Stability and compatibility of morphine with bupivacaine

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ABSTRACT

The stability and compatibility of 0.05 mg/mL morphine sulphate plus 1.0 mg/mL bupivacaine hydrochloride diluted in 0.9% sodium chloride was tested at 4°C and 23°C. Over a 28-day study period, in addition to visual inspection and pH, the concentrations of morphine and bupivacaine in the mixtures were determined by a stability-indicating liquid chromatographic method on days 0, 1, 2, 5, 6, 7, 9, 12, 14, 19, 21, and 28. Within and between days analytical error, determined on replicate sample analysis, averaged less than 5% for both drugs.

Morphine and bupivacaine were physically compatible and retained greater than 90% of the initial concentration of both morphine and bupivacaine for 28 days when stored at either 4°C or 23°C. The pH in these compatible solutions changed by less than 0.5 of a pH unit over the study period.

In summary, we recommend a 28-day expiration date for the combination of morphine, 0.05 mg/mL and bupivacaine, 1 mg/mL. However, expiry dates at any given institution should be established after giving consideration to the contamination rate within that institution's own IV additive program.

RÉSUMÉ

La stabilité et la compatibilité du sulfate de morphine (0,5 mg/mL) et du chlorhydrate de bupivacaïne (1,0 mg/mL) dilués dans du chlorure de sodium à 0,9 % ont été testées à des températures de 4 °C et 23 °C, sur une période de 28 jours. Outre les inspections visuelles et à la vérification du pH, on a déterminé la concentration des solutions en morphine et en bupivacaïne, au moyen d'une épreuve de stabilité par chromatographie liquide, aux jours 0, 1, 2, 5, 6, 7, 9 12, 14, 19, 21 et 28. La marge d'erreur analytique pour une même journée ou entre deux journées, déterminée par une analyse d'échantillon répété, était inférieure à 5 % en moyenne pour les deux médicaments.

La morphine et la bupivacaïne se sont révélées physiquement compatibles et ont conservé plus de 90 % de leurs concentrations initiales de morphine et de bupivacaïne durant 28 jours, entreposées à des températures soit de 4 °C, soit de 23 °C. Le pH de ces solutions compatibles a varié de moins de 0,5 unité pH au cours de la période d'étude.

En résumé, une durée de conservation maximale de 28 jours est recommandée pour les mélanges de morphine (0,5 mg/mL) et de bupivacaïne (1 mg/mL). Cependant, chaque établissement devra tenir compte du taux de contamination relatif à son programme d'additifs aux solutés dans la détermination des durées de conservation.

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INTRODUCTION

Injectable morphine is a commonly used narcotic analgesic which is often used alone or mixed with other medication and administered intravenously, subcutaneously or epidurally. The combination of morphine and bupivacaine for epidural infusion has been used for many years for patients whose pain cannot be controlled by morphine alone.[1] The stability of morphine alone, stored in a refrigerator or at room temperature for up to 31 days, is well documented.[2–5] The stability of bupivacaine alone, stored in a refrigerator or at room temperature for 32 days has also been previously reported.[6] However, the chemical stability and compatibility of the combination of morphine and bupivacaine is unknown.

The combination of morphine and bupivacaine has been reported to be visually compatible for 30 days at room temperature.[7] In this study, Neels reported only the lack of microbial contamination and the absence of visual incompatibility over 30 days with continued effectiveness of the solution in a patient over 19 days.[7] Therefore, while it is apparent that both drugs are stable in intravenous solutions alone[2–6] and since Neels[7] has only indicated that the combination did not precipitate, it was the intent of this study to test the chemical stability and compatibility of a combination of morphine and bupivacaine over a 28-day period. Extension of the expiry date of morphine-bupivacaine solutions was expected to reduce wastage. In this study the concentrations of both morphine and bupivacaine were evaluated by a validated stability-indicating liquid chromatographic method.

METHODS

Assay validation

Accelerated degradation of morphine and bupivacaine.

Degradation of morphine was achieved by diluting 100 mg of morphine sulfate (BDH, lot 92239/8203, USP Grade) in 20 mL of normal saline and adjusting the pH of this solution to 11 with 1M sodium hydroxide. This solution was heated at 950C

for 125 hours. Samples were drawn prior to incubation and 8 other times during incubation. Chromatograms were inspected for the appearance of additional peaks and the morphine peak was compared between samples for changes in concentration, retention time and peak shape.

