Hydromorphone use for acute pain: Misconceptions, controversies, and risks

Maryann Mazer-Amirshahi, PharmD, MD, MPH; Sergey Motov, MD; Lewis S. Nelson, MD

ABSTRACT

Hydromorphone (HM) is a potent opioid analgesic that is commonly administered in the emergency department (ED) and other acute care settings, such as medical surgical wards. In recent years, there has been a significant increase in the ED administration of HM relative to other opioids. Although HM is an effective analgesic, its use has been commonly implicated in adverse drug events and medication errors. In addition, intravenous HM has potent euphoric effects that may contribute to its abuse liability. There are limited data regarding how acute parenteral administration of opioid analgesics in the setting of high rates of preexisting chronic opioid use (medical or nonmedical) may contribute to or reinforce addictive behavior, making the potential contribution of rising HM administration to subsequent prescription opioid abuse and overdose uncertain. This review addresses the pharmacology of HM, recommended dosing, its efficacy for acute pain, as well as its tolerability, safety, and abuse profiles. Controversies and strategies for appropriate use of this medication are also described.

INTRODUCTION

In recent years, there has been a debate regarding the expanded administration of opioid analgesics in the emergency department (ED) and its contribution to the opioid epidemic.1-6 This controversy has been fueled by a variety of factors, including accreditation requirements, patient satisfaction, the undertreatment of pain, and the implication for subsequent misuse and addiction.7,8 In addition, administration of opioid analgesics for acute pain presents a risk of iatrogenic overdose and adverse drug events (ADEs), including oversedation, respiratory depression, and even death.9-12

Of individual opioid analgesics, hydromorphone (HM) has had the largest proportional increase in the past two decades, and this has been driven largely by administration in the ED.1-4 One study demonstrated a 102 percent increase in ED HM administration from 2005-2010, which was much larger than the relative increases in administration for other opioids.1 Inpatient use for medical and surgical patients has been increasing as well.13,14 There are limited data regarding how acute parenteral administration of opioid analgesics, particularly in the setting of high rates of preexisting chronic opioid use (medical or nonmedical), initiates or reinforces substance use disorders. This raises concerns for the potential contribution of rising HM administration in the acute care setting to prescription opioid use disorder and overdose nationally, particularly because HM has significant abuse liability.15,16 Additionally, there are data that suggest HM is more commonly associated with ADEs compared to other opioids.17-19

This review addresses the pharmacology of HM, particularly by the intravenous (IV) route, recommended dosing, and efficacy for acute pain, as well as its tolerability, safety, and abuse profiles. Controversies and strategies for appropriate use of this medication are also described. Although the ED literature serves as the basis for much of this review, similar questions about efficacy and safety apply to its inpatient use for the management of acute pain.19
HM PHARMACOLOGY

Pharmacodynamics

HM is a potent semisynthetic opioid analgesic that is structurally similar to morphine. It exerts its actions primarily via the μ-opioid receptors and to a lesser extent on δ-opioid receptors. As such, it has the same physiologic effects as other opioids, including analgesia, sedation, euphoria, miosis, gastrointestinal distress, slowed gastrointestinal motility, histamine release, and respiratory depression. It is a full agonist at the mu opioid receptor, and therefore there is no ceiling effect to its analgesic properties, but its therapeutic dosing is limited by adverse effects.20,21 Although HM’s mechanism of action is similar to that of the other opioid analgesics, there are certain clinically important differences. Of particular importance is HM’s potency—it is approximately 7 to 11 times more potent than morphine via the IV route and up to 8 times more potent orally.21,22,23 HM is 10 times more lipophilic than morphine, which contribute to its rapid and potent central nervous system effects.20,21

HM is most commonly used in acute care in the parenteral form, either via the IV or intramuscular routes, but it can also be used by the subcutaneous and epidural routes.24 It is available as a parenteral formulation, and orally as a solution, immediate release tablets, as well as an extended-release tablet (Exalgo). The extended-release formulation is indicated for the management of chronic pain in patients who are opioid tolerant and require around the clock analgesia.25 As such, this HM preparation should only be prescribed from the ED in the rarest circumstances, only to someone already prescribed and using it therapeutically, and will not be discussed further in this review. Of note, the first FDA-approved extended-release HM product was removed from the market in 2005 due to safety concerns due to “dose-dumping,” particularly with concomitant alcohol consumption.26,27

