Evaluation of the Incidence of Ibuprofen Administration in Alcohol and Opioid Detoxification Patients With Concomitant Thrombocytopenia

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Sheheryar Muhammad¹, John R. Tomko¹,
and Laura M. Wilson¹

Abstract

Purpose: The purpose of this study was to determine the incidence of ibuprofen administration in patients who are undergoing alcohol and opioid detoxification, and have concomitant alcohol-related thrombocytopenia. **Methods:** This was a single-center, cross-sectional, prospective, observational study. A daily manual review of electronic health records was conducted for patients admitted to the detoxification unit of the hospital. Patients who (1) were of age 18 years or more, (2) were ordered both alcohol and opioid detoxification protocols, and (3) had a platelet count of less than 150 000/ μ L were included in the study. The incidence of ibuprofen administration was evaluated. **Results:** Twenty-five patients were included in the analysis. More than 70% of patients had an active ibuprofen order and 50% of patients received ibuprofen. Patients with a platelet count of <100 000/ μ L were more likely to receive ibuprofen in the presence of an active ibuprofen order and received a higher dose of ibuprofen than patients who had a platelet count of $\geq$ 100 000/ μ L. **Conclusion:** This study highlights a potential medication safety concern in patients with alcohol-related thrombocytopenia who are unintentionally ordered ibuprofen. Future, long-term studies are warranted to further investigate this issue.

Keywords

drug/medical use evaluation, medication process, physician prescribing

Introduction

A normal platelet count in humans ranges from 150 000 to 450 000/ μ L; thrombocytopenia is defined as a platelet count below 150 000/ μ L.¹ Alcohol use disorder is a common cause of thrombocytopenia, occurring in 3% to 43% of nonacutely ill, well-nourished alcoholic patients and 14% to 81% of acutely ill, hospitalized patients with alcohol use disorder.² However, except for the most severe cases, these patients typically do not exhibit manifestations of excessive bleeding.² Alcohol affects not only platelet production but also platelet function; therefore, patients with alcohol use disorder can exhibit a wide spectrum of platelet abnormalities when admitted to a hospital.² These abnormalities include impaired platelet aggregation, decreased secretion or activity of platelet-derived proteins involved in blood clotting, and prolongation of bleeding in the absence of thrombocytopenia.² Moreover, the susceptibility to develop alcohol-induced thrombocytopenia appears to be variable among individuals.² Alcohol-related thrombocytopenia generally is transient, and platelet count usually returns to normal level within 1 week of abstinence.² The exact mechanisms underlying alcohol-related thrombocytopenia are unknown.

Administration of medications that prolong bleeding time or prevent coagulation in the setting of alcohol-related thrombocytopenia may heighten the risk of bleeding in a patient. One such class of medications is nonsteroidal anti-inflammatory drugs (NSAIDs), which impair thromboxane-dependent platelet aggregation by inhibiting platelet cyclooxygenase, thereby blocking the formation of thromboxane A₂.³ Consequently, this produces a prolongation in bleeding time.³ Nonaspirin NSAIDs, such as ibuprofen, inhibit cyclooxygenase reversibly; thus, their effects on platelet aggregation and prolongation of bleeding time are transient.⁴ The extent and duration of these effects depend on the dose and half-life of the particular NSAID.^{4,5} After a single 300 mg dose of ibuprofen, platelet aggregation is inhibited within 2 hours, and this effect is lost within 24 hours.⁶

¹University of Pittsburgh Medical Center, PA, USA

Corresponding Author:

Sheheryar Muhammad, Department of Pharmaceutical Services, Mercy Hospital, University of Pittsburgh Medical Center, 1400 Locust St, Pittsburgh, PA 15219-5114, USA.
Email: sheheryar@umaryland.edu

Table 1. Demographic Variables.

Demographic	Value
Male gender, no. (%)	19 (76)
Age, years, mean $\pm$ SD	48.5 $\pm$ 10.1
Actual body weight, kg, mean $\pm$ SD	86.8 $\pm$ 17.7
Platelet count, $\times 10^3/\mu\text{L}$, mean $\pm$ SD	117.0 $\pm$ 30.4
Serum creatinine, mg/dL, mean $\pm$ SD	0.80 $\pm$ 0.19

An estimated 1.1% of the United States population has an alcohol use disorder with a co-occurring drug use disorder.⁷ Pharmacological management of withdrawal from alcohol and opioids involves treatment symptoms of withdrawal, where withdrawal symptoms can be quantified to allow symptom-triggered therapy.⁸ Medications used to treat alcohol withdrawal symptoms include benzodiazepines, anticonvulsants, β -blockers, and α_2 -adrenergic agonists.⁸ Medications used in the management of opioid withdrawal symptoms include α_2 -adrenergic agonists, benzodiazepines, NSAIDs, and antiemetics.⁹

Problem

At our institution, patients with thrombocytopenia (platelet count $<150\,000/\mu\text{L}$) related to alcoholism undergoing both alcohol and opioid detoxification are likely to be inadvertently ordered ibuprofen, as it is an automatic/preselected standard order within the opioid withdrawal protocol order set, where it is included to treat bone, muscle, joint, or other pain.⁸ Furthermore, these patients may be routinely receiving benzodiazepines and α_2 -adrenergic agonists to manage other alcohol and opioid withdrawal symptoms, such as anxiety and insomnia.^{8,9} Administration of these medications can cause hypotension, sedation, and depression of central nervous system, which can heighten the risk of falls.¹⁰ The unintentional combination of ibuprofen and thrombocytopenia, coupled with an increased risk of falls, can compound the risk for bleeding in these patients.