Degradation of bupivacaine was achieved by diluting 20 mg of bupivacaine hydrochloride (Marcaine; Sanofi Winthrop; Lot M070RB) in 20 mL of 0.3 N hydrochloric acid. The final pH of this solution was 0.89. This solution was heated at 86°C for 124 hours. Samples were drawn prior to incubation and 12 other times during incubation. Chromatograms were inspected for the appearance of additional peaks and the bupivacaine peak was compared between samples for changes in concentration, retention time, and peak shape.

Chromatographic system and separation

Following the formation of degradation products, a chromatographic separation was developed which allowed analysis of morphine and bupivacaine simultaneously and ensured the separation of bupivacaine and morphine from their degradation products. The mobile phase consisted of a mixture of a monobasic potassium phosphate (Sigma Chemical Co., St Louis MO), acetonitrile (OmniSolv, EM Science, Toronto, ON) and tetrabutylammonia hydrogen sulphate (Sigma Chemical Co., St Louis MO). To prepare 1 L of mobile phase, 850 mL of 0.01M monobasic potassium phosphate the phosphate buffer was mixed with 150 mL of acetonitrile and 3.396 g of tetrabutylammonia hydrogen sulphate (0.01 M) was added. This ratio of buffer to organic was held constant during a chromatographic run. The mobile phase was pumped at 1.0 mL/min through a 25 cm x 4.6 mm C18, 5μm column (Hypersil ODS, Alltech, Guelph, ON) using a liquid chromatographic pump (SpectraSystem P4000, Thermo Separation Products, Fremont, CA). Morphine and bupivacaine were detected at 230 nm using a variable wavelength detector (Series 1050 Hewlett Packard, Mississauga, ON) and chromatograms were recorded directly on computer using PC-1000 software (Thermo Separation Products, Freemont, CA). Using this separation, samples containing morphine and its degradation

products and bupivacaine and its degradation products, produced through accelerated degradation, were mixed and the separation confirmed.

Assay validation, accuracy and reproducibility

Validation of the method, with respect to accuracy and reproducibility was tested over 4 days. During this period, system suitability criteria (theoretical plates, tailing and retention time) were also established for each compound of interest to ensure consistency between study days. Each sample was chromatographed in duplicate. Inter- and intraday reproducibility were assessed using the coefficient of variation of the peak area for samples determined in duplicate and accuracy was determined based on deviations from the known concentration of both standards and quality control samples.

STABILITY STUDY

The stability and compatibility of the combination of morphine sulfate (1 mg/mL, Morphine LP Epidural,™ Lot #: 1096084; Sabex., Boucherville, PQ) and bupivacaine injection (Marcaine™, 5 mg/mL, Lot # M070RB; Sanofi Winthrop, Mississauga, ON) diluted in 0.9% sodium chloride in water (NS), was determined. Three 80-mL aliquots of solution were prepared for each of the 2 study temperatures. These solutions had initial nominal morphine and bupivacaine concentrations of 0.05 mg/mL and 1.0 mg/mL, respectively. Equal numbers of solutions were stored at room temperature (23°C) and in the refrigerator (4°C). One container of each temperature was used to complete the physical inspection and pH while all were used to determine the concentration of morphine and bupivacaine by liquid chromatographic analysis on days 0, 1, 2, 5, 6, 7, 9, 12, 14, 19, 21, and 28. Between sampling days and during storage at room temperature or in the refrigerator, each bag was wrapped in an amber PVC bag and placed within a zip-lock bag. This simulated actual in-use storage conditions designed to reduce water loss from the container. The bags stored at room temperature were exposed to ambient fluorescent light for approximately 12 hours during each study day.

Liquid chromatographic analysis

On each study day, fresh standards of morphine and bupivacaine were prepared and chromatographed to construct a standard curve. On each study day the bags were sampled and the pH, physical analysis and chromatographic analysis was completed within 4 hours of sampling.

For morphine, an accurate weight of approximately 30 mg was weighed and a stock solution of 15 mg/mL was prepared and diluted to create concentrations of 0.012, 0.025, 0.045, 0.055, 0.065, and 0.075 mg/mL. Twenty microlitres of each of these 6 standards and a blank were directly chromatographed in duplicate and the concentration of morphine determined.

