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Apr 5th, 8:00 AM - 12:00 PM

Refrigerated Stability of Diluted Cisatracurium, Rocuronium, and Vecuronium for skin testing after perioperative anaphylaxis

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Dinsmore, Kristen; Campbell, Bethany; Archibald, Timothy; Mosier, Greg; Brown, Stacy PhD; and Gonzalez-Estrada, Alexei MD, "Refrigerated Stability of Diluted Cisatracurium, Rocuronium, and Vecuronium for skin testing after perioperative anaphylaxis" (2018). *Appalachian Student Research Forum*. 146.
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Refrigerated Stability of Diluted Cisatracurium, Rocuronium, and Vecuronium for Skin Testing After Perioperative Anaphylaxis



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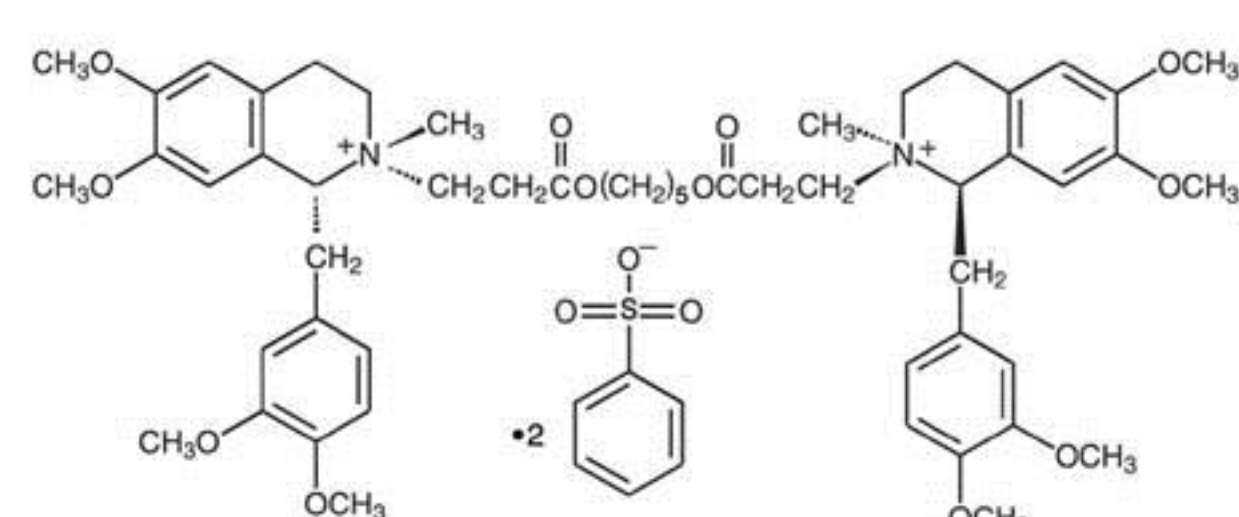
Introduction

Perioperative anaphylaxis is a life-threatening allergic reaction that may occur during surgery. Reports from several countries point to neuromuscular blocking agents (NMBAs) as a leading cause of anaphylaxis. Skin testing with different diluted concentrations of NMBAs are utilized during an allergy evaluation.

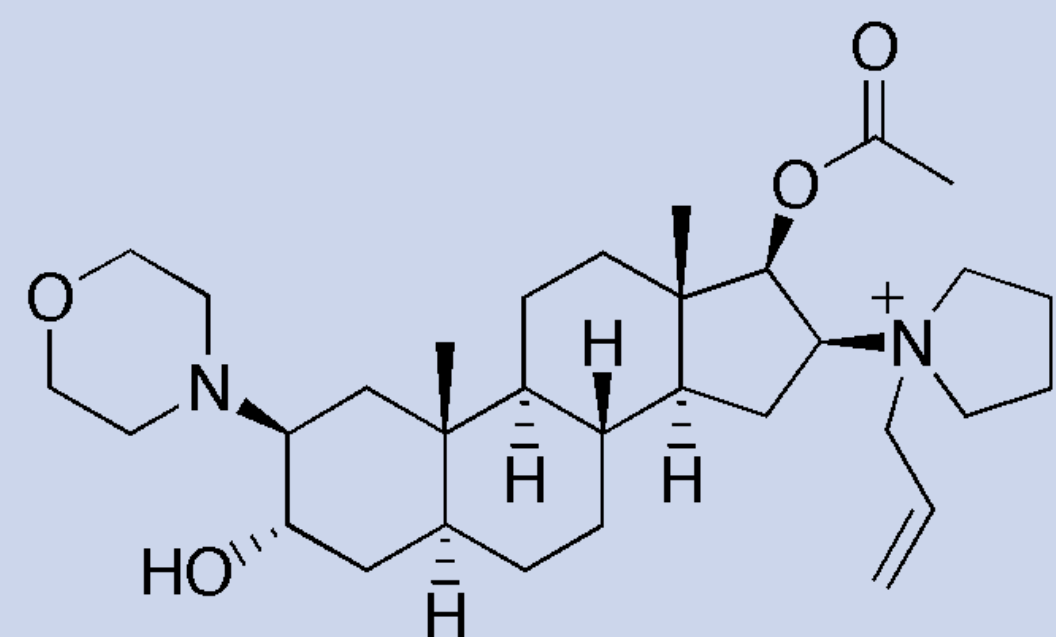
The purpose of this study is to investigate the refrigerated stability of these drugs when diluted by various factors and stored under refrigerated conditions.

