A Quality Assurance Evaluation of Hydromorphone Adverse Events Post-Implementation of a Safety Initiative

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ABSTRACT:

Purpose: Hydromorphone is a potent opioid that may lead to respiratory and central nervous system depression prompting naloxone use. The primary objective of this study was to evaluate whether a safety initiative implemented at Windsor Regional Hospital involving interchanging hydromorphone intravenous or subcutaneous doses of 1 mg or greater to low dose (0.5 mg) in opioid naïve, medical and surgical patients was associated with naloxone events. The secondary objective was to assess whether there was a compromise in patient pain control with the low dose.

Methods: We conducted a retrospective, multicenter, observational study of medical and surgical opioid-naïve patients admitted to Windsor Regional Hospital who received intravenous or subcutaneous hydromorphone within an eighteen-month timeframe. To determine if there is an association between naloxone events and implementation of the safety initiative, we compared patients who experienced a naloxone event (cases) with patients who did not experience a naloxone event (controls) in approximately 1:4 ratio. Efficacy outcomes assessed changes in patient pain control before and after interchange policy implementation (i.e. need for increase in dose, frequency or additional analgesics).

Results: Of the 4343 patients who received hydromorphone, 143 opioid naïve patients were included in the final analysis. Of the 27 patients who experienced a naloxone event, 0% of patients were interchanged. In contrast, of the 116 patients who did not experience a naloxone event, 52% were interchanged (OR = 0, 95% 0 to 0.13, $p<0.01$). There were no significant differences in terms of patient pain control before and after interchange policy implementation.

Conclusions: The pharmacist-led safety initiative of interchanging all opioid naïve patients to low dose hydromorphone was not associated with naloxone events and did not compromise patient pain control.

Keywords: hydromorphone, naloxone, opioid, safety, pain management

Introduction:

The Institute of Safe Medication Practices (ISMP) defines opioids as high-alert medications because of the potential to cause serious adverse drug events (ADEs) such as accidental overdoses and respiratory depression.[1] Hydromorphone, a potent opioid, is the most common medication voluntarily reported to ISMP Canada for causing patient harm.[2] From January 2000 to September 2013, ISMP received 233 incidents involving hydromorphone with an outcome of harm or death.[2]

The hydromorphone package insert suggests a dose of 1-2 mg[6]; this dose is roughly equivalent to 7-14 mg of morphine – an excessive amount for many opioid naïve patients[7]. Several studies have suggested that currently recommended starting doses of hydromorphone or the recommended conversions are too high.[8-10] Meisenberg et al reduced opioid-induced respiratory depression by implementing the use of lower doses of hydromorphone for high-risk patients through creating new pain order sets that default to morphine and implementing alerts that define opioid naïve when ordering opioids.[11] Similarly, Guelst et al. identified that hydromorphone was often being prescribed intravenously in excessive doses to opioid-naïve patients. Therefore, they re-packaged hydromorphone in 0.2 mg syringes and removed all 2 mg vials from patient care units and aggressively educated health care professionals. This intervention minimized severe cases of respiratory depression without compromising analgesic

efficacy through implementing system-related and educational changes over a three-year time period.[12]

At Windsor Regional Hospital (WRH), there were 86 reported naloxone-related events secondary to opioid use from 2016 to 2017.[3] The majority of these events were attributed to hydromorphone use. Pain guidelines state that patients who are opioid naïve are most at risk of opioid-related harm.[4-5] These findings prompted the implementation of a safety initiative at WRH, whereby pharmacists can interchange all prescribed hydromorphone intravenous or subcutaneous doses of 1 mg or greater to low dose (0.5 mg) hydromorphone in opioid naïve medical or surgical patients in order to minimize opioid-related adverse effects.

We conducted a retrospective, observational study to 1) assess the impact of the policy on safety by identifying if there is an association between naloxone events (the outcome) and implementation of the interchange (the exposure) and 2) to evaluate efficacy outcomes regarding patient pain control with the low dose interchange. We predict that implementation of our interchange policy will not be associated with naloxone events and will not compromise patient pain control.

METHODS:

Selection and Description of Participants

A retrospective, case-control study was conducted at two separate hospital sites: Ouellette and Metropolitan campus at Windsor Regional Hospital (WRH). This study was approved by the WRH Research Ethics Board (REB) #18-345. The computerized pharmacy software (Solcom®, WORX, and Horizon's Medical Manager®, Pyxis® automated dispensing cabinet reports) was used to identify all medical and surgical adult patient (≥18 years) admitted to Windsor Regional Hospital who experienced a naloxone-related event within 24 hours of receiving a dose of

hydromorphone nine months before and after interchange policy implementation. We excluded all critically ill patients admitted to the intensive care unit as well as oncology, trauma or palliative patients since these patients typically have higher analgesic requirements.

Data Collection

Computerized pharmacy records were used to extract patient and drug data. Specific demographic and clinical outcome information was entered into an electronic case report form: age, sex, type of patient (i.e. medical or surgical), hospital length of stay and mortality were collected. Patient comorbidities that could affect safety and efficacy outcomes including obesity, sleep apnea, chronic obstructive pulmonary disease, renal or liver impairment and chronic pain were collected. Medication information at baseline and throughout hospital stay including benzodiazepine, NSAID, acetaminophen, antidepressant, neuropathic agent or marijuana use at baseline and throughout hospital stay was also collected.

