Stability of dexmedetomidine 4 μg/mL in polypropylene syringes

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Purpose. The results of a study to determine the long-term (up to 14 days) stability of diluted dexmedetomidine kept in polypropylene syringes under typical pharmacy storage conditions are presented.

Methods. Four samples of dexmedetomidine injection diluted to 4 μg/mL in 0.9% sodium chloride were prepared and divided into 25-mL portions for storage in syringes at ambient room temperature (20–25 °C) with light exposure or under refrigeration (5 °C) in darkness. At 24 and 48 hours, the percentage of the initial dexmedetomidine concentration remaining in all samples was assessed via high-performance liquid chromatography with diode-array detection; further stability testing of the refrigerated samples was performed on days 7 and 14. At each time point, the test samples were visually inspected for color, clarity, and signs of formation of particulate matter.

Results. As determined by chromatographic analyses, the samples of diluted dexmedetomidine stored in syringes at room temperature exhibited a loss of drug concentration of <10% over 48 hours; the refrigerated samples exhibited a loss of drug concentration of <5% over 14 days. All of the syringe-stored samples remained clear and colorless on visual inspection for the duration of the study.

Conclusion. Dexmedetomidine diluted to 4 μg/mL in 0.9% sodium chloride injection was stable for at least 48 hours at 20–25 °C and 14 days at 5 °C when stored in polypropylene syringes.

Index terms: Chromatography, liquid; Concentration; Dexmedetomidine hydrochloride; Diluents; Polypropylene; Refrigeration; Sodium chloride; Stability; Storage; Sympathomimetic agents; Syringes; Temperature

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Dexmedetomidine is a selective α_2-adrenergic agonist indicated for the initial sedation (less than 24 hours) of patients receiving mechanical ventilation in the intensive care unit (ICU) and for the procedural sedation of patients not receiving mechanical ventilation.[1] Dexmedetomidine was approved for ICU use by the Food and Drug Administration (FDA) in 1999, and studies demonstrating its safety and efficacy outside of critical care units led to the approval of a supplemental indication for procedural sedation in 2008. Although not approved by the FDA, the use of dexmedetomidine in pediatric patients and for periods longer than 24 hours is supported by published evidence.[2,3]

The use of dexmedetomidine in critically ill patients has increased during the past decade. The results of a cohort study indicated that dexmedetomidine was administered in 7.2% of continuous-infusion sedation procedures in 2007, compared with 2% of such procedures in 2001.[4] The increased use of dexmedetomidine has been observed at our home institution, a freestanding 289-bed pediatric facility, where 3231 dexmedetomidine infusions were dispensed in 2010, compared with 1778 dispensed infusions in 2008. The use of dexmedetomidine for sedation during radiological imaging studies and short procedures, coupled with longer durations of use in critically ill patients, has contributed to this increase. These trends of rising use prompted us to investigate the stability of dexmedetomidine 4 μg/mL in 0.9% sodium chloride injection. Although the package insert for dexmedetomidine does not contain extended stability data,[1] a representative of the drug's manufacturer has indicated 48-hour stability of 4-μg/mL dilutions in 0.9% sodium chloride injection at ambient room temperature (Tamayo W, Hospira, personal communication, 2011 Jul 12). To our

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knowledge, no stability studies of dexmedetomidine are reported in the literature. The advance preparation of syringes of prediluted dexmedetomidine, to be kept ready for use in anticipation of orders from prescribers, could expedite the delivery of the drug, enhance patient care, and improve the efficiency of pharmacy operations.

The purpose of the study described here was to determine the stability of dexmedetomidine diluted to 4 µg/mL in 0.9% sodium chloride injection using high-performance liquid chromatography (HPLC) with diode-array detection (DAD).

Analytical methods for the quantification of dexmedetomidine, alone or within various matrixes, using either gas chromatography or liquid chromatography coupled with mass spectrometry have been published.[5-7] The HPLC method used in our study was developed to determine the stability of a standard dexmedetomidine dilution under typical pharmacy storage conditions.

The administration or storage of dexmedetomidine using syringes with components containing natural rubber should be avoided due to the possibility of absorption.[1] Our study used commercially available, natural rubber-free, polypropylene syringes that are appropriate for syringe pump use.

Methods

Materials. Dexmedetomidine hydrochloride,[a] 0.9% sodium chloride for injection,[b] and syringes[c] were obtained commercially. HPLC-grade water,[d] methanol,[e] sodium phosphate,[f] and hydrochloric acid[g] were used in the preparation of the HPLC mobile phase. Forced-degradation studies were performed with sodium hydroxide,[h] hydrochloric acid,[g] hydrogen peroxide,[i] and heat (60 °C). Chromatographic analyses were conducted using an HPLC system with a quaternary pump,[j] an autosampler,[k] a thermostatted column compartment,[l] and a DAD system[m] with controlling software[n] and a 4.6 × 100 mm, 3.5-µm column.[o]

Chromatographic analysis. The concentration of dexmedetomidine was quantified by HPLC using a stability-indicating assay. The sample injection volume was 5 µL. Isocratic elution (1 mL/min) of dexmedetomidine was accomplished on the HPLC column with methanol and 10 mM sodium phosphate monobasic adjusted to a pH of 4[p] with 0.1 *N* hydrochloric acid (50:50, v/v) as the mobile phase. The column compartment was maintained at 25 °C. The detection wavelength was set at 210 nm. The retention time for dexmedetomidine was 2.3 minutes, with a total run time of 2.6 minutes.