Stability was investigated over a 14 day period using liquid chromatographic-tandem mass spectrometric (LC-MS/MS) determination of the stored drugs versus freshly prepared reference standards.

Cisatracurium (shown as besylate)
[M+2H⁺] m/z = 464.29



Rocuronium
[M+H⁺] m/z = 529.42



Vecuronium (shown as bromide)
[M+H⁺] m/z = 279.23

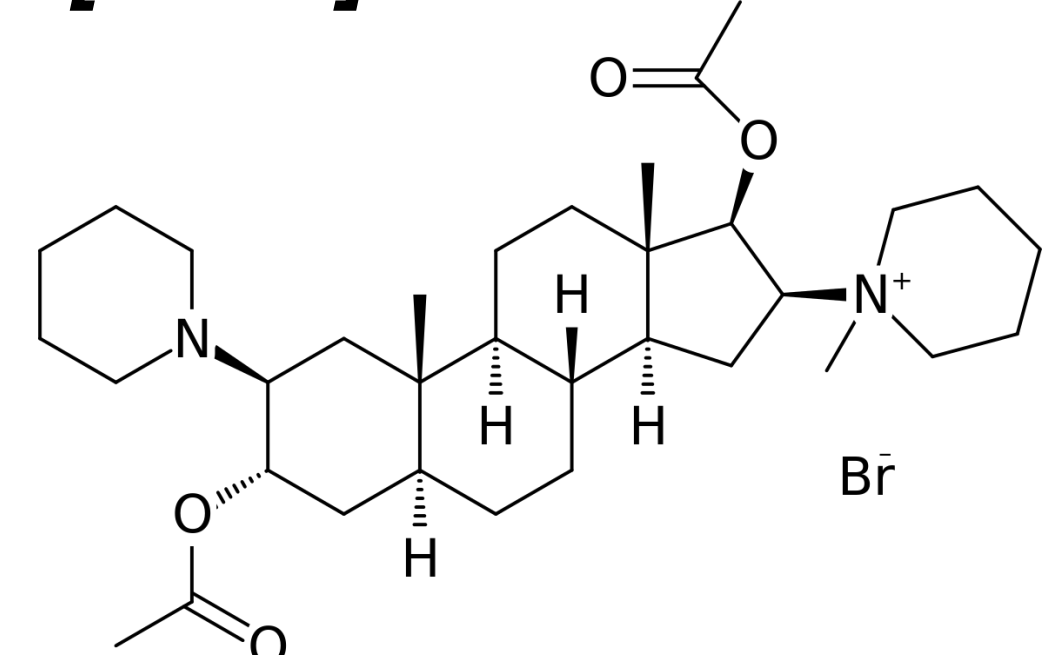


Figure 1: Chemical structures of neuromuscular blocking agents included in dilution investigation

Methods

Dilutions of NMBAs were prepared by serial dilution in normal saline by factors of 10x, 100x, 1,000x, 10,000x, and 100,000x; (n = 5 of each)

Diluted drug preparations were stored in laboratory refrigerator and 1 mL aliquots were periodically removed over a 14 day storage period

Potency of stored dilutions was compared to a fresh reference standard using LC-MS/MS

