Original Article

Stability of Admixture Containing Morphine Sulfate, Bupivacaine Hydrochloride, and Clonidine Hydrochloride in an Implantable Infusion System

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Abstract
Intrathecal infusion is often performed using drug combinations. This study was conducted to evaluate the stability of the admixture of morphine sulfate, bupivacaine hydrochloride, and clonidine hydrochloride when used in an implantable pump under simulated clinical use conditions. SynchroMed implantable pumps were filled with an admixture and incubated at 37°C for a period of 90 days. Drug admixture stored in glass vials at 4°C and at 37°C served as controls. Samples which included pump reservoir and catheter delivered aliquots were collected every 30 days and analyzed for drug concentrations using a stability-indicating HPLC method. All drugs contained in the admixture were stable and the original concentrations remained greater than 96%. Over 90 days, and with the pump at the simulated body temperature of 37°C, there were no evident heat catalyzed or device catalyzed reactions.

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Key Words
Implantable pump, stability, morphine sulfate, clonidine, bupivacaine

Introduction
Administration of multiple analgesic drugs concurrently into the cerebrospinal fluid on a continuous basis from an implantable programmable infusion system has become an accepted method of therapy over the past decade.1,2 This practice of polyanalgesia is supported by only a few publications, but now is commonly employed for the treatment of chronic pain.2,3 Morphine frequently is used for neuraxial infusion, but may produce unwanted side effects, particularly at relatively high doses.4–7 Patients receiving high intrathecal doses of morphine can develop a state of hyperalgesia and are at an increased risk of developing an inflammatory mass.8
Bupivacaine is the drug most commonly used in combination with morphine for the treatment of neuropathic pain. The augmentation in pain relief by this combination is perhaps related to the additional effect of bupivacaine, which directly inhibits neuronal voltage-gated sodium channels, as opposed to stimulating selected receptors. This combination has been shown to reduce the need for escalating doses of morphine when used alone.

More recently, clonidine, an alpha2-adrenergic receptor agonist, has been shown to be effective against neuropathic pain. One mechanism suggests that clonidine increases mechanical threshold via activation of muscarinic m1 receptors in the spinal cord. The combination of clonidine and morphine via intrathecal administration has proven to be effective for chronic pain by producing a synergistic antinoceptive interaction. In addition, preclinical studies demonstrate decreased rates of inflammatory mass formation when clonidine is added to morphine intrathecal infusions. Further, clonidine in combination with bupivacaine and morphine seems to fill a therapeutic deficit in the treatment of neuropathic cancer pain where other combinations have failed.

The safe intrathecal delivery of morphine via implantable infusion pumps has become widely accepted for the treatment of intractable pain. In addition, the safety of the administration of bupivacaine via an implantable delivery system has been investigated and shown to be stable and compatible with the delivery device and well tolerated when administered chronically in patients. However, the stability of the admixture of morphine, bupivacaine, and clonidine has been shown only in plastic reservoir bags at room temperature for the treatment of chronic pain syndromes.

This study investigates the stability and compatibility of these agents with each other and in an infusion pump system designed for intrathecal delivery.

Methods

Drug Preparation

The drug solutions employed in this study were prepared by Hartley Medical Center, Long Beach, California, to simulate drug combination solutions used by physicians for intrathecal administration. Stock solutions of USP morphine sulfate, bupivacaine hydrochloride, and clonidine hydrochloride were prepared in sterile water for injection. The concentrations for the above solutions were morphine sulfate at 50 mg/mL, bupivacaine hydrochloride at 25 mg/mL, and clonidine hydrochloride at 2 mg/mL. (Note: These concentrations are relatively high, but clinically relevant to maximize any potential drug–drug or drug–device interactions). Each solution was verified by our validated analytical method to be within 5.5% of the stated concentrations prior to use.

Equipment

The implantable drug delivery system evaluated was the 18 mL reservoir SynchroMed EL pump (Medtronic, Minneapolis, MN, USA) with a silicone infusion catheter (model 8709, Medtronic). The pump allows programming by a noninvasive technique that also facilitated infusion rate changes during the study.

