

Chemical Stability Testing of Solutions for Intraventricular Irrigations via IRRFlow Ventricular Drain System

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Abstract

Purpose: Advances have been made with delivery of medications via continuous intrathecal irrigating ventricular drains such as IRRFlow (IRRAS). Medications including vancomycin, tobramycin, daptomycin and nicardipine are currently being used as ventricular irrigations via the IRRFlow device. The purpose of this study was to evaluate the chemical stability of minute concentrations of daptomycin, nicardipine, tobramycin, and vancomycin for administration via IRRFlow intrathecal catheters. **Methods:** Commercially available formulations of daptomycin, nicardipine, tobramycin, and vancomycin were each diluted in separate normal saline (NS) 1000 mL bags to final concentrations of daptomycin 2 mg/1000 mL NS, nicardipine 2.5 mg/1000 mL NS, tobramycin 4 mg/1000 mL NS, and vancomycin 4 mg/1000 mL NS. Samples from each compound were transferred into 2.5 mL glass vials and evaluated in triplicate fashion using ultra-performance liquid chromatography and tandem mass spectrometry (LC-MS/MS). Each injection was analyzed in comparison to its respective calibration curve and a mean result for each time point was determined. The concentration of the samples was tested at 0, 6 and 12-hours for vancomycin, daptomycin, and tobramycin and 0, 4 and 8-hours for nicardipine. All irrigations were kept at room temperature and were not protected from light. **Results:** All samples tested were found to be chemically stable at various testing time points. Daptomycin retained a mean of 94.3% of initial concentration at 12 hours while tobramycin retained 93.1% of its initial concentration at 12 hours. Vancomycin samples were found to be 92.9% of initial concentration at 12 hours and nicardipine maintained a mean of 90.6% of initial concentration at 8 hours. Future studies could assess these conditions to potentially further stability data. **Conclusion:** With use of LC-MS, we demonstrated that dilute concentrations of vancomycin, daptomycin, and tobramycin maintain at least 90% of initial concentration for 12 hours at room temperature, whereas nicardipine remained chemically stable for 8 hours at room temperature.

Keywords

compounding, critical care, drug stability, medication safety, neurology

Introduction

Use of intraventricular and intrathecal medications has been routine for decades since this route bypasses the blood brain barrier and ensures appropriate levels of drug in the cerebrospinal fluid. Intermittent boluses of medication into the intraventricular space via external ventricular drain has been used for multiple indications.¹⁻³ Continuous intrathecal infusions of baclofen, opiates and other medications via surgically implanted pumps are commonly used in practice for treatment of spasticity and pain. Compounding of these products requires extended periods of stability testing to be established due to the length of time patients go between refills of their surgically implanted intrathecal pumps. The storage requirements of these compounded products also must account for temperature of the body.⁴⁻⁷

Recently, advances have been made with delivery of medications via continuous intrathecal irrigating ventricular drains such as IRRFlow (IRRAS).⁸ Medications including vancomycin, tobramycin, daptomycin and nicardipine are currently being used as ventricular irrigations via the IRRFlow device. The indication for these irrigations ranges from treatment of ventriculitis to management of cerebral vasospasm associated with aneurysmal subarachnoid

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hemorrhage. Contrary to medications intended for use in implanted intrathecal pumps, IRRFlow irrigations reach the intrathecal space via an external ventricular catheter. The irrigations are hence stored at room temperature and are far more dilute than intrathecal pump products. Regardless of the type of intrathecal preparation, compounding and administration of these medications must be performed with attention to the potential complications such as over or under dosing and risk of infection when administering drugs via this route^{9,10}.

The concentration of medications in the irrigations must be carefully selected to be based on the amount of drug that could be delivered via the intraventricular route per day when irrigating. The IRRFlow device can irrigate up to a maximum of 180 mL/hour. At this rate, 24-hour drug to brain exposure must fall within the confines of previously published data which results in very dilute concentrations of the irrigants.¹¹⁻¹³ Given that previous stability studies have not analyzed such low concentrations of these drugs, the purpose of this paper was to provide evidence of chemical stability of these dilute compounds.

