Intrathecal Hydromorphone for Chronic Nonmalignant Pain: A Retrospective Study

Valerie C. Anderson, PhD, Beverly Cooke, RN, BA, and Kim J. Burchiel, MD
Department of Neurological Surgery, Oregon Health Sciences University, Portland, Oregon

ABSTRACT

Objective. Ten percent to 15% of patients with chronic pain experience intolerable side effects or inadequate analgesia with continuous intrathecal morphine therapy. Although clinical experience suggests that rotation to hydromorphone (Dilaudid) can reduce side effects and recapture analgesia, there have been only scattered reports of long-term intrathecal hydromorphone use in patients with nonmalignant pain. The purpose of this study is to review the safety and effectiveness of continuous intrathecal hydromorphone in the management of patients with nonmalignant pain in whom continuous intrathecal morphine therapy has failed.

Design. A retrospective review of 37 patients with chronic nonmalignant pain managed with intrathecal hydromorphone after failure of intraspinal morphine.

Results. The mean age of patients was 64 years ± 12 SD. All patients suffered from severe nonmalignant pain, most from failed lumbosacral spine operations (19/37; 51%). Morphine was replaced with hydromorphone because of pharmacological complications (21/37; 57%) or inadequate analgesic response (16/37; 43%) after an average of 11 months ± 11 SD of intrathecal therapy. Pharmacological complications, particularly nausea and vomiting, pruritus, and sedation were reduced by hydromorphone in most patients. Peripheral edema was improved by hydromorphone but tended to recur with prolonged hydromorphone exposure. Analgesic response was improved by at least 25% in six of 16 patients who were switched to hydromorphone because of poor pain relief.

Conclusions. Hydromorphone can be a safe, analgesic alternative for long-term intrathecal management of nonmalignant pain among patients in whom morphine fails because of pharmacological side effects or inadequate pain relief.

Key Words. Hydromorphone; Intrathecal; Analgesia; Opioids; Chronic Pain

Hydromorphone (HM) is a semisynthetic derivative of morphine that has been used extensively for the management of cancer pain [1,2]. The drug is more soluble than morphine in both aqueous and lipophilic media [3], has a slightly shorter duration of action [1], and is approximately five times more potent than morphine when delivered systemically [4–6]. Like morphine, HM binds primarily at μ-opioid receptors and produces analgesia by presynaptic inhibition of neurotransmitter release in small primary afferents and hyperpolarization of postsynaptic neurons in the dorsal horn [7]. Clinically, HM has been shown to provide effective analgesia when delivered by oral, subcutaneous, and intravenous routes [8–10].

Intraspinal opioids are being increasingly used for the management of chronic severe pain conditions, with morphine as the first-line analgesic [11–14]. The drug is effective and tolerated by most patients and is relatively inexpensive [15]. Additionally, clinical experience with morphine is extensive and complications are well known [16–18]. In many patients, pharmacological side effects are transient and can be managed medically [19]. Currently, morphine is the only drug
approved by the Food and Drug Administration for use in permanent intrathecal (IT) infusion systems.

Nevertheless, approximately 15% to 20% of patients experience persistent pharmacological complications of IT morphine at or below analgesic doses [20]. Among the most problematic of these, peripheral edema, nausea and vomiting, micturition disturbances, sedation, and decreased mental status generally respond only to decreased opioid dose, thus limiting therapeutic benefit. In addition, many patients report decreased analgesic response with prolonged morphine exposure. Although the time course of tolerance development and the opioid dose at which it becomes problematic tend to be highly variable, we have observed that patients who require morphine dose in excess of 8 to 10 mg/day generally experience increased pharmacological side effects with little or no increase in analgesic effect [11]. For the most part, these patients continue to report poor pain relief at all tolerated doses.