Pharmacokinetics

HM is well absorbed orally from the small intestine, but is subject to approximately 60 percent of first pass hepatic metabolism. The onset of analgesia for immediate release oral HM is approximately 30 minutes, with a duration of action of up to 4 hours.28 The oral to IV conversion is estimated to be approximately 5:1; however, significant interpatient variability exists.29 The onset of action of IV HM is within 5 minutes, but the peak effect may be delayed up to 20 minutes due to distribution into the central nervous system. Despite the delay, this is still much faster than morphine.30

HM is metabolized primarily by phase II glucuronidation. The primary metabolite is hydromorphone-6-glucuronide (H6G), which lacks analgesic activity.31 There are limited data regarding the analgesic activity of other metabolites. Another metabolite, hydromorphone-3-glucuronide (H3G), has been associated with neuroexcitatory effects, such as myoclonus and seizures.31,32 HM metabolites are renally eliminated. As such, they can accumulate in patients with renal failure and lead to nausea, delirium, and seizures.33,34 In fact, H3G is more potent than the similar morphine metabolite, morphine-3-glucuronide.35 One advantage of HM is that it does not undergo metabolism by cytochrome P450 as do other opioid analgesics and is therefore subject to fewer drug-drug interactions.31

Recommended dosing and administration

The prescribing information for HM recommends a wide range of dosages based on patient age, the severity of pain, and the presence of opioid tolerance and/or renal and hepatic impairment.36,37 When given IV, it is recommended that HM be administered over a minimum of 2 to 3 minutes to avoid nausea, pruritus, and rapid sedation. Parenteral dosing is generally titrated to effect and then repeated every 2 to 3 hours as needed.36 The dosing interval for oral administration is every 3-6 hours.37 (Table 1)36,37 Lower doses and longer dosing intervals are recommended for older patients or those with moderate to severe renal or hepatic impairment.36,37 In addition, although there does not seem to be a difference in efficacy when comparing

<table>
<thead>
<tr>
<th>Route of administration</th>
<th>Dose</th>
<th>Frequency</th>
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<tr>
<td>Intramuscular</td>
<td>1-2 mg</td>
<td>Every 3-4 hours; titrate every 30-45 min</td>
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<tr>
<td>IV</td>
<td>0.1-1 mg</td>
<td>Every 2-3 hours; titrate q 15-20 min</td>
</tr>
<tr>
<td>Oral</td>
<td>2-4 mg</td>
<td>Every 4-6 hours</td>
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weight based or fixed dosing, large doses in obese patients (following weight-based dosing regimens) may lead to safety concerns. Specifically, the concerns for hypoventilation and hypoxia are greater in this population due to obstructive sleep apnea, and this is complicated by the potential for more difficult airway management. In patients on chronic opioid therapy, when converting from another opioid to HM, it is also reasonable to decrease the dose of HM to allow for incomplete cross-tolerance between opioids. Higher titrated doses can be considered for patients that are opioid tolerant or are in severe pain. Frequent reassessment and dose adjustment should occur to identify and minimize adverse effects.

Efficacy of HM in the ED

The efficacy of IV HM in the ED has been examined in several studies. Overall, and not surprisingly, HM is an efficacious analgesic. Given in equianalgesic doses to another full opioid agonist, HM should be expected to provide comparable pain relief. A 1 mg IV bolus of HM plus a repeat bolus in 15 minutes if needed (1 + 1) was effective and acutely safe in nonelderly ED patients with acute pain. A similar study comparing the 1 + 1 mg IV protocol to a single 2 mg IV bolus of HM noted similar analgesic efficacy, but the 1 + 1 group had a significantly lower opioid requirement. IV HM has also provided effective analgesia in a patient-driven anesthesia protocol in the ED. A single IV bolus dose of 2 mg HM administered in the ED for severe pain was associated with significant pain relief, but this dose was associated with significant oxygen desaturation.