Methods

Preparation of Samples

All samples were prepared as Category 2 compounded sterile preparations in a USP-797 compliant ISO Class 5 hood within a cleanroom suite to be consistent with standard sterile compounding practice¹⁴. Three separate bags were compounded for testing on each drug. All samples were compounded and stored at room temperature for the entirety of testing. Stability testing methods, structure and results are displayed in accordance with published stability and compatibility guidelines.¹⁵ There was no means of protecting samples from light. Time points for testing samples were dictated by high-performance liquid chromatography (HPLC) calibration studies prior to testing. Preparation of samples was done in the following fashion.

A vial of Vancomycin 1 g (Vancomycin 1 g/vial, 10 mL vial, lot 7608977A; Mylan Institutional LLC Morgantown, WV, USA) was reconstituted with 10 mL of PF sterile water to a concentration of 100 mg/mL. An aliquot was prepared with 9 mL of PF normal saline (NS) and 1 mL of the 100 mg/mL reconstituted solution to a final concentration of 10 mg/mL. Lastly, 0.4 mL of the 10 mg/mL aliquot was injected into 1000 mL of normal saline (0.9% sodium chloride for injection, 1000 mL in polyvinyl chloride bag, Baxter International, Deerfield, IL, USA). The final concentration prepared was Vancomycin 4 mg/1000 mL normal saline.

Daptomycin 500 mg (Daptomycin for injection 500 mg/vial, 10 mL vial, lot: 3167787; Xellia Pharmaceuticals LLC Buffalo Grove, IL, USA) was reconstituted with 10 mL of PF

NS to prepare a 50 mg/mL concentration. An aliquot was then prepared by mixing 1 mL of 50 mg/mL daptomycin with 9 mL PF NS to create a 5 mg/mL concentration dilution. 0.4 mL of this 5 mg/mL dilution was injected into 1000 mL of NS (0.9% sodium chloride for injection, 1000 mL in polyvinyl chloride bag, Baxter International, Deerfield, IL, USA) to create a final concentration of Daptomycin 2 mg/1000 mL normal saline.

One milliliter of PF Nicardipine 2.5 mg/mL (Nicardipine 25 mg/10 mL, 10 mL vial, lot: 10002374; Hikma, Berkeley Heights, NJ, USA) was injected into 1000 mL NS (0.9% sodium chloride for injection, 1000 mL in polyvinyl chloride bag, Baxter International, Deerfield, IL, USA). The final concentration was nicardipine 2.5 mg/1000 mL normal saline.

Tobramycin 1.2 g (Tobramycin 1.2 g/vial, 30 mL vial, lot AT8778B; XGEN Pharmaceuticals DJB, Inc., Big Flats, NJ 14814, USA) was reconstituted with 30 mL of PF sterile water for a final concentration of 40 mg/mL. A 0.1 mL sample from this vial was injected into 1000 mL NS (0.9% sodium chloride for injection, 1000 mL in polyvinyl chloride bag, Baxter International, Deerfield, IL, USA) to prepare a final concentration of Tobramycin 4 mg/1000 mL normal saline. Of note, Tobramycin is also commercially available in a multidose vial in-solution; however, care must be taken to choose a preservative-free formulation for intraventricular preparation.

Sample Analysis

Standards for Vancomycin (>99.0%), Daptomycin (>99.0%), Tobramycin (>99.0%), and Nicardipine (>99.0%) were obtained from Sigma Aldrich (St. Louis, MO, USA). Optima[®] LC/MS grade water, Optima[®] LC/MS grade acetonitrile, and LC/MS grade formic acid were purchased from Fisher Scientific Chemicals (Fair Lawn, NJ, USA). Analytical columns, Accucore C₁₈, 2.6 μ m, 2.1 mm \times 50 mm (Part No. 17126-052130) were purchased from Thermo Fisher Scientific Inc. (San Jose, CA, USA) and Acquity BEH Amide Column, 1.7 μ m, 2.1 mm \times 50 mm (Part No. 186004800) was purchased from Waters Corporation (Milford, MA, USA).

Ultra-Performance Liquid Chromatography and Tandem Mass Spectrometry (LC-MS/MS) Methodology. A Thermo Fisher Scientific Q-Exactive mass spectrometer (MS), featuring a high-performance quadrupole precursor ion selection and subsequent collision induced dissociation fragmentation, with high resolution, accurate mass (HR/AM) Orbitrap detection, with a Vanquish Ultra-performance Liquid Chromatography (UHPLC) system for compound separation (Thermo Fisher Scientific Inc., San Jose, CA, USA) was used for the acquisition of mass-to-charge (*m/z*)

Table 1. Sample Columns.

