Extended Stability of Epinephrine Hydrochloride Injection in Polyvinyl Chloride Bags Stored in Amber Ultraviolet Light-Blocking Bags

Hospital Pharmacy
2017, Vol. 52(8) 570–573
© The Author(s) 2017
Reprints and permissions:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/0018578717721121
journals.sagepub.com/home/hpx

Edward T. Van Matre¹, Kang C. Ho², Clark Lyda²,
Beth A. Fullmer², Alan R. Oldland², and Tyree H. Kiser¹

Abstract

Objective: The objective of this study was to evaluate the stability of epinephrine hydrochloride in 0.9% sodium chloride in polyvinyl chloride bags for up to 60 days. **Methods:** Dilutions of epinephrine hydrochloride to concentrations of 16 and 64 µg/mL were performed under aseptic conditions. The bags were then placed into ultraviolet light-blocking bags and stored at room temperature (23°C–25°C) or under refrigeration (3°C–5°C). Three samples of each preparation and storage environment were analyzed on days 0, 30, 45, and 60. Physical stability was performed by visual examination. The pH was assessed at baseline and upon final degradation evaluation. Sterility of the samples was not assessed. Chemical stability of epinephrine hydrochloride was evaluated using high-performance liquid chromatography. To determine the stability-indicating nature of the assay, degradation 12 months following preparation was evaluated. Samples were considered stable if there was less than 10% degradation of the initial concentration. **Results:** Epinephrine hydrochloride diluted to 16 and 64 µg/mL with 0.9% sodium chloride injection and stored in amber ultraviolet light-blocking bags was physically stable throughout the study. No precipitation was observed. At days 30 and 45, all bags had less than 10% degradation. At day 60, all refrigerated bags had less than 10% degradation. Overall, the mean concentration of all measurements demonstrated less than 10% degradation at 60 days at room temperature and under refrigeration. **Conclusion:** Epinephrine hydrochloride diluted to 16 and 64 µg/mL with 0.9% sodium chloride injection in polyvinyl chloride bags stored in amber ultraviolet light-blocking bags was stable up to 45 days at room temperature and up to 60 days under refrigeration.

Keywords

epinephrine hydrochloride, sodium chloride, stability, injections, storage, concentration

Introduction

Epinephrine hydrochloride is a sympathomimetic agent and replicates the actions of the sympathetic nervous system.¹ Its potent β_1 , β_2 , and α_1 agonist properties lead to vasoconstriction and increase cardiac inotropy and chronotropy.² Due to these effects, epinephrine hydrochloride is commonly used for hemodynamic support in a variety of disease states particularly when bradycardia is present.^{3–5} Epinephrine hydrochloride can be administered as an intramuscular injection, an intravenous bolus, and/or intravenous infusion. Concentrated epinephrine hydrochloride, typically 1:1000 concentration (1 mg/mL), must be further diluted for intravenous administration. Epinephrine hydrochloride for intravenous infusion is commonly diluted to concentrations ranging from 16 to 64 µg/mL.

Epinephrine contains a catechol moiety which is susceptible to oxidative reactions catalyzed by ultraviolet light,

oxygen, increases in temperature, and basic conditions.⁶ Efforts to mitigate these degradation mechanisms include temperature control, minimizing air introduction during compounding, and storage of compounded solution within amber ultraviolet light-blocking bags. Previous stability studies have shown epinephrine hydrochloride at concentrations from 25 to 100 µg/mL are stable for at least 30 days within polyvinyl chloride bags at room temperature and under refrigeration.⁷ However, no stability-indicating studies

¹University of Colorado, Aurora, USA

²University of Colorado Hospital, Aurora, USA

Corresponding Author:

Tyree H. Kiser, Associate Professor, Department of Clinical Pharmacy, Skaggs School of Pharmacy and Pharmaceutical Sciences, University of Colorado, Anschutz Medical Campus, 12850 E. Montview Blvd, Mail Stop C238, Aurora, CO 80045, USA.