The efficacy of HM has also been compared to other opioid analgesics, particularly morphine. A meta-analysis of morphine versus HM suggested a small analgesic advantage to HM. In a comparative safety and efficacy trial, HM and morphine performed equally well. In addition, morphine and HM were similarly efficacious in a study of older adults presenting to the ED with severe acute pain. Of note, the majority of HM efficacy trials in the ED were not supported by the pharmaceutical industry.

Although available studies support the efficacy of HM as an analgesic, there are some notable limitations. Several of the studies that demonstrated HM’s superiority to morphine compared a set dose of HM to “usual” care with morphine dosed at the providers’ discretion. In addition, the doses of morphine were often variable and not equianalgesic (and usually lower) when compared to HM. In general, morphine tended to be underdosed in these studies, and the doses of HM used were at the high end of the recommended dosing range, which could bias efficacy data in favor of HM. There is a paucity of data regarding oral or intramuscular HM. A review of the efficacy of HM in ED trials is presented in Table 2.

Safety and tolerability of IV HM

Over the past 10 years, significant attention has been paid to the safety of HM administration in various acute pain management settings including the ED. The available data demonstrates a significant increase in rates of oversedation, administration of naloxone, respiratory depression, and apnea as well as increase in misuse, abuse, diversion, and addiction related to HM. The error data report from Pennsylvania Patient Safety Authority revealed 1,694 medication errors associated with HM administration from January 2008 to October 2009 of which wrong (excessive) dosing represented the majority of events (17 percent, n = 287) with 6 percent of these dosing errors (n = 17) involving the ED. A subsequent analysis of 499 ADEs related to HM that resulted in respiratory and central nervous system depression revealed that 292 (65 percent) of these ADEs were related to excessive dosing and could have been prevented.