Compound	Vancomycin	Daptomycin	Tobramycin	Nicardipine
Column	Thermo accucore C18	Thermo accucore C18	Waters acquity BEH amide	Thermo accucore C18
Column temperature (°C)	40.0	40.0	40.0	40.0
Sampler temperature (°C)	22.0	4.0	4.0	22.0
Flow rate (mL/min)	0.350	0.300	1.000	0.400
Gradient	0-0.8 min 95% A 0.8-1.8 min 95-10% A 1.8-3.8 min 10% A 3.8-3.9 min 10-95% A 3.9-5.2 min 95% A	0-2 min 70-5% A 2-3 min 5% A 3-3.1 min 5-70% A 3.1-5 min 70% A	0-0.5 min 5% A 0.5-2 min 5-40% A 2-3.5 min 40% A 3.5-3.6 min 40-5% A 3.6-5 min 5% A	0-0.5 min 90% A 0.5-3 min 90-10% A 3-3.5 min 10% A 3.5-3.6 min 10-90% A 3.6-5 min 90% A
MS inlet temperature (°C)	250	268	300	262
Probe heater temperature (°C)	418	438	512	425
Sheath gas (arbitrary units)	48	52	52	50
Auxiliary gas (arbitrary units)	12	14	18	12
Sweep gas (arbitrary units)	2	2	3	2
Spray voltage (kV)	3.5	3.5	3.8	3.4

Table 2. Selective Ion Monitoring.

Compound	Precursor ion adduct	Precursor ion (<i>m/z</i>)	Product ion (<i>m/z</i>)
Vancomycin	[M + 2H] ²⁺	724.7	144.1
Daptomycin	[M + 2H] ²⁺	810.9	339.2
Tobramycin	[M + H] ⁺	468.3	324.2
Nicardipine	[M + H] ⁺	480.2	315.1

measurements. Refer to Table 1 for UHPLC gradient elution parameters utilized for each analysis, where mobile phase A (A) consisted of 0.1% formic acid in water and mobile phase B (B) consisted of 0.1% formic acid in acetonitrile. MS instrument conditions for the tune file were optimized using the auto defaults in the XCalibur software suite for the respective UHPLC flow rates for each compound and are also listed in Table 1.

LC-MS/MS Methodology Evaluation/Sample Analysis. LC-MS/MS methods were developed for each compound and were evaluated to assess linearity, precision, and accuracy. Standard solutions were prepared in 0.9% saline for each compound with serial dilutions ranging from 2.0 mg/L to 5.3 mg/L for Vancomycin, 0.4 mg/L to 3.0 mg/L for Daptomycin, 2.8 mg/L to 4.8 mg/L for Tobramycin, and 0.25 mg/L to 3.5 mg/L for Nicardipine. Calibration curves were generated utilizing the concentration ranges of standards listed above and utilizing selective ion monitoring (SIM) mode to monitor specific precursor ions corresponding to the molecular weights of the target compounds. In addition, collision induced dissociation (CID) of the precursor ion was conducted to evaluate product ions to verify the identity of the compound by confirming the presence of characteristic product ions (Table 2).

Intensities for each serial dilution, injected in triplicate, were determined using the X-Calibur software suite by using exact mass comparisons for retention time (t_R) resolved mass spectra. Extracted ion chromatograms (XICs) were obtained for each respective compound and concentration where the monoisotopic mass for each was used to extract the chromatogram by summing the intensities for each m/z value across the t_R range (Figure 1).

Calibration curves were constructed by plotting the signal intensity of the monitored ions against the known concentrations ensuring the linearity of the methods with R^2 values of greater than .995. Triplicate injections of quality control samples (prepared at 80%, 100%, and 120% concentrations of the prepared samples) were also conducted to ensure accuracy and precision of each respective method. The linearity of each method (R^2) and results obtained for quality control samples are listed in Table 3.

