Stability of Ketamine 2 and 10 mg/mL Diluted in 0.9% Sodium Chloride and Stored in Polypropylene Syringes for 90 Days at 4 and 25°C

Vera Riss[1], Roxanne Hook[1], Ashleigh Neault[1], Shirley Law[2], Nathan H Ma[2]

Department of Pharmacy, Hospital for Sick Children, Toronto, Ontario[1]; Department of Pharmacy, Sunnybrook Health Sciences Centre, Toronto, Ontario[2].

INTRODUCTION

Ketamine is a rapid-acting general anaesthetic that is indicated for use as the sole anaesthetic agent, for the induction of anaesthesia, or to supplement low potency agents (e.g. nitrous oxide). It is used for its opioid-sparing properties with patients requiring high dose, continuous opioids for analgesia, and as a fourth-line agent in the treatment of status epilepticus.

Inpatient pharmacies often require concentrations of ketamine that are not commercially available. In order to meet patient needs, these must be compounded and assigned an appropriate beyond-use date. Previous studies have evaluated the stability of ketamine, but not when diluted with 0.9% sodium chloride to concentrations of 2 and 10 mg/mL and stored in polypropylene syringes.

OBJECTIVES

The objective of the study was to evaluate the chemical stability of ketamine diluted with 0.9% sodium chloride to concentrations of 2 and 10 mg/mL stored in polypropylene syringes for 90 days in a refrigerator (4°C) and at room temperature (25°C).

METHODS

Liquid Chromatographic Method

The liquid chromatographic system was composed of a solvent delivery pump and autoinjector system (Waters Alliance 2695 Separations Module, Waters Scientific, Toronto ON) which pumped the mobile phase through a 150mm x 4.6mm reverse-phase C18, 5 µm column (Poroshell 120 EC-C18, Agilent, Toronto ON) at a rate of 1 mL/min. The effluent was monitored with UV detection (Waters 998 photodiode array detector, Waters Scientific, Toronto ON) at 215 nm. The mobile phase consisted of 40% acetonitrile and 60% 0.05M sodium phosphate dibasic with the pH adjusted to 6.2 using concentrated H_3PO_4.

Assay Validation

The method was evaluated to ensure reproducibility, accuracy and assay specificity. The system was shown to separate carbetocin 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 (CV) and the standard deviation of regression.

Stability Study

On study day 0, eight BD polypropylene syringes containing ketamine 2 mg/mL (Sandoz, lot: AA0702, Exp: Sept 2026) diluted in 0.9% sodium chloride (Baxter, lot: W4A25B0, exp: April 2025) and an additional eight BD polypropylene syringes containing ketamine 10 mg/mL diluted in 0.9% sodium chloride were prepared. Four syringes of each concentration were stored in a refrigerator (4°C) and four syringes were stored at room temperature (25°C). The concentration of ketamine was evaluated on study days 0, 1, 7, 14, 21, 28, 42, 56, 72, and 90 using a validated, stability-indicating liquid chromatographic method with UV detection. The fourth syringe for each concentration and storage condition was used to evaluate the physical stability.

Data Reduction and Statistical Analysis

Ketamine's chemical stability was calculated using the intersect of the lower limit of the 95% confidence interval of the degradation rate and the time to achieve 90% of the initial concentration. Linear regression was used to determine if study day, initial concentration and/or storage temperature were independent predictors of percent remaining.

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RESULTS

Table 1. Percent Remaining of Initial Ketamine Concentration[1]

Temperature		4°C	4°C	25°C	25°C
Nominal concentration (mg/mL)		10	2.0	10	2.0
Actual concentration (mg/mL)		10.07	1.96	10.05	1.91
Study Day	0	100.00	100.00	100.00	100.00
	2	97.61±1.68	99.74±1.60	98.32±0.50	101.55±1.19
	7	97.17±2.07	99.84±1.59	96.35±0.46	97.73±1.74
	14	97.15±1.71	97.09±1.19	96.80±1.02	100.28±2.56
	21	99.19±1.72	99.97±1.31	97.96±0.47	99.72±1.51
	28	96.41±2.10	98.70±0.09	98.91±2.13	98.02±1.35
	42	98.72±0.74	99.32±0.34	98.77±1.89	100.89±1.90
	56	97.50±1.35	99.34±0.31	99.34±1.77	99.68±0.92
	72	97.06±0.87	99.50±0.25	99.18±2.07	101.58±0.78
	90	98.69±0.82	101.22±1.46	97.68±0.69	98.19±1.00
Rate of change of concentration (%/day)		-0.003	0.012	0.006	-0.002
Intercept		98.044	99.072	98.134	99.846
Correlation (r)		-0.078	0.353	0.159	-0.054
Standard Deviation of Regression (Sy.x)		1.203	1.053	1.203	1.487
Confidence Interval for slope		0.02985	0.02613	0.02986	0.03691
Fastest Slope 95% Confidence		-0.0327	-0.0140	-0.0240	-0.0394
Shortest T-90 (95% CI)		305.63	712.22	417.34	254.00