Traditional parenteral HM dosing regimens for patients between the ages of 18-65 the ED (1-2 mg IV push) have been associated with significant rates of hypoxia and bradypnea as well as less severe adverse effects such as nausea, vomiting, pruritus, sedation, and dizziness. HM given to adult patients (18-55 years of age) as a 1 + 1 titration regimen resulted in abnormalities in vital signs in 17 percent of patients. Ten percent of patients were noted to have bradycardia and 5 percent of patients had hypoxia (O2 sat<95 percent). However, when a similar titration protocol was compared in older adults to opioid administration based on physician discretion, greater rates of hypoxia (22 percent vs 5 percent), respiratory depression (30 percent vs 17 percent), and physician interventions (26 percent vs 17 percent) were observed in the HM titration group with similar change in pain score between the two groups.
<table>
<thead>
<tr>
<th>Authors</th>
<th>Design</th>
<th>Intervention (N of patients assigned)</th>
<th>Comparator (N of patients assigned)</th>
<th>Primary Analgesic Outcome</th>
<th>Results</th>
<th>Conclusion</th>
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<tr>
<td>Chang et al., 2006</td>
<td>RCT: IV HM vs IV morphine sulfate (MS), 198 patients</td>
<td>HM: 0.015 mg/kg (N = 97)</td>
<td>MS: 0.1 mg/kg (94)</td>
<td>11-point NRS reduction at 30 min (difference and CI)</td>
<td>HM: -5.5, MS: -4.1 (difference: -1.3; 95% CI -2.2 to -0.5)</td>
<td>IV HM at 0.015 mg/kg is a feasible alternative to IV MS at 0.1 mg/kg</td>
</tr>
<tr>
<td>Chang et al., 2009</td>
<td>RCT: IV HM vs IV morphine in geriatric patients (&gt;65yo), 194 patients</td>
<td>HM: 0.0075 mg/kg (N = 93)</td>
<td>MS: 0.05 mg/kg (90)</td>
<td>11-point NRS reduction at 30 min (difference and CI)</td>
<td>HM: -3.8, MS: -3.5 (difference: 0.5; 95% CI, -0.2 to 1.3)</td>
<td>IV HM at 0.0075 mg/kg is neither clinically nor statistically different from IV MS at 0.05 mg/kg in older adults in the ED</td>
</tr>
<tr>
<td>Chang et al., 2009</td>
<td>Prospective interventional: HM 2mg IVP, 269 patients</td>
<td>HM: 2 mg IV (N = 269)</td>
<td>N/A</td>
<td>11-point NRS reduction at 5 and 30 min (IQR)</td>
<td>NRS Baseline Pain score 10 [IQR 8-10] to 1 [IQR 0-5] to 1 [IQR 0-3]</td>
<td>2 mg of IV HM provides efficacious and rapid pain relief in nonelderly patients</td>
</tr>
<tr>
<td>Chang et al., 2009</td>
<td>Prospective interventional: “1 + 1”Titration protocol, 223 patients</td>
<td>1 mg HM IV with optional 1 mg HM IV at 15 min (N = 223)</td>
<td>N/A</td>
<td>11-point NRS reduction at 15 and 60min (percentage of patients and CI)</td>
<td>HM: 1 mg IV adequate analgesia for 77% (95% CI: 71% to 82%) within 15 minutes; for 96% (95% CI: 92% to 98%) at 1h</td>
<td>Rapid “1 + 1” titration protocol using IV HM is efficacious in nonelderly ED patients with acute severe pain</td>
</tr>
<tr>
<td>Chang et al., 2009</td>
<td>RCT: Patient-driven titration protocol vs physician-driven analgesia, 224 patients</td>
<td>1 mg HM IV with optional 1 mg HM IV at 15 min (N = 108)</td>
<td>Physician-driven analgesia (any opioid) (N = 110)</td>
<td>11-point NRS reduction at 60 min (difference and CI)</td>
<td>HM titration: -5.6; Physician-driven: -4.5 (difference: -1.1; 95% CI 0.3 to 1.9)</td>
<td>“1 + 1” patient-driven protocol is statistically superior and at least as clinically efficacious and safe as traditional physician-driven treatment of ED patients with acute severe pain</td>
</tr>
<tr>
<td>O’Connor-or et al., 2010</td>
<td>Prospective cohort trial: MS and HM prescribing practices in the ED</td>
<td>HM dosing: 1 mg (N = 121); 2 mg (N = 64)</td>
<td>MS dosing: 4 mg (N = 291), 2 mg (N = 131)</td>
<td>&gt;50 percent reduction in pain score (odds ratios and CI)</td>
<td>HM 1 mg: 1.27 (0.78-2.09) HM 2 mg: 0.70 (0.38-1.31) MS 4 mg: 1.04 (0.68-1.57)</td>
<td>Marked opioid dosing variability with substantial number of ED patients with severe pain responding well to relatively low opioid dosages</td>
</tr>
<tr>
<td>Authors</td>
<td>Design</td>
<td>Intervention (N of patients assigned)</td>
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| Chang et al., 2011 | RCT: “1 + 1” Titration vs usual care, 350 patients                     | HM: “1 + 1” Titration (N = 167)        | Usual care (N = 171)                | Proportion of patients with successful treatment (declined analgesia at 15 and 60 min; difference and CI) | “1 + 1” titration: 92.3 percent with successful treatment
Usual care: 76.6 percent successful treatment (difference: -15.7%; 95% CI: 7.9% to 23.3%). | “1 + 1” HM protocol is statistically and clinically more efficacious than usual care |
| Chang et al., 2013 | RCT, 2 mg HM vs “1 + 1” titration protocol, 334 patients               | 2 mg HM IVP (N = 166)                 | “1 + 1” HM titration (N = 168)      | Proportion of patients with successful treatment (declined analgesia at 60 min; difference and CI) | 2 mg HM IVP: 67.5 percent success “1 + 1” titration:
67.3 percent success;
difference 0.2%; 95% CI: -9.7% to 10.2%). | HM’s “1 + 1” titration protocol provides similar pain relief to an initial 2 mg bolus dose |
| Chang et al., 2015 | Prospective interventional nongeriatric cohort, 215 patients, dosing: 1 mg-4 mg | HM 1 mg IVP q 30 min up to
4 doses based upon patient’s response | NA                                  | Proportion of patients achieving satisfactory pain control (declining analgesia on one or more occasions; difference and CI) | 205 of 207 patients: satisfactory pain control (99% 95% CI: 97% to 100%) | Titration of 1 mg IV HM driven solely by patient response resulted in achievement of satisfactory analgesia on at least one occasion in 99 percent of patients |
| Deitch et al., 2015 | RCT: “1 + 1” Titration vs Physician discretion analgesia in geriatric patients (>65yo), 104 patients | 1 mg HM IV with optional 1 mg
HM IV at 15 min (N = 50) | Physician discretion analgesia (N = 54) | 100 mm-VAS at 15 min and 60 min (difference and CI) | “1 + 1” Titration: -31.7 mm at 15 min; Physician discretion: -30.4 mm
Difference: 6 mm (95% CI: 6.1-18.1 mm) at 15 min;
7.9 mm (95% CI: -4.5-20.5 mm) at 60 min | No significant differences between groups in terms of VAS pain scores at 15 or 60 minutes |

