Stability and Compatibility of Hydromorphone Hydrochloride in an Implantable Infusion System

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Abstract
With the exception of morphine, hydromorphone is the most commonly used intrathecal opioid for the treatment of intractable pain. The purpose of this study was to evaluate the stability and compatibility of hydromorphone in the implantable infusion system that is most commonly used in these patients. Hydromorphone solution was incubated at 37°C in infusion system reservoirs and with individual materials which comprise the fluid pathway of the infusion system. Stability was analyzed using high performance liquid chromatography; mechanical integrity of device materials was evaluated after drug exposure. After 4 months of exposure to device materials or intact devices, hydromorphone concentration remained greater than 95% of starting material. All device materials retained acceptable mechanical performance. These results demonstrate that hydromorphone is stable at physiological temperatures for at least 4 months in an implantable infusion system and that current clinical practice of refilling the pump every 3 months is appropriate.

Key Words
Hydromorphone, opioid, stability, compatibility, intrathecal, implantable pump

Introduction
Intrathecal delivery of opioids using implantable infusion systems has become an accepted method for long-term management of severe malignant pain.1-4 The intrathecal route of delivery significantly increases the therapeutic index of this class of analgesics as compared to oral or other parenteral routes of administration.5 In addition, implantable infusion technology allows much lower doses of medication to be infused chronically with reduced risk of infection and without the patient inconvenience associated with ambulatory infusion systems.

Opioids are the most commonly used agents for intrathecal management of pain. Morphine sulfate is the most frequently used and only approved agent for long-term intrathecal infusion. Another opioid that is commonly used, though, is hydromorphone hydrochloride.2,3,6,7 Hydromorphone (HM) is a semisynthetic hydrogenated ketone of morphine (Figure 1) that is approximately five times more analgesic...
than morphine.8–10 The duration of action (4–5 hours) and plasma half life (2–3 hours) of HM following parenteral administration are comparable to morphine.11 Moreover, the opioid-receptor selectivity of HM is similar to morphine. Both are considered high-affinity, selective mu-receptor agonists.

The stability of HM and its compatibility with implantable infusion systems have not been confirmed. Because of the low intrathecal doses needed to manage chronic pain and the fixed volume of the infusion pump, refill is generally required only 3 to 5 times per year. Therefore, it is important that the preservative-free drug solution remain stable at body temperature for prolonged intervals. Drugs that degrade significantly or form precipitates within the infusion reservoir are not suitable for prolonged intrathecal use. In addition, although materials which comprise the fluid pathway of the infusion systems are selected because of their mechanical and chemical robustness, unless the specific pump and catheter system is tested with the drug solution of interest, it cannot be assured that material degradation or system failure will not occur.

The stability and compatibility of morphine sulfate (Infumorph®) with a commonly used implantable infusion system (SynchroMed®, Minneapolis, MN) has been previously demonstrated (Medtronic data on file). The purpose of this study is to investigate the stability of HM in this delivery system and the compatibility of drug with device materials.

**Methods**

The stability of HM (Dilaudid®, Mount Olive, NJ) was evaluated in vitro using two different yet complementary methods. In the first method (drug–material stability), the effect of materials present along the drug-device interface on HM stability was evaluated. In the second method (drug–device stability), stability was evaluated using an intact pump-catheter system. As tested, the formulation contained HM at a concentration of 2 (Dilaudid, Wilmington, DE) or 10 mg/mL (Dilaudid-HP) in a 0.2% sodium citrate buffer solution, pH 4.1.

**Equipment and Conditions**

Stability analyses were performed using high performance liquid chromatography (HPLC). A Hewlett Packard (Palo Alto, CA) 1090A liquid chromatograph with a diode array detector was used. The stationary phase was a Dupont 5 micron, C18 reverse-phase column (150 × 4.6 mm); the mobile phase was a 59/49/1 (V/V/V) mixture of 5 mM heptane sulfonic acid/methanol/acetic acid. The detector was set at 280 nm. Flow rate of the mobile phase was constant at 1 ml/min; sample injection volume was 10 μl. This method displayed good linearity (correlation coefficient 0.999) and precision (coefficient of variation 1.98%) with 3% accuracy during duplicate injections. The limit of detection was approximately 10 μg/ml.