In an effort to decrease morphine-related pharmacological complications and improve analgesic response, the use of alternate opioids, most commonly HM, has been reported [12]. Mechanistically, HM and morphine are very similar; however, the latter has a number of advantages that make it an important alternative to morphine, particularly for long-term intraspinal use. First, HM has greater potency than morphine. Although not established specifically for intrathecal delivery, an oral equianalgesic ratio of 1:4 to 1:8 HM/morphine is commonly reported [4,21,22]. As a first approximation then, an intrathecal HM dose approximately 20% that of morphine can be expected to provide roughly equivalent pain relief and, because of the reduced dose requirements, decreased side effects. When delivered epidurally, the two drugs have, in fact, been shown to provide equivalent analgesia of postoperative pain but with improved side effect profile among patients receiving HM [1,23]. Another advantage of HM is that it has no known active metabolites, in contrast to morphine, for which increased levels of the morphine-3-glucuronide have been shown to be associated with drowsiness, hyperalgesia, allodynia, and myoclonus during chronic oral, intravenous, and intrathecal administration [24–26]. Finally, the increased lipid solubility of HM results in more rapid entry into the spinal cord, shorter onset of analgesia, and potentially fewer central nervous system (CNS) side effects than morphine because of rostral spread of the drug [21,27,28]. In combination, these features suggest that intrathecal HM may provide analgesia at least as effective as that of morphine but with fewer side effects. Indeed, systemic HM is known to be an effective alternative analgesic for patients who experience encephalopathy, sedation, nausea and vomiting, hyperalgesia, or myoclonus to systemic morphine [26,29–31].

In spite of its widespread clinical use, there have been only scattered reports of continuous intrathecal HM for pain management, and no study has focused exclusively on the response of nonmalignant pain to long-term HM therapy [11,13,14,20,32]. The purpose of the current study, therefore, is to provide a retrospective assessment of the safety and analgesic effectiveness of long-term HM in the management of patients with severe, nonmalignant pain in whom IT morphine has failed.

Methods

Clinical Methods

Between January 1996 and December 1999, 112 patients were implanted with a permanent infusion system at Oregon Health Sciences University for delivery of intraspinal morphine. All patients had chronic pain (defined as pain of at least 6 months duration) refractory to a wide variety of medical and surgical treatments and sensory loss in an anatomical distribution. All patients had been exposed to systemic opioids before being considered for infusion system implant; the majority (>80%) were taking systemic opioids at the time of initial assessment. After neurological evaluation and review of relevant imaging studies, candidates for continuous intrathecal opioid therapy (CIOT) were referred for psychological evaluation to exclude those with severe depression, history of drug abuse, or significant unresolved issues of secondary gain central to the pain complaint.

Patients without medical or psychological contraindications to CIOT were then admitted for a 1- to 2-day inpatient trial of intraspinal morphine (epidural catheter or IT injection) to assess analgesic response before implantation of permanent infusion system [11]. In patients with good pain relief but unmanageable side effects (typically nausea and vomiting or pruritus), morphine was discontinued and the trial repeated or continued with HM. Patients who reported at least 50% pain relief during trial were offered implant of a permanent infusion system (Synchromed; Medtronic, Inc., Minneapolis, MN). Implantation of the infusion system proceeded via standard surgical procedures [33].

Patients were started on IT morphine immediately after implant. Routinely, the starting dose was 1 mg/day. This dose allowed most patients to be discharged within 1 or 2 days of surgery with adequate, if not entirely optimal, pain control. Patients
who showed good analgesic response to morphine during the trial but experienced unmanageable side effects were started on HM, typically 0.2 mg/day. Systemic opioid analgesics were prescribed for breakthrough pain during the perioperative period, but the prolonged use of systemic in addition to IT opioids was strongly discouraged. Typically, patients were weaned off of all oral opioids within 2 months of beginning IT therapy.

Patients returned to the clinic within 10 days of discharge for suture removal and dose adjustment, as necessary. Subsequent clinic visits were scheduled based on pain report, pharmacological complications, or when reservoir refill was necessary. Although the vast majority of patients experienced some degree of drug-related side effects immediately after infusion system implant (most commonly constipation, diaphoresis, and micturition disturbances), they tended to be mild and resolved medically over the first few months of therapy.

