Stability of Procainamide Injection in Clear Glass Vials and Polyvinyl Chloride Bags

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Abstract

Objectives: The objective of this study was to evaluate the chemical stability of procainamide hydrochloride, 100 mg/mL, when repackaged in clear glass vials or diluted to 3 mg/mL with normal saline and packaged in polyvinyl chloride (PVC) bags when stored at either 23°C and exposed to light (ETL) or 5°C and protected from light (PFL).

Methods: Solutions were assayed using a stability-indicating high-performance liquid chromatography method. Samples (5 mL) were collected from triplicate containers on days 0, 7, 14, 21, 28, 56, 91, and 193. Color/clarity and pH changes were also monitored at each time interval.

Results: During the study, all samples remained clear and there was only a slight pH change. The color of the solutions stored at 23°C intensified but did not correlate with a significant decrease in concentration, while solutions stored at 5°C remained unchanged. Solutions repackaged in glass vials were stable for 193 days when stored at 23°C and ETL or 5°C and PFL. When further diluted to 3 mg/mL with normal saline and packaged in PVC bags, procainamide was also stable for 193 days at either 23°C and ETL or 5°C and PFL.

Conclusions: The stability of procainamide, 100 mg/mL, repackaged in clear glass vials was 193 days when stored at either 23°C and ETL or 5°C or PFL. If diluted further to 3 mg/mL with normal saline and packaged in PVC bags, the drug was also stable for 193 days at either 23°C and ETL or 5°C and PFL.

Keywords

procainamide hydrochloride, normal saline, glass vials, polyvinyl chloride bags, drug stability, high-performance liquid chromatography

Introduction

The antiarrhythmic drug, procainamide, can be administered intravenously or orally to treat supraventricular and ventricular arrhythmias and to convert atrial fibrillation. *N*-acetylprocainamide, the active metabolite, is equipotent to the parent drug as an antiarrhythmic agent.

The stability of procainamide hydrochloride, when diluted in 5% dextrose in water (D5W) or normal saline (NS) to 2 to 4 mg/mL, is reported by the manufacturer to be 24 hours at room temperature or 7 days when refrigerated.¹ An earlier study reported the stability of procainamide when diluted in NS, 1 mg/mL, to be 32 hours in glass bottles.² The same study also reported the stability in D5W to only be 8 hours while 2 others studies^{3,4} report stability ranging from 4 to 24 hours. When diluted in D5W, the reported instability was due to possible hydrolysis or complexation of the drug with the sugar and occurs at a slower rate when under refrigeration and pH is adjusted.⁵⁻⁷ Unused vials of undiluted procainamide (500 mg/mL) cycled through temperatures ranging from –6°C to 54°C every 24 hours in ambulances were stable for 28 days.⁸ Procainamide hydrochloride is subject to oxidation causing the solution to darken from the normal colorless

to a slightly yellow color. During the manufacturing process, the air in vials is purged out with nitrogen,¹ but there is no information regarding the repackaging of the solution into clear glass vials.

This study was undertaken to determine the effects of repackaging solutions of procainamide hydrochloride (100 mg/mL) in clear glass vials when stored at either 23°C and exposed to light (ETL) or 5°C and protected from light (PFL). Also the physical compatibility and chemical stability of procainamide diluted with NS to 3 mg/mL and packaged in polyvinyl chloride (PVC) bags was evaluated at 23°C and ETL or 5°C and PFL. Chemical stability of the solutions was assessed using a validated stability-indicating high-performance liquid chromatography (HPLC) method. These data were required so that blinded containers could be prepared for an in-hospital clinical trial in an economical manner.

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Methods

Materials

Procainamide injection (Sandoz Inc, Boucherville, Canada), NS (Baxter Inc, Mississauga, Canada), sterile glass vials (Allergy Laboratories, Oklahoma City, Oklahoma), and PVC bags (Baxter Inc) were used to compound all sample solutions. Procainamide reference material (United States Pharmacopeia, Rockville, Maryland) was used to prepare stock solutions for validation and standard curves. Metronidazole powder (Professional Compounding Centers of America, London, Canada) was used to prepare the internal standard solution. All other chemicals used were HPLC or American Chemical Society (ACS) grade.

Physical Tests

Sample pH was recorded on days 0, 7, 14, 21, 28, 56, 91, and 193 using a calibrated pH meter (Fisher Scientific Model Accumet 25 pH meter; Fisher Scientific Ltd, Nepean, Canada). The instrument was calibrated each time before pH measurements were taken using buffers 4.00 and 7.00.

At each time period, color and clarity was monitored with the aid of a luminated 4× magnifying glass. Samples were observed against a black background for particulate matter and a white background for color change.

Sample Preparation

Stock solutions of procainamide, 100 mg/mL, were aseptically transferred to clear glass vials, in triplicate. Stock solutions were also further diluted with NS to a final concentration of 3 mg/mL and then packaged in PVC bags, in triplicate.

