ARTICLE

Physical Compatibility and Chemical Stability of Bupivacaine and Hydromorphone in Polypropylene Syringes

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ABSTRACT

Background: Narcotics are combined with local anesthetic agents for epidural administration during many surgical procedures. A literature review revealed one chemical stability study for bupivacaine combined with hydromorphone and packaged in polyvinyl chloride bags and one physical stability study for this drug combination packaged in polypropylene syringes.

Objective: A physical compatibility and chemical stability study was undertaken to determine a shelf life that would allow batch preparation of this drug combination, for storage in polypropylene syringes, without significant wastage.

Methods: Bupivacaine (0.5%) was diluted with normal saline (0.9% sodium chloride) to prepare a 0.25% solution, which was then combined with hydromorphone such that the final concentration of the latter was either 0.02 or 0.04 mg/mL. These mixtures were then packaged in polypropylene syringes and stored either at 22°C with exposure to fluorescent light or at 6°C with protection from light. Five-millilitre samples were taken from each syringe on days 0, 7, 14, 28, 56, and 91 and frozen at –70°C. All samples were monitored for colour, clarity, and changes in pH, in addition to undergoing duplicate analysis with a stability-indicating high-pressure liquid chromatography assay.

Results: All samples remained colourless and free of precipitate throughout the study. There were no significant changes in pH under either of the storage conditions. Both the bupivacaine (0.25%) and the hydromorphone (0.02 or 0.04 mg/mL) stored in combination at either 22°C with exposure to light or 6°C with protection from light remained stable for 91 days.

Conclusions: Bupivacaine (0.25%) with hydromorphone (0.02 or 0.04 mg/mL) packaged in polypropylene syringes and stored either at 22°C with exposure to light or at 6°C with protection from light were considered stable for at least 91 days. At the author's institution, a 30-day expiry date has been established on the basis of the institutional sterile packaging policy. Facilities

RÉSUMÉ

Historique : On administre des narcotiques en association avec des anesthésiques locaux par voie épidurale dans le cadre de nombreuses interventions chirurgicales. Une revue de la littérature a fait état d'une étude de stabilité chimique pour la bupivacaïne associée à l'hydromorphone et conditionnées dans des sacs de polychlorure de vinyle, et une étude de stabilité physique pour cette même association médicamenteuse conditionnée dans des seringues de polypropylène.

Objectif : Une étude de compatibilité physique et de stabilité chimique a été menée pour déterminer la durée de conservation qui permettrait de préparer par lots et de conserver dans des seringues de polypropylène cette association médicamenteuse, sans pertes significatives.

Méthodes : On a dilué de la bupivacaïne (à 0,5 %) dans une solution physiologique salée (chlorure de sodium à 0,9 %) pour obtenir une solution à 0,25 %, qu'on a alors mélangée à de l'hydromorphone pour obtenir une concentration finale de cette dernière de soit 0,02, soit 0,04 mg/mL. Ces préparations ont ensuite été conditionnées dans des seringues de polypropylène et conservées soit à une température de 22 °C sous lumière fluorescente, soit à une température de 6 °C à l'abri de la lumière. On a prélevé des échantillons de cinq millilitres de chaque seringue aux jours 0, 7, 14, 28, 56 et 91, qu'on a ensuite congelés à une température de –70 °C. Tous les échantillons ont été examinés pour un changement de couleur, de limpidité ou de pH, et soumis à une double analyse au moyen d'une épreuve de stabilité par chromatographie liquide à haute pression.

Résultats : Tous les échantillons sont demeurés incolores et n'ont présenté aucun précipité tout au long de l'étude. On n'a observé aucun changement significatif du pH dans les deux conditions de stockage. Les mélanges de bupivacaïne (à 0,25 %) et d'hydromorphone (à 0,02 ou 0,04 mg/mL) conservés à une température de 22 °C avec exposition à la lumière ou à une température de 6 °C à l'abri de la lumière sont demeurés stables pendant 91 jours.

wishing to use the physical compatibility and chemical stability information provided here should first perform their own institution-specific sterile packaging testing.