In all patients, the decision to replace morphine with HM was made by the managing physician and was based on complication profile and analgesic response. In the absence of intolerable side effects, reports of ineffectual analgesia were not considered an immediate indication for opioid rotation but rather for morphine dose escalation, typically 5% to 20% depending on pain severity. However, when patients consistently failed to experience inadequate pain relief despite repeated dose increases, rotation to HM was considered [34]. In either case, after the decision was made to rotate from morphine to HM, the starting dose of HM was based on the current IT morphine dose, assuming a relative potency of 1 mg HM per 5 mg morphine [5,22].

**Study Methods**

Pharmacy prescription logs of all IT schedule II drugs were matched with the 112 patients implanted with an infusion system during the review period. Accordingly, 48 of 112 (43%) patients with a chronic nonmalignant pain diagnosis were identified who received HM at some time during the period. Of these, 11 (23%) were no longer being monitored in our clinic and were excluded from detailed analysis. However, attempts were made to contact the treating physician for brief clinical status follow-up. Four of 11 patients continued to be managed with IT opioids: two on HM and two who had been switched back to morphine (the reason was not documented). Another two patients had been weaned off all IT opioids secondary to poor pain relief, one with and another without explantation of the infusion system. No additional follow-up was available for the remaining five patients.

Overall, 37 patients were implanted with an IT infusion system and were managed in our clinic throughout CIOT. All patients had chronic nonmalignant pain managed with intrathecal HM for at least 1 month at the time of chart review. Demographics and pain history were collected, including age, gender, diagnosis, and dosing history. Pain rating, routinely documented at each clinic visit, was available at the time of rotation to HM (T₀) and throughout follow-up. Clinically, one of two pain rating scales was used to document average pain over the previous week: a verbal numerical analogue scale (NAS) ranging from 1 to 10 or 100-mm visual analogue scale (VAS).

Statistical analyses were performed using JMP Statistical Visualization Software (SAS Institute, Cary, NC). All P values are two-tailed. Nonparametric analyses were used when data were nonnormally distributed or when data could not be normalized by common transformations [35].

**Results**

Demographics of the study population (N = 37) are summarized in Table 1. The mean age at time of implant was 64 years ± 12 SD (range: 43–85). The majority of patients (27/37; 73%) had undergone at least one prior surgery for pain (median: 2). Most patients were female (23/37; 62%). Pain was chronic in all patients, with duration of 5 years or longer (median: >10 years) in 31 of 37 (84%) patients. On average, pain had been managed with IT morphine for 11 months ± 1 SD before rotation to HM.

Most patients (19/37; 51%) presented with mixed nociceptive/neuropathic pain as the result of failed back surgery syndrome (FBSS; n = 17) or degenerative lumbar spine disease (n = 2). Another 15 patients (41%) had pain of predominantly neuropathic origin as a result of peripheral neuropathy (n = 4), arachnoiditis (n = 3), traumatic spinal cord injury (n = 2), or neurofibromatosis, sciatric nerve damage, myeloradiculopathy, genitourinary pain, brachial plexus avulsion, or postherpetic neuralgia.

**Table 1. Clinical features of study patients (N = 37)**

<table>
<thead>
<tr>
<th>Demographic</th>
<th>M ± SD</th>
<th>Median (N,%)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>64 ± 12</td>
<td>—</td>
<td>43–85</td>
</tr>
<tr>
<td>Pain duration (yr)</td>
<td>—</td>
<td>&gt;10 (23,62)</td>
<td></td>
</tr>
<tr>
<td>Previous surgeries</td>
<td>—</td>
<td>2</td>
<td>0–28</td>
</tr>
<tr>
<td>Female</td>
<td>—</td>
<td>23 (62)</td>
<td></td>
</tr>
<tr>
<td>Duration of morphine use (mo)</td>
<td>11 ± 11</td>
<td>—</td>
<td>0–49</td>
</tr>
</tbody>
</table>
Finally, three patients (8%) had nociceptive pain complaints as a result of joint pain (n = 2) or multiple knee operations (n = 1).

The topographical distribution of pain among the study group is shown in Figure 1. Most patients (28/37; 76%) reported a significant component of pain in the low back. The majority of these (24/37; 65%) reported radicular symptoms, with radiation to one (n = 15) or both (n = 9) lower extremities. In the remaining patients (9/37; 24%), pain was localized to the lower extremities, feet or hands, arm, groin, or penis.