Assay Validation

The results of assay validation demonstrated that ketamine was separated from its degradation products (Figure 1).

Ketamine was measured specifically, accurately (deviations from known averaged 1.35%), and reproducibly (within day replicate error averaged 0.50% and between day replicate error averaged 1.22%). A second estimate of between day reproducibility, the standard deviation of the study samples, averaged 1.24%. Thus, the assay was deemed to be stability indicating.

Concentration Results

The percent remaining of the initial ketamine concentration for each concentration and storage temperature are reported in Table 1. Ketamine retained at least 96% of its initial concentration for the entire 90 day study duration. Physical inspection did not identify any precipitation, evolution of gas or changes in colour.

The calculated time to achieve 90% of the initial concentration with 95% confidence exceeded the 90 day duration of the study. Linear regression identified concentration ($p<0.01$) as a predictor of percent remaining but not study day ($p=0.63$) or temperature ($p=0.38$).

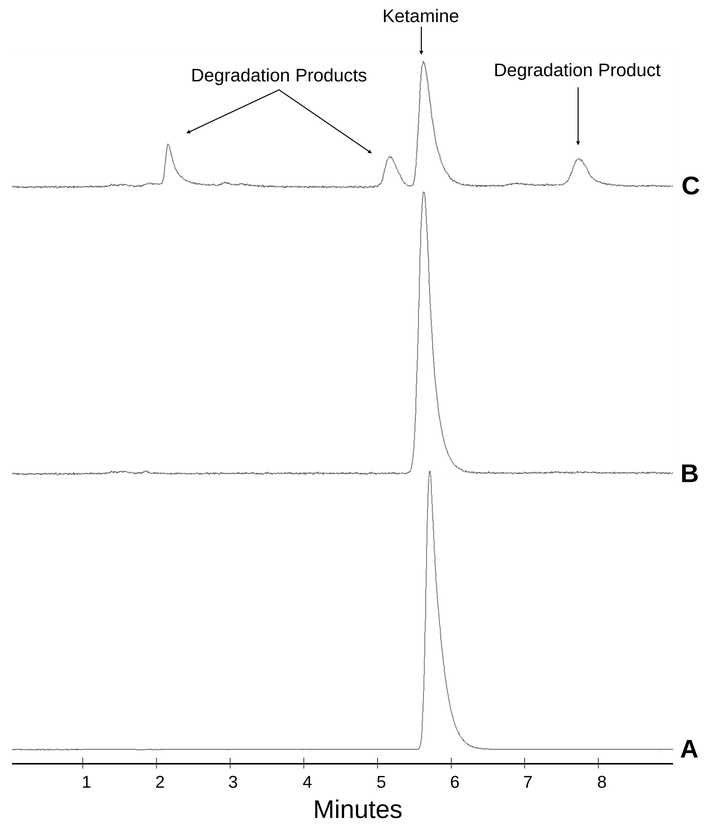

Figure 1: Representative chromatograms.

Chromatogram A shows a sample of ketamine 10 mg/mL on study day 0. Ketamine eluted at approximately 5.6 minutes. Chromatogram B shows the same sample after storage at room temperature (25°C) for 90 days with 97.68% of the initial concentration remaining. No degradation products were observed.

Chromatogram C shows accelerated degradation of 1 mL sample of ketamine 10 mg/mL with 100 µL of sodium hypochlorite and heated at 90°C. After 10.3 hours, 43.85% of the initial concentration remain and degradation products were noted to elute at 2.1, 5.2 and 7.7 minutes.

CONCLUSIONS

Ketamine 2 and 10 mg/mL solutions diluted with 0.9% sodium chloride and stored in polypropylene syringes is stable for at least 90 days when stored in a refrigerator (4°C) and at room temperature (25°C).

DISCLOSURES

Authors of this poster have the following to disclose concerning possible personal or financial relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation:

Vera Riss- Nothing to disclose
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