# Compatibility and Stability of Ketamine in Lactated Ringer's at Room Temperature (25°C)

Nathan H Ma[1], William Perks[1], Romina Marchesano[1], Shirley Law[1], and Scott E. Walker[1,2]

*Department of Pharmacy Sunnybrook Health Sciences Centre[1] and the Faculty of Pharmacy, University of Toronto[2], Toronto, Ontario.*

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## INTRODUCTION

IV Ketamine is widely used in our institution for both pain and sedation. Many patients may receive ketamine administered via Y-site with a simultaneous infusion of Lactated Ringers (RL). However, the compatibility of ketamine with RL is unknown.

The usual dose for pain ranges from 0.1 to 0.3 mg/kg/hour as a continuous infusion. The dose for sedation can range as high as 5 mg/kg/hour.

Depending on the indication and doses required, ketamine IV bags are prepared in 0.9% sodium chloride (NS) in concentrations that range from 1.5 to 7.6 mg/mL.

Since ketamine solutions in NS are generally intended for infusion at rates between 2.6 and 99 mL/hr and RL infusions are intended for infusion at rates between 25 and 200 mL/hr, ketamine solutions diluted in NS and solutions of RL were mixed in a range of volumes, such that the final solution consisted of 20.16% to 98.72% RL. These solutions simulate the possible range of ketamine concentrations in NS and RL solutions after the Y-site within infusion tubing.

## OBJECTIVES

To evaluate the compatibility and stability of 1.5 and 7.6 mg/mL solutions of ketamine in NS mixed with RL across a range of infusion rates. The percentage of RL in the final solutions ranged from 20.16% to 98.72% and the ketamine concentration ranged from 0.019 mg/mL to 6.058 mg/mL. Stability and compatibility of these solutions was evaluated over 24 hours at room temperature (25°C).

The concentration of ketamine was evaluated using a validated, stability-indicating, liquid chromatographic method using UV detection.

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The ketamine used in this study was purchased by the Department of Pharmacy, Sunnybrook Health Sciences Centre.

## METHODS

### Liquid Chromatographic Method

The liquid chromatographic system consisted of a mixture of 50% acetonitrile and 50% 0.05 mol/L potassium phosphate ($K_2HPO_4$) adjusted to pH 7.3 with 85% phosphoric acid which was pumped through 25 cm x 4.6 mm reverse-phase Supelcosil LC-18 (Sigma-Aldrich Canada Inc. Oakville, Ont.) at 1.0 mL/min. The effluent was monitored at 280 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 ketamine from its degradation products (Figure 1). Accuracy and reproducibility of standard curves was tested over 5 standard curves. Inter- and intra-day errors of reproducibility were assessed by the coefficients of variation and the standard deviation of regression.

### Stability Studies

Ketamine Injection (Sandoz Canada; lot:JR3989; Exp Date: Feb 2020), was diluted in NS (Baxter; Lot # W9H15b1; Exp. Mov 2020) to created two concentrations (1.5385 and 7.5785 mg/mL), intended for infusion at rates between 2.6 and 99 mL/hr. These solutions were mixed with RL (Baxter; Lot W9H23MO; Exp Feb 2021) intended for infusion at rates between 25 and 200 mL/hr.

This created eight different ketamine concentrations ranging from 0.019 mg/mL to 6.058 mg/mL. These solutions also differed in the percentage of RL in the final solution ranging from 20.16% to 98.72%.

At time zero, 8 solutions were prepared in triplicate and the concentration evaluated at 0, 2, 4, 6, 8, and 24 hours using the validated reverse-phase stability-indicating liquid chromatographic method. Solutions were also evaluated for precipitate, changes in colour, temperature and evolution of gas at multiple times over a 24-hour period.

### 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. Multiple linear regression analysis was used to test differences in degradation rate between concentration, percentage of RL in the final solution and study day.

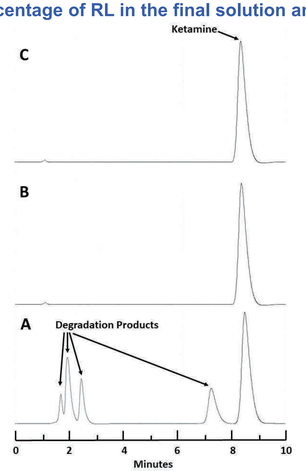


**Figure 1.**
Chromatogram A represents a solution of 5.0 mg/mL ketamine in water at pH 12.5 after incubation at 94°C for 24 hours, when 43.5% of the initial concentration of ketamine remains. Four degradation products are clearly visible and separated from ketamine. Chromatogram B represents a 2.5 mg/mL solution of ketamine at time zero. Chromatogram C represents the same 2.5 mg/mL solution of ketamine after 24 hours of storage at room temperature (25°C).

The degradation products observed in Chromatogram A are not present in either Chromatograms B and C. All of the degradation products elute prior to 8 minutes and are separated from ketamine and do not interfere with quantification of ketamine, which elutes at 8.3 minutes.

## CONCLUSIONS

Ketamine has been shown to be a stable drug retaining more than 90% of the initial concentration over 24 days at 4°C or 23°C (CJHP 2001;54(3)).

In this study, ketamine was also shown to be stable, although only over 24 hours at room temperature (25°C) in all solutions ranging from 20.16% to 98.72% of RL. However, the shortest time to achieve 90% of the initial concentration with 95% confidence was 19.35 hours. Contact time between solutions in a Y-site during an infusion should be less than 1 hour.

Over the 24-hour study period all solutions remained clear and colourless, free of precipitate, evolution of gas or change in temperature.