For bupivacaine, a stock solution of 5 mg/mL was diluted to prepare 6 concentrations of 0.32, 0.60, 0.99, 1.16, 1.32 and 1.46 mg/mL. These 6 standards plus a blank were used to construct a standard curve. Twenty microlitres of each standard and a blank were directly chromatographed in duplicate on each study day.

Morphine and bupivacaine were quantified simultaneously on each study day using the same reverse phase liquid chromatographic separation described above. The average peak area of bupivacaine and morphine from each of 2 replicates from each standard were subjected to least-squares linear regression and the concentration of samples was interpolated from the standard curves and recorded. Concentrations were recorded to the nearest 0.001 mg/mL.

Three quality control samples were run on each study day. Two quality control samples were prepared fresh each day from the stock solutions of morphine, 0.055 mg/mL and bupivacaine 0.99 mg/mL. The third quality control sample was prepared on day zero by mixing equal parts of a 0.055 mg/mL morphine solution with a 1.0 mg/mL bupivacaine solution.

pH and physical inspection

Physical inspection was completed on solutions as they were drawn for pH analysis. On each of the study days a 1-mL sample was drawn and placed in a 10 x 75 mm glass test tube. Each solution was inspected visually for colour and clarity. The pH of each solution was then measured. The pH meter (Accumet-model 925; Fisher Scientific, Toronto, ON) was equipped with a

microprobe glass body electrode (cat# 13-639-280; Fisher Scientific, Toronto, ON) and was standardized each day with 2 commercially available buffer solutions. The pH was recorded to the nearest 0.001 of a pH unit.

Data reduction and statistical analysis

Means (± standard deviation) were calculated for replicated analyses. Reproducibility was assessed by coefficient of variation (CV). Mean concentration results for each solution were analysed by least-squares linear regression to determine the percent of initial concentration remaining on the last day of the study. All concentrations in the study were subjected to analysis of variance to determine the significance of temperature and time on the change in concentration. The 5% level was used as the a priori cut-off for significance.

Morphine and bupivacaine concentrations were considered "within acceptable limits" if the concentration on any day of analysis was not less than 90% of the initial (day-zero) concentration. A solution was judged to be physically compatible if there was no visual change in the colour or clarity of the mixture and no precipitate or other particulate formation was visually apparent.

RESULTS

Assay validation

Accelerated degradation of morphine and bupivacaine

At the end of the 125-hour accelerated degradation study period, approximately 60% of the initial morphine concentration remained and there was chromatographic evidence of a degradation product in the solvent front (Figure 1, Panel B).

At the end of the 124-hour accelerated degradation study period, approximately 98% of the initial bupivacaine concentration remained, but there was minor chromatographic evidence of a degradation
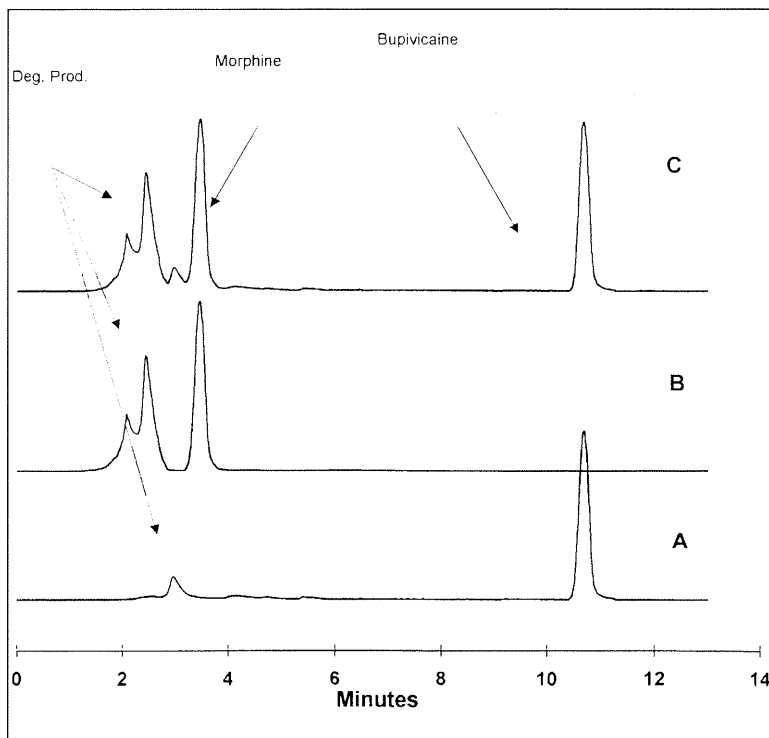