Email: ty.kiser@ucdenver.edu

have evaluated the stability of epinephrine hydrochloride in polyvinyl chloride bags for greater than 30 days.

The purpose of this study was to determine the physical and chemical stability of epinephrine hydrochloride at concentrations of 16 and 64 $\mu\text{g/mL}$ in 0.9% sodium chloride when stored at room temperature or refrigerated for 60 days while in amber ultraviolet light-blocking bags.

Methods

Sample Preparation

Dilution of epinephrine hydrochloride (epinephrine hydrochloride injection, 1 mg/mL, 30 mL vial, lot DT078G6; IMS Limited Brand, Danbury, Connecticut) to a nominal concentration of 16 and 64 $\mu\text{g/mL}$ was performed by the University of Colorado Hospital pharmacy under aseptic conditions in an International Standards Organization class 7 environment by adding 4 and 16 mg of epinephrine hydrochloride, respectively, to 246 and 234 mL of 0.9% sodium chloride for injection (0.9% sodium chloride for injection, 250 mL in polyvinyl chloride bag, lot C984294; Baxter Healthcare Corporation, Deerfield, Illinois). Accurate volumes were achieved by removing all 0.9% sodium chloride for injection from all polyvinyl chloride bags, and exact volumes of 0.9% sodium chloride for injection were then injected into the polyvinyl chloride bags utilizing a graduated syringe. This preparation was repeated 6 times for each concentration. The prepared solutions were then placed in amber ultraviolet light-blocking bags (Amber UV Protection Zippit Bags; Health Care Logistics, Circleville, Ohio). The bags were then refrigerated (3°C - 5°C) or stored at room temperature (20°C - 25°C) under normal florescent lighting. Refrigerated samples were allowed to warm to room temperature before sampling. No external source of heat was used to warm the bags. Three bags for each of the storage conditions were assessed for physical and chemical stability over 60 days. Stability was assessed on days 0, 30, 45, and 60. Sterility of the samples was not assessed.

Physical Evaluation

Physical stability of epinephrine hydrochloride was assessed by visual examination. Solutions were evaluated against black and white backgrounds for visible particulate matter, cloudiness, and color change. The pH was assessed on day 1 and at the time of high-performance liquid chromatographic analysis.

High-Performance Liquid Chromatographic Analysis

Epinephrine concentrations were determined using high-performance liquid chromatography (HPLC) with ultraviolet light detection based on a previously published method,⁷ with only minor modifications made. The HPLC system consisted of an autosampler (Model 508 autosampler; Beckman Coulter,

Fullerton, California), a delivery pump (Model 118 delivery module; Beckman Coulter), a C_{18} column (Phenomenex Luna 5- μm C_{18} 150 $\times$ 4.6-mm column, serial 80836-8, batch 5291-32; Phenomenex, Torrance, California) with a guard column (guard column containing $\mu\text{Bondapak C}_{18}$ 10- μm inserts, lot 0201342791; Waters Corporation, Milford, Massachusetts), a variable wavelength ultraviolet light detector set to 273 nm (Model 166 detector; Beckman Coulter), a controller (32 Karat software, version 5.0; Beckman Coulter), and a solvent waste container. The mobile phase consisted of an 88:2:10 (v/v/v) mixture of water, acetonitrile, and a 100 mmol/L solution of ammonium acetate at a pH of 7.20. The flow rate was set at 0.75 mL/min. Analytical grade epinephrine hydrochloride powder (Epinephrine Hydrochloride, $\geq 98\%$ pure, 329-63-5; Sigma-Aldrich, St. Louis, Missouri) was used for validation and quality control of the HPLC assay. Epinephrine hydrochloride samples (20 μL) were then injected into the HPLC system for analysis. Unknown compounds (assumed to be sodium chloride, chlorobutanol, sodium metabisulfite, and sodium hydroxide) eluted between 1.2 and 3.5 minutes, and epinephrine hydrochloride eluted at 5.3 minutes. These unidentified compounds did not interfere with the detection or quantitation of epinephrine hydrochloride by the HPLC method used in this study.

