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Incidence of Hydromorphone-Induced Neuroexcitation in Hospice Patients

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Abstract

Background and Objective: To date, there are no known published studies that prospectively followed hospice patients receiving hydromorphone to evaluate the development of hydromorphone-induced neuroexcitation (HINE). The first objective of this study was to determine the incidence of HINE. The second objective was to identify factors influencing the presence or absence of HINE symptoms in hospice patients.

Methods: This was a noninterventional, prospective study. This study population included hospice patients 18 years of age or older who were admitted to one of two Nathan Adelson Hospice inpatient units in Las Vegas, Nevada, and were initiated on a scheduled regimen of hydromorphone. A total of 156 patients were enrolled and analyzed in this study. Data collection was performed by the study investigators using a standard data tracking form, including hospice diagnosis, gender, renal function, hydromorphone regimen, and whether or not the patient experienced neuroexcitatory symptoms. Data collection occurred from November 2010 to March 2011.

Results and Conclusions: Based on the data collected in this study, it appears that the likelihood of HINE does increase with larger doses, increasing age, increasing serum creatinine, and the presence of malignant neoplasm. However, after adjusting for the variables in the logistic regression model, diagnosis of malignant neoplasm was not a significant predictor of HINE. Future studies may focus on evaluating metabolite levels, such as hydromorphone-3-glucuronide (H3G), in patients developing HINE symptoms. This may help to determine if the metabolites of opioids, such as H3G, are involved in the development of the neurotoxic symptoms.

Introduction

Pain, due to various conditions, is a common symptom observed in hospice patients. These patients often require high doses of opioid pain medications. Administration of opioids often leads to adverse reactions, and high doses can lead to opioid-induced neuroexcitatory symptoms.[1–3] However, little is known about the incidence of this infrequent, but serious neuroexcitatory adverse reaction, particularly in hospice patients. Morphine has been the drug of choice for pain management in hospice patients because of its therapeutic efficacy and availability in multiple dosage forms, as well as for its low cost. Accumulation of morphine's toxic metabolite (morphine-3-glucuronide; M3G) is more likely to occur when high doses are being used in patients with renal insufficiency,[5–8] and could lead to opioid-induced neuroexcitation.[9–12] Hydromorphone is a semisynthetic opioid that is milligram per milligram more potent than morphine but has similar metabolic patterns.[9,10] The toxic metabolite of hydromorphone (hydromorphone-3-glucuronide; H3G) could also be accumulated and potentially cause opioid-induced neuroexcitation.[9,11–13] The clinical study by Lee and colleagues despite a limited sample size, showed hydromorphone to be safe and effective in patients with renal insufficiency.[14] Perhaps, this finding is the initial step to evaluate and suggest that hydromorphone may be a safer therapeutic option than morphine in hospice patients with renal insufficiency.

Two retrospective studies of hospice patients receiving parenteral hydromorphone found symptoms of neuroexcitation to be more likely with larger doses and longer durations of therapy.[3,4] The study by Paramanandam et al. specifically looked at hospice patients with chronic kidney disease.[4] Comparing the data from this study with that from the study conducted by Lee and coworkers leads to conflicting observations regarding the safety of hydromorphone used in patients with renal insufficiency. Animal studies showed that high levels of H3G caused myoclonus jerks, shakes, tonic-clonic convulsions, and touch-evoked agitation in rats.[13] These

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symptoms are similarly seen in patients with hydromorphone-induced neuroexcitation (HINE) and this situation could be misinterpreted as subtherapeutic doses of hydromorphone, and result in a dose increase to better manage the pain, which could lead to severe neuroexcitation. Allodynia, along with myoclonus jerks, or seizures could also be misinterpreted as disease progression, thus complicating patient management. These symptoms need to be recognized as adverse reactions of the opioid, and a treatment regimen change, such as rotating to a different opioid, is necessary. Clinicians caring for patients exhibiting these symptoms should broaden their differential diagnosis to include opioid-induced neuroexcitation as a possible cause. Establishing the likelihood and a threshold dose at which neuroexcitation may occur in hospice patients being treated with hydromorphone can provide clinicians with beneficial information for treating patients.

To date, there are no known published studies that prospectively followed hospice patients receiving hydromorphone to evaluate the development of HINE. The objective of this study was twofold. The first objective was to determine the incidence of HINE. The second objective was to identify factors influencing the presence or absence of HINE symptoms in hospice patients.