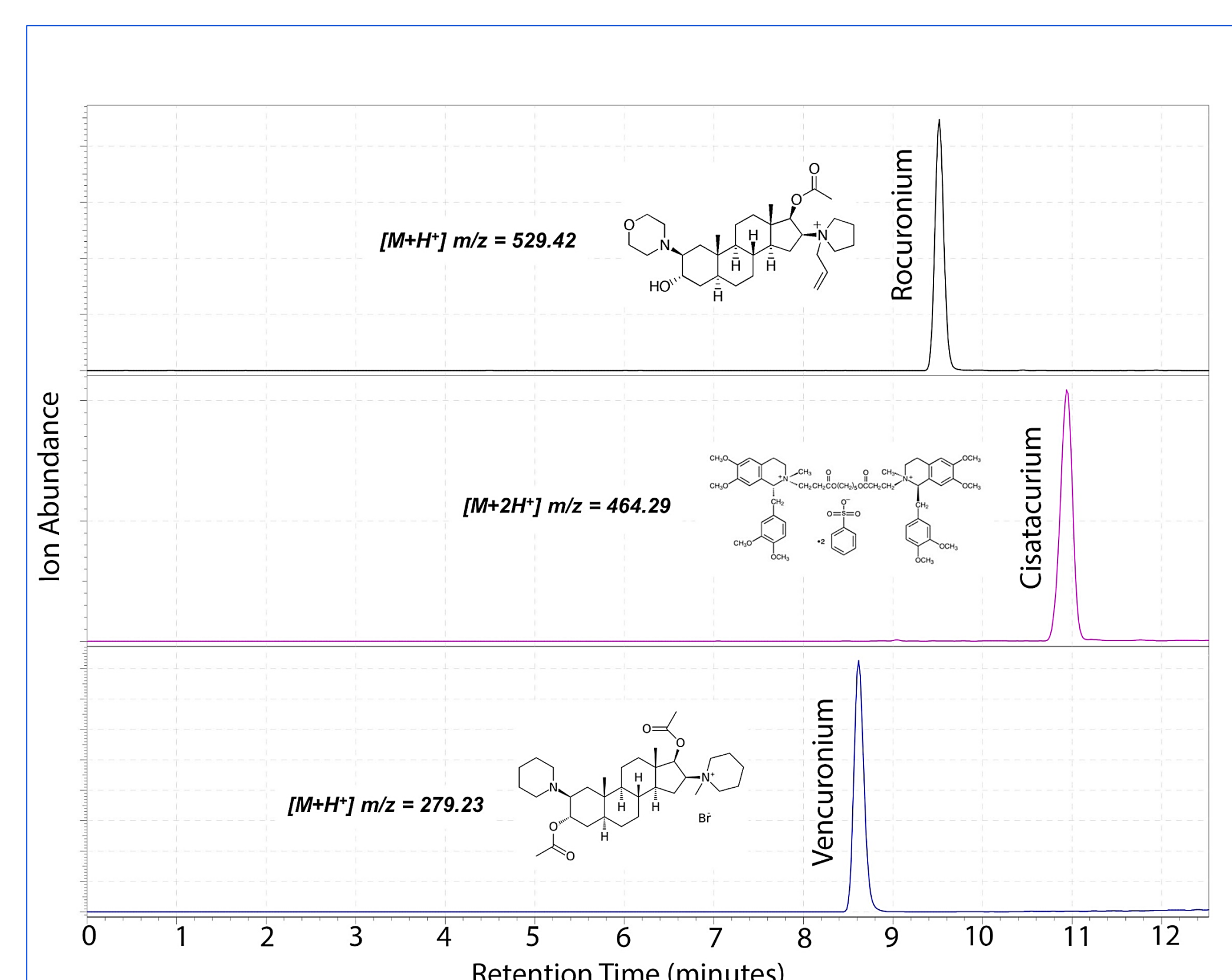


Figure 2: Extracted ion chromatogram of rocuronium, cisatracurium, and vecuronium diluted in saline (100x dilution shown)

LC-MS/MS Parameters:

Column: Agilent Zorbax Eclipse XDB-C18 column (4.6 x 150mm; 3.5 micron particle size), 50°C

Gradient Separation: Using 0.01% trifluoroacetic acid (TFA) (A) and acetonitrile (B), 10 – 90% B over 15 minutes, flow rate = 0.400 mL/min

Detection: Direct MS2 channels relative to specific drugs (see Figure 1)