A linear standard curve was constructed from dilutions of dexmedetomidine of 2, 3, 4, 5, and 6 µg/mL in 0.9% sodium chloride injection (r^2 = 0.9997). Precision of the analytical method was evaluated by assaying 10 replicate injections of dexmedetomidine 4 µg/mL. The resultant coefficient of variation was 0.99%. Blank injections of 0.9% sodium chloride injection were systematically included in the analysis.

Subjecting dexmedetomidine samples to heat, 0.1 *N* hydrochloric acid, and hydrogen peroxide for 24 hours did not result in the detection of decomposition peaks. The forced degradation of samples in 0.1 *N* sodium hydroxide resulted in an unidentified degradation peak at 1.5 minutes.

Four separate vials of commercially available dexmedetomidine were used to prepare four dilutions of 4 µg/mL in 0.9% sodium chloride injection; each of the 50-mL dilutions was divided into 25-mL portions, which were placed in separate polypropylene syringes[c] for storage at ambient room temperature (20–25 °C) exposed to light or under refrigeration (5 °C). The room-temperature samples were analyzed in triplicate initially and on days 1 and 2 after preparation, and the refrigerated samples were analyzed in triplicate initially and on days 1, 2, 7, and 14. A sample was considered stable if its dexmedetomidine concentration was >90% of the original concentration; triplicate determinations using duplicate quality-control samples (4 µg/mL) were performed on each day of analysis. The interday and intraday coefficients of variation were 1.6% and 0.5%, respectively.

Physical assessment. A visual inspection of the samples for particulate matter, clarity, and color against a light background and without instrumentation or magnification was conducted at each time point of analysis.

Results and discussion

All dexmedetomidine samples were stable under their respective storage conditions and remained clear and colorless on visual inspection for the duration of the study (Table 1).

The chromatographic peak at 1.5 minutes that had been observed in association with forced degradation by sodium hydroxide was not detected in any of the analyzed study samples. As the study progressed, an unidentified chromatographic peak at 1.9 minutes was detected in the samples and increased in prominence as the remaining percentage of the initial dexmedetomidine concentration diminished. Neither of the aforementioned chromatographic peaks (at 1.5 and 1.9 minutes) interfered with the dexmedetomidine peak, which eluted at 2.3 minutes. The DAD system was used to obtain peak spectra throughout the dexmedetomidine signal at 2.3 minutes. The ultraviolet spectrum for dexmedetomidine was consistent in all analyzed samples throughout the study period.

The study results indicate that assigning beyond-use dates for dexmedetomidine 4 µg/mL in 0.9% sodium chloride injection of 48 hours for

room-temperature storage and 14 days for refrigerated storage would be appropriate. Such practices would be consistent with sterility guidelines for low-risk-level compounded sterile preparations, as outlined in *The United States Pharmacopeia*.[8]

Conclusion

Dexmedetomidine diluted to 4 µg/mL in 0.9% sodium chloride injection was stable for at least 48 hours at 20–25 °C and 14 days at 5 °C when stored in polypropylene syringes.

Table 1.
Stability of Dexmedetomidine 4 µg/mL in 0.9% Sodium Chloride Injection

Storage Temperature (°C)	Mean ± S.D. Initial Conc.[a] (µg/mL)	% Initial Concentration Remaining[a]			
		1 Day	2 Days	7 Days	14 Days
20–25	3.97 ± 0.03	97.4 ± 1.4	95.1 ± 1.3	. . .[b]	. . .
5	3.96 ± 0.02	99.5 ± 1.4	99.8 ± 0.6	98.3 ± 2.6	97.9 ± 2.0

[a]Triplicate determinations of four samples.
[b]Not evaluated.

[a]Dexmedetomidine hydrochloride, 200 µg/2 mL, Hospira, Lake Forest, IL, lot 94-490-DK.
[b]0.9% sodium chloride injection, USP, Hospira, lot 04-194-JT.
[c]BD Luer-Lok syringe, 60 mL, BD, Franklin Lakes, NJ, ref. no. 309680.
[d]Water, HPLC grade, Fisher Scientific, Fair Lawn, NJ, lot 110757.
[e]Methyl alcohol for HPLC, Acros Organics, Morris Plains, NJ, lot B0520302.
[f]Sodium phosphate, monobasic monohydrate, 98+%, for analysis ACS, Acros Organics, lot A0292690.
[g]Hydrochloric acid, 0.1 *N*, Spectrum Laboratory Products, New Brunswick, NJ, lot YF1196.
[h]Sodium hydroxide, 0.1 *N*, Acros Organics, lot B00K6696.
[i]Hydrogen peroxide, 3%, AmerisourceBergen, Valley Forge, PA, lot B3224AC.
[j]1260 Infinity quaternary pump, Agilent Technologies, Santa Clara, CA, model G1311B.
[k]1260 Infinity standard autosampler, Agilent Technologies, model G1329B.
[l]1260 Infinity thermostatted column compartment, Agilent Technologies, model G1316A.
[m]1260 Infinity diode-array detector, Agilent Technologies, model G4212B.
[n]HPLC ChemStation, version B.04.03, Agilent Technologies.
[o]Zorbax Eclipse SDB-CN, 4.6 × 100 mm, 3.5-µm column, Agilent Technologies.
[p]pH 213 Microprocessor pH meter, Hanna Instruments, Ann Arbor, MI.

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