Each infusion pump received from the manufacturer contained sterile water and was emptied prior to use. Each pump was filled with the admixture, warmed to 37°C and rinsed with 10 mL of the admixture prior to filling. The incubator system used for this study was a Forma-Scientific model 3932 which was maintained at 37 ± 2°C to mimic in vivo temperatures.

The analysis was performed using a Hewlett Packard (Wilmington, DE, USA), model 1050 high performance liquid chromatograph equipped with a diode array detector. The column employed was a Phenomenex Luna C18(2) 150mm × 4.6 mm with a 5µ particle size.

The pH of the solutions was obtained using a Corning model 350 pH/ion analyzer. The osmolality of the solutions was obtained using a Wescor model 5500 vapor pressure osmometer.

Drug Solution Stability

Drug solution stability was determined at two different temperatures, 4°C and 37°C to establish the stability of the drug solution stored in glass and protected from light. These serve as controls for the primary experiment. A standard containing morphine sulfate, bupivacaine hydrochloride, and clonidine hydrochloride was assayed to determine their initial concentrations. This standard was transferred to two glass vials. One vial was protected from light and
stored at 4 ± 2°C. The second vial was protected from light, and stored at 37 ± 2°C. Each solution was sampled at 0, 30, 60, and 90 days. Another identical admixture solution was subjected to a freeze-thaw cycle by placing it in the freezer for 4 hours, removing and then thawing for 4 hours. Upon completion of the thaw, the samples were reanalyzed and compared to the zero time-point analysis. This freeze-thaw cycle was performed because all samples were frozen and analyzed at one time at the end of the study. The temperature control samples allowed the evaluation of the stability of the drugs in solution independent of the infusion system.

**Drug Stability in Device**

In order to compare the stability of the admixture in the pump to the inherent stability of the admixture, the control admixture solutions (4°C and 37°C) of morphine sulfate, bupivacaine hydrochloride, and clonidine hydrochloride were assayed in parallel with the pump solution at designated intervals. Three SynchroMed pump systems were evaluated at 37°C. These were compared against identical solutions protected from light at 37°C to determine any device-induced degradation. A third identical solution protected from light, but at 4°C, was used to determine any heat-related degradation.

The relevant drug infusion system consists of a pump-reservoir and catheter. Three of these infusion systems were utilized and sampled at 0, 30, 60, and 90 days. One-milliliter samples were taken from each control solution and two 1-mL samples were collected from each infusion system at the designated time interval. The first sample was taken directly from the pump reservoir via the septum port. The second was taken through the catheter by setting the pump at the maximum flow rate to produce 1 mL and then shutting off at the completion of each collection. This procedure also assessed the delivery function and accuracy of the device after admixture exposure. The samples were collected into pre-labeled glass vials. The time zero solution for each was analyzed at the beginning of the study and then stored in the freezer at −20°C until the end of the study. All samples were then thawed and allowed to come to room temperature and assayed as a batch.

**Physical Stability of Solution**

The physical stability of each admixture was evaluated by visual inspection for color and particulate matter. The pH of each solution was measured at each time interval and osmolality was assessed only for the time-zero and 90-day samples.

**Analytical Methods**

An HPLC stability-indicating method was developed and validated for morphine sulfate, bupivcaine hydrochloride, and clonidine hydrochloride quantitation. USP guidelines, Validation of Compendial Methods (Chapter 1225), Chromatography (Chapter 621), FDA, and ICH guidelines were followed in the validation of this stability indicating method. Separate source analytical standards were used in the validation of the analytical method. A gradient elution method allowed resolution of the above drugs using a single method. The established analytical range was from 25–125% of the target value for each drug. The mobile phase was composed of two solutions. Solution A was 39 mM K2HPO4 at pH 9. Solution B was HPLC-grade methanol (Pharmco Inc., lot no. HM020502). The flow rate was at 1.0 mL/min with an injection volume of 20 µL. The detection wavelength was 210 nm. The total run time was 13 minutes per sample.