Results

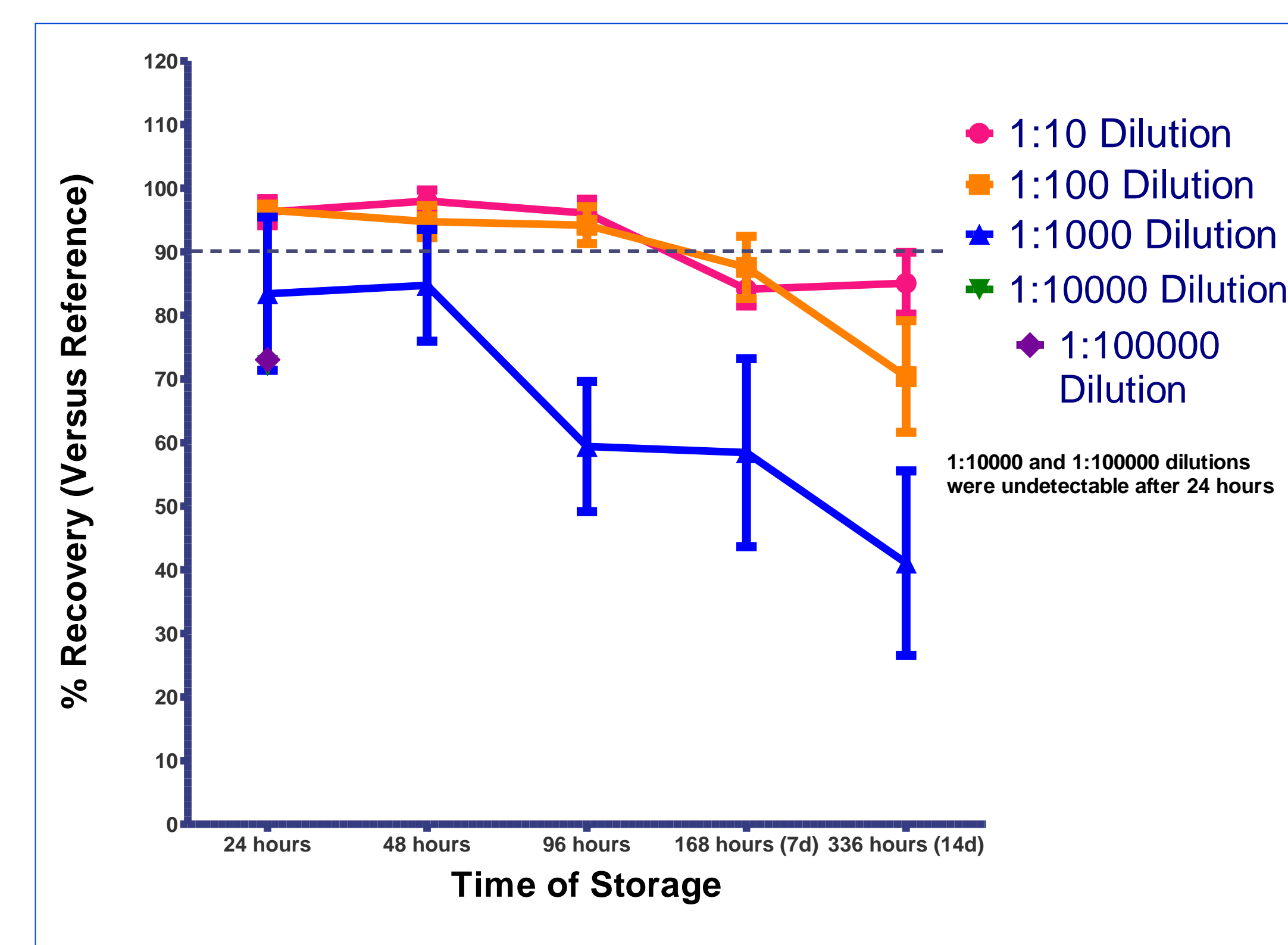


Figure 3: Percent recovery of diluted cisatracurium stored in refrigerated temperatures (4.00°C ± 0.28)

