Stability of 4 and 10 mcg/mL Remifentanil Solutions Stored in Syringes at Room Temperature (23^{0}C).

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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. Furthermore, having medications in a Ready-To-Administer format on nursing units is important for safe and timely administration.

A previous publication [Stewart et al Anesth Analg 2000; 90: 1450-1] reported that the stability of 5mcg/mL and 50 mcg/mL solutions retained more than 90% of the initial concentration for 36 hours in BD polypropylene syringes at room temperature (22-24C). However, in PVC containers more than 90% of the 50 mcg/mL solution remained for 36 hours but the 5 mcg/mL solution retained more than 90% for only 24 hours at room temperature (22-24C). 95% confidence intervals were not calculated in this study and analytical performance (reproducibility and accuracy) was not provided. Furthermore, no proof that this method is stability indicating is provided.

Paediatric patients require lower concentrations of opioid continuous infusions than adults and while previous publications have demonstrated the stability of remifentanil, data for lower concentrations stored in syringes beyond 36 hours has not been reported.

OBJECTIVES

The objective of this study was to evaluate the stability of remifentanil concentrations of 4 mcg/mL and 10 mcg/mL in polypropylene syringes over a 90 day storage period at room temperature.

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

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The remifentanil and polypropylene syringes used in this study were purchased by the Department of Pharmacy, Hospital for Sick Children.

Liquid Chromatographic Method

The liquid chromatographic system consisted of a mixture of 45% acetonitrile and 55% 0.05 mol/L phosphoric acid with 0.01 M sodium lauryl sulfate which was pumped through a 15 cm x 4.6 mm reverse-phase C18, 3-µm column (Supelcosil; Supelco, Toronto, Ontario) at 1.0 mL/min. The effluent was monitored at 216 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 remifentanil from its degradation products (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, 3 sample solutions of remifentanil 4 mcg/mL and 10 mcg/mL of remifentanil, diluted with 0.9% sodium chloride injection, were prepared and drawn into polypropylene Becton-Dickinson syringes in 5 mL aliquots. Three units from each container were stored at room temperature. Concentration and physical inspection were completed on days 0, 1, 3, 7, 14, 24, 38, 56, 76, and 90.

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.

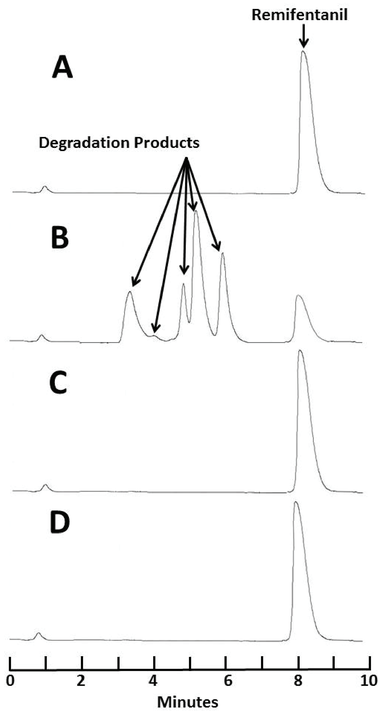

Figure 1.
Chromatogram A represents a 10 mcg/mL concentration of remifentanil at time zero prior to incubation at 90C.
Chromatogram B represents the same 10 mcg/mL remifentanil solution after 70 hours incubation at 90C when 32% of the initial concentration remains. Several degradation products are evident.
Chromatogram C represents a 10 mcg/mL solution of remifentanil in a syringe on study day zero.
Chromatogram D represents the same 10 mcg/mL solution of remifentanil in a syringe after 90 days of storage at room temperature.

Note. After 90 days of storage at room temperature *additional peaks are not present* in the chromatogram indicating the lack of observed degradation of remifentanil during storage .

CONCLUSIONS

This study has demonstrated that concentrations of 4 mcg/mL and 10 mcg/mL remifentanil (diluted in saline), stored in polypropylene syringes, retain more than 96.5% of the initial concentration, with 95% confidence, over the 90-day study period.

The results of this study demonstrate extended chemical stability of remifentanil admixtures, exceeding USP General Chapter <797> BUD limits.

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 deviate by less than 3.04% over the study period (90 days) when stored at room temperature.

The calculated use-before-date, with 95% confidence, exceeds 156 days, exceeding the 90 day study - storage period for all concentrations.

Assay Validation

Assay validation demonstrated that numerous other narcotics are separated from remifentanil (Figure 1). Standards and quality control samples over the study period showed an average absolute deviation of 2.65% from the expected concentration. Analytical error with replicate measurement (as measured by coefficient of variation) averaged 0.81% within a day and 1.98% between days. A second estimate of between days analytical error, as measured by the standard deviation of regression averaged 1.19%.

Analysis of variance revealed significant differences in percent remaining due to study day ($p = 0.0026$), but not concentration ($p = 0.203$). The study was capable of detecting a 1.4% difference in concentration due to study day and concentration or container. The difference due to concentration is less than 0.5% and may be unimportant.

Table 1. Percent Remaining of the Initial Remifentanil Concentration.

Container		Syringe	Syringe
Storage Temperature		RT	RT
Nominal Concentration (mcg/mL)		4 mcg/mL	10 mcg/mL
Study Day	Initial concentration (mcg/mL)	4.4 ± 0.1	10.8 ± 0.5
1		100.36±0.37	99.32±0.89
3		98.82±1.55	99.23±3.18
7		100.03±1.58	99.06±1.25
14		100.05±1.19	100.66±1.72
24		99.75±0.59	101.93±1.73
38		100.32±1.38	102.27±1.12
56		97.17±0.87	97.68±0.17
76		97.21±0.63	98.15±0.66
90		96.96±0.75	96.97±0.78
	Degradation rate (%/day) [Slope]	-0.036	-0.027
	Intercept (Percent of Initial Concentration)	100.184	100.367
	Correlation coefficient (r)	-0.840	-0.516
	Standard Deviation of Regression (Sy.x)	0.815	1.574
	Std Error in Slope (Sb)	0.008257	0.015946
	Confidence Interval for slope	0.01904	0.03677
	Fastest Slope 95% Confidence	-0.0552	-0.0639
	Upper Limit 95% Confidence	-0.0171	0.0096
	T-90 (point Estimate) in days	276.51	368.31
	Shortest T-90 (95% CI) in days	**181.14**	**156.44**
	Longest T-90 (95% CI) in days	584.00	1039.55