Stability of Morphine Solutions of 20, 40, 100, 200 and 1,000mcg/mL In Syringes Following Dilution with 0.9% Sodium Chloride or D5W at Room Temperature (25°C).

Roxanne Hook[1], Vera Riss[1], Ashleigh Neault[1], Nathan H Ma[2], Shirley Law[2] and Scott E. Walker[2,3]

Departments of Pharmacy, Hospital for Sick Children [1] and Sunnybrook Health Sciences Centre [2], and the Faculty of Pharmacy [3], University of Toronto, Toronto, Ontario.

INTRODUCTION

Inpatient hospital pharmacies must compound intravenous products and assign an appropriate beyond-use-date (BUD) as per NAPRA standards, when products are not commercially available. Having infusions available as ready-to-administer (RTA) products on nursing units is important for safe and timely administration of medication.

Pediatric patients require lower concentrations than adults. Multiple publications have demonstrated the stability of morphine, but none with storage in polypropylene syringe for periods longer than 14 days.

We required such data to be in compliance with current NAPRA/USP regulations.

OBJECTIVES

The objective of this study was to evaluate the chemical stability of morphine prepared in polypropylene syringes at concentrations of 20 mcg/mL and 40 mcg/mL diluted in D5W and concentrations of 100, 200 and 1,000 mcg/mL, diluted in 0.9% sodium chloride, while solutions were stored at room temperature (25°C).

The concentration of morphine was evaluated during storage using a validated, stability indicating, liquid chromatographic method using UV detection.

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NONE of the authors of this poster have any personal or financial relationships with any commercial entities that may have a direct or indirect interest in the subject matter of this presentation. The morphine and syringes used in this study were purchased by the Department of Pharmacy, Hospital for Sick Children.

METHODS

Liquid Chromatographic Method

The liquid chromatographic system consisted of a mixture of 30% acetonitrile and 70% 0.05 mol/L phosphoric acid which was pumped through a 15 cm x 4.6 mm reverse-phase C18, 3-µm column (Supelco, Supelcosil LC-18, Mississauga, Ontario) at 1.0 mL/min. The effluent was monitored at 285 nm.

Assay Validation

A chromatographic separation was developed and evaluated to ensure reproducibility, accuracy and assay specificity. The system was shown to be capable of separating morphine from many other narcotics (Figure 1). Accuracy and reproducibility of standard curves was tested over 5 days. Inter and intra-day errors of reproducibility were assessed by the coefficients of variation and the standard deviation of regression.

Stability Study

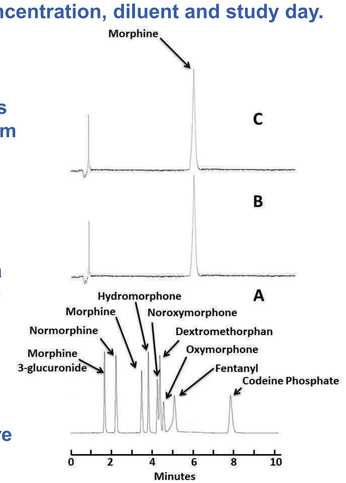
On study day 0, three batches of morphine solutions (20 and 40 mcg/mL diluted in D5W) and three batches of 100, 200 and 1,000 mcg/mL solutions diluted in 0.9% sodium chloride were prepared using Sandoz Canada; 10 mg/mL Morphine Injection (Lot: GS0278; Exp: 10/19) and 50 mg/mL Morphine Injection (Lot: JB2588; Exp. 12/19 and Lot: JD3586; Exp: 02/20). Three BD syringes of each concentration were stored at room temperature (25°C). Concentration analysis was completed on study days 0, 2, 7, 14, 21, 28, 42, 56, 72 and 91 using a validated stability-indicating liquid chromatographic method with UV detection.

Data Reduction and Statistical Analysis

Chemical stability was based on the intersection of the lower limit of the 95% confidence interval of the observed degradation rate, determined by linear regression, and the time to achieve 90% of the initial concentration (T-90). Multiple linear regression analysis was used to test differences in degradation rate between concentration, diluent and study day.

Figure 1. Representative Chromatograms

Chromatogram A demonstrates the separation of morphine from 7 other narcotics with similar structure. The elution time in this figure for morphine is 3.5 min. In the study this was extended to 6.1 minutes. Chromatogram B represents a 200 mcg/mL morphine sample on day zero Chromatogram C represents the same 200 mcg/mL morphine sample on day 91. No degradation products are apparent in solution after room temperature storage for 91 days.