Samples for each compound, prepared as referenced above, were transferred into 2.5-mL glass vials and injected in triplicate onto the UHPLC-MS. Each injection was analyzed in comparison to its respective calibration curve and a mean result for each time point was determined. XICs for each injection were obtained for each respective compound identical to each respective calibration curve utilizing SIM mode and confirmation of the peak of interest through

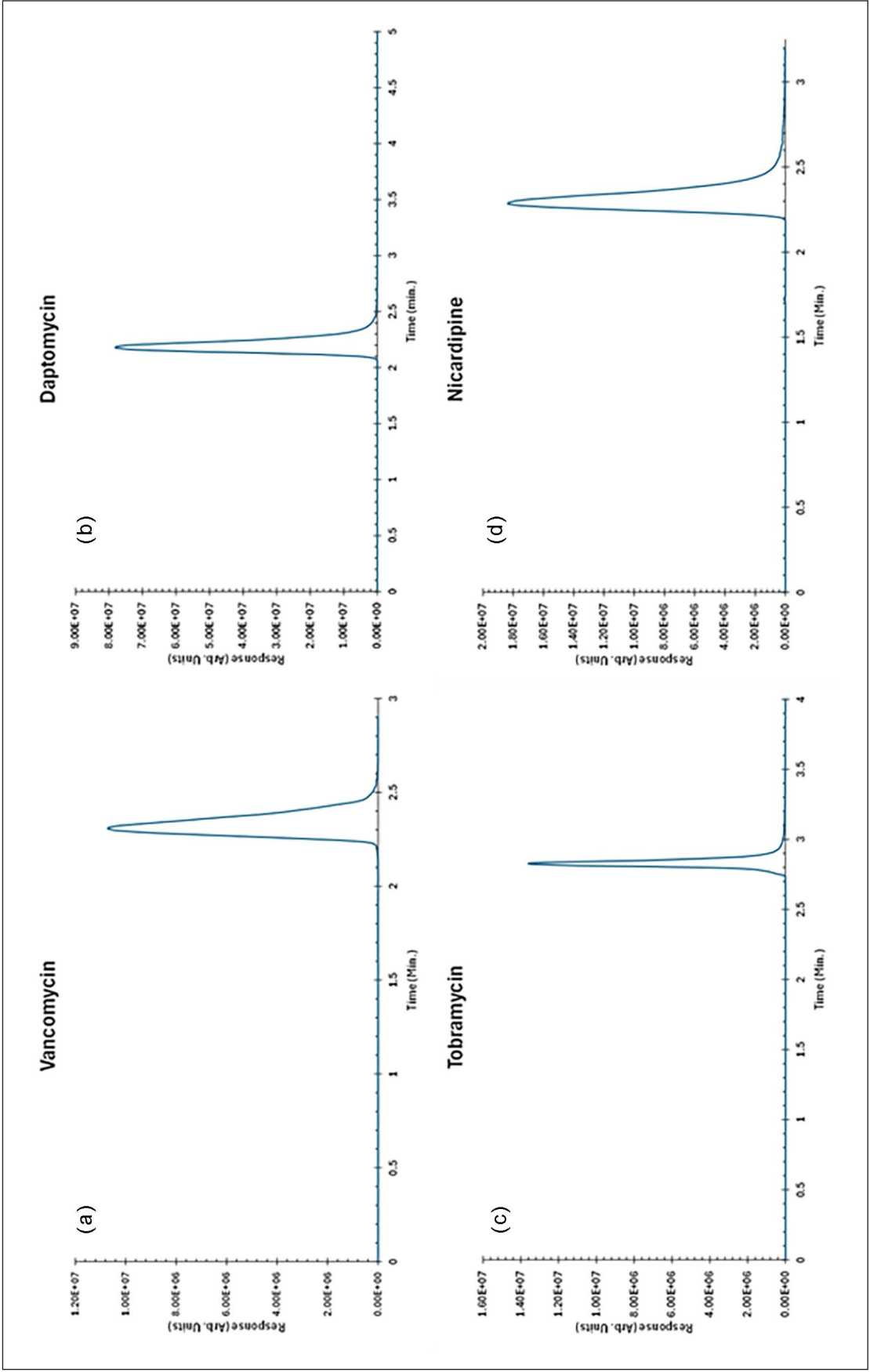


Figure 1. Extracted ion chromatograms of: (a) vancomycin, (b) daptomycin, (c) tobramycin, and (d) nicardipine.