Key words: bupivacaine, hydromorphone, stability, normal saline, high-pressure liquid chromatography, epidural administration

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Conclusions : L'association bupivacaïne (à 0,25 %) et hydromorphone (à 0,02 ou 0,04 mg/mL) conditionnée dans des seringues de polypropylène et conservée soit à une température de 22 °C avec exposition à la lumière, soit à une température de 6 °C à l'abri de la lumière a été jugée stable pendant une période d'au moins 91 jours. L'établissement où est rattaché l'auteur a établi une date de péremption de 30 jours, conformément à sa politique de conditionnement stérile. Les établissements qui souhaitent utiliser l'information sur la compatibilité et la stabilité chimique présentée ici devraient d'abord mener leurs propres essais sur les conditionnements stériles qu'ils utilisent.

Mots clés : bupivacaïne, hydromorphone, stabilité, solution physiologique salée, chromatographie liquide à haute pression, administration épidurale

INTRODUCTION

Local anesthetic agents, such as bupivacaine, are frequently combined with narcotics to reduce the amount of narcotic required to produce analgesia and to decrease the possibility of adverse effects. Although the combination of bupivacaine and hydromorphone has been used in the clinical setting for several years, its long-term chemical stability in polypropylene syringes has never been reported. At the author's institution, syringes are aseptically prepared to final concentrations of bupivacaine 0.25% and hydromorphone either 0.02 or 0.04 mg/mL and the mixtures are assigned an arbitrary 14-day expiry date based on a 72-h chemical stability study[R1] and a 30-day physical stability study.[R2] A study was therefore undertaken to determine the physical compatibility and chemical stability of bupivacaine (0.25%) and hydromorphone (0.02 or 0.04 mg/mL) when packaged in polypropylene syringes. Storage conditions were either 22°C with exposure to light or 6°C with protection from light.

METHODS

Preparation of Admixtures

Test admixture solutions were aseptically prepared by diluting bupivacaine 0.5% (Astra Pharma Inc, Mississauga, Ontario, lot D177A, expiry January 2002) and hydromorphone 2 mg/mL (Sabex Inc, Boucherville, Quebec, lot 105525, expiry September 2003) with enough 0.9% sodium chloride (normal saline [NS]; Baxter Corporation, Mississauga, Ontario, lot W0J11C0, expiry October 2001) to yield an admixture of bupivacaine 0.25% and hydromorphone 0.02 or 0.04 mg/mL. Polypropylene syringes (60 mL; Becton Dickinson, Franklin Lakes, New Jersey) were then filled with 50 mL of the admixture and stored at either 22°C with exposure to light or 6°C with protection from light.

Sample Collection

Immediately after packaging (day 0), one 5-mL sample was collected from 3 syringes in each of the 4 groups of syringes (bupivacaine 0.25% with hydromorphone 0.02 mg/mL stored at either 22°C with exposure to light or 6°C with protection from light and bupivacaine 0.25% with hydromorphone 0.04 mg/mL stored at either 22°C with exposure to light or 6°C and protected from light). Samples were frozen at –70°C in a scientific freezer (model 8433, Forma Scientific Inc, Marietta, Ohio) for analysis at a later time. On days 7, 14, 28, 56, and 91, additional samples were collected, inspected, and frozen in a similar manner.

Physical Compatibility

Each sample was inspected for particulate matter against a black background and for colour change against a white background. pH was determined on each sampling day by means of a calibrated pH meter with a silver–silver chloride electrode (Accumet model 25, Fisher Scientific Ltd, Nepean, Ontario). Buffers at pH 4.00 (Fisher Scientific Ltd, lot SC0241230, expiry August 2002) and 7.00 (Fisher Scientific Ltd, lot SC0257318, expiry September 2002) were used to calibrate the pH meter before each use.

