Stability of 1.0, 0.2 and 0.025 mg/mL Milrinone Solutions Stored in Syringes at 4ºC and at Room Temperature (25ºC).

Roxanne Hook[1], Vera Riss[1], Erica Scharrer[1], Jonathan Robillard[1], 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.

Previous publications have demonstrated the stability of 0.2 mg/mL of milrinone for 72 hours in polyethylpolypropyl copolymer plastic containers, (AJHP 86); 0.4 – 0.8 mg/mL for 14 days in PVC minibags (Compounding Ophthalmics – 1998). Compatibility of a 0.4 mg/mL solution has also been reported with numerous other drugs for 7 days (AJHP – 1999).

Paediatric patients require lower concentrations than adults. Since the stability of milrinone has not been reported at concentrations below 0.2 mg/mL, has never been reported beyond 14 days and has never been reported for solutions stored in syringes, we required such data to be in compliance with current regulations.

OBJECTIVES

The objective of this study was to evaluate the chemical stability milrinone prepared in syringes at concentrations of 1 mg/mL (undiluted), 0.2 and 0.025mg/mL (diluted in either 0.45% sodium chloride or 5% dextrose in water (D5W)) at both room temperature and in the refrigerator.

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

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 milrinone 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 with 0.01M sodium lauryl sulfate which was pumped through a 15 cm x 4.6 mm reverse-phase C18, 5-µm column (Agilent Zorbax SB-CN, Mississauga, Ontario) at 1.0 mL/min. The effluent was monitored at 325 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 milrinone from its degradation product (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, 60mL solutions of 1, 0.2 and 0.025mg/mL concentrations of milrinone were prepared in 50mL BD syringes using Fresenius Kabi; Milrinone Lactate Injection (Exp: 01-Sept-18). 3 units of each container and concentration were stored at room temperature (25C) and 3 were stored at 4C. Concentration analysis was completed on study days 0,1,7,14,21,28,42,54,75 and 90 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 and the time to achieve 90% of the initial concentration. Analysis of variance was used to test differences in degradation rate.

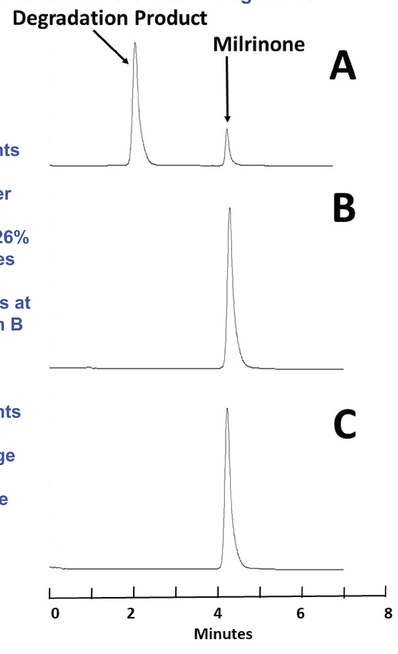

Figure 1. Representative Chromatograms

Chromatogram A represents a solution of 1.0 mg/mL milrinone immediately after the addition of sodium hypochlorite showing 18.26% remaining. Milrinone elutes at 4.45 minutes and the degradation product elutes at 2 minutes. Chromatogram B represents a 1 mg/mL solution of milrinone on study day zero. Chromatogram C represents the same solution after 90 days of storage in a syringe at room temperature. No degradation products were observed.

CONCLUSIONS

In this study the concentration was observed to change by no more than 4% during the 90 day study period and the BUD, calculated with 95% confidence, exceeded 155 days for storage of all concentrations, temperatures and diluents.

We conclude that 1 mg/mL (undiluted), 0.2 and 0.025mg/mL diluted in either 0.45% sodium chloride or D5W, stored at either room temperature or in the refrigerator in polypropylene BD syringes are physically and chemically stable for 90 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 were observed to vary by 4% or less from the initial concentration throughout the 90-day study period.

Multiple linear regression revealed significant differences in percent remaining due to study day (p=0.008) and temperature (p = 0.0276) but not concentration (p= 0.108) or diluent (p= 0.635). The calculated T-90, with 95% confidence, exceeded 155.61 days for all concentrations, temperatures and diluents.