**Drug–Material Stability**

HM (10 mg/mL) was exposed to each of 6 different materials that comprise the infusion pathway of the delivery system for 16 weeks. Samples of each material were incubated with HM in glass ampules sealed to prevent evaporation and maintained at 37°C with continuous agitation. HM incubated in the absence of any device material served as a control. Fluid samples were collected after 1, 2, 4, 8, and 16 weeks. HM concentration was determined in each and expressed as a percentage of the concentration of HM contained in a fresh solution of the same lot.

**Drug–Device Stability**

Three SynchroMed infusion systems were tested. Attached to each pump was a silicone catheter (Model 8703, Medtronic, Inc.). The reservoirs of the pumps (18 ml) were filled with HM (2 mg/ml). The infusion systems

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**Fig. 1.** Chemical structures of morphine and hydromorphone. Hydromorphone differs structurally from morphine by the substitution of an oxygen for the 6-hydroxyl group and hydrogenation of the 7–8 double bond.
were maintained at 37°C to simulate implant conditions and programmed to deliver at a constant rate of 90 μl/day. HM aliquots were collected every two weeks over 16 weeks from two different locations: the reservoir of the pump and the exit port of the catheter. No re-fills were made to the pump reservoirs during this time. Control solution was maintained in a sealed vial at room temperature and protected from light. Concentrations in the reservoir and at the catheter tip were expressed as percentages of the control concentration.

**Drug–Device Compatibility**

To evaluate effects of prolonged HM exposure on materials that comprise the fluid pathway of the infusion system, the following tests were conducted. Each material was immersed in HM (10 mg/ml) contained in sealed glass ampules (5 pieces of material per ampule). Ampules were maintained at 37°C with constant agitation for 16 weeks. Material samples were collected at 1, 2, 4, 8, and 16 weeks after immersion. Tensile strength and percent elongation at break point of elastomers were assessed using a pull-tester machine. Flow rate (water at 10 psi) through the in-line filters was evaluated. Hardness of the septum through which drug solution is added to the reservoir was evaluated to ensure proper sealing following needle puncture.

**Results**

**Drug–Material Stability**

After 16 weeks of incubation with each material that comprises the fluid pathway of the infusion system, none of the HM samples analyzed demonstrated significant loss of drug (Figure 2). HM concentration was ± 3% of that measured in fresh solution. As shown, control solution unexposed to device materials demonstrated HM concentrations of 99.8% and 98.5% at 8 and 16 weeks, respectively. In addition, none of the material-exposed HM samples demonstrated a consistent time-dependent decrease in concentration. The reason for the slight decrease in concentration observed after exposure to one type of elastomer (filled circles) is not clear but may be due to adsorption to the material. At 16 weeks, material-exposed samples and the control solution pH was 4.2 (compared to 4.1 in fresh solution).

![Fig. 2. Concentrations of material-exposed hydromorphone over time.](image)

Fig. 2. Concentrations of material-exposed hydromorphone over time. Each material of the delivery system was incubated with hydromorphone for 16 weeks at 37°C. The concentration was expressed as a percentage of drug contained in fresh solution (control). Open squares, filled squares = pump elastomers, open triangles = catheter material, filled triangles = refill septum, open circles = titanium, filled circles = pump filter, open diamonds = control.

**Drug–Device Stability**

Samples collected from 3 SynchroMed infusion systems maintained at 37°C are shown in Figure 3. When expressed as percent concentrations of control, all 16-week samples collected from either the pump reservoir or the catheter exit port had mean HM concentrations > 95%. No individual sample exhibited a concentration < 92.5% of control. HPLC chro-
matograms of device-exposed HM revealed no additional peaks. In contrast, HM degradation peaks were identified after exposure to electric current. In addition, HM samples did not demonstrate a time-dependent decrease in concentration.

Drug–Device Compatibility

All device materials exposed to HM solutions for 16 weeks demonstrated acceptable mechanical performance. Tensile strength and elongation of the 3 different elastomers displayed no significant changes from initiation to completion of the experiment (Table 1). Throughout the test period, the elastomers exhibited physical properties that were within the qualification specification of each material required for use in the delivery system.12 Hardness of the access septum and flow rate of the pump filter were likewise unaffected by chronic HM exposure (Table 1).

Discussion

Long-term intrathecal opioid administration by means of implantable infusion systems presents several unique challenges in terms of stability of the pharmaceutical agent being delivered. Two major challenges include: 1) the requirement to use preservative-free formulations, and 2) prolonged storage of the formulation at elevated temperature (i.e., body temperature) within the reservoir of the delivery system.