Methods

Patient population

This study population included hospice patients 18 years of age or older who were admitted to one of two Nathan Adelson Hospice inpatient units in Las Vegas, Nevada, and were initiated on a scheduled regimen of hydromorphone. The treatment regimen was based upon the prescribing practitioner's knowledge, experience, and preference. Selection of their pain medication regimen was not influenced by this study. Because the study was noninterventional, optimal pain management was performed in all patients admitted to the inpatient unit regardless of whether or not they were enrolled in this study. Any patient meeting the aforementioned criteria was offered enrollment in this study and informed consent was obtained for any enrolled patient. Exclusion criteria were: patients receiving scheduled hydromorphone prior to the time of inpatient unit admission, patients already exhibiting signs and symptoms of opioid-induced neuroexcitation, or incomplete or lack of signed consent form. The study was approved by Roseman University of Health Sciences Institutional Review Board.

Study design and data collection

This was a noninterventional, prospective study. Physician assessment of each enrolled patient was performed daily for pain relief and neuroexcitation symptoms of hyperalgesia, allodynia, myoclonus, and seizures. The primary outcome was whether or not enrolled patients developed neuroexcitation with hydromorphone. Exhibiting any of the aforementioned symptoms (hyperalgesia, myoclonus, allodynia, and seizures) would meet the criteria for HINE. The secondary outcomes were to determine the dose and duration at which patients were at risk for developing HINE, and any characteristics that may have been associated with developing HINE. Data collection was performed by the study investigators using a standard data tracking form, including hospice diagnosis, gender, renal function, hydromorphone regimen, and whether or not the patient experienced any of the aforementioned symptoms. Data collection occurred from November 2010 to March 2011.

Statistical analysis

Differences in demographic characteristics and other variables of interest in patients with HINE and without HINE were compared using Pearson's χ^2 and independent t tests for categorical and continuous data, respectively. Factors influencing the presence of HINE symptoms were examined using a logistic regression. The rule of thumb that logistic regression models should be evaluated with a minimum of 10 participants per independent variable was used in the present study. In this regard, several variables indicating the presence of hospice diagnosis were collapsed into separate variables based on clinical judgment. For instance, end-stage Alzheimer's dementia and end-stage dementia were combined together under the diagnosis of dementia. Cirrhosis and end-stage liver disease were combined together under the diagnosis of cirrhosis. End-stage cerebral vascular accident (CVA) and subdural hematoma were combined together under the diagnosis of cerebral injury. Different types of cancer diagnosis (lymphoma, Kaposi's sarcoma, melanoma, osteosarcoma, squamous head/neck, squamous mouth/tongue, endometrial, pancreatic, lung, renal cell, bladder, breast, paranasal sinuses, prostate, colon, liver, esophageal, peritoneal, vaginal, ovarian, glioblastoma, stomach, cholangiocarcinoma, adenocarcinoma, and multiple myeloma) were combined together under the diagnosis of malignant neoplasm. Presence of chronic obstructive pulmonary disease (COPD), end-stage cardiac disease, debility not otherwise specified, end-stage renal disease, encephalopathy, peripheral

Table 1. Variables of Interest among Those with HINE Symptoms ($N=10$) and Those without HINE Symptoms ($N=146$)

Variable of interest	*Presence of HINE (%)*	*Absence of HINE (%)*	P *value*
Age[a,b]	73.70 (11.59)	70.57 (14.03)	0.492
Gender (male)	60	46.6	0.41
Dose[a,b]	2.15 (2.50)	0.88 (1.68)	0.03*
Serum Creatinine[a,b]	3.21 (1.90)	1.35 (1.53)	0.02*
COPD	0.0	3.4	0.55
End-stage cardiac disease	0.0	8.9	0.32
Debility NOS	0.0	13.7	0.21
End-stage renal disease	10	2.1	0.12
Encephalopathy	0.0	0.7	0.79
PVD	0.0	0.7	0.79
Lymphadenopathy	0.0	0.7	0.79
Dementia	0.0	3.4	0.55
Malignant neoplasm	90	56.8	0.04*
Cerebral injury	0.0	2.7	0.60
Cirrhosis	0.0	7.5	0.37

*$p < 0.05$.
[a]Mean values (standard deviation).
[b]Independent t test.
COPD, chronic obstructive pulmonary disease; HINE, hydromorphone-induced neuroexcitation; NOS, not otherwise specified; PVD, peripheral vascular disease.