Chemical Stability

High-Pressure Liquid Chromatography System

The bupivacaine samples were analyzed by means of a modified USP 24 method.[R3] The modified method used a 4.6 mm x 25 cm column instead of the 4.0 mm x

30 cm specified in the monograph. All other conditions and monitoring parameters remained the same.

The hydromorphone samples were analyzed by means of an in-house high-pressure liquid chromatography (HPLC) method that used a combination of 35 parts acetonitrile (EM Science, Gibbstown, New Jersey, lot 36065) and 65 parts of a phosphate buffer. The phosphate buffer was prepared by dissolving 25 mmol/L of monobasic phosphate (monohydrate) (BDH, Toronto, Ontario, lot 115184/38578) in HPLC-grade water. The pH of the final solution was adjusted to 3.0 ± 0.1 with concentrated orthophosphoric acid (BDH, lot 91892); the solution was then filtered through a 0.45-µm nylon filter and degassed.

Mobile phases were passed through a 4.6 mm x 25 cm, 5-µm C_{18} column (Luna ODS [octadecylsilane] 18[2], lot 256161; Phenomenex, Torrance, California) at a rate of 1.5 mL/min using an isocratic delivery pump (model LC-10AS, Shimadzu Corporation, Kyoto, Japan). A photodiode array detector (model SPD-M6A, Shimadzu Corporation) was set at either 230 or 263 nm to monitor peaks of hydromorphone or bupivacaine, respectively. An autoinjector (model SIL-10A_{XL}, Shimadzu Corporation) was used to analyze 20-µL samples. Di-*n*-butyl phthalate (1.3 mg/mL; BDH, lot 108649/1376) and propylhydroxybenzoate (1 mg/mL; BDH, lot 98382/11273) were used as the internal standards for the bupivacaine and hydromorphone assays, respectively.

Assay Validation

Both assay methods were validated as stability-indicating by analysis of forcibly degraded samples of bupivacaine and hydromorphone. Three stock solutions containing 0.225% of bupivacaine (Medisca, Montreal, Quebec, lot 9807094) were prepared. One solution was adjusted to a pH of approximately 1.2 with concentrated hydrochloric acid (BDH, lot 109521/11031) and heated on a hot plate (Thermix stirring hot plate, model 210T, Fisher Scientific Ltd) for 286 h. A second solution was adjusted to a pH of about 8.1 with 5N sodium hydroxide (BDH, lot 9112019) and heated for 286 h. One millilitre of 30% hydrogen peroxide (BDH, lot 113439-30995) was added to the final solution, which was stirred at 22°C for 48 h. All solutions were analyzed at time 0 and at 7 other points over the course of the study for interfering peaks.

Three stock solutions containing 0.2 mg/mL of hydromorphone (Sabex Inc, lot 1018581) were prepared. One solution was adjusted to a pH of approximately 1.0 with concentrated hydrochloric acid (BDH, lot 109521/11031) and heated on a hot plate (Thermix stirring hot plate, model 210T, Fisher Scientific Ltd) for 120 h. The second solution was adjusted to pH 13.0 with 5N sodium hydroxide (BDH, lot 9112019) and heated for 120 h. The final solution was stirred at 22°C for 48 h after 1 mL of 30% hydrogen peroxide (BDH, lot 113439-30995) had been added. All solutions were monitored at time 0 and at 7 subsequent points over the study period for interfering peaks.

The purity of all peaks was determined by multiwavelength (230 and 263 nm) and ultraviolet (UV) spectral analysis (200 to 350 nm). The UV spectra of the