Patients were classified as opioid naïve if they did not have an opioid listed on their medication history or filled within the 30 days prior to their hospital admission. Hydromorphone prescription information collected included: the dose administered, whether it was interchanged to 0.5 mg or less and whether the patient was discharged on hydromorphone or another opioid.

To evaluate safety outcomes, a report of all the naloxone removals from the Pyxis® automated dispensing cabinets with corresponding opioid use was generated. Only naloxone administration associated with respiratory depression were included in the analysis. To evaluate pain control in all patients who received an interchange to low-dose hydromorphone, the data collected included patient hydromorphone requirements such as increase in dose, frequency or additional analgesics 24 hours post-interchange. These analgesic requirements were compared pre vs post-interchange policy implementation.

DATA ANALYSIS

For the safety analysis, patients who experienced a naloxone event were categorized as cases, and were compared in approximately a 1:4 ratio with patients who did not experience a naloxone event as the controls. Continuous variables were reported as means with standard deviations or medians with interquartile ranges, which were compared using unpaired T-test and Mann Whitney U Test, respectively. Categorical and binary variables were reported as counts and percentages and compared using Chi squared test. A p-value of < 0.05 was considered statistically significant. A multivariable regression analysis was conducted in order to identify and adjust for any potential confounders. For the safety analysis, there were no naloxone events in the intervention arm, therefore the data was un-analyzable with a lower bound of zero and upper bound of infinity.

RESULTS

Population

As shown in Table 1, 143 patients were included in the final analysis. The median age was 70 years (IQR=11.3) and 41.9% were female. Twenty-seven patients required naloxone administration secondary to respiratory depression 24 hours post-hydromorphone administration. These 27 cases were compared with approximately four controls. There were no significant differences between cases and controls at baseline in terms of risk factors for respiratory depression such as obesity, sleep apnea, chronic obstructive pulmonary disease, renal or liver impairment etc. There were no patients receiving non-opioid analgesics in the group that experienced a naloxone event in comparison to the control group (0% vs. 30.2%, respectively, $p<0.001$). The average hydromorphone dose was found to be significantly higher in the group of

patients who experienced a naloxone event in comparison to controls (2.2 mg vs. 0.8 mg, p <0.001).

Safety Results

Table 2 outlines the association between naloxone events and implementation of interchange. Amongst the 27 patients who experienced a naloxone-related event, zero of these individuals were interchanged to low dose hydromorphone. In contrast to the group of patients that did not result in a naloxone event, 52% of patients were interchanged, indicating a statistically significant difference in the implementation of interchange between cases and controls ($X^2 = 27.3$, $p<0.01$).

Table 3 outlines the naloxone-related events at Windsor Regional Hospital nine months before and after the hydromorphone interchange policy was implemented. There was an overall 24% reduction in naloxone related events post-interchange policy implementation amongst both hospital sites (OR = 0.68, 95% CI 0.60-3.82). The Ouellette site demonstrate a 32% reduction (OR=0.68, 95% CI: 0.60-3.82) in comparison to the Metropolitan site which showed a 14% increase in naloxone-related events (OR= 0.76, 95% CI 0.61 – 2.91).

Efficacy Results

Table 4 outlines the efficacy in pain control in opioid naïve patients before and after the hydromorphone interchange policy was implemented. There were no significant differences in need for an increase in dose, frequency or additional analgesics pre vs. post policy implementation. There were no differences in concurrent use of other analgesics throughout patient hospital stay. There were significantly less patients being discharged on hydromorphone pre vs. post-policy implementation (16.7% vs. 6.1%, p = 0.041).

DISCUSSION

We determined that the implementation of a pharmacist-led safety initiative whereby interchanging all hydromorphone intravenous or subcutaneous doses of 1 mg or greater to low dose (0.5 mg) was not associated with naloxone-related events and did not compromise efficacy in patient pain control.

Ricket et al conducted a pilot evaluation of hydromorphone dose substitution on patient safety and pain management in a community hospital in Kentucky, USA. The results of this study suggest that utilizing lower initial doses of hydromorphone may provide similar efficacy for patients who are opioid naïve. Although this pilot study did not achieve adequate statistical power, they concluded that initiating low dose hydromorphone in opioid-naïve patients may prevent adverse drug events while adequately controlling pain.[13] Our study, which implemented a similar substitution policy found that substituting to low dose hydromorphone in opioid naïve patients was not associated with naloxone events. The patients in the naloxone-event group were receiving significantly higher doses of hydromorphone at baseline and none of these patients were interchanged. To confirm this implicating factor, the dose of hydromorphone administered was the only significant difference found between cases and controls at baseline other than the use of non-opioid analgesics. This demonstrates that there was a failure to use a multi-modal analgesic approach in order to provide opioid-sparing effects and minimize harm along with excessive doses of hydromorphone in the group of patients that experienced a naloxone-related event.

