Predictors of naloxone use for respiratory depression and oversedation in hospitalized adults

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The Joint Commission released a Sentinel Event Alert in August of 2012 that highlighted the problems of opioid-related oversedation and respiratory depression among hospital inpatients. Opioid analgesics are frequently used for pain control in hospitals. While they are efficacious analgesics, there is a strong potential for adverse drug events (ADEs), and opioids are frequently mentioned in reports on the most commonly implicated medications involved in ADEs or medication errors. These ADEs can range from minor symptomatic nuances such as drowsiness to serious or life-threatening events or death.

The frequency of opioid-induced respiratory depression has been reported in the literature to be less than 1% overall but depends on the population being evaluated postoperative, general medicine, patient-controlled analgesia). In the case of more severe opioid-related adverse events, naloxone, an opioid antagonist, can be used. This injectable medication has a strong affinity for μ-opioid receptors and can reverse opioid activity within minutes. Naloxone use for the treatment of opioid-induced respiratory depression was cited in 4.6% of all ADEs reported in one analysis. Even with the availability of this antidote, opioid-induced adverse events can lead to increased costs of care due to an increased length of stay, the need for additional medications, and lawsuits. A study evaluating over 4000 patients admitted to two tertiary care hospitals found that the more ser-
ous ADEs were typically regarded as preventable. Clinicians have sought to optimize the detection and prevention of ADEs related to opioid use through various efforts. Oftentimes the first step in such a process involves analyzing the incidents reported in a specific population or environment. The data collected can provide insight on risk factors and the potential predictability of certain ADEs. Opioid-related risk factors for oversedation and respiratory depression have been documented in the literature and are believed to include obesity, sleep apnea, smoking, snoring, older age, opioid naivety, recent surgery (especially thoracic or upper abdominal surgery), usage of other central nervous system (CNS)–depressant medications, longer duration of anesthesia, and preexisting major organ disease.

The objective of the study described in this article was to determine the influence of established risk factors for opioid-related oversedation and respiratory depression in patients who were admitted to a tertiary care hospital over a one-year period.

Methods

Study population. In this retrospective case–control study, we analyzed records for patients admitted to Kent Hospital, a 359-bed community teaching hospital in Rhode Island, who received at least one dose of naloxone between October 1, 2011, and September 30, 2012. Patients who received naloxone hydrochloride 0.1 or 0.4 mg i.v. were identified using a report generated by the pharmacy informatics system. This report included data on patients for whom naloxone was charged and dispensed, either directly from the pharmacy or from an automated dispensing cabinet. The case population consisted of patients at least 18 years of age who received at least one dose of i.v. naloxone and whose records after naloxone administration contained a composite indicator of oversedation (defined as documentation of difficulty arousing the patient or clinical improvement after naloxone administration) or respiratory depression (defined as a respiratory rate of ≤8 breaths/min or documentation of clinical response to naloxone administration). All data for this study were collected through the use of electronic medical records; therefore, patient records were excluded from analysis if the specific information was captured only on paper (i.e., was not available through electronic systems). In addition, patient records were excluded from analysis if the dose of naloxone was administered within 24 hours of admission or was administered in the emergency department, operating room, or postanesthesia care unit or if the patient's medication profile did not document administration of an opioid analgesic within 24 hours before naloxone administration. Each patient in the case group was matched with a control patient who received 80–120% of the case patient's 24-hour opioid consumption, as determined in oral morphine equivalents. For both groups, the analysis included patients who had been admitted to any unit within the hospital, provided that they had not received naloxone while in the emergency department, operating room, or postanesthesia care unit.

Data collection and analysis. All data were collected through a review of electronic medical records. The demographic and study-variable data collected included the following: the nursing unit within the hospital to which the patient was admitted; patient age, sex, body mass index (BMI), and smoking status; data on concurrent use of CNS-depressant medications and degree of opioid tolerance (defined by prior use of opioids per admission medication reconciliation records); and the presence of respiratory disease (defined as chronic obstructive pulmonary disease, emphysema, chronic bronchitis, asthma, lung cancer, or pulmonary fibrosis), renal disease (defined as a creatinine clearance of <30 mL/min, receipt of dialysis, or documentation of chronic kidney disease in the patient chart), cardiac disease (defined as a documented diagnosis of atrial fibrillation or another arrhythmia, coronary artery disease, history of stent placement, history of myocardial infarction, congestive heart failure, hypertension, cardiomyopathy, valvular replacement, or the use of a pacemaker or implantable cardioverter defibrillator), or hepatic disease (defined as a documented diagnosis of cirrhosis, hepatitis, fatty liver, or abnormal findings on liver function tests). A BMI of ≥30 kg/m² was considered a positive risk factor for (i.e., indicator of) obesity. Patient age was subclassified as follows: >60 years, ≤70 years, >70 years, ≤80 years, and ≥80 years.

Pearson chi-square tests and logistic regression analysis using odds ratios with 95% confidence intervals were used to determine the significance of differences between groups for risk factor variables, and t tests were used to determine the significance of continuous variables, with an a priori level of significance of 0.05. Statistical tests were performed using SPSS, version 20 (IBM Corporation, Armonk, NY). Kent Hospital's institutional review board approved this study.