**Results**

**Drug Solution Stability**

When combined, morphine sulfate, bupivacaine hydrochloride, and clonidine hydrochloride did not change by more than ±5% when compared to their respective concentrations at time zero. After 90 days at 4°C, the mean concentration of morphine sulfate, bupivacaine hydrochloride and clonidine hydrochloride were 100.7%, 100.7% and 98.0% respectively, compared to the concentration at time zero. The 4°C results are graphically represented in Figure 1.

At 90 days and 37°C, morphine sulfate retained 100.0% of its original concentration.
from time zero. For the same conditions, bupivacaine hydrochloride maintained 104.2% of its original concentration and clonidine hydrochloride maintained 99.0% of its original concentration with respect to time zero. The 37°C results are graphically represented in Figure 2.

**Drug Stability in Device**

After 90 days of incubation at simulated body temperature (37°C) within the implantable pumps, the concentrations of the drugs of interest did not deviate by more than 4.4% from the time zero concentration.

Morphine sulfate showed reservoir concentration values of 49.60 mg/mL, 49.60 mg/mL, 49.21 mg/mL, and 49.53 mg/mL for the 0, 30, 60, and 90-day intervals, respectively. The 90-day reservoir concentration of morphine sulfate did not deviate more than 0.8% when compared to initial concentrations at time zero. Catheter concentrations of morphine sulfate were 48.76 mg/mL, 50.04 mg/mL, 49.57 mg/mL, and 49.31 mg/mL for day 0, 30, 60, and 90, respectively. The 90-day catheter concentrations of morphine sulfate did not deviate more than 2.2% when compared to initial concentrations at time zero. Morphine sulfate results are graphically represented in Figure 3.

Bupivacaine hydrochloride had reservoir concentration values of 25.33 mg/mL, 25.59 mg/mL, 25.56 mg/mL, and 25.39 mg/mL for the 0, 30, 60, and 90-day intervals, respectively. The 90-day reservoir concentration of bupivacaine hydrochloride did not deviate more than 1% when compared to its initial concentration at time zero. Catheter bupivacaine hydrochloride concentration values were 24.65 mg/mL, 25.72 mg/mL, 25.73 mg/mL, and 25.68 mg/mL for days 0, 30, 60 and 90, respectively. The 90-day catheter concentration of bupivacaine hydrochloride did not deviate more than 4.4% when compared to its initial concentration at time zero. Bupivacaine hydrochloride results are graphically represented in Figure 4.
Clonidine hydrochloride showed reservoir concentration values of 1.90 mg/mL, 1.88 mg/mL, 1.90 mg/mL, and 1.83 mg/mL for the 0, 30, 60, and 90-day intervals, respectively. At 90 days, the reservoir concentration of clonidine hydrochloride did not deviate more than 3.2% when compared to reservoir concentrations at time zero. Catheter concentrations of clonidine hydrochloride were 1.83 mg/mL, 1.94 mg/mL, 1.88 mg/mL, and 1.86 mg/mL for days 0, 30, 60, and 90, respectively. At 90 days, the catheter concentration of clonidine hydrochloride did not deviate more than 6.6% when compared to catheter concentrations at time zero. Clonidine hydrochloride results are graphically represented in Figure 5.

Table 1 is a comparison of the above data versus the data collected for the 37°C control group as seen in Figure 2.

**Physical Stability of Solution**

Table 2 lists the results of the pH of the solutions that were obtained for each sample at each time point.

Table 3 lists the observations for color and particulate matter made for the solutions collected from the pumps with respect to the source and time.

In addition to these tests and observations, the osmolality for the beginning solution and a sample from the 37°C stored for 90 days were analyzed. The initial osmolality was 273 mmol/Kg and the osmolality of the 90-day sample was 270 mmol/Kg. The results for the samples removed from the reservoir of the infusion pump were 100.1%, 100.2%, and 96.8% relative to time zero for morphine sulfate, bupivacaine hydrochloride, and clonidine hydrochloride, respectively. The results for the samples
removed from the catheter of the infusion pump were 100.1%, 100.2%, and 96.8% relative to time zero for morphine sulfate, bupivacaine hydrochloride, and clonidine hydrochloride, respectively. The results of all the samples were within 5% of the results of time zero.