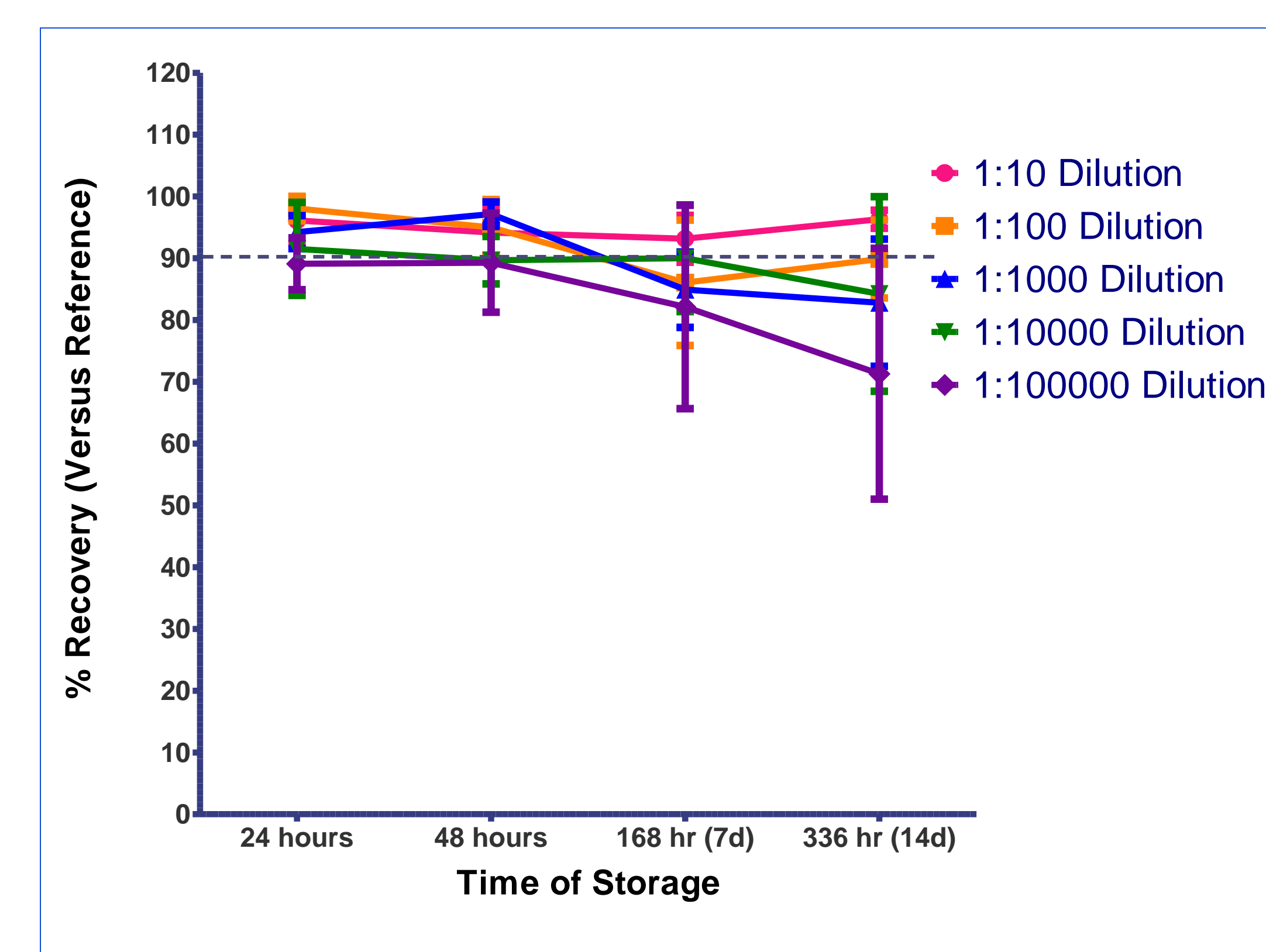


Figure 4: Percent recovery of diluted rocuronium stored in refrigerated temperatures (3.88°C ± 0.15)