Chromatogram peak heights were used to determine epinephrine hydrochloride concentrations. All samples for each storage condition were assayed in triplicate. Calibration of the HPLC system was performed by construction of a standard curve using 11 known concentrations of epinephrine hydrochloride (range, 0-100 $\mu\text{g/mL}$) and was conducted on each of the 4 study days. Coefficients of determination (r^2) for the standard curve were 0.95 or greater for the entire study. Our assay met the best practice standards set for bio-analytical method validation.⁸

To demonstrate the stability-indicating nature of the assay, passive long-term degradation of epinephrine hydrochloride was accomplished by keeping all prepared bags at room temperature in amber ultraviolet light-blocking bags for 12 months following the 60-day stability study. The samples had a mean pH of 4.42 ± 0.02 for the 16 $\mu\text{g/mL}$ concentration and a mean pH of 4.02 ± 0.04 for the 64 $\mu\text{g/mL}$ concentration at the time of degradation evaluation. Samples injected into the HPLC system showed a reduction of approximately 25% in the epinephrine hydrochloride chromatographic peak and the development of new peaks, representing apparent degradation products. These unidentified degradation products did not interfere with the detection or quantitation of epinephrine hydrochloride by HPLC method used in this study.

Stability Analysis

The percentage of epinephrine hydrochloride remaining at each time point was determined. Samples were considered stable if there was less than 10% degradation of the initial concentration.

Table 1. Stability of Epinephrine Hydrochloride in 0.9% Sodium Chloride Injection.

Epinephrine hydrochloride concentration	Storage conditions	Actual initial drug concentration ($\mu\text{g/mL}$)	% initial concentration remaining		
			Day 30	Day 45	Day 60
16 $\mu\text{g/mL}$	Room temperature	16.2 ± 0.8	97.4 ± 1.4	95.8 ± 3.2	91.4 ± 2.8
	Refrigeration	16.3 ± 0.5	98.2 ± 1.1	96.9 ± 2.9	94.3 ± 2.5
64 $\mu\text{g/mL}$	Room temperature	64.7 ± 1.4	99.1 ± 1.7	95.8 ± 2.9	92.6 ± 3.7
	Refrigeration	64.8 ± 1.3	98.9 ± 1.9	97.9 ± 2.4	95.7 ± 2.7

Results

Epinephrine hydrochloride diluted to 16 and 64 $\mu\text{g/mL}$ with 0.9% sodium chloride injection was physically stable throughout the study. Solutions kept under refrigeration or at room temperature remained clear throughout the study. No precipitation was observed. The mean $\pm$ SD pH of the 16 $\mu\text{g/mL}$ concentration at baseline was 4.78 ± 0.06 , day 30 was 4.92 ± 0.07 , day 45 was 4.81 ± 0.03 , and day 60 was 4.70 ± 0.05 . The mean $\pm$ SD pH of the 64 $\mu\text{g/mL}$ concentration at baseline was 4.40 ± 0.06 , day 30 was 4.45 ± 0.01 , day 45 was 4.34 ± 0.03 , and day 60 was 4.31 ± 0.04 .

The results of the HPLC analysis are shown in Table 1. Minimal degradation was seen in both storage conditions and epinephrine hydrochloride concentrations at day 30, and less than 10% degradation was seen at day 60 for both concentrations and storage conditions. No new degradation peaks were observed, and concentrations of the unidentified peaks did not increase.