CONCLUSIONS

In this study the concentration was observed to change by less than 2% during the 91-day study period. The BUD, calculated with 95% confidence, exceeded the 91-day study period for all concentrations. After 91-days of storage at 25°C, more than 97.8% of the initial concentration will remain, with 95% confidence.

We conclude that morphine solutions stored at room temperature in a syringe, in concentrations ranging between 20 mcg/mL and 40 mcg/mL diluted in D5W or concentrations of 100, 200 or 1,000 mcg/mL diluted in 0.9% sodium chloride are physically and chemically stable for 91 days.

When establishing a BUD in your institution, the sterile compounding environment and sterility testing of the final product must be considered

RESULTS

Concentration Results

Concentrations on each study day are reported in Table 1 and retained more than 98.42% from the initial concentration throughout the 91-day study period at 25°C.

Multiple linear regression failed to reveal significant differences in percent remaining due to study day (p=0.062), concentration (p=0.851) or diluent (p=0.654). The calculated T-90, with 95% confidence, exceeded the 91-day study period for all concentrations at 25°C, estimated to be between 280 and 977 days.

Assay Validation

The analytical method was judged to be stability-indicating. The method was specific for morphine, capable of separating morphine from morphine degradation products and other narcotics of similar structure.

The concentration was measured specifically, accurately (deviations from known averaged 2.17%) and reproducibly (replicate error within a day averaged 0.45% [CV(%)]). The standard deviation of regression, another measure of between days reproducibility averaged 0.64%.

Table 1. Percent Remaining of the Initial Morphine Concentrations.[1]

Diluent	D5W	D5W	0.9% NaCl	0.9% NaCl	0.9% NaCl
Container	Syringe	Syringe	Syringe	Syringe	Syringe
Nominal Initial concentration (µg/mL)	20ug/mL	40ug/mL	100ug/mL	200ug/mL	1000mg/mL
Study Day / Initial concentration (µg/mL)	19.62±0.59	40.14±0.71	99.55±0.10	199.47±0.18	999.17±0.06
2	99.88±0.95	100.29±0.22	99.64±0.50	99.88±0.18	100.01±0.05
7	99.52±2.46	101.29±1.23	99.40±1.10	100.33±0.64	99.89±0.09
14	100.23±1.46	98.48±0.06	99.72±0.13	99.70±0.17	100.56±0.17
21	100.55±1.47	99.54±1.23	99.45±0.32	100.48±1.80	100.29±0.39
28	101.45±0.64	98.42±0.40	99.19±0.31	99.17±0.56	100.13±0.34
42	100.24±0.66	99.78±2.39	100.59±1.05	99.66±0.16	100.19±0.36
56	100.79±1.00	99.18±0.24	101.08±1.09	99.29±0.75	100.30±0.58
72	100.85±1.26	100.74±1.42	101.82±0.49	101.28±1.85	99.36±0.31
91	99.31±1.78	100.05±0.46	100.79±0.49	101.04±1.73	100.17±0.66
Degradation Rate (%/day) [Slope]	0.001	0.001	0.022	0.010	-0.002
Standard Deviation of Regression (Sy.x)	0.686	0.972	0.572	0.659	0.327
Confidence Interval for slope	0.01691	0.02397	0.01410	0.01625	0.00807
Fastest Degradation Rate-95% Confidence	-0.0157	-0.0227	0.0075	-0.0060	-0.0102
Slowest Degradation Rate-95% Confidence	0.0181	0.0252	0.0357	0.0265	0.0059
Shortest T-90 in days (95% CI)	551.75	396.37	280.22	377.55	977.49

1. Concentrations are expressed as a percentage of initial concentration ± the Coefficient of Variation (CV)

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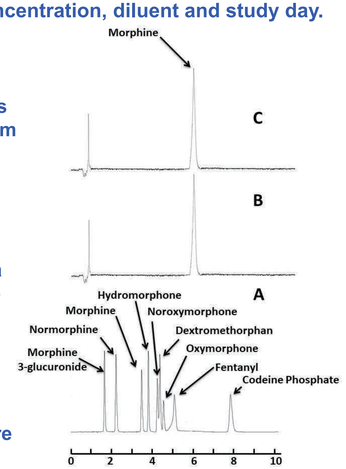

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