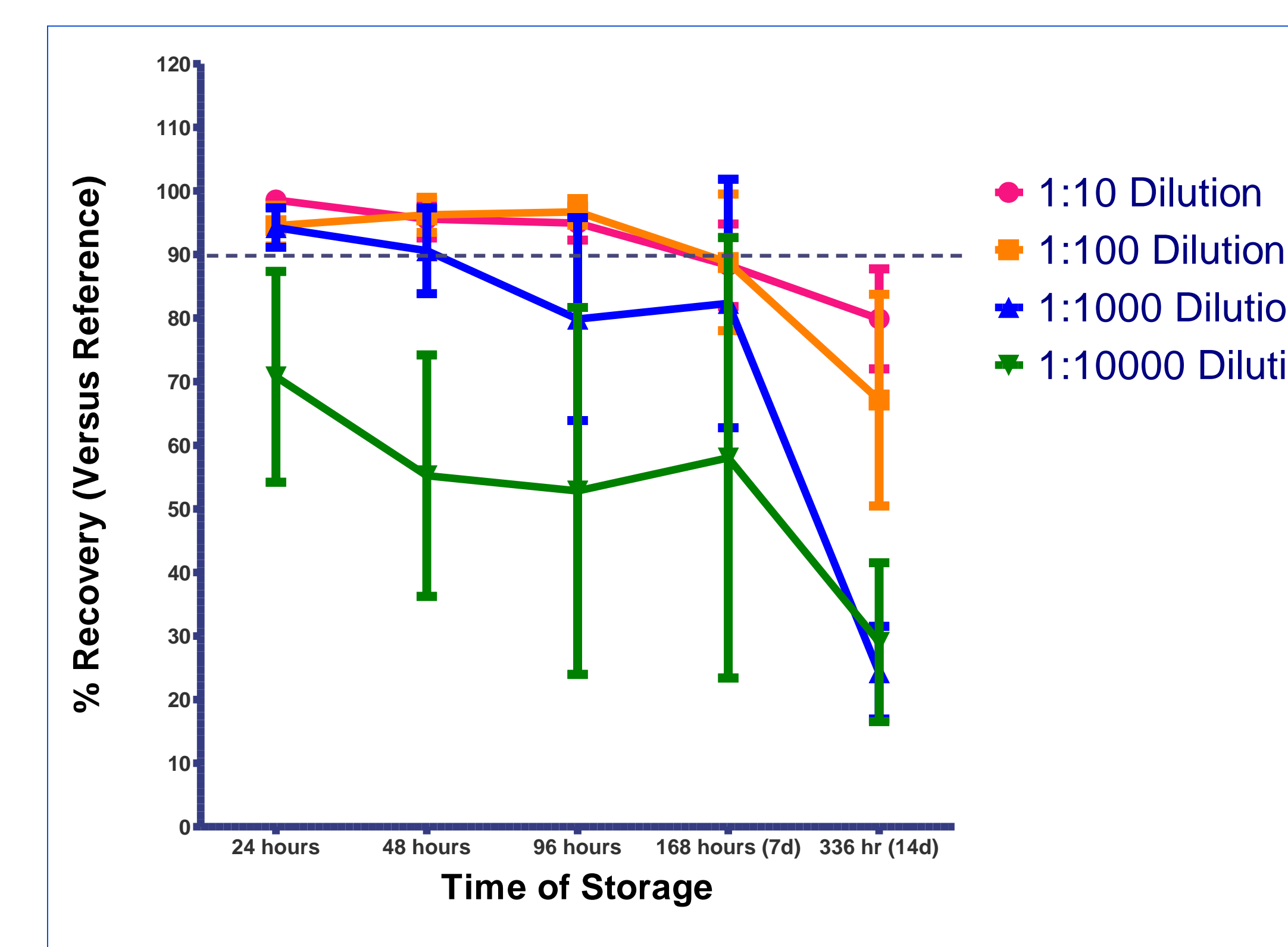


Figure 5: Percent recovery of diluted vecuronium stored in refrigerated temperatures (3.80°C ± 0.17)

Results

The results are expressed as beyond-use-date (BUD), which is defined as 90 – 100% recovery of the drug versus a reference.

Drug	1:10	1:100	1:1000	1:10K	1:100K
Cisatracurium	96hr	96hr	<24hr	<24hr	<24hr
Rocuronium	48hr	48hr	48hr	<24hr	<24hr
Vecuronium	96hr	96hr	24hr	<24hr	unknown

Table 1: Summary of recommended BUD for dilutions of study drugs in saline, stored in refrigerated temperatures

- Both cisatracurium and vecuronium can be prepared and stored up to 96 hours at the 10x and 100x dilution levels
- Rocuronium has a slightly shorter BUD for the 10X and 100x dilution (48 hours), but the 1000x dilution lasts longer than the other study drugs
- Higher dilution factor preparations have the most limited stability, and should be used immediately

Conclusions

The stability of cisatracurium, rocuronium, and vecuronium in saline decreases with higher dilution factors. Additionally, the variability between study samples (as reflected by standard deviation) increases with higher dilutions and with time. Dilutions of 10x and 100x were most stable for all of these drugs. Limitations in long-term stability of these drugs in aqueous solution is likely due to their vulnerability to hydrolysis.

Acknowledgements

The authors would like to acknowledge The Bill Gatton College of Pharmacy at East Tennessee State University for funding associated with this project.