Table 3. Linearity and Accuracy Evaluation.

Compound	Linearity R^2	Quality control samples (n = 3)		
		80%; recovery (%)—RSD*	100%; recovery (%)—RSD*	120%; recovery (%)—RSD*
Vancomycin	.9989	99.5—1.484	99.7—1.50	98.5—0.860
Daptomycin	.9975	98.7—0.601	99.2—0.954	98.6—0.590
Tobramycin	.9981	99.2—0.179	98.4—1.019	99.1—1.42
Nicardipine	.9952	98.5—1.76	98.7—0.599	99.0—0.947

*RSD: relative standard deviation = standard deviation/average.

Table 4. Vancomycin Results.

Sample	Time point (hours)	Concentration (mg/L)	% Initial concentration remaining
Mean concentration, n = 3 (% initial concentration): 3.98 mg/L (100%)			
Vancomycin Sample 1	0	3.96	100
Vancomycin Sample 2	0	3.98	100
Vancomycin Sample 3	0	3.99	100
Mean concentration, n = 3 (% initial concentration): 3.78 (95%)			
Vancomycin Sample 1	6	3.78	95.4
Vancomycin Sample 2	6	3.78	94.9
Vancomycin Sample 3	6	3.78	94.7
Mean concentration, n = 3 (% initial concentration): 3.69 (92.9%)			
Vancomycin Sample 1	12	3.72	93.9
Vancomycin Sample 2	12	3.67	92.2
Vancomycin Sample 3	12	3.70	92.7

Table 5. Daptomycin Results.

Sample	Time point (hours)	Concentration (mg/L)	% Initial concentration remaining
Mean concentration, n = 3 (% initial concentration): 2.09 mg/L (100%)			
Daptomycin Sample 1	0	2.10	100
Daptomycin Sample 2	0	2.09	100
Daptomycin Sample 3	0	2.08	100
Mean concentration, n = 3 (% initial concentration): 2.03 (97.0%)			
Daptomycin Sample 1	6	2.04	97.1
Daptomycin Sample 2	6	2.02	96.7
Daptomycin Sample 3	6	2.02	97.1
Mean concentration, n = 3 (% initial concentration): 1.97 (94.3%)			
Daptomycin Sample 1	12	2.01	95.7
Daptomycin Sample 2	12	1.97	94.3
Daptomycin Sample 3	12	1.93	92.8

detection of characteristic product ions via CID fragmentation analysis. The concentration of the samples at 6-hours and 12-hours for Vancomycin, Daptomycin, and Tobramycin and 4-hour and 8-hour for Nicardipine were compared to the initial sample preparation concentration (0-hour) to evaluate the stability of the compounded sample preparations consistent with typical usage. The results for each compound stability study are summarized in Tables 4 to 7.

Physical stability was assessed by visual evaluation of the samples for changes in color or the presence of any precipitate. This evaluation was conducted at each time point that samples

were collected for subsequent UHPLC/MS analysis. Solutions were considered stable if mean concentrations of n = 3 injections were greater than 90% of the initial sample concentration.

Results

LC-MS Methodology Validation

The LC-MS methods were validated for each compound to assess linearity, precision, and accuracy. Standard solutions were prepared in 0.9% saline for each compound with serial

Table 6. Nicardipine Results.

Sample	Time point (hours)	Concentration (mg/L)	% Initial concentration remaining
Mean concentration, n = 3 (% initial concentration): 2.50 mg/L (100%)			
Nicardipine Sample 1	0	2.52	100
Nicardipine Sample 2	0	2.49	100
Nicardipine Sample 3	0	2.48	100
Mean concentration, n = 3 (% initial concentration): 2.37 (94.7%)			
Nicardipine Sample 1	4	2.39	94.8
Nicardipine Sample 2	4	2.35	94.3
Nicardipine Sample 3	4	2.36	95.2
Mean concentration, n = 3 (% initial concentration): 2.26 (90.6%)			
Nicardipine Sample 1	8	2.27	90.0
Nicardipine Sample 2	8	2.25	90.4
Nicardipine Sample 3	8	2.27	91.5

Table 7. Tobramycin Results.