Figures 1 and 2 show that the control samples were stable over the 90-day time period. Figures 3 and 4 show that the infusion pump samples were stable over the 90-day period. The results indicate no degradation occurred in any of the samples. This conclusion also extends to the stability of the solution stored in the infusion pump. This indicates that no degradation is apparent over the 90 day time period and thus had no effect on the analysis of the sample.

Table 2 lists the results of the pH of the samples collected at each time point. The 37°C control samples and catheter samples showed the only significant changes over time. The 37°C control samples had a change of -1 to 3.6 pH units over the 90-day time period whereas the 37°C catheter samples rose from 3.8 to 5.1 pH units between 0 and 30 days. The other time points had less than 1 pH unit change. These variations had little or no effect on the concentrations of the drugs in the solutions.

A change in the color of the solutions from colorless to light yellow was observed between the 30- and 60-day time points. This has been observed in injectable solutions of morphine sulfate and identified as pseudomorphine. This color change did not affect the stability of the solution. The examination for particulate matter was performed to determine if any of the components of the matrix were precipitating during storage of the solutions. No particulate matter was noted over the 90-day period.

Osmolality tests were performed at time zero and 90 days after being stored at 37°C. The slight difference of the results between these samples is not clinically significant. The calculations for the results were based on the data obtained by analysis of the samples using the validated HPLC method. Reference standards of each analyte were prepared and the peak areas of these reference standards were compared against the peak areas of the study samples. This

Table 1
Results of Catheter and Reservoir Concentrations for Morphine Sulfate, Bupivacaine HCl, Clonidine HCl, and 37°C Control Samples at 0, 30, 60, and 90-Day Intervals

<table>
<thead>
<tr>
<th>Day</th>
<th>Bupivacaine HCl</th>
<th>Clonidine HCl</th>
<th>Morphine Sulfate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Reservoir</td>
<td>Catheter</td>
<td>37°C</td>
</tr>
<tr>
<td>0</td>
<td>25.33</td>
<td>24.65</td>
<td>25.64</td>
</tr>
<tr>
<td>30</td>
<td>25.59</td>
<td>25.72</td>
<td>26.16</td>
</tr>
<tr>
<td>60</td>
<td>25.56</td>
<td>25.73</td>
<td>26.46</td>
</tr>
<tr>
<td>90</td>
<td>25.39</td>
<td>25.68</td>
<td>26.71</td>
</tr>
</tbody>
</table>
Stability of Admixture in an Infusion System

### Table 2
Results of pH Determinations for Different Sample Groups 4°C, 37°C, 37°C Reservoir, and 37°C Catheter, at 0, 30, 60 and 90 Days

<table>
<thead>
<tr>
<th>Time Period</th>
<th>pH Sample Groups</th>
<th>4°C Control</th>
<th>37°C Control</th>
<th>37°C Reservoir</th>
<th>37°C Catheter</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td>4.6</td>
<td>4.6</td>
<td>4.8</td>
<td>3.8</td>
</tr>
<tr>
<td>30</td>
<td></td>
<td>5.0</td>
<td>5.2</td>
<td>5.2</td>
<td>5.1</td>
</tr>
<tr>
<td>60</td>
<td></td>
<td>3.9</td>
<td>5.1</td>
<td>4.7</td>
<td>4.8</td>
</tr>
<tr>
<td>90</td>
<td></td>
<td>3.6</td>
<td>4.7</td>
<td>4.5</td>
<td>4.6</td>
</tr>
</tbody>
</table>

Each result is the mean of 3 pH determinations.

Comparison yielded the concentration of the analytes in the study solutions. Overall stability of the solutions was established by determining the percent difference between the results from 90 days to the results obtained from time zero. In order for the solutions to be considered stable, there must not be a change in the concentration of any analyte greater than 10%. Based on these calculations and this criterion all solutions remained stable for at least 90 days.