Table 2. Dose and Duration of Hydromorphone in Patients with HINE

Average[a] *hydromorphone dose on day 1*	*Average*[a] *hydromorphone dose during entire therapy*	*Day of hydromorphone therapy at time of HINE diagnosis*	*Average*[a] *hydromorphone dose on day of HINE diagnosis*
1.10 mg/hour	1.5 mg/hour	6	1.65 mg/hour
1.88 mg/hour	1 mg/hour	4	1.5 mg/hour
9.29 mg/hour	8.8 mg/hour	11	17.2 mg/hour
0.09 mg/hour	0.6 mg/hour	5	0.6 mg/hour
1.03 mg/hour	3.4 mg/hour	4	10.8 mg/hour
0.22 mg/hour	1.4 mg/hour	5	2.96 mg/hour
0.17 mg/hour	0.26 mg/hour	4	0.4 mg/hour
1 mg/hour	1.97 mg/hour	5	2.5 mg/hour
0.25 mg/hour	0.64 mg/hour	8	0.45 mg/hour
0.97 mg/hour	1.95 mg/hour	9	4.33 mg/hour

[a]Average dose includes both scheduled and breakthrough doses.
HINE, hydromorphone-induced neuroexcitation.

vascular disease (PVD), and lymphadenopathy were not collapsed into any variable.

Data were analyzed using SPSS version 19.0 (SPSS, Inc., Chicago, IL), and the a priori alpha was set at $p < 0.05$.

Results

A total of 156 patients were enrolled and analyzed in this study, with no patients being excluded after enrollment. The mean age of the patients in the study was 70 years (range: 36–95 years) with nearly 47% ($n = 74$) of the patients being male. Of 156 patients treated with hydromorphone, 10 patients (6.4%) developed symptoms of HINE. The symptoms observed in HINE patients were hyperalgesia ($n = 7$), myoclonus ($n = 8$), allodynia ($n = 1$), or a combination of these symptoms (note: each patient could demonstrate > 1 symptoms). None of the HINE patients experienced seizures. Table 1 presents the comparison of patients developing HINE symptoms ($n = 10$) with those not developing HINE symptoms ($n = 146$). All variables presented in Table 1 were found to be similar across patients developing HINE symptoms and those not developing HINE symptoms, except when comparing the dose of hydromorphone (t-value = –2.24, $p = 0.03$), serum creatinine (t-value = –2.31, $p = 0.02$) and in those with the diagnosis of malignant neoplasm ($\chi^2 = 4.25$, $p = 0.04$); see Table 1.

The average dose and duration of hydromorphone was 2.15 mg/hour continuously for 6 days for the patients who experienced HINE and 0.88 mg/hour continuously for 5.48 days in the non-HINE patients. Table 2 presents the initial dose of hydromorphone, the average daily dose of hydromorphone for the entire course of hydromorphone therapy, and the day of therapy as well as the dose of hydromorphone therapy when HINE was diagnosed. Mean serum creatinine in HINE patients was 3.2 mg/dL versus 1.4 mg/dL in non-HINE patients.

Factors influencing patients developing neuroexcitatory symptoms

The logistic regression model predicting HINE symptoms was adjusted for patient's age, gender, dosage, and the presence of the following diagnoses: COPD, end-stage cardiac disease, debility not otherwise specified, end-stage renal disease, encephalopathy, PVD, lymphadenopathy, dementia, cerebral injury, and cirrhosis. Each 1-unit (1-year) increase in patient's age was associated with a higher likelihood of developing HINE symptoms compared with patients not developing HINE symptoms. Likewise, a 1-unit (0.01 mg/hour) increase in dose was associated with a greater likelihood of patients developing HINE symptoms compared with those patients not developing HINE symptoms. None of the hospice diagnoses improved the prediction of the model and were not presented.

Discussion

The frequency of HINE in our study was 6.4%. Based on the data collected in this study, it appears that the likelihood of HINE does increase with larger doses, increasing age, increasing serum creatinine, and the presence of malignant neoplasm (Table 1). However, after adjusting for the variables in the logistic regression model, diagnosis of malignant neoplasm was not a significant predictor of HINE. One explanation for the increased risk of HINE symptoms in the studied hospice patients with a diagnosis of malignant neoplasm could possibly be due to the higher doses of hydromorphone required to manage pain in malignant neoplasm patients versus other diagnoses such as heart disease, pulmonary disease, and dementia. To summarize, it appears that age and dose were better predictors of the presence of HINE (Table 3) compared with the diagnosis of malignant neoplasm alone.