Results

Initial order-dispense reports identified 169 patients who received naloxone and met the study inclusion criteria. Subsequent exclusions included 25 patients who received naloxone within 24 hours of admission, 13 patients who did not receive an opioid within 24 hours before naloxone administration, and 66 patients who received naloxone in the operating room or postanesthesia care unit. After those exclusions, 65
records remained for inclusion in the study. The average amount of opioid used in a 24-hour period for these 65 patients was 88.57 mg, as expressed in oral morphine equivalents; the mean difference in opioid consumption between case and control patients was 13.1%. The average age of all patients (65 cases and 65 controls) was 63.8 years (range, 22–100 years) (Table 1). Both groups comprised mostly women, and the fraction of patients with a BMI of ≥30 kg/m² was similar in the two groups. Current smoking and concurrent use of a CNS-depressant medication were more common in case patients. Concurrent CNS-depressant medications included benzodiazepines (lorazepam, alprazolam, temazepam, clonazepam, and diazepam), antipsychotics (chlorpromazine, olanzapine, quetiapine, haloperidol, and fluphenazine), zolpidem, gabapentin, pregabalin, mirtazapine, amitriptyline, diphenhydramine, trazodone, butalbital–acetaminophen–caffeine, primadone, and cyclobenzaprine.

Patients who received naloxone during their admission had an average of 5.1 risk factors for opioid-induced oversedation or respiratory depression. Among these patients, there were high rates of concomitant CNS-depressant medication use, positive smoking history, renal disease, cardiac disease, and respiratory disease. In contrast, patients who did not receive naloxone had a significantly lower average number of risk factors, 3.3 (p < 0.001).

Significant associations were found between administration of naloxone and smoking status, concurrent use of a CNS-depressant medication, and documentation of renal disease, cardiac disease, or respiratory disease (Table 2).

### Discussion

This study sought to examine identifiable risk factors for opioid-related ADEs (oversedation and respiratory depression) in an adult hospital population. In the hospital setting, analyzing trends in ADEs can be accomplished by review of patient medical records combined with pharmacy dispensing reports. For opioid-specific analyses, studying naloxone use as an indicator of potential opioid-related events has been found to be an effective and appropriate method. The study described here analyzed naloxone dispensing to identify patients with opioid-related adverse events in a hospital inpatient setting. Specific exclusion criteria were designed to remove from the analysis incidents resulting from patient behavior prior to admission, so that only those incidents related to care provided by the institution would be captured. When oversedation or respiratory depression occurs after opioid administration, it is typically classified as having resulted from overdosage. While the
definition of an opioid overdose may seem straightforward, difficulty can arise when attempting to make a correct diagnosis. One study found that among patients initially suspected of having received an opioid overdose, the majority were subsequently determined not to have received an overdose but rather had pulmonary conditions that were misdiagnosed as an opioid overdose.\textsuperscript{15} The investigators concluded that pulmonary, neurologic, cardiovascular, and electrolyte abnormalities can be misdiagnosed as an opioid overdose in hospitalized patients. Another study found that after careful review of patient records on naloxone utilization, 25\% of the cases were later determined to involve a new diagnosis that could have contributed to sedation.\textsuperscript{16} In our study, patient records that met the inclusion criteria were reviewed thoroughly for documentation of situations that would clinically justify the use of naloxone (e.g., staff had difficulty arousing the patient, the patient had a decreased respiratory rate, a clinical response to naloxone administration was noted).

After proper identification, ADEs are often differentiated by categorization of their preventability. Although a small but significant fraction of ADEs are determined to be nonpreventable, it is worthwhile to continue tracking them as they may be deemed preventable with future advances in medicine.\textsuperscript{13} Further classification of ADEs has focused on the determination of preventable versus nonpreventable events. Several authors have concluded that many ADEs are preventable.\textsuperscript{10,17} Bobb et al.\textsuperscript{3} concluded that opioids were one of the drug classes most commonly involved in clinically significant prescribing errors; of these errors, approximately two thirds were deemed to have been likely preventable with the use of computerized prescriber order entry. Rothschild et al.\textsuperscript{9} determined that clinical pharmacists potentially could have prevented 64\% of the inpatient ADEs evaluated in a study of medication-related malpractice claims.

Nevertheless, some patients experience severe adverse reactions to opioids even when they are prescribed, dispensed, and administered appropriately.\textsuperscript{18} Data captured by the study described here can assist with the identification of patients at high risk for ADEs; our study found that patients who required naloxone had significantly more identifiable risk factors than those who did not require naloxone. Of note was the lack of a significant association of opioid naïvety with naloxone use, since that has been identified as a risk factor for opioid-related ADEs.\textsuperscript{1,11} We believe that the retrospective nature of the study and the reliance on data from electronic medication reconciliation records may explain this finding; that is, the determination of opioid tolerance by patient interview would likely provide more thorough information about which medications and, in the case of analgesics, how many doses the patient was actually taking prior to admission. Finally, grouping analysis was unable to find any common clustering of risk factors that had significant associations with naloxone use.

In summary, patients in this sample who required naloxone therapy in response to opioid-related oversedation or respiratory depression were more likely to have had respiratory, cardiac, or renal disease; to have been smokers; and to have received concurrent CNS-depressant medications. The overall number of risk factors—but not the type of risk factor combinations—played a large role in determining risk. Analysis of such overdosage incidents, coupled with a review of patient-specific factors, could lead to the development of predictive screening tools to identify the patients at greatest risk. Potential implications for future work could include the development of clinical pathways for patients found to reach a cutoff or threshold number of risk factors on initial clinical screenings.

Conclusion

Hospitalized patients on general medical units who required naloxone to reverse opioid-induced oversedation or respiratory depression had significantly more risk factors than matched patients who did not require naloxone.

References