Assay Validation

The analytical method separated degradation products from milrinone such that the concentration was measured specifically, accurately (deviations from known averaged 2.24%) and reproducibly (replicate error averaged 0.66%(CV(%)) and standard deviation of regression averaged 0.75%). The analytical method was judged to be stability-indicating.

Table 1. Percent Remaining of the Initial Milrinone Concentration.

Diluent	Undiluted	NaCl	D5W	NaCl	D5W	Undiluted	NaCl	D5W	NaCl	D5W
Container	Syringe	Syringe	Syringe	Syringe	Syringe	Syringe	Syringe	Syringe	Syringe	Syringe
Temperature	4C	4C	4C	4C	4C	RT	RT	RT	RT	RT
Nominal Concentration	1mg/mL	0.2mg/mL	0.2mg/mL	0.025mg/mL	0.025mg/mL	1mg/mL	0.2mg/mL	0.2mg/mL	0.025mg/mL	0.025mg/mL
Observed Initial Conc.	1.02±0.52	0.20±0.07	0.20±0.21	0.024±0.28	0.025±0.03	1.03±0.08	0.20±0.02	0.20±0.09	0.024±0.04	0.024±0.04
Study Day										
1	100.09±0.00	100.09±0.00	100.09±0.00	98.15±0.01	98.16±0.00	100.10±0.00	100.09±0.00	100.09±0.00	98.14±0.00	98.15±0.00
7	100.42±0.18	100.74±0.43	100.07±0.19	99.11±0.15	98.95±0.18	99.60±0.33	99.94±0.02	100.15±0.12	99.48±0.19	100.01±0.19
14	101.20±0.18	102.07±0.53	100.77±0.40	98.42±0.34	101.22±1.46	100.41±0.24	100.22±0.08	100.69±0.38	98.48±0.24	99.57±0.60
21	99.35±0.71	101.37±0.04	100.33±0.52	99.71±0.38	103.77±0.40	100.30±0.08	100.20±0.11	100.42±0.32	99.98±0.18	101.23±1.75
28	99.90±0.20	101.01±0.88	100.39±0.58	101.70±0.18	101.14±0.39	101.29±0.94	100.32±0.37	100.02±0.19	101.15±0.21	101.83±0.84
42	100.09±0.66	102.18±0.10	101.24±0.41	102.63±0.96	102.35±0.58	100.57±0.33	100.91±0.06	100.32±0.12	101.77±0.07	101.91±0.53
54	100.55±0.68	102.64±0.04	101.72±0.57	101.14±0.78	101.86±0.87	100.76±0.53	101.30±0.03	100.65±0.31	100.43±0.08	100.70±0.23
75	100.09±0.92	102.00±0.06	101.11±0.45	100.92±0.76	101.41±0.35	100.11±0.59	100.69±0.11	99.98±0.41	100.44±0.15	100.56±0.12
90	99.62±0.65	101.65±0.03	100.80±0.66	102.22±0.65	102.01±0.13	99.71±0.47	100.20±0.18	99.52±0.37	101.68±0.28	101.64±0.13
Rate of Change of Concentration (%/day – Slope)	**-0.004**	**0.019**	**0.013**	**0.036**	**0.028**	**0.000**	**0.007**	**-0.004**	**0.027**	**0.022**
Intercept	100.259	100.747	100.227	99.203	100.172	100.291	100.141	100.322	99.274	99.843
Correlation (r)	-0.239	0.659	0.694	0.722	0.521	-0.012	0.529	-0.372	0.682	0.574
Standard Deviation of Regression (Sy.x)	0.525	0.718	0.440	1.150	1.498	0.534	0.397	0.345	0.949	1.023
Confidence Interval for slope	**0.01288**	**0.01760**	**0.01079**	**0.02819**	**0.03671**	**0.01309**	**0.00973**	**0.00845**	**0.02325**	**0.02508**
Fastest Slope 95% Confidence (%/day)	**-0.0168**	**0.0013**	**0.0019**	**0.0079**	**-0.0092**	**-0.0133**	**-0.0023**	**-0.0126**	**0.0033**	**-0.0035**
Upper Limit95% Confidence	0.0090	0.0365	0.0235	0.0643	0.0642	0.0129	0.0172	0.0043	0.0498	0.0467
Shortest T-90 (95% CI) days	596.73	274.02	424.97	155.61	155.72	752.48	582.46	793.57	200.69	214.30

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