Rationale for the Study

Based on several case reports within our institution, we believe that patients who are undergoing alcohol and opioid detoxification and have concomitant alcohol-related thrombocytopenia may routinely be prescribed and administered ibuprofen. To date, there have been no studies published that evaluate the incidence of ibuprofen administration in this patient population within a health-systems setting. The purpose of this study is to evaluate the incidence of ibuprofen administration in this patient population.

Methods

This study was a single-center, cross-sectional, prospective, observational study, conducted from November 1, 2016, to

March 31, 2017. Approval was granted by the Quality Improvement Review Committee of the institution prior to the start of data collection. During the study period, a daily manual review of electronic health records was conducted for patients admitted to the detoxification unit of the hospital. Patients who (1) were of age 18 years or more, (2) were ordered both alcohol and opioid detoxification protocols, and (3) had a platelet count of less than $150\,000/\mu\text{L}$ were included in the study. For each patient meeting the inclusion criteria, the following data were collected: age, gender, actual body weight, platelet count, serum creatinine, administration of any anticoagulant and/or antiplatelet medications, presence of an active order for ibuprofen, dosage strength, and the number of ibuprofen doses administered, if any. Descriptive statistics were used to express the data as frequency, percentage, and mean with standard deviation (SD).

Results

Five hundred twenty-six patients' electronic health records were reviewed within the study period. A total of 25 patients met the inclusion criteria. The demographic characteristics of patients included in the analysis are shown in Table 1. Eighteen (72%) patients had an active order for ibuprofen as a preselected order within the opioid withdrawal protocol order set. Ibuprofen order was discontinued by a physician in 7 (28%) patients. Of the 18 patients with an active ibuprofen order, 9 (50%) patients received ibuprofen. The mean $\pm$ SD ibuprofen dose received within was 481.8 mg $\pm$ 159.3 mg. All patients who received ibuprofen received only 1 dose. None of the patients who met the inclusion criteria received any other NSAID besides ibuprofen. Furthermore, none of the patients received any anticoagulant or antiplatelet medication.

Because the bleeding risk may be higher when the platelet count is $<100\,000/\mu\text{L}$, which could be further compounded by concomitant ibuprofen administration, the patients were divided into 2 groups based on the platelet count—one with a platelet count of $<100\,000/\mu\text{L}$ and the other with a platelet count of $\geq 100\,000/\mu\text{L}$. Of the 18 patients with an active ibuprofen order, 3 (16.7%) had a platelet count of $<100\,000/\mu\text{L}$ and 15 (83.3%) had a platelet count of $\geq 100\,000/\mu\text{L}$. Within the group with a $<100\,000/\mu\text{L}$ platelet count, all 3 (100%) patients received ibuprofen, whereas only 10 (66.7%) patients received ibuprofen order within the $\geq 100\,000/\mu\text{L}$ platelet count group, as illustrated in Table 2. Hence, the likelihood of receiving ibuprofen in presence of an active ibuprofen order was higher in $<100\,000/\mu\text{L}$ platelet count group as compared with the $\geq 100\,000/\mu\text{L}$ platelet count group, 100% and 66.7%, respectively. Furthermore, patients within the $<100\,000/\mu\text{L}$ platelet count group received a higher mean $\pm$ SD ibuprofen dose when compared with patients within the $\geq 100\,000/\mu\text{L}$ platelet count group, 666.7 mg $\pm$ 188.6 mg and 452.6 mg $\pm$ 130.7 mg, respectively.

Table 2. Ibuprofen Administration in Patients With an Active Ibuprofen Order, and a Platelet Count of <100 000/ μ L or $\geq$ 100 000/ μ L.

	Platelet count of <100 000/ μ L (n = 3)	Platelet count of $\geq$ 100 000/ μ L (n = 15)
Ibuprofen administration, no. (%)	3 (100)	10 (66.7%)
Ibuprofen dose administered, mg, mean $\pm$ SD	666.7 $\pm$ 188.6	452.6 $\pm$ 130.7

Note. n = number of patients with an active ibuprofen order.

Discussion

This study demonstrated that including ibuprofen as an automatic/preselected standard order within the opioid withdrawal protocol order set resulted in patients receiving ibuprofen which may put patients with concomitant thrombocytopenia at a higher risk for bleeding. One recommendation to mitigate this risk is to remove ibuprofen as an automatic standard order within predetermined order sets. In addition, acetaminophen could be considered as a potential alternative, at least until the platelet count rebounds, though the data for acetaminophen use in this patient population is not as robust as it is with NSAIDs.¹⁰ Of note, the use of acetaminophen in patients with an alcohol use disorder may be questioned, especially when there is an evidence of liver disease. However, several studies have demonstrated that ingestion of acetaminophen within recommended doses (up to 4 grams per day) did not produce an increase in hepatic aminotransferase enzyme levels or any clinical manifestations of hepatic toxicity among patients with alcohol use disorder.^{11,12}

Limitations

There are limitations to this study that are worth noting. One limitation of this study is its small sample size. Another limitation is the potentially high cut-off value for platelet count of <150 000/ μ L for the study definition of thrombocytopenia. Even though this platelet count meets the definition of thrombocytopenia, the risk of bleeding may be relatively lower until platelet count drops further.^{1,13} Another limitation of this study is that the physicians' reasoning for discontinuation of ibuprofen in certain patients was unclear.

Conclusion

More than 70% of patients identified had an active order for ibuprofen and 50% of these patients received ibuprofen. Patients with a platelet count of <100 000/ μ L were more likely to be receive ibuprofen in presence of an active ibuprofen order and received a higher dose of ibuprofen than those who had a platelet count of $\geq$ 100 000/ μ L. This study illustrates a potential medication safety concern in patients with alcohol-related thrombocytopenia who are inadvertently ordered ibuprofen. Future, long-term studies are warranted to confirm the findings.

Declaration of Conflicting Interests

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