On day 0, samples (1 × 5 mL) were removed from each container and transferred to clean, dry test tubes. The glass vials and PVC bags were then stored at either 23°C and ETL or 5°C and PFL. This procedure was then repeated on days 7, 14, 21, 28, 56, 91, and 193. All samples were diluted further and analyzed by HPLC. Metronidazole (100 µL of 0.5 mg/mL) was added to each sample as an internal standard.

Chromatographic Conditions

Chemical assay was conducted using a modified literature HPLC assay method.⁹ The modification consisted of adding triethylamine (2 mL/L of 99% solution) and adjusting the pH of the final solution to 7.5 ± 0.1 with phosphoric acid. The column used was an analytical column (Phenomenex Luna 5µ C18 4.6 × 250 mm column, Serial No. 611960-66; Phenomenex Inc, Torrance, California). The HPLC system consisted of an isocratic pump (Shimadzu Model LC-10ATVP Delivery Module; Shimadzu Corp, Kyoto, Japan), photodiode array detector (Shimadzu Model SPD-M20A Photodiode Array Detector; Shimadzu Corp) set at 280 nm, and an autosampler

(Shimadzu Model SIL-20AC Autosampler; Shimadzu Corp) which injected 20 µL samples. The flow rate was set at 1.0 mL/min. Class-VP software (version 7.1, Shimadzu Scientific Instruments Inc, Columbia, MD) was used for data collection and analysis.

Assay Validation

Enough procainamide reference standard was accurately weighed out to prepare an approximately 0.2 mg/mL stock solution in HPLC water.

Samples of procainamide were stress tested to validate the stability-indicating ability of the HPLC assay method. Samples of procainamide stock solution were exposed to acid, alkali, an oxidizing agent, heat, or ultraviolet (UV) light. An acidic sample of solution was prepared by adding concentrated hydrochloric acid to 10 mL of stock solution of procainamide (pH ≈ 1.5) and heating in a dry heat block set at 65°C. An alkali degradation sample was prepared by adding 5N sodium hydroxide to 10 mL of procainamide stock solution (pH ≈ 11.6) and heating in a dry heat block set at 65°C. An oxidized sample was prepared by adding 0.2 mL of 30% hydrogen peroxide to 9.8 mL of procainamide stock solution while being kept at 23°C. A fourth sample was ETL generated from a UV lamp. A fifth sample was heated to 65°C to see the effects of exposure to heat. Samples were chromatographed, over time, to determine whether there were any degradation peaks that would interfere with the parent peak or internal standard.

The linearity over the concentration ranges of 0.005 to 0.04 mg/mL was determined. Peak purity and identification of the parent compound was determined for all the procainamide peaks in the degradation samples by UV multiwavelength analysis (280 nm and 220 nm) and spectral overlay (200 nm–350 nm).

Intraday variation was assessed by comparison of average areas ratios of 5 replicate injections at 3 separate time periods and then calculating the coefficient of variance (CV). The interday variation was accessed based on the CV for the slopes, linear coefficients, and the average area ratios from 5 separate days. Accuracy was determined from recovery samples assayed on 5 separate days. The limit of quantitation (LOQ) was defined as the concentration that generated a detectable peak while still retaining a linear relationship.

USP formulas were used to calculate relative standard deviation and tailing factors. Standard curve linearity (R^2) was calculated using Microsoft Excel 2010 software.

Triplicate sample results, assayed in duplicate, for each concentration and storage condition were averaged then compared with the day 0 values. Values are reported as an average percent of initial concentration remaining ± standard deviation. Day 0 values were set as 100% potency.

Solutions were considered to be stable if the concentrations remained greater than 90% or less than 110% of the initial (day 0) concentrations.

Table 1. Stability of Procainamide Hydrochloric Acid (100 mg/mL) Repackaged in Clear Glass Vials.

Temperature, °C	Initial concentration, ^a mg/mL	% of initial concentration remaining ^a					
		Day 7	Day 14	Day 28	Day 56	Day 91	Day 193
23 ^b	100.2 ± 0.13	96.5 ± 1.1	94.6 ± 1.9	98.4 ± 1.8	98.9 ± 1.4	97.7 ± 1.7	97.5 ± 1.0
5 ^c	94.7 ± 1.5	99.9 ± 1.0	99.6 ± 0.7	99.8 ± 1.1	100.0 ± 1.7	101.1 ± 0.7	99.5 ± 1.2

^aMean ± standard deviation (N = 6).**Table 2.** Stability of Procainamide Hydrochloric Acid (3 mg/mL) Diluted in Normal Saline Packaged in Polyvinyl Chloride Bags.