In terms of efficacy results, there was no difference in patient pain control pre vs. post policy implementation, indicating that we can comfortably initiate opioid naïve patients with a reduced dose of hydromorphone and potentially prevent life-threatening respiratory depression.

Doses may be titrated if the patient's pain is not adequately controlled after the initial dose. Furthermore, once our interchange policy was implemented, there were significantly less patients being discharged home on hydromorphone post-policy implementation. This is important because multiple studies have reported an increased risk of new persistent opioid use after prescription of opioids for acute pain in opioid naïve patients.[14-17] Even patients who undergo relatively minor low-pain surgery are at increased risk of long-term opioid use.[16]

The strengths of this study include a large number of patients screened who received hydromorphone. We also looked at a variety of possible confounding factors such as obesity, sleep apnea, COPD and found no confounders. Furthermore, we implemented an initiative of forcing function which is highest on ISMP's hierarchy of effectiveness[2] in achieving safety outcomes indicating that the hydromorphone dose cannot be processed without the pharmacist's review. In addition to the safety benefits for patients, this intervention is easy to implement at any institution, requires minimal resources, may be cost-saving and may potentially prevent the development of opioid use disorder.

Our study is limited by its retrospective nature since not all interventions were documented. Although the order cannot be processed without pharmacist review, the order requires pharmacist discretion of whether to interchange. It is possible that not all pharmacists were interchanging patients, particularly when the policy was first implemented. Furthermore, we used surrogate markers of respiratory depression i.e. naloxone use. Despite this, naloxone is the best surrogate marker available since its use is easily captured by the automated pharmacy dispensing system. Surrogate markers of pain control were also used because pain scores were poorly documented in the charting and would result in incomplete information. Furthermore, pain perception may also vary based on ethnicity and the type of surgery or reason for admission which varied amongst patients.

CONCLUSION

We determined that the implementation of a pharmacist-led safety initiative whereby interchanging all hydromorphone intravenous or subcutaneous doses of 1 mg or greater to low dose was not associated with naloxone-related events and did not compromise efficacy in patient pain control.

Table 1 – Baseline Demographics

	All Patients N = 143	Naloxone Event N = 27	No Naloxone Event N = 116	P-value
Age, years (median, IQR)	70 (11.3)	67 (12.2)	74 (10.3)	0.561
Sex, female	60 (41.9)	11 (40.7)	49 (42.24)	0.915
Type of patient				
Medical	59 (41.3)	11 (40.7)	48 (41.4)	0.914
Surgical	84 (58.7)	16 (59.3)	68 (58.6)	0.914
Obesity	54 (37.7)	10 (37.0)	44 (37.9)	0.913
Sleep apnea	12 (8.4)	3 (11.1)	9 (7.8)	0.581
COPD	21 (14.7)	4 (14.8)	17 (14.7)	0.883
Renal impairment	25 (17.5)	6 (22.2)	19 (16.4)	0.492
Liver impairment	7 (4.9)	2 (7.4)	4 (3.4)	0.199
Chronic pain	28 (19.6)	2 (7.4)	26 (22.4)	0.083
Benzodiazepine use	22 (15.4)	5 (18.5)	17 (14.7)	0.470
NSAID/Acetaminophen use	35 (24.5)	0 (0.0)	35 (30.2)	<0.001
Antidepressant, neuro agent, marijuana use	43 (30.1)	8 (29.6)	35 (30.2)	0.908
Hydromorphone Dose, mg (mean, SD)	1.2 (1.01)	2.2 (1.7)	0.8 (0.6)	<0.001
Hospital LOS (median, IQR)	6 (8.2)	7 (9.3)	6 (7.8)	0.681
Death	18 (10.5)	2 (7.4)	16 (13.8)	0.431

Table 2 – Association between naloxone events and implementation of interchange

Variable	Naloxone Event	No Naloxone Event	Total	χ^2	P-value
Interchange					
Yes	0 (0)	60 (52)	60 (42)	27.3	<0.001

No	27 (100)	56 (48)	83 (58)		

Table 3- Naloxone Related Events Pre vs. Post Policy Implementation

		Pre (May 2017 to Jan 2018)	Post (Feb 2018 to Oct 2018)	OR
Ouellette	Yes	12	8	0.68 (0.60 – 3.82)
	No	1288	1268	
Metropolitan	Yes	3	4	1.15 (0.16 – 4.23)
	No	838	975	
Total	Yes	15	12	0.76 (0.61 – 2.91)
	No	2111	2232	

Table 4 – Efficacy Data – Pain Control (Opioid Naïve only)

	Pre – Interchange Policy N= 61 (15+46)	Post – Interchange Policy N = 82 (12+70)	
Interchanged to 0.5 (or less)	6 (9.8)	54 (65.8)	<0.001
Increase in Dose	13 (21.3)	13 (15.9)	0.451
Increase in Frequency	5 (8.2)	7 (8.5)	0.881
Additional analgesics	10 (16.4)	12 (14.6)	0.729
Concurrent use of other analgesics			
≤1	50 (82)	56 (68)	0.068
2+	11 (18)	15 (18)	0.913
Discharge on hydromorphone	10 (16.7)	5 (6.1)	0.041

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