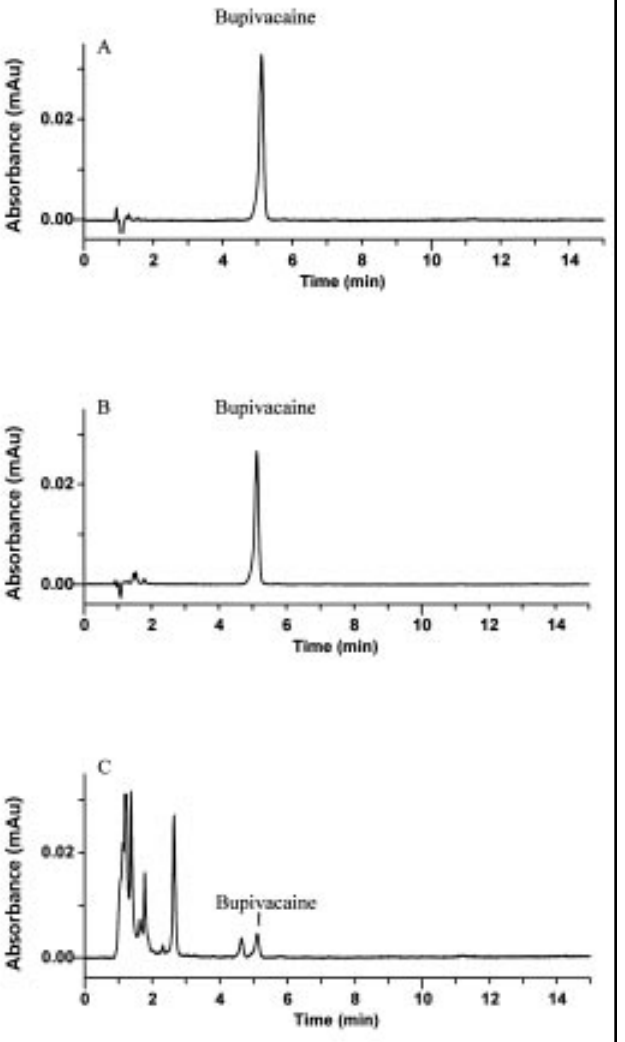

Figure 1. Degradation diagrams of bupivacaine. A: After exposure to acidic conditions (pH about 1.2) and heating for 286 h. B: After exposure to alkaline conditions (pH about 8.1) and heating for 286 h. C: After exposure to an oxidizing agent for 48 h.

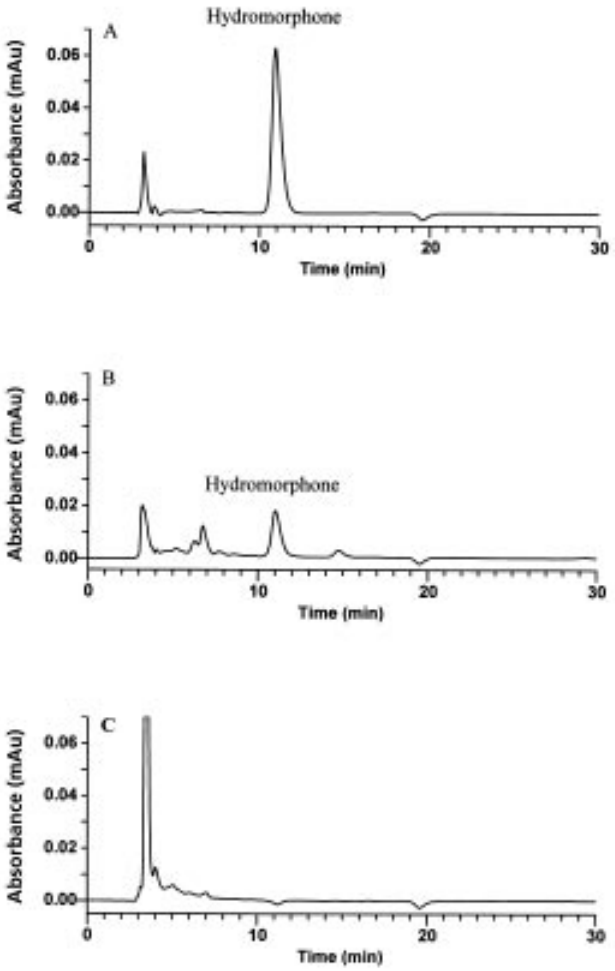

Figure 2. Degradation diagrams of hydromorphone. A: After exposure to acidic conditions (pH about 1.0) and heating for 120 h. B: After exposure to alkaline conditions (pH about 13.0) and heating for 120 h. C: After exposure to an oxidizing agent for 48 h.

bupivacaine and hydromorphone peaks from the degradation samples were compared with bupivacaine and hydromorphone reference materials, and correlation coefficients were determined.