Patients receiving an average hydromorphone dose of 2.15 mg/hour. (approximately 1032 mg of oral morphine equivalents per day) were statistically more likely to develop symptoms of HINE than patients receiving an average hydromorphone dose of 0.88 mg/hour (approximately 422 mg of oral morphine equivalents per day).

Table 3. Predictor of HINE[a]

	β (SE)	P *value*	*OR*	*95% CI for OR*	
Age	0.08 (0.04)	0.04	1.09	1.01	1.17
Dose	0.36 (0.15)	0.02	1.43	1.06	1.93

[a]Variables not found to be significant predictors of HINE are not presented in this table.
CI, confidence interval; β (SE), parameter estimate (standard error); HINE, hydromorphone-induced neuroexcitation; OR, odds ratio.

The exact mechanism of how opioids cause these infrequent but serious adverse reactions is not known or clearly understood. Some studies have shown that metabolites of morphine and hydromorphone (M3G and H3G, respectively), can cause these reactions, whereas others have shown that the symptoms may be caused by some fully unknown and not elicited mechanisms.[15,16] Both M3G and H3G have been implicated in causing adverse reactions with no analgesic properties.[9,17–19] These metabolites are hydrophilic and under normal circumstances easily removed by the kidneys, thus causing no adverse reactions. When given in large doses or in patients with renal insufficiency, these metabolites can be accumulated[5–7,20,21] and it is presumed that the likelihood of adverse reactions increases with accumulation.

Although the treatment of HINE was not the objective of this study, it is described as follows. All patients who experienced HINE had hydromorphone immediately discontinued. Patients were opioid rotated to either parenteral fentanyl or methadone at approximately half of the equivalent hydromorphone dose they were receiving at the time of the HINE diagnosis. In addition to opioid rotation, any patient who developed myoclonus was treated with lorazepam.[22–27] Although parenteral hydration is often considered as part of the treatment regimen,[28] none of our patients were given parenteral hydration as it was deemed by the attending physician to not align with their overall goals of care. This treatment resulted in resolution of the HINE symptoms in each of the 10 patients within approximately 24 to 36 hours after discontinuation of hydromorphone.

Some limitations exist in our study. First, there was limited access to patient medical information. This resulted in incomplete medical histories or missing lab values, including renal function. Because serum creatinine was not available in all of the patients, this variable was omitted from the logistic regression model, therefore limiting our ability to determine renal function as a predictor of HINE. We believed it was inappropriate to draw lab values in our patients as it is not standard care in hospice to do lab studies unless it is clinically meaningful. A second limitation of the study was observation bias. In clinical practice, symptoms of HINE are not easily recognizable and can be easily dismissed until exaggerated symptoms, such as myoclonus and allodynia, are present. The fact that we were looking for subtle clues that might have attributed to the development of HINE could have given us a higher incidence of HINE than otherwise observed outside of a study setting. Finally, though not specifically a limitation, one other factor may have affected the results and deserves discussion. We did not include agitation or delirium in our symptom criteria for the diagnosis of HINE as has been done before.[3,4] Hospice patients are already at a very high risk of developing delirium and/or agitation regardless of opioid administration and delirium has been reported in as high as 85% of patients in the last few weeks of life.[29] We felt including delirium may give us a falsely high number of HINE patients.

Future studies may focus on evaluating metabolite levels, such as H3G, in patients developing HINE symptoms. This may help to determine if the metabolites of opioids, such as H3G, are involved in the development of the neurotoxic symptoms. One small pilot study by McCann and colleagues concluded that serum levels of M3G and H3G did not appear to correlate with myoclonus.[30] However, the neuroexcitatory effects of opioid metabolites are not likely to be solely explained by serum metabolite levels. It would also be beneficial if complete and accurate medical information for all patients was available, including renal and liver function. The aim of any future study should be to collect information that will allow clinicians to more easily identify patients at risk for developing symptoms of HINE and thus be able to potentially avoid this infrequent but serious adverse reaction.

Conclusion

Data from this study show that use of hydromorphone in hospice patients in high doses and/or with increasing age, may lead to an increased risk of developing HINE symptoms. Therefore, data from this study, along with clinical experience and judgment, may dictate the use of opioids other than hydromorphone for the management of hospice patients with increasing age requiring large opioid doses.

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Author Disclosure Statement

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