Temperature, °C	Initial concentration, ^a mg/mL	% of initial concentration remaining ^a						
		Day 7	Day 14	Day 21	Day 28	Day 56	Day 91	Day 193
23 ^b	2.9 ± 0.03	100.8 ± 2.1	100.9 ± 2.8	100.9 ± 1.3	98.9 ± 1.0	103.1 ± 0.6	107.5 ± 0.6	109.6 ± 2.0
5 ^c	3.0 ± 0.02	100.8 ± 1.1	100.0 ± 1.6	96.9 ± 0.7	98.6 ± 0.9	96.5 ± 2.0	100.9 ± 1.3	101.3 ± 1.1

^aMean ± standard deviation (N = 6).^bContainers were exposed to light.^cContainers were protected from light using brown ultraviolet bags.

Results

During the study, all samples remained clear. However, there was an increase in the yellow color of the solutions when stored at 23°C and ETL with the color appearing more intense for the solution in vials probably due to the higher concentration. There was no color change for solutions stored at 5°C and PFL. For containers stored at 5°C and PFL, there was a slight pH change (≈ 0.7 units). The change in pH of solutions stored at 23°C with ETL was less (≈ 0.4 units).

Several new peaks appeared in acidic, alkaline, oxidized, and UV samples; however, none would interfere with the parent or internal standard peaks (Figure 1). The retention time of the internal standard was 11.1 minutes. Heating the sample had the least effect on chemical stability only decreasing the concentration to 96.9% after 382 hours. Under acidic, alkaline, and oxidative conditions, the initial concentration decreased to 85.4%, 75.6%, and 83.9%, respectively. Exposure of procainamide to UV light caused a darkening in yellow color with time, and the concentration slowly decreased to 73.0% after 382 hours of exposure. UV multiwavelength and spectral overlay analysis confirmed that the procainamide peak in all degradation samples remained pure ($\geq 99\%$).

The procainamide standard curve remained linear ($R^2 > 0.99$) over the concentrations studied. Reproducibility of the method over a 31-hour period was 0.6% while the interday coefficients of variances were 1.5% (slope), 0.01% (linearity), and 1.8% (area ratio). The accuracy of the method was $99.0\% \pm 2.0\%$. The LOQ was determined to be 2 ng. All tailing factors were less than 2.

The mean results of the percent of initial concentration remaining for all storage conditions and concentrations have been summarized in Tables 1 and 2. The concentration of all

solutions remained above 94.6% when stored at either temperature for 193 days.

Discussion

All degradation samples produced faster eluting peaks with some peaks being common between all the degradation solutions. The UV conditions caused the greatest degradation of the procainamide. Acidic and oxidative conditions caused much less degradation while exposure to alkaline conditions caused the second most decrease in the initial concentration. Heating the solution had the least effect of all the degradation conditions.

The only stability data for procainamide diluted with NS² reported that 100% of the drug was still present after 32 hours storage at room temperature. Because there was no change in the concentration after 32 days, the first sample selection time of 7 days was chosen as a responsible first time period.

During the stability study, solutions stored at 23°C and ETL showed an increase in the darkening of the color; however, there was only a slight change in concentrations. The increase in the concentration of the solution packaged in the PVC bags after 28 days storage at 23°C and ETL may have been the result of loss of water from the bags under these conditions as this is a known phenomenon.¹⁰ The effect was not as apparent in the bags stored at 5°C.

The manufacturer packages the commercial solution in amber glass vials and several references^{11,12} recommend protecting procainamide from light, so some changes in the color could be expected over a short time period. According to the manufacturer (Sandoz Canada Inc, oral communication, September 2012) and the American Hospital Formulary System Drug Information,¹ the solution is packaged under

Figure 1. Sample chromatograms of procainamide hydrochloride and degradation products.

Note. Panel A represents a procainamide sample after 382 hours of exposure to acidic conditions, Panel B represents the alkaline-degraded procainamide sample after 310 hours, Panel C represents oxidized sample after 310 hours exposure, and Panel D represents the UV light exposed sample after 310 hours. Peak 1 is procainamide. mAu = milli absorbance units.

nitrogen to minimize the effect of exposure to air. In this study, the exposure to air in the vials may have been a contributing factor to the decrease in concentration and more so when stored at 23°C rather than when refrigerated. Storage under refrigeration is reported to retard the oxidation process.¹

It had previously been reported¹ that procainamide (2-4 mg/mL) was stable for 24 hours at room temperature and 7 days under refrigeration when prepared in D5W and NS. The beyond-use date of procainamide at 3 mg/mL when diluted in NS was extended to 193 days at both room temperature and 5°C. Procainamide that is repackaged in clear glass vials

was also found to be stable for 193 days. These beyond-use dates should only be used after appropriate assessment of sterility and contamination rates at the compounding facility are determined, as outlined in United States Pharmacopeia Chapter 797 (USP 797).¹³ Without this additional information, the maximum beyond-use dates are governed by the risk levels within USP 797.

Conclusions

The results from this study establish the stability of procainamide solution, 100 mg/mL, when repackaged in clear glass vials and stored at either 23°C and ETL or 5°C and PFL, to be 193 days. Subsequently when diluted further to 3 mg/mL in NS and packaged in PVC bags, the stability has been extended to 193 days when stored at either 23°C and ETL or 5°C and PFL.

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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