The linearity of all concentration versus area response curves were determined by least squares regression analysis. The accuracy of each method was measured on 5 separate days using a sample of known weight. Intraday variation was determined from the average areas of 5 replicate injections at 3 separate time points for each method. Replicate injections of a standard solution on 5 separate days were used to determine interday variation for each method. The sensitivity of each assay was determined by serial dilutions of a stock solution until no peaks could be detected and the linear relationship was maintained.

Stability Study

On the day of analysis, the samples were allowed to warm to room temperature (minimum 2 h). The internal standard was then added to an aliquot of each sample, and the aliquot was further diluted with mobile phase and assayed in duplicate.

RESULTS

Physical Compatibility

All admixture samples remained clear and colourless over the 91-day study period. There were no significant changes in pH in any of the admixture samples under any of the storage conditions.

Chemical Stability

Assay Validation

Heating of the acidic solutions resulted in no degradation of bupivacaine (Figure 1A) and some degradation of hydromorphone (Figure 2A) after 286 and 120 h, respectively. Alkaline conditions produced a slight degradation of the bupivacaine after 286 hours of heating (Figure 1B) and significantly more degradation of the hydromorphone after 120 h of heating (Figure 2B). Oxidation with hydrogen peroxide resulted in near-complete destruction of the bupivacaine (Figure 1C) and complete destruction of the hydromorphone (Figure 2C). Under all conditions, none of the degradation peaks interfered with the parent compound. The purity of all parent peaks was confirmed by multichannel (230 and 263 nm) and UV spectral analysis (200 to 350 nm). Good correlation (similarity index > 0.990) was observed when the parent peaks were compared with the respective reference material. UV spectral analysis and retention times were used to distinguish parent peaks from degradation products.

The linearity of the concentration versus area response curves had an r^2 value of at least 0.996. The average recovery of bupivacaine and hydromorphone was 98.9% (standard deviation [SD] 1.78) and 99.4% (SD 2.9%), respectively. Intraday and interday coefficients of variation were 0.51% and 1.97% for bupivacaine and 1.10% and 2.68% for hydromorphone when area ratios were compared. The sensitivity of the assay was determined to be 2.5 µg for bupivacaine and 0.06 µg for hydromorphone.

Table 1. Stability of Bupivacaine 0.25% with Hydromorphone 0.02 mg/mL in 0.9% Sodium Chloride Packaged in Polypropylene Syringes and Stored at 22°C with Exposure to Light

Drug	Initial Conc'n* (mg/mL)	% of Initial Concentration Remaining*				
		Day 7	Day 14	Day 28	Day 56	Day 91
Bupivacaine	2.71 (0.026)	100.2 (0.70)	99.0 (0.59)	97.5 (0.56)	98.3 (1.01)	98.9 (0.30)
Hydromorphone	0.02 (0.00)	99.7 (0.58)	100.0 (0.82)	99.5 (0.72)	99.1 (0.75)	98.6 (0.46)

*Mean of 6 determinations and standard deviation.

Table 2. Stability of Bupivacaine 0.25% with Hydromorphone 0.02 mg/mL in 0.9% Sodium Chloride Packaged in Polypropylene Syringes and Stored 6° C with Protection from Light

Drug	Initial Conc'n* (mg/mL)	% of Initial Concentration Remaining*				
		Day 7	Day 14	Day 28	Day 56	Day 91
Bupivacaine	2.70 (0.050)	98.5 (1.13)	98.7 (1.18)	98.3 (0.83)	97.5 (0.71)	96.6 (0.25)
Hydromorphone	0.02 (0.00)	99.9 (0.67)	99.7 (0.83)	98.7 (1.68)	96.9 (0.38)	96.0 (0.35)

*Mean of 6 determinations and standard deviation.