HM = Hydromorphone; MS = morphine sulfate; NRS = numerical rating scale; RCT = randomized controlled trial.
HM administration as a single IV push dose of 2 mg to ED patients suffering from acute pain resulted in hypoxia in 32 percent of patients, out of which 26 percent had oxygen saturation between 90-94 percent, 6 percent of patients had oxygen saturation of less than 90 percent, and the lowest recorded saturation was 82 percent. None of these patients required naloxone administration but all received supplemental oxygen and stimulation. Additionally, 16 percent of patients had nausea, 7 percent vomiting, 13 percent bradycardia, and 8 percent pruritus.18

A prospective cohort trial evaluating IV opioid (morphine and HM) dosing and outcomes in the ED demonstrated that among patients receiving 1 mg of IV HM (N = 121), 15 percent of patients were oversedated, and 4 percent were noted to be confused. Among 62 patients receiving 2 mg of HM, 11 percent were sedated, 2 percent confused, and 5 percent complained of dizziness.54

A retrospective study of 73 patients with opioid-related adverse events that occurred in the ED and resulted in patient harm revealed that 62 percent had received IV HM with half of these patients requiring naloxone reversal. Of note, 75 percent of these adverse effects were related to medication errors (excessive dosing).55 Although not all of the ED studies of HM were powered to evaluate safety, a summary of adverse events associated with HM in ED trials is presented in Table 3.

Abuse liability

The increase in prescription (261 percent) and therapeutic use of HM nationwide parallels the alarming increase in HM misuse, diversion, and development of addiction.56 Data from Automation of Reports and Consolidated Orders System (ARCOS) and Drug Abuse Warning Network (DAWN) assessing the trends in medical use and misuse of opioid analgesics from 2004 to 2011 demonstrated an increase in medical use of HM (route unspecified) by 140 percent accompanied by an increase in misuse by 438 percent.57 Similarly, diversion of HM is on the rise,58 with the demand presumably linked to its abuse liability.59 As a result, the street price for 1 mg of HM is $3.29, which is six times higher than the street price of 1 mg morphine ($0.52).59

HM’s high potency and lipophilicity reflect its ability to more rapidly penetrate the blood brain barrier and saturate μ-receptors. These pharmacokinetic parameters account for the significant reinforcing effects (euphoria, tranquility, and reward), that lead to recreational abuse.20 The rapid penetration into the central nervous system and short half-life of HM lead to very rapid onset and offset of the pleasurable effects, which contribute to repeat self-administration. The faster reward reinforces and promotes continued self-administration (ie, abuse) in a dose-escalating pattern (ie, tolerance) as well as addiction and overdose.20,59 On a public health scale, these positive reinforcing effects lead to high street value and diversion, and ultimately epidemic morbidity and mortality.60,61

Studies that examined the reinforcing and euphoric effects of HM (enteral and parenteral) in comparison to morphine in patients with opioid-related abuse and addiction demonstrated ten times greater potency (euphoria and reinforcement) of HM compared to that of morphine.62,63 A study of 12 patients comparing the subjective, psychomotor, and physiological effects of IV HM and morphine in healthy volunteers demonstrated slightly higher potencies on nonanalgesic endpoints, specifically “having pleasant bodily sensations” and “liking of the drug” of HM.64 At the same time, another study demonstrated no difference in abuse liability between HM and morphine, and this represents an area in need of further prospective study.65

Unfortunately, studies evaluating the analgesic efficacy and adverse effects of HM did not include the euphoric properties of this opioid. The lack of such comparison undermines the greater abuse liability, likeability, and addiction potential of HM in comparison to morphine. However, the practical experience and observations as well as data from the Internet-based drug and addiction network (Bluelight and Erowid) clearly describe the drug-enabled gratification related to HM use.66-68

COMMON MISCONCEPTIONS

Several misconceptions exist among healthcare providers regarding proper equianalgesic conversion of HM to morphine and safety of HM in patients with renal insufficiency.

