Stability of 2 mg/mL Adenosine Solution in Polyvinyl Chloride and Polyolefin Infusion Bags

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Abstract

Adenosine is a potent endogenous mediator of vasodilation. Compounded sterile solutions of adenosine are used in cardiac catheterization lab to perform stress tests on the heart. These tests are used to determine the fractional flow reserve (FFR) and are commonly used in the management and diagnosis of cardiovascular conditions. The purpose of this study was to assess the physical and chemical stability of 2 mg/mL adenosine in 0.9% Sodium Chloride Injection, USP in polyvinyl chloride (PVC) and polyolefin infusion bags stored at room temperature (20°C–25°C) and under refrigeration (2°C–8°C). The compounding and analytical methods used in this study were very similar to those described in the prior publications from the authors' laboratory. To ensure a uniform starting concentration of all stability samples, a batch of 2 mg/mL adenosine solution was prepared and then packaged into empty PVC and polyolefin infusion bags. These stability samples were prepared in triplicate for each bag type and storage temperature (a total of 12 samples). The infusion bag samples were assessed for stability immediately after preparation and after 1 day, 3 days, 7 days, and 14 days. At each time point, the infusion bags were first visually inspected against a light background for color change, clarity, and particulates. Aliquots were drawn from each sample at each time point for pH analysis and high-performance liquid chromatography (HPLC) analysis. Over 14 days of storage at room temperature or refrigeration, no considerable change in visual appearance or pH was observed in any bags. All samples retained 90% to 110% of the initial drug concentration. No significant degradation peaks were observed in the HPLC chromatograms.

Keywords

cardiovascular, cardiac agents, drug stability, drug information

Purpose

Adenosine is a potent endogenous mediator of vasodilation. Compounded sterile solutions of adenosine are used in cardiac catheterization lab to perform stress tests on the heart. These tests are used to determine the fractional flow reserve (FFR) and are commonly used in the management and diagnosis of cardiovascular conditions.¹ In previous studies conducted in the authors' laboratory, stability and compatibility was established for 10 to 220 µg/mL adenosine solutions in commonly used intravenous (IV) diluents and infusion bags.^{2,3} The first study conducted assessed adenosine 50, 100, and 220 µg/mL solutions in polyvinyl chloride (PVC) infusion bags containing 0.9% sodium chloride injection or 5% dextrose injection stored at room temperature (23°C–25°C) or under refrigeration (2°C–8°C).¹ The second study conducted assessed adenosine 10 and 50 µg/mL solutions in polyolefin infusion bags using both diluents and storage conditions in the first study.² A forced-degradation study was conducted in Almagambetova et al.³ Neither study found any significant signs of degradation or loss. This study was a continuation of the previous studies but at a higher adenosine concentration

of 2 mg/mL. This high concentration became necessary due to the flow rate limitation on certain IV infusion pumps used for FFR lab procedures. The purpose of this study was to assess the physical and chemical stability of 2 mg/mL adenosine in 0.9% Sodium Chloride Injection, USP in PVC and polyolefin infusion bags stored at room temperature (20°C–25°C) and under refrigeration (2°C–8°C).

Methods

The compounding and analytical methods used in this study were very similar to those described in the prior publications from the authors' laboratory.^{2,3} The main differences are noted below. Adenosine Injection, USP, 90 mg/30 mL vials from Teva (NDC# 0703-8777-01, Lot# 31320652B) were

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Table 1. Stability of Adenosine 2 mg/mL in 0.9% Sodium Chloride Injection Stored in Polyvinyl Chloride (PVC) and Polyolefin Infusion Bags at Room Temperature (20°C–25°C) and Under Refrigeration (2°C–8°C) (n = 3).

Packaging type and storage temperature	Actual initial concentration (mg/mL)	% initial concentration remaining			
		1 day	3 days	7 days	14 days
PVC bag at room temperature	1.959 ± 0.0011	99.0 ± 0.5	98.2 ± 0.1	102.3 ± 1.5	104.8 ± 0.4
PVC bag under refrigeration	1.964 ± 0.0019	99.2 ± 0.6	97.1 ± 1.4	100.5 ± 2.1	102.4 ± 1.7
Polyolefin bag at room temperature	2.008 ± 0.0004	98.5 ± 0.5	97.5 ± 0.4	101.3 ± 3.0	101.6 ± 0.9
Polyolefin bag under refrigeration	1.981 ± 0.0031	99.7 ± 1.3	97.7 ± 0.7	102.8 ± 1.7	102.8 ± 0.4

Note. Data reported as mean of 3 samples under the same conditions ± standard deviation.

used as the drug source, and 0.9% Sodium Chloride Injection, USP from Baxter (NDC# 0338-0049-38, Lot# P332106) was used as the diluent. Sterile empty polyolefin bags (50-mL capacity) were obtained from Baxter (Product# 2B8019, Lot# UR15E27088). Sterile empty PVC bags were not available commercially; therefore, 50-mL PVC bags of 0.9% Sodium Chloride Injection, USP (Baxter, NDC# 0338-0049-31, Lot# P329979) were drained completely through the medication port before the filling of stability samples. To ensure a uniform starting concentration of all stability samples, a batch of 2 mg/mL adenosine solution was prepared by diluting 390 mL source adenosine solution with 195 mL diluent in a 1-L glass beaker. About 8% volume overage was included for the batch size to account for any potential loss of transfers. The 2 mg/mL adenosine solution was then packaged and sealed into the empty PVC and polyolefin bags, 45 mL each. These stability samples were prepared in triplicate for each bag type and storage temperature (a total of 12 samples). Five standard solutions were prepared from adenosine powder (Acros Organics, lot# A0263503) in deionized water. The standards were used to build a calibration curve and replicate samples were frozen on the first day. A set of standards was thawed prior to high-performance liquid chromatography (HPLC) analysis each day of the study.

The infusion bag samples were assessed for stability immediately after preparation and after 1 day, 3 days, 7 days, and 14 days. At each time point, the infusion bags were first visually inspected against a light background for color change, clarity, and particulates. A 1-mL aliquot was withdrawn from each bag using aseptic compounding technique. The bags were then resealed and returned to their respective storage conditions. For each aliquot sample, 0.1 mL was accurately transferred and diluted with 0.9 mL purified water for HPLC analysis.^{2,3} The pH of the remaining aliquot sample was measured and recorded.

Results and Discussion

At time zero, the 2 mg/mL adenosine solution in both bag types appeared clear, colorless, and free of particulates. The pH values of the samples ranged from 6.1 to 6.7. Over 14 days of storage at room temperature or refrigeration, no

considerable change in visual appearance or pH was observed in any bags. Based on the HPLC analysis results shown in Table 1, all samples retained 90% to 110% of the initial drug concentration. No significant degradation peaks were observed in the HPLC chromatograms.

Conclusion

Adenosine solutions of 2 mg/mL in 0.9% Sodium Chloride Injection, USP stored in 50-mL PVC and polyolefin infusion bags were physically and chemically stable for up to 14 days at room temperature or under refrigeration. Two important reminders must be made for the sterile compounding of adenosine IV bags for use in patients. First, 50-mL bags of 0.9% Sodium Chloride Injection, USP often contain >10% overfill. To obtain an accurate final drug concentration, it is recommended to withdraw the overfill volume prior to the addition of drug source solution. Second, pertinent USP <797> requirements must be followed to minimize microbial contamination during compounding.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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