Table 3. Stability of Bupivacaine 0.25% with Hydromorphone 0.04 mg/mL in 0.9% Sodium Chloride Packaged in Polypropylene Syringes and Stored at 22° C with Exposure to Light

Drug	Initial Conc'n* (mg/mL)	% of Initial Concentration Remaining*				
		Day 7	Day 14	Day 28	Day 56	Day 91
Bupivacaine	2.71 (0.037)	98.9 (0.74)	98.1 (0.77)	97.1 (0.63)	95.9 (0.47)	96.0 (0.56)
Hydromorphone	0.04 (0.00)	101.1 (1.07)	99.5 (1.55)	100.8 (0.69)	101.4 (0.87)	99.6 (1.21)

*Mean of 6 determinations and standard deviation.

Table 4. Stability of Bupivacaine 0.25% with Hydromorphone 0.04 mg/mL in 0.9% Sodium Chloride Packaged in Polypropylene Syringes and Stored 6° C with Protection from Light

Drug	Initial Conc'n* (mg/mL)	% of Initial Concentration Remaining*				
		Day 7	Day 14	Day 28	Day 56	Day 91
Bupivacaine	2.63 (0.019)	98.9 (0.84)	98.2 (0.98)	96.0 (0.26)	95.0 (0.37)	94.6 (0.41)
Hydromorphone	0.04 (0.00)	100.2 (0.81)	99.4 (0.45)	99.5 (0.63)	98.1 (0.55)	97.8 (0.92)

*Mean of 6 determinations and standard deviation.

Stability Study

The results of the chemical stability study are summarized in Tables 1 through 4. Both bupivacaine (0.25%) and hydromorphone (0.02 or 0.04 mg/mL) in the admixtures were stable for 91 days when diluted with NS, packaged in polypropylene syringes, and stored at 22°C with exposure to light. These admixtures were also stable for 91 days when stored at 6°C with protection from light.

DISCUSSION

Two groups of investigators have reported the stability of bupivacaine mixed with hydromorphone. Christen and others[1] studied the chemical stability of mixtures containing bupivacaine 0.625% or 1.25% and hydromorphone 0.020 or 0.1 mg/mL in polyvinyl chloride bags, stored at 22°C; they reported a 72-h expiry date. Neels[2] reported a 30-day expiry period, on the basis of visual inspection, for a solution containing bupivacaine 0.75% and hydromorphone 65 mg/mL packaged in a polypropylene syringe and stored at 25°C. The results reported here extend both chemical stability and physical compatibility to 91 days.

During the HPLC analysis, degradation products were adequately separated from parent compounds and internal standards under all conditions. Bupivacaine was

stable under acidic conditions; however, it showed signs of some destruction under alkaline conditions and was almost completely destroyed under oxidative conditions. Hydromorphone was most stable under acidic conditions, whereas alkaline conditions caused more severe degradation, and oxidation caused complete destruction of the starting material. The pH of the bupivacaine and hydromorphone combinations was in the range of 5 to 6, which supports the physical compatibility findings and the chemical stability of the mixtures. All of the parent peaks of bupivacaine and hydromorphone were confirmed as pure by multichannel and UV spectral analysis.

This study demonstrates that in admixtures of bupivacaine (0.25%) and hydromorphone (either 0.02 or 0.04 mg/mL) prepared in normal saline, both drugs are physically compatible and chemically stable for 91 days when packaged in polypropylene syringes and stored at either 22°C with exposure to light or 6°C with protection from light. This expiry date is based on physical compatibility and chemical stability. Individual institutional expiry dates should also take into consideration the sterility data for the particular institution. For example, at the author's institution, a 30-day expiry date has been established on the basis of the institutional sterile packaging policy.

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