As noted previously, long-term stability of morphine sulfate in the SynchroMed system has been previously established (Medtronic data on file). Aqueous preservative-free morphine at room temperature has been reported to be stable for 12 days,13 6 weeks,14 3 months,15,16 and 18 months.17 Morphine has also been reported to be stable for 2 months at 32°C18 and 1 month at 37°C.19 Long-term stability of morphine and similarity in chemical structure between morphine and HM (Figure 1) suggest similar stability properties of aqueous HM solutions.

This is the first report that specifically addresses the stability and compatibility of HM with an implantable delivery system. Coombs and colleagues suggested that HM is stable at body temperature when chronically administered via an implantable infusion pump.6 Unfortunately, these data and the specifics of their methodology were not reported. Admixtures of HM with fluorouracil (an antineoplastic) and with ondansetron (an antiemetic) have been demonstrated to be stable at 32°C for at least 7 days and at least 31 days at room temperature.20,21 Admixtures of HM and bupivacaine have been shown to be stable at 24°C for 72 hours in polyvinyl-chloride containers.22

Results of the present study indicate that commercially available preservative-free HM hydrochloride solution is stable within the SynchroMed infusion system for at least 4 months. Three to four months is a typical interval between pump reservoir refills (outpatient appointments) for implantable infusion pumps used for treatment of chronic pain. Drug-material testing using the compositional materials of the delivery system also corroborate the stability of the HM formulation. All HM solutions evaluated after 16-week exposure to either infusion systems or infusion system materials exhibited concentrations > 95% of control solutions.

| Table 1

Mechanical Performance of Device Materials Before and After 16-Week Hydromorphone Exposure

<table>
<thead>
<tr>
<th>Material</th>
<th>Tensile Strength (psi)</th>
<th>% Elongation</th>
<th>Flow rate (ml/30 sec)</th>
<th>Hardness (durometer)</th>
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<tr>
<td></td>
<td>Before</td>
<td>After</td>
<td>SD</td>
<td>Before</td>
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<tr>
<td>Elastomer A&lt;sup&gt;e&lt;/sup&gt;</td>
<td>1586</td>
<td>1600</td>
<td>36</td>
<td>771</td>
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<tr>
<td>Elastomer B</td>
<td>1420</td>
<td>1330</td>
<td>60</td>
<td>870</td>
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<tr>
<td>Catheter</td>
<td>589</td>
<td>570</td>
<td>26</td>
<td>669</td>
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<tr>
<td>Pump filter</td>
<td>—</td>
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<tr>
<td>Refill septum</td>
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<sup>a</sup> Hydromorphone concentration = 10 mg/ml, T = 37°C.
<sup>b</sup> Mean force measured at breaking point.
<sup>c</sup> Mean percent elongation at breaking point versus unstretched condition.
<sup>d</sup> Standard deviation from 5 samples per material.
<sup>e</sup> Elastomers A and B are components of the internal pump mechanism.
The HPLC-UV detection method used to quantify HM in device- or material-exposed samples proved to be sensitive, accurate, and precise. HPLC has been the method of choice for quantifying opioids in a variety of matrices with methods of detection including diode array, fluorescence, electrochemical, and mass spectrometry. Another proven method of opioid analysis is gas chromatography with mass spectrometry detection. Although mass spectrometry is more expensive than other traditional methods of detection, when combined with either liquid or gas chromatography, it can significantly lower the limit of quantification, an advantage which is often desired with biological matrices.

This study also demonstrates the compatibility of device materials with HM after chronic incubation at temperatures representative of clinical use. All materials that comprise the fluid pathway of the delivery system demonstrated appropriate mechanical integrity after 16 weeks. Moreover, the infusion system maintained appropriate function throughout the course of the in vitro testing. Clinical practice demands longevity of implantable infusion systems for at least 5 years. The 4-month HM-device compatibility data and the clinical history of the SynchroMed infusion system to deliver morphine, a chemically similar opioid, chronically in patients suggest that long-term patient management with HM is reasonable.

In conclusion, these results demonstrate that a commercially available formulation of HM has acceptable stability and material compatibility when tested over a 16-week period. Based on these data, the current clinical practice of refilling the reservoir of the pump every three months is acceptable from a stability–compatibility perspective.

Acknowledgments

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References