We conclude that concentrations of ketamine in NS of 1.5 and 7.6 mg/mL, mixed with RL to simulate the possible range of ketamine concentrations and percentage of RL in the final solutions, are physically compatible and chemically stable up to 19 hours at room temperature (25°C).

## RESULTS

**Table 1. Percent Remaining of the Initial Ketamine Concentration in Normal Saline and Lactated Ringers[1]**

| Temperature | RT (25°C) | RT (25°C) | RT (25°C) | RT (25°C) | RT (25°C) | RT (25°C) | RT (25°C) | RT (25°C) |
|---|---|---|---|---|---|---|---|---|
| Concentration of Ketamine in Normal Saline (mg/mL) | 1.5385 | 1.5385 | 7.5758 | 7.5758 | 7.5758 | 7.5758 | 7.5758 | 7.5758 |
| Volume of Lactated Ringers Tested (mL) | 25 | 200 | 25 | 200 | 25 | 200 | 25 | 200 |
| Volume of Ketamine in Normal Saline Tested (mL) | 2.6 | 2.6 | 99 | 99 | 52.8 | 52.8 | 20.4 | 20.4 |
| Percentage of Solution Volume as Lactated Ringers | 90.58 | 98.72 | 20.16 | 66.89 | 32.13 | 79.11 | 55.07 | 90.74 |
| Expected concentration (mg/mL) | 0.1449 | 0.0197 | 6.0484 | 2.5083 | 5.1414 | 1.5833 | 3.4041 | 0.7012 |
| Time (hour) / Observed Concentration (mg/mL) | 0.1393 ± 0.0015 | 0.01987 ± 0.008 | 6.0579 ± 0.0106 | 2.4969 ± 0.0047 | 5.235 ± 0.0079 | 1.5197 ± 0.0012 | 3.3590 ± 0.0069 | 0.7018 ± 0.0074 |
| 1 | 101.03 ± 0.38 | 99.47 ± 1.99 | 99.52 ± 0.04 | 100.02 ± 0.18 | 100.00 ± 0.32 | 101.19 ± 1.23 | 99.87 ± 0.12 | 100.14 ± 0.66 |
| 2 | 100.05 ± 0.83 | 104.18 ± 5.84 | 99.55 ± 0.24 | 100.37 ± 0.19 | 99.98 ± 0.18 | 101.21 ± 0.56 | 99.68 ± 0.27 | 102.08 ± 0.60 |
| 4 | 99.25 ± 1.76 | 98.98 ± 4.02 | 99.87 ± 0.12 | 100.48 ± 0.71 | 100.02 ± 0.08 | 100.63 ± 0.08 | 99.82 ± 0.78 | 104.70 ± 0.99 |
| 6 | 99.65 ± 0.32 | 100.28 ± 3.27 | 99.80 ± 0.22 | 100.51 ± 0.37 | 100.12 ± 0.19 | 101.37 ± 0.56 | 100.25 ± 0.93 | 103.85 ± 2.27 |
| 8 | 98.95 ± 1.41 | 104.55 ± 4.23 | 99.81 ± 0.20 | 100.91 ± 0.68 | 100.13 ± 0.22 | 100.92 ± 0.12 | 100.14 ± 0.63 | 103.63 ± 1.79 |
| 24 | 97.89 ± 0.83 | 96.53 ± 1.08 | 99.94 ± 0.31 | 100.47 ± 0.20 | 100.29 ± 0.14 | 100.73 ± 0.87 | 100.35 ± 0.79 | 102.61 ± 3.39 |
| | | | | | | | | |
| Degradation Rate (%/hour) (Slope) | -0.104 | -0.164 | 0.009 | 0.016 | 0.013 | 0.001 | 0.022 | 0.070 |
| Standard Deviation of Regression (Sy.x) | 0.532 | 2.767 | 0.185 | 0.310 | 0.035 | 0.512 | 0.181 | 1.893 |
| | | | | | | | | |
| Fastest Degradation Rate - 95% Confidence | -0.1722 | -0.5167 | -0.0145 | -0.0232 | 0.0083 | -0.0643 | -0.0015 | -0.1712 |
| Slowest Degradation Rate - 95% Confidence | -0.0366 | 0.1878 | 0.0325 | 0.0556 | 0.0172 | 0.0660 | 0.0445 | 0.3108 |
| Shortest T-90 (95% CI) (hours) | 58.08 | 19.35 | 307.52 | 179.72 | 581.19 | 151.57 | 32.17 | 58.40 |

1. Concentrations are shown as mean ± the Coefficient of variation (CV), expressed as a percentage

### Assay Validation

Assay validation demonstrated that degradation products are separated from ketamine (Figure 1). Standards and quality control samples over the study period showed an average absolute deviation of 2.08% from the expected concentration. Analytical error with replicate measurement (as measured by coefficient of variation) averaged 0.21% within a sample time and 0.40% between sampling times. The standard deviation of regression, another measure of between days reproducibility averaged 0.80%. The analytical method was judged to be stability-indicating.

### Stability Study Results

Over the 24-hour study period all solutions remained clear and colourless, free of precipitate, evolution of gas or change in temperature.

Concentrations on each study day are reported in Table 1. During the study period all solutions retained more than 96.5% of the initial concentration. The shortest calculated use-before-date was (shortest T-90, with 95% confidence - Table 1) was 19.35 hours (range: 19.35 – 581.19 h; average 323 h).

Multiple linear regression revealed significant differences in the percent remaining of ketamine due to the observed initial ketamine concentration (p=0.0024) and the percentage of RL in the final solution (p=0.0015), but not study hour (p=0.456). This study was capable of detecting a 1.39% difference in the percent remaining of ketamine. Differences are detected between the expected initial ketamine concentration of 0.70 mg/mL and all other concentrations.