger. Therefore, the results of this project were dependent on the triggers to assist the students in determining if trigger medication categories, to reduce variances in review and charting improve overall consistency. Additionally, a screening tool was utilized for each of the triggers to assist the students in determining if an ADE was found. This screening tool ensured that ADEs were determined objectively.