Except for three patients who were switched to HM during trial screening because of severe morphine-related side effects (uncontrollable nausea and vomiting or pruritus), all patients began CIOT with morphine, and every attempt was made to provide satisfactory analgesia without adjuvant intraspinal agents. However, because of the reported potentiation of opioid analgesia by local anesthetics in patients with a prominent neuropathic pain component, combination morphine/0.75% bupivacaine was assessed in 11 patients with neuropathic or mixed neuropathic/nociceptive pain [36–38]. Diagnoses included FBSS (n = 5), spinal cord injury (n = 2), arachnoiditis, peripher- nal neuropathy, neuropathic penile pain, and neuropathic sciatic pain. Daily IT bupivacaine dose ranged from 0.98 to 6.39 mg/day. On average, these patients continued to receive combination morphine/bupivacaine for 13 months ± 8 SD (range: 2–28 months), with mild to moderate improvement in pain report. Ultimately, however, analgesic response diminished and bupivacaine was discontinued. Similar results have been reported by Hassenbusch and others [39,40]. Finally, in two patients with neuropathic pain resulting from arachnoiditis and sciatic neuropathy response to combination intraspinal morphine/clonidine (50 or 100 µg/day) was evaluated [41–43]. Unfortunately, neither patient reported improved analgesia with the addition of the α₂-adrenergic agonist, and it was abandoned after 1 month in both cases. No other intraspinal combinations were used in this patient series.

Rotation to HM was considered when intolerable side effects developed or when reports of inadequate pain relief were persistent despite repeated morphine dose increase. Of the 37 patients in this series, morphine was discontinued in 21 (57%) because of pharmacological side effects. Among all patients, peripheral edema and intractable nausea and vomiting were the most problematic and, combined, were the primary reasons for morphine discontinuation in more than 38% (14/37) of all patients (Figure 2).

In the remaining 16 patients, pain was unrelieved by repeated morphine dose increases. Because of the possibility of hardware malfunction, system patency was assessed in all patients with persistent report of poor pain control. Return of cerebrospinal fluid from the pump side port, diagnostic x-ray film, and technetium flow study were used to confirm proper operation of infusion system before consideration of opioid rotation [28]. In this series, eight patients (22%) experienced catheter displacement, kinking, or occlusion that reduced flow to the IT space at some time during morphine infusion. After surgical revision, IT therapy was reinstituted. Ultimately, however, 16 patients experienced inadequate analgesia from IT morphine despite proper functioning of the infusion system.

Among all patients, HM infusion was begun after 11 months ± 11 SD (range: 0–49 months) of IT morphine. The final morphine dose before rotation to HM was 4.8 mg/day ± 5.0 SD (median: 3.1 mg/ day; range: 0–23). The starting dose of HM was 1.1 mg/day ± 1.1 SD (range: 0–4.6 mg/day). At the most recent follow-up, an average of 10 months ± 9 SD after beginning intrathecal HM, 33 of 37 patients (89%) continued to be managed with HM. Mean daily dose among these patients was 3.2 mg ± 3.3 SD (range: 0.1–12.8 mg). In the remaining four patients, HM was discontinued after a median of 4 months (range: 1–12 months) and morphine reinstituted. Three of these patients, switched to HM because of inadequate analgesia, reported unimproved pain and requested return to intraspinal morphine. After reinstallation of IT morphine, all three reported analgesia superior to that experienced before rotation. The remaining patient was switched back to morphine after 2 months because of a metallic odor and taste that developed shortly after rotation to
Intrathecal Hydromorphone

Symptoms resolved within 2 weeks of rotation to morphine.

**Analgesic Response to Intrathecal HM**

Numerical pain ratings were available for 32 patients at the time of rotation to HM (T₀) and at the most recent follow-up. Because of changes in clinic procedures, 16 of 32 patients were asked to rate initial pain by verbal NAS, and the remaining 16 completed the written VAS assessment. At the most recent follow-up, all patients completed VAS rating. Mean T₀ NAS/VAS rating was 72 ± 15 (range: 30–100). At most recent follow-up, VAS pain rating was 65 ± 15 (range: 4–100), an insignificant change from the T₀ pain report (P = 0.9; Wilcoxon signed ranks).