Figure 1 — Lower panels A and B show chromatograms observed using the accelerated studies. Panel A shows the chromatogram observed after 124 hours of incubation of bupivacaine at 86ºC in 0.3 N HCl at a pH of 0.89. Panel B shows the chromatogram observed after 125 hours of incubation of morphine 95ºC in 0.9% saline adjusted to a pH of 11 with sodium hydroxide. Panel C shows a mix of the solutions chromatographed in panels A and B to demonstrate the separation of morphine and bupivacaine from degradation products.

product in the solvent front. The pH during accelerated degradation was at 0.89 and the temperature was held constant at 86.0°F. The chromatographic separation of morphine from bupivacaine and the degradation products of both compounds (Figure 1) demonstrated that this analytical separation was stability-indicating for morphine and bupivacaine.[8,9]

Assay validation: Morphine

Duplicate analysis of morphine quality control samples (concentrations of 0.05 and 0.055 mg/mL), demonstrated that concentrations were estimated with less than a 6% deviation between the observed and known concentrations and the coefficient of variation (CV) on duplicate analysis was approximately 1%, within a day, and less than 6.2% between days. Accuracy and reproducibility for standards was similar. Deviations from the known concentration were

routinely within 3% and error (CV) of duplicate analysis, within a day, ranged from 1.29% to 2.52%, and averaged less than 2% for all concentrations. These analyses indicated that the morphine concentrations were measured accurately and reproducibly and that differences of 10% or more could be confidently detected with acceptable error rates.[10,11]

Assay validation: Bupivacaine

The accuracy of bupivacaine, based on duplicate analysis of quality control samples (concentrations of 1.0 and 0.99 mg/mL), demonstrated that concentrations were estimated with deviations of less than 3.25% and the error (CV) on duplicate analysis was less than 1.8% within a day for 15 of 17 results, and was less than 3.25% between days. Accuracy and reproducibility for standards was similar. Deviations from known concentration were routinely within 2% and error (CV) of duplicate analysis, within a day, ranged from 0.11% to 7.5%, averaging approximately

1.3% for all concentrations. These analyses indicated that the bupivacaine concentrations were measured accurately and reproducibly and that differences of 10% or more could be confidently detected with acceptable error rates.[10,11]

Compatibility/stability studies

At room temperature over a 24-hour period, solutions of morphine and bupivacaine were observed to be physically compatible. No precipitate was visible in any solution, no colour changes occurred and no gas was produced on mixing during the study period.

During the 28-day stability study period, neither morphine nor bupivacaine degraded to a measurable extent. Degradation products observed in the accelerated degradation study during assay validation were not observed during the 28-day stability study. In all samples, greater than 90% of the initial morphine and bupivacaine concentrations remained on the last study day (Table I). Least-squares linear regression of the change in concentration with time demonstrated that there was less than a 6.5% change in concentration for either bupivacaine or morphine. For each solution–temperature combination, the fluctuation in concentration was similar to assay error, averaging 3.2% (range: 2.29%–4.76%). There was no significant trend for the concentration to change with time (p = 0.708) and there was no significant effect of storage temperature on the concentration of either drug (4°C vs. 23°C; p = 0.899).

pH and physical inspection

The pH of the 0.05 mg/mL morphine and 1 mg/mL bupivacaine solution stored at room temperature was initially 5.50 and did not

Table I — Mean concentrations of morphine and bupivacaine in normal saline solutions