### Discussion

Although management of intractable pain using long-term intrathecal analgesic administration by implantable infusion systems has become accepted clinical practice, this method presents unique challenges regarding the stability of the pharmaceutical agent(s) delivered. Two major challenges include: 1) the requirement to use preservative-free formulations to avoid neurotoxicity, and 2) prolonged storage of the formulation at elevated temperature (i.e., body temperature) within the reservoir of the delivery system. Adjunctive analgesics such as bupivacaine and clonidine are frequently added to the infusate because of inadequate efficacy or intolerable side effects associated with opioid monotherapy. Moreover, the use of polyanalgesia may limit morphine exposure and thus reduce the risks of opioid tolerance and catheter-tip inflammatory mass formation. When using drug combinations, the chemical and physical compatibility of the individual drug components of the admixture also must be carefully assessed.

Long-term stability and compatibility of morphine-clonidine admixtures (20 mg morphine sulfate + 0.05 mg clonidine hydrochloride per mL and 2.0 mg morphine + 1.84 mg clonidine per mL) in the SynchroMed system, the same system as employed in our studies, has been previously reported. These authors reported that morphine and clonidine concentrations remained at >94% of initial concentration after storage in the infusion system at 37°C for 90 days. The stability of bupivacaine hydrochloride (7.5 mg/mL) in the SynchroMed infusion system also has been reported. Bupivacaine concentrations remained greater than 96% of the initial concentration when stored for 90 days at 37°C. Moreover, the compatibility of the individual analgesics, namely morphine, clonidine, and bupivacaine with the SynchroMed delivery system also has been confirmed.

The stability of admixtures containing morphine (6.66 mg/mL), bupivacaine (3 mg/mL), and clonidine (30 µg/mL) has been previously reported. These solutions were preservative-free, stored for 90 days, protected from light, and analyzed using HPLC. Although the chemical and physical stability of these agents combined in aqueous solution was confirmed, there are several important distinctions between the previous study and the one reported here. The previous study used morphine hydrochloride (commonly available in Europe), rather than morphine sulfate (the only morphine salt available in the U.S.). As both clonidine and bupivacaine are also hydrochloride salts, the chance of unfavorable interactions is less than with the sulfate form of morphine. Moreover, relatively low concentrations of each analgesic were used and most importantly, the drug solution was stored in plastic ambulatory pump cassettes at room temperature.

The study presented herein is significant in several ways. It represents the first study that...
specifically addresses the long-term stability of a commonly used analgesic trimixture. Furthermore, it evaluates the stability of each component at the highest clinically relevant concentration (morphine sulfate, 50 mg/mL; bupivacaine hydrochloride, 25 mg/mL; and clonidine hydrochloride, 2 mg/mL) to ensure that the potential of degradation processes involving intermolecular interactions in solution are maximized (i.e., worst-case scenario). It should be appreciated that in actual clinical practice, it is unlikely that each analgesic of a three-drug combination would be present at maximal concentration. On the other hand, high concentrations of at least the primary opioid analgesic but often the adjuvant analgesics as well are used in implantable pumps in order to maintain reasonable refill intervals. Because dosing is a function of concentration and infusion rate, high concentration infusates are able to maintain effective analgesia while minimizing the volume of infusate expended. However, because high concentration morphine sulfate may be associated with inflammatory mass formation, using adjuvants such as bupivacaine and clonidine allow opioid exposure (dose and concentration) to be reduced without sacrificing adequate pain control. The results of this study provide assurance that combinations of these three commonly used analgesics at clinically relevant maximal concentrations maintain appropriate chemical and physical stability when stored in an implantable SynchroMed infusion system under simulated clinical conditions.

**Conclusion**

The admixture containing morphine sulfate, bupivacaine hydrochloride, and clonidine hydrochloride is stable when stored at 4°C and 37°C in vitro for 90 days. In addition, it is stable at 37°C in the SynchroMed EL infusion pump for 90 days and no heat- or device-catalyzed reactions were evident. Accurate pump delivery function was maintained throughout the study. The study thereby indicates that these drugs are stable with the SynchroMed EL infusion pump.

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**References**