Equianalgesic dosing

A misunderstanding about equianalgesic dosing of HM is the most important factor leading to overdosing and harm from HM.57,52 The common equianalgesic conversion is that 1 mg of oral HM equals

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<table>
<thead>
<tr>
<th>Authors</th>
<th>Design</th>
<th>Nausea/Vomiting</th>
<th>Hypoxia</th>
<th>Respiratory Depression</th>
<th>Hypotension/Bradycardia</th>
<th>CNS Depression</th>
<th>Pruritus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chang et al., 2006</td>
<td>RCT: IV HM vs IV morphine, 198 patients</td>
<td>54% (55) -HM</td>
<td>1% (1) -HM</td>
<td>None</td>
<td>1.5% (2) -HM</td>
<td>None</td>
<td>0%-HM</td>
</tr>
<tr>
<td>Chang et al., 2009</td>
<td>RCT: IV HM vs IV morphine in geriatric patients (&gt;65yo), 194 patients</td>
<td>10.4% (5) -HM</td>
<td>9.7% (9) -HM</td>
<td>1.1% (1) -HM</td>
<td>3.2% (3) -HM</td>
<td>Not reported</td>
<td>4.3% (4)</td>
</tr>
<tr>
<td>Chang et al., 2009</td>
<td>Prospective interventional: 2 mg IVP, 269 patients</td>
<td>2% (30)</td>
<td>26%-O2 90-94%</td>
<td>4% (12)</td>
<td>1% (2)</td>
<td>Not reported</td>
<td>8% (22)</td>
</tr>
<tr>
<td>Chang et al., 2009</td>
<td>RCT, “1 + 1” Titration protocol, 223 patients</td>
<td>20% (34)</td>
<td>5% (11)</td>
<td>1% (3)</td>
<td>1% (2)</td>
<td>Not reported</td>
<td>5% (12)</td>
</tr>
<tr>
<td>Chang et al., 2009</td>
<td>RCT: Titration protocol vs physician-driven analgesia, 224 patients</td>
<td>22% (14) -Titration</td>
<td>4.6% (5) -Titration</td>
<td>0.9% (1 in each group)</td>
<td>1.8% (2) -Physician driven</td>
<td>Not reported</td>
<td>6.5% (7)</td>
</tr>
<tr>
<td>Chang et al., 2011</td>
<td>RCT: “1 + 1” Titration vs usual care, 327 patients</td>
<td>13% (13) -Titration</td>
<td>0.6 percent (1-Titration</td>
<td>0%-Titration 1.2% (2)-Usual care</td>
<td>1.8% (3) -Titration</td>
<td>Not reported</td>
<td>2.9% (5)</td>
</tr>
<tr>
<td>Chang et al., 2013</td>
<td>RCT, 2 mg vs “1 + 1” Titration Protocol, 334 patients</td>
<td>44% (26/58) in 2 mg group</td>
<td>0.6% (1) in “1 + 1” group</td>
<td>1% (2) in each group</td>
<td>1% (2) in “1 + 1” titration protocol</td>
<td>Not reported</td>
<td>17% (28)</td>
</tr>
<tr>
<td>Chang et al., 2015</td>
<td>Prospective interventional nongeriatric cohort, 215 patients, dosing: 1 mg–4 mg</td>
<td>1 mg-35% (10) 2 mg-73% (19) 3 mg-100% (2) 4 mg-73% (3)</td>
<td>8% (9)</td>
<td>1% (1)</td>
<td>1% (1)</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Chang et al., 2015</td>
<td>RCT: “1 + 1” Titration vs Physician discretion analgesia in geriatric patients (&gt;65yo), 104 patients</td>
<td>Not reported</td>
<td>22% (11/50)- Titration</td>
<td>30% (15/50)-Titration</td>
<td>17% (19/54)- Physician discretion</td>
<td>Not reported</td>
<td>Not reported</td>
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</table>