Change in pain intensity was analyzed separately for those patients who were switched to HM because of inadequate analgesia (n = 16) and pharmacological complications (n = 21). Among the former, pain decreased from 75 ± 19 at T₀ to 59 ± 27 at most recent follow-up (P = .04; Wilcoxon signed ranks) for the 15 patients for whom complete pain ratings are available. Of these, six patients reported a decrease of more than 25%, whereas only one reported increased pain after rotation to HM. Among patients switched because of morphine-related side effects, four reported pain improved by at least 25% at most recent follow-up, although, as a whole, patients who began HM because of morphine-related side effects did not report significantly improved analgesia (68 ± 11 at T₀ vs. 67 ± 17 at most recent follow-up; P = .74; Wilcoxon signed ranks). Figure 3 shows the percentage of pain relief from T₀ to most recent follow-up for patients in each group.

**Pharmacological Complications of Intrathecal HM**

Complications of HM were noted at each clinic visit. Figure 4 shows the percentage of patients reporting each complication at any time after initiation of HM infusion and again after more than 1 month of HM. The latter represents complications of long-term HM, whereas the former includes complications experienced in the short term after discontinuation of morphine. Overall, the most common complications associated with HM were drowsiness and nausea, experienced by 30% to 40% of patients. As shown in Figure 4, however, reports of both were significantly reduced within 1 month of beginning HM infusion. Similarly, diaphoresis, pruritus, and mental status changes, which continued to be problematic immediately after rotation to HM, were reported with decreased frequency in subsequent months. In contrast, five of eight patients with morphine-related nausea reported that symptom severity was reduced by HM but tended to recur periodically while on HM. In these patients, symptoms were controlled with standard medical management and CIOT continued. Likewise, for some patients, constipation tended to be a recurrent problem that, despite improvement with decreased opioid dose, was not resolved by HM (see Figure 4). Like nausea, however, constipation tended to be more manageable and shorter lived after rotation to HM. Importantly, no patient in this series requested discontinuation.
of CIOT because of constipation, nausea, drowsiness, pruritus, diaphoresis, or mental status change after rotation to HM.

One of the most problematic complications of long-term opioid therapy is peripheral edema. In this series, eight of 37 patients reported extremity or joint edema at some time during HM infusion. Six had experienced edema while on morphine, and in these patients it was the primary reason for opioid rotation. As indicated in Figure 5, only one of six patients experienced complete resolution of edema after rotation to HM. In this patient, resolution was rapid; edema dissipated almost immediately after morphine discontinuation. In the remaining five patients, however, HM did not permanently resolve peripheral symptoms and edema tended to occur periodically. Temporary HM dose reduction improved symptoms although generally not without diminution of analgesic effect.

Finally, no complications were associated with HM that had not been reported during morphine infusion. Notably, however, a metallic taste or odor developed after 2 to 14 months in three patients who were asymptomatic on morphine. In two patients, symptoms resolved spontaneously. However, in one, symptoms were so bothersome that HM was discontinued and morphine infusion re instituted.

![Figure 3](https://academic.oup.com/painmedicine/article-abstract/2/4/287/1876359)

**Figure 3** Change in pain from initial rating at the time of rotation to HM to the most recent follow-up for patients switched to HM because of morphine-related side effects (solid; n = 17) and ineffective analgesia (open; n = 15). See Results for additional description.

![Figure 4](https://academic.oup.com/painmedicine/article-abstract/2/4/287/1876359)

**Figure 4** Percentage of patients reporting pharmacological complications of HM therapy at any time (solid) and after 1 month of HM (dotted) (N = 37).
Effectiveness of HM as an Alternative to Morphine

Figure 5 shows the primary reason for morphine discontinuation among all patients and the extent to which the problem was resolved by HM. Among the 16 patients switched because of poor analgesic response, six reported pain reduction of at least 25% at the most recent follow-up. Among the 21 patients for whom pharmacological side effect was the primary reason for morphine discontinuation, 11 reported no bothersome symptoms after rotation to HM. Although some patients did report periodic pruritus, diaphoresis, urinary difficulty, and CNS side effects of HM, all those who discontinued morphine because of these complications reported no further difficulties after rotation to HM.