| Variable | Observed concentrations* (Mg/mL) | | | |
| | Morphine (0.05 mg/mL) | | Bupivacaine (1 0 mg/mL) | |
	Refrigerated	Room temperature	Refrigerated	Room temperature
Day 0	0.046 ± 0.001	0.048 ± 0.001	0.990 ± 0.085	1 008 ± 0.055
Day 1	0.048 ± 0.002	0.047 ± 0.001	1 023 ± 0 023	1 046 ± 0 012
Day 2	0 049 ± 0 000	0 052 ± 0.002	0.981 ± 0.015	1 021 ± 0 017
Day 5	0.050 ± 0.000	0.051 ± 0.000	0.947 ± 0 006	0.933 ± 0 004
Day 6	NDA†	0 050 ± 0.002	1 010 ± 0 004	1 016 ± 0 026
Day 7	0 044 ± 0.001	0.046 ± 0.001	1 000 ± 0.018	0 968 ± 0 019
Day 9	0 045 ± 0.003	0.046 ± 0.027	1 008 ± 0.005	0 992 ± 0 000
Day 12	0 051 ± 0.000	0.050 ± 0.001	1 038 ± 0 019	1 004 ± 0 003
Day 14	0 049 ± 0.001	0.049 ± 0.000	1 010 ± 0 004	1 009 ± 0 003
Day 19	0 049 ± 0.001	0.049 ± 0.000	0 987 ± 0 030	1 002 ± 0 020
Day 21	0 051 ± 0 004	0.051 ± 0.002	0 998 ± 0 008	1 002 ± 0 001
Day 28	0.048 ± 0 001	0 047 ± 0.001	1 009 ± 0 005	1 008 ± 0 006
CV(%)‡	4 76	2.96	2 29	2 78
% remaining§ on Day 28	106 13	93 49	101 35	99 78

* Mean based on 3 replicates determined in duplicate.
† No data available
‡ Coefficient of variation (standard deviation/mean) expressed as a %
§ Based on least squares linear regression (100 x regression determined day 28 concentration/regression determined day 0 concentration)

change through the duration of the study. The refrigerated sample of same concentration had a pH that was 0.5 higher than the room temperature samples and also remained constant throughout the study.

DISCUSSION

Least-squares linear regression of the change in concentration with time demonstrated that there was less than a 6.5% change in concentration for both bupivacaine and morphine over the 28-day study period. In studies where no change in the concentration of the drugs of interest can be detected, assurance that the analytical method is specific for the compound of interest is important. This was demonstrated in the accelerated degradation portion of the study where we were able to separate degradation products of both drugs from both morphine and bupivacaine. Therefore, this method was specific for the compounds of interest and was stability-indicating.

The stability of morphine in à range of concentrations and in a variety of containers and solutions has been previously reported.[2–5] All studies have demonstrated that intravenous solutions of morphine are stable. Bupivacaine is also a very stable compound.[6] Furthermore, morphine[12–18] and bupivacaine[7,19–25] have each been shown to be visually or chemically compatible with a variety of other drugs. However, only visual evidence of compatibility of the combination of morphine and bupivacaine has been reported.[7] Neels reported that 7.5 mg/mL of bupivacaine and 129 mg/mL of morphine were visually compatible and remained effective for 19 days. However, we believe that routine storage of an intravenous medication for an extended period should be based on more that visual physical compatibility. This current study demonstrates the chemical compatibility and stability of the combination of morphine with bupivacaine for 28 days at both room temperature and 4°C in NS solutions using a validated liquid chromatographic method. These solutions will retain more than 90% of the initial morphine and bupivacaine concentration for 28 days.

Extension of expiry dates has been demonstrated to reduce wastage of both antibiotics and chemotherapy.[26,27] This reduction in wastage should also reduce drug expenditures and, for intravenous medications, should reduce intravenous preparation time. Several factors likely affect the relationship between waste and the expiry date. Extending an expiry date can only reduce wastage if the shelf life, on average, is longer than the interval between orders or prescriptions. For this reason, expiry dates for an infrequently used product must be longer[27] and the cost advantages of a large multi-dose vial will not be realised for a low-frequency usage medication.[28] The impetus of the current study of morphine and bupivacaine stability was the night-cupboard wastage of morphine and bupivacaine. While usage is generally more frequent than once every 28 days, realisation of a maximum reduction in wastage required an expiry of at least 28 days. However, while this study provides information to demonstrate the stability of the combination, expiry dates at each institution should be established after giving consideration to the contamination rate within their own IV additive program. This is especially true for this combination which is intended for epidural use, since it will be stored at room temperature and does not contain any preservative. Individual institutions are encouraged to evaluate their own microbial contamination rate because, unlike chemical stability, the equipment, procedures and personnel at each site determine a unique, site-specific contamination rate. Only after consideration of the contamination rate should an expiry date of 28 days be used.

ACKNOWLEDGEMENTS

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