HM = Hydromorphone; MS = morphine sulfate; RCT = randomized control trial.
to 6-8 mg of morphine and 1 mg of parenteral (IV) HM equals to 8 mg (7-11 mg) of morphine. Thus, HM must be given in much smaller doses than morphine. However, these smaller numerical doses of HM (1-2 mg) may falsely reassure providers that a lesser functional amount of opioids is being administered to patients. Such practices result in average 50 percent higher dosing of HM than morphine leading to overdose and subsequent complications. In addition, this misconception is fueled by observations that ED physicians are much more comfortable and less concerned about administering HM in supra-analgesic doses than equianalgesic dose of morphine. Furthermore, several research papers misleadingly stated that it would be easier to combat undertreatment of acute pain by introducing a different parenteral opioid such as HM rather than educate providers to “use higher, more appropriately therapeutic doses of morphine.” A comparison of the initial doses of IV HM and the most commonly used parenteral alternatives morphine and fentanyl is provided in Table 4.

### Renal insufficiency and renal failure

HM’s active metabolite, H3G, is renally excreted, and as such, accumulates in patients with various degrees of renal insufficiency. Plasma concentrations may be four times higher than in patients with normal kidney function, and patients with renal insufficiency may develop severe neurotoxicity defined as myoclonus and seizures. Thus, a lower starting dose, as well as an increased dosing interval, along with close clinical monitoring is strongly recommended when HM is used for acute analgesia. In patients on hemodialysis, HM given by any route should be used with great caution and proper monitoring as the H3G accumulates between dialysis treatments but is effectively removed during hemodialysis.

### RECOMMENDATIONS FOR SAFE PRACTICE

All providers should strongly consider the nonopioid analgesic modalities as a first-line for patients with all but the most severe forms of pain and resort to an opioid only in cases of intractable pain. In addition, nonopioid analgesics can be used as adjuncts to lower opioid requirements.

Given the relatively concerning risk-benefit of HM, both in isolation and in comparison to morphine, which was discussed in this review, there appears to be a need for reconsideration of current practices of IV HM administration for acute pain. Several recommendations with primary emphasis on limited use and safety of this opioid analgesic are discussed below.

Since HM does not possess analgesic superiority over morphine for patients with acute pain and has a significantly inferior adverse effect profile, its use for this indication should be discouraged for patients with acute pain and for patients with chronic non-cancer pain. HM might be considered for patients with refractory cancer-related pain, refractory sickle-cell pain, and patients requiring palliative care on case-by-case bases and in conjunction with the patient’s oncologists, hematologists, or palliative care team, particularly in situations when morphine’s side effects (primarily pruritus and tolerance) become severe enough to jeopardize its analgesic efficacy.

The commonly used initial dosing of IV HM of 1-2 mg should be changed to smaller doses of 0.2-0.5 mg, especially for opioid-naïve patients. If HM must be used, the medication should be administered as a slow IV push. These dosing regimens are advised by Purdue Pharma and by the Institute for Safe Medication Practices.

Healthcare providers should become more familiar with the potency of HM as it applies to dosing and equianalgesic conversion to morphine milligram equivalents to provide safe, judicious, and effective analgesia.

Healthcare providers should not coadminister IV diphenhydramine with HM to prevent or treat opioid-induced pruritus, as it minimally alleviates pruritus but potentiates sedation and may lead to further alteration in mental status. If required for pruritus, oral diphenhydramine should suffice, though neither oral or IV administration of this drug has been systematically evaluated. Rescue naloxone should be readily available, especially if IV HM is used above the recommended dosing range.
CONCLUSION

HM is a potent opioid with similar analgesic efficacy to morphine when given in equianalgesic doses but with greater potential for abuse, diversion, and addiction. Current practices of IV HM administration are associated with 50-70 percent of higher doses that lead to significant hypoxia and respiratory depression. Every effort should be made to ensure a safe and rational IV HM use in the ED and throughout the hospital by reserving it for patients with intractable pain and palliation, by administering smaller effective analgesic doses, and by educating providers with ordering privileges about appropriate therapeutic dosing of morphine.

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