Discussion

Traditionally, morphine has been the opioid of choice for systemic management of severe pain. The demonstration of the drug’s long-term stability at physiologic temperatures [44] combined with its compatibility with a variety of implantable infusion systems [45] has extended its role, making morphine the mainstay drug for long-term IT management of severe nonmalignant pain. However, pharmacological complications or reduced analgesic response can diminish its benefit, leaving patients with few options for pain control. In these cases, an alternative analgesic is needed [34].

The current report represents the first review focused exclusively on the clinical response of nonmalignant pain to long-term intrathecal HM. The major findings of this retrospective study are twofold. First, rotation to HM can provide analgesia to some patients for whom pain relief is inadequate with morphine. In this series, six of 16 patients switched to HM because of poor pain relief with IT morphine reported at least a 25% reduction in pain at most recent follow-up. Improved analgesia after systemic morphine/HM rotation is well known and has been attributed to differential opioid receptor affinities of the two drugs. Whereas morphine is a pure µ-receptor agonist, HM has intrinsic activity at µ-, κ-, and δ-opioid receptors [46]. It has also been suggested that the improved analgesic response may be due to changes in the receptor–effect relation that develops with prolonged morphine administration [21,47].

The second major finding of this study is that pharmacological complications of IT morphine, particularly nausea and vomiting, pruritus, and sedation, can be reduced or, in some patients, eliminated by HM. Even among patients for whom the side effect was not completely resolved, nausea and vomiting tended to improve rapidly after rotation to HM. Gastrointestinal complications such as nausea and vomiting are known to be associated with cephalad migration of morphine and binding to brainstem nausea centers and the medullary chemoreceptor trigger zone [18,48]. In addition, it has been suggested that accumulation of the 3- and 6-glucuronide metabolites of
morphine may produce side effects through nonopioid receptor mechanisms [18,25,49,50]. In contrast, neither the pharmacological activity nor accumulation of the major metabolite of HM, hydromorphone-3-glucuronide, have been established [51,52]. Certainly, the current results suggest that if HM metabolites do accumulate during chronic IT infusion in patients with normal renal function, their pharmacological activity is of minimal clinical significance.

Fluid retention was more problematic in our patients than previously reported; morphine was discontinued in 16% of patients because of peripheral edema [15]. In most of these patients, edema was only transiently improved after rotation to HM and tended to recur with prolonged exposure. Pharmacokinetic studies suggest that morphine stimulates release of vasopressin from the posterior pituitary [18]. Given the similarities of the two opioids, it is likely that HM, only slightly less hydrophilic than morphine [3], also diffuses to higher order brain centers, producing peripheral edema via a similar mechanism.

Our data also suggest that endocrine disturbances associated with chronic IT morphine, including decreased libido and erectile dysfunction, are not improved by rotation to HM [15,53,54]. Although this is probably underreported, two patients in our series described problems with sexual function that contributed to the decision to discontinue morphine; however, both patients continued to experience problems while on HM. All of our patients are now explicitly questioned about changes in sexual function at each clinic visit, with referral for endocrine work-up as required.

Overall, our data are consistent with earlier observations that HM is associated with less severe side effects than morphine [1,23,32,55]. This finding is of particular relevance in the context of IT therapy, for which the risks and relatively high cost of the infusion system demand that the benefit be sustained [56]. Our data suggest that HM, with its improved side effect profile and analgesic properties, can extend the benefit of IT therapy among patients who experience intolerable side effects with long-term IT morphine.

It is important, however, to view these results within the limitations of the retrospective study design. First, inclusion criteria were not rigidly defined by protocol, and all patients in whom IT morphine had failed and who had pain managed with HM for at least 1 month were included. As such, the study population reflects the biases inherent in the patient selection methods used in our clinic to identify patients for continuous IT therapy. In our center, patients are offered CIOT only after failure of all other reasonable pain management approaches, a neurological finding of sensory loss in an anatomical distribution, absence of psychological contraindications to invasive pain management, and demonstration of successful pain response to intraspinal morphine trial. Although these selection criteria are by no means universal [57], they are nevertheless standard, accepted methods of choosing patients who are most likely to respond to CIOT.