Discussion

The manufacturer of epinephrine hydrochloride recommends that unopened vials of epinephrine hydrochloride be stored at controlled room temperature.¹ Opened multi-dose vials are to be stored at controlled room temperature and discarded within 30 days of initial use, or earlier if precipitation or discoloration occurs. Compounded epinephrine hydrochloride solutions should be stored in ultraviolet light-blocking bags. This is an essential storage step to ensure stable epinephrine hydrochloride concentrations by minimizing oxidation of the catechol functional group.⁶ Carr and colleagues utilized a stability-indicating HPLC assay to evaluate epinephrine hydrochloride diluted in 5% dextrose in water to concentrations of 25, 50, and 100 $\mu\text{g/mL}$ at room temperature and refrigeration. Ninety-three percent or greater of the epinephrine hydrochloride concentrations were retained for both storage environments at day 30.⁷ To the authors' knowledge, no current data are published utilizing a stability-indicating methodology regarding epinephrine hydrochloride stability in 0.9% sodium chloride. The present study showed that all refrigerated bags at both concentrations retained greater than 90% epinephrine hydrochloride concentration out to 60 days and all room temperature bags at both concentrations retained greater than 90% epinephrine hydrochloride concentration

out to 45 days. Overall, the mean concentration in all storage conditions was greater than 90% of the original concentration at 60 days for all storage conditions. Despite this extended stability for 30 and 60 days based on product environment, the sterility of the prepared epinephrine hydrochloride solution must be assessed according to the standards in chapter 797 of the *U.S. Pharmacopeia* (USP).⁹

Due to the inexpensive cost of epinephrine hydrochloride, a cost minimization analysis was not conducted in this study. This stability study allows for a 31-day room temperature shelf life or a 46-day refrigerated shelf life, given the need for a 14-day sterility assessment for low-risk batched products per USP 797 requirements. Epinephrine hydrochloride bags can be batched centrally and placed within automated dispensing cabinet at desired locations or stored in satellite pharmacies within the facility. This proximity to the patient allows for the clinical team to have rapid access to epinephrine hydrochloride infusions, reducing the amount of time to drug delivery and administration. The ability to batch epinephrine hydrochloride may possibly reduce drug waste and medication errors due to improper dilution of the drug.

Conclusion

Epinephrine hydrochloride diluted to concentrations of 16 and 64 $\mu\text{g/mL}$ with 0.9% sodium chloride injection in ultraviolet light-blocking bags was stable for 45 days at room temperature and 60 days when refrigerated.

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.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

References

1. Epinephrine [package insert]. Chestnut Ridge, NY: Par Pharmaceutical Companies, Inc. September 2016.
2. Lipman J, Roux A, Kraus P. Vasoconstrictor effects of adrenaline in human septic shock. *Anaesth Intensive Care*. 1991;19(1):61-65.

3. Dellinger RP, Levy MM, Rhodes A, et al. Surviving sepsis campaign: international guidelines for management of severe sepsis and septic shock: 2012. *Crit Care Med*. 2013;41(2):580-637.
4. Unverzagt S, Wachsmuth L, Hirsch K, et al. Inotropic agents and vasodilator strategies for acute myocardial infarction complicated by cardiogenic shock or low cardiac output syndrome. *Cochrane Database Syst Rev*. 2014(1):CD009669.
5. Zilberstein J, McCurdy MT, Winters ME. Anaphylaxis. *J Emerg Med*. 2014;47(2):182-187.
6. Hoellein L, Holzgrabe U. Ficts and facts of epinephrine and norepinephrine stability in injectable solutions. *Int J Pharm*. 2012;434(1-2):468-480.
7. Carr RR, Decarie D, Ensom MH. Stability of epinephrine at standard concentrations. *Can J Hosp Pharm*. 2014;67(3):197-202.
8. van de Merbel N, Savoie N, Yadav M, et al. Stability: recommendation for best practices and harmonization from the Global Bioanalysis Consortium Harmonization Team. *AAPS J*. 2014;16(3):392-399.
9. The USP Compounding Expert Committee. Pharmaceutical compounding—sterile preparations (general information chapter 797). In: *The United States Pharmacopeia, 27th rev., and the National Formulary*. 22nd ed. Rockville, MD: U.S. Pharmacopeial Convention; 2004:2350-2370.