Sample	Time point (hours)	Concentration (mg/L)	% Initial concentration remaining
Mean concentration, n = 3 (% initial concentration): 4.00 (100%)			
Tobramycin Sample 1	0	3.99	100
Tobramycin Sample 2	0	4.00	100
Tobramycin Sample 3	0	4.01	100
Mean concentration, n = 3 (% initial concentration): 3.86 (96.5%)			
Tobramycin Sample 1	6	3.85	96.5
Tobramycin Sample 2	6	3.86	96.3
Tobramycin Sample 3	6	3.88	96.8
Mean concentration, n = 3 (% initial concentration): 3.72% (93.1%)			
Tobramycin Sample 1	12	3.66	91.7
Tobramycin Sample 2	12	3.74	93.5
Tobramycin Sample 3	12	3.77	94.0

dilutions ranging from 0.4 mg/L to 3.0 mg/L for Daptomycin, 0.25 mg/L to 3.5 mg/L for Nicardipine, 2.8 mg/L to 4.8 mg/L for Tobramycin, and 2.0 mg/L to 5.3 mg/L for Vancomycin. The method validation results are presented in Table 1.

All samples were found to be chemically stable within their respective time points. LC-MS results are presented for each compound. All concentrations remained above 90% of their initial concentration within the tested time points.

Discussion

To date, there have not been any published data highlighting the stability of such low concentrations of vancomycin, daptomycin, tobramycin and, nicardipine. These extremely dilute concentrations are clinically necessary for irrigation of ventricles when using continuous irrigating external ventricular drains such as the *IRRAflow* to limit overall drug exposure to the brain. When compounding these irrigations, measures must be taken in sterile preparation to ensure these minute concentrations are accurately measured and prepared properly. This includes use of dilutional techniques utilizing fresh vials of PF products and minimizing entries into each vial to reduce the potential for bacterial contamination. All

samples compounded for testing adhered to these practices and were performed in a USP-797 compliant cleanroom suite to best replicate clinical practice. As Category 2 compounded sterile preparations, the room temperature storage periods studied were within the 4-day beyond-use date limitation for sterile preparations using sterile ingredients in the absence of sterility testing. Given that the risk of chemical degradation, absorption of drug into PVC bags and uncertainty of microbiologic sterility is higher in dilute preparations, our paper established shorter beyond use dates to match with chemical stability.¹³

Previous stability data is readily available for all the compounds we studied; however, our samples were far more dilute. Numerous stability studies have been performed with vancomycin with the most dilute concentrations being 1 mg/mL.¹⁶ We found that vancomycin was stable at a concentration as low as 4 mcg/mL. Previous daptomycin stability showed that the medication was stable for 12 hours when diluted to 20 mg/mL in PVC at room temperature.¹⁷ Our data also demonstrated stability when daptomycin was diluted to 2 mcg/mL. Baaske et al. reported the lowest recorded concentration of nicardipine at 50 mcg/mL as compared to our data demonstrating stability at 2.5 mcg/mL.¹⁸ Lastly, our

results with tobramycin demonstrated stability of a 4 mcg/mL concentration which is more dilute than previous studies that validated 200 mcg/mL.¹⁹

Our study did have several limitations. Mainly, all irrigations were kept at room temperature and without protection from light. Future studies could assess these conditions to potentially extend stability data. Color change and inspection for precipitation was done visually and not by validated instruments due to availability. Our data did not assess microbiologic stability. However, all preparations were aseptically compounded with sterile ingredients within the ISO Class 5 hood in a USP-797 compliant cleanroom suite in accordance with the requirements of USP Chapter <797>, 2023 to maintain microbial sterility. Lastly, it would be possible, with our current resources, to study stability of the irrigations past 12 hours and we did not pursue this with our testing. While interesting, the clinical utility of this testing does not justify additional expense since the preparations are never infused beyond the 12-hour time point.

Conclusion

With use of LC-MS, we demonstrated that dilute concentrations of vancomycin, daptomycin, and tobramycin maintain less than 10% degradation for 12 hours at room temperature, whereas nicardipine remains chemically stable for 8 hours at room temperature. These results demonstrate beyond use dating guidance for safely compounding these dilute solutions for continuous ventricular irrigation.

Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Jeffrey Garavaglia is a pharmacist consultant for IRRAS.

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