Consistent with prevalence demographics, the majority of patients in our clinic who are considered for CIOT have low back pain. Not surprisingly, then, the majority of patients described herein had low back pain with radiation to the lower extremities and clinical signs and symptoms consistent with mixed neuropathic/nociceptive pain; however, we and others have observed that some neuropathic pain conditions can also be managed quite effectively with long-term CIOT [11,20]. Thus, this series consists of patients with diverse pain types and causes. Although we realize that the prognostic significance of our results are somewhat obscured by this diversity, we believed that the first report to focus on long-term intrathecal HM use should provide a broad basis for clinical conclusions concerning its use as an alternative to morphine. More specific prognostic conclusions await a prospective study design.

A second limitation of this study is the lack of rigid criteria for the rotation to HM, an issue of obvious clinical importance. In our clinic, observation of severe morphine-related toxicities prompts immediate consideration of an alternative IT drug [34]. However, when a patient reports poor pain relief, the decision to change opioid is less clear-cut and is frequently based on a combination of subjective, sometimes seemingly inconsistent, factors. For example, in the 16 patients in this series who were switched to HM because of ineffective analgesia, we also considered morphine dose, adjuvant medication use, duration of therapy, psychological health of the patient, family support, coexisting medical problems, and frequency of pump refills before morphine replacement. No one factor was consistently used as the basis for the decision to rotate to HM. Thus, some patients were switched to HM after morphine dosage exceeded 20 mg/day and others at 2 mg/day; some patients were rotated after pain report of 100, others at 50.

As a further complication, clinical practice in IT therapy is evolving rapidly [12]. Before 1998, for example, we considered a second-line IT therapy only when morphine dosage approached 20 mg/day, unless complications were bothersome at lower doses. Although 20 mg/day is still the generally accepted upper limit for IT morphine dosage [34], one survey
found that the mean morphine dosage was 7.1 mg/day among 13,342 whose pain was managed long-term with CIOT [12]. This trend to provide analgesia at lower IT opioid dose is reflected in our data by the relatively low 5 mg/day morphine at which patients were rotated to HM.

Thus, although we realize that the subjectivity of the timing of rotation obscures interpretation, we believe that the decision to replace morphine with a second-line opioid or combination analgesic will always remain somewhat subjective and is likely to vary with physician experience and prescribing practices, patient–physician interaction, and family support, all of which can have a large influence on pain management decisions. It is unlikely that more objective criteria for opioid rotation, particularly in the face of inadequate analgesia, will be defined in the absence of a controlled, prospective study.

A further limitation of the study is the potential for underreporting complications as a result of the retrospective design. Typically, only the most bothersome side effects are recorded in the clinical setting, and, in the absence of direct questioning, many pharmacological complications may not be reported at all. Nevertheless, it is unlikely that the retrospective nature of the study significantly influences the relative complications of the morphine and HM because clinical procedures and reporting were relatively consistent throughout.

Finally, the results of our study suggest that chronic intrathecal HM can provide analgesia comparable to that of morphine in patients with severe nonmalignant pain. We do appreciate, however, that this conclusion is based on pain report that is a combination of visual and numerical analogue scales. Whereas the VAS has shown to be a valid and reliable measure of pain intensity that is sensitive to changes over time [58], the verbal NAS rating reflects both an intensity and an unpleasantness component of the pain that is not distinguished by the VAS [59]. Thus, comparison of combination NAS/VAS scores with follow-up, purely VAS data may have little psychometric validity.

In conclusion, our study suggests that HM can be a safe, clinically useful analgesic for long-term IT infusion among patients in whom morphine CIOT has failed. Pharmacological side effects are reduced with HM, extending the IT dose that can be safely delivered. The study also demonstrates that HM can provide analgesia to patients whose pain has become unresponsive to morphine. Taken together, these results suggest that HM can be a clinically useful alternative to morphine among a carefully selected population of patients with severe nonmalignant pain managed by CIOT.

References

49 Ekblom M, Gardmark M, Hannarlund-Udenaes M.
Intrathecal Hydromorphone


