Clinical Trial/Experimental Study

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Stability study of dezocine in 0.9% sodium chloride solutions for patient-controlled analgesia administration

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Abstract

Background: Dezocine, a mixed agonist/antagonist of opioid receptors, has been used in iv patient-controlled analgesia (PCA) pumps for postoperative pain control. The aim of this study was to investigate the physicochemical stability of dezocine solutions in 0.9% sodium chloride for injection for PCA administration.

Methods: Solutions of dezocine (0.3, 0.45, or 0.6 mg/mL in 0.9% sodium chloride for injection) were stored in polyolefin bags and glass bottles. Their stabilities at storage conditions of 4°C for 14 days and 25°C for 72 hours were studied. For all preparations, physical characteristics (including pH, color, and presence of precipitates) were evaluated. Each preparation of dezocine was also analyzed using a stability-indicating high-performance liquid chromatography method. A solution was considered stable if it maintained at least 90% of its initial concentration.

Results: No notable changes in pH, color, or precipitation were observed in any of the prepared solutions over the testing period. All formulations maintained >97% of the initial dezocine concentration under the storage conditions evaluated.

Conclusions: Dezocine solutions at 0.3, 0.45, or 0.6 mg/mL in 0.9% sodium chloride for PCA administration were stable for 72 hours at 25°C and for 14 days at 4°C when packaged in polyolefin bags or glass bottles and protected from light.

Abbreviations: HPLC = high-performance liquid chromatography, PCA = patient-controlled analgesia, QC = quality control, RSD = relative standard derivation.

Keywords: dezocine, drug stability, high-performance liquid chromatography, patient-controlled analgesia

1. Introduction

Dezocine (Fig. 1), (5R,11S,13S)-13-amino-5,6,7,8,9,10,11,12-octahydro-5-methyl-5,11-methanobenzocyclodecen-3-ol, a mixed agonist/antagonist of opioid receptors, was first developed in the 1970s.[1] Although its specific mechanism of action is still not completely understood,[2] there is no doubt that dezocine has potent analgesic effects. Numerous studies and systemic reviews have shown that the analgesic efficacy of dezocine is just as effective as that of morphine, meperidine, fentanyl, and sufentanil for the management of acute postoperative pain.[3–11] As with other opioid analgesics, the administration of dezocine via intravenous pumps for patient-controlled analgesia (PCA) is now commonplace for the long-term management of severe, malignant postoperative pain.[7–11] This route of administration allows the patient to maintain safe and appropriate levels of analgesia, and this is a major advantage over conventional analgesia techniques. Hence, knowledge of the compatibility and stability of these drug mixtures is important to ensure patient safety. Currently, only 1 published study has evaluated the stability of the combination of dezocine and ketorolac tromethamine in 0.9% sodium chloride for injection,[12] and no published information is available on the stability of dezocine in solutions. Thus, the aim of the study was to determine the stability of dezocine, at 3 different concentrations, prepared in 0.9% solutions of sodium chloride injection and stored in polyolefin bags and glass bottles over a period of 14 days at 4°C and 72 hours at 25°C.

2. Methods

2.1. Materials and reagents

The working standards of dezocine were purchased from the National Institutes for Food and Drug Control (Beijing, China). A commercial formulation of dezocine for injection (5 mg/mL) was supplied by Yangtze River Pharmaceutical Co, Ltd (Jiangsu, China). The 0.9% sodium chloride injections were in 100 mL

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B-XF and L-HW contributed equally to this work and should be considered as first authors equally.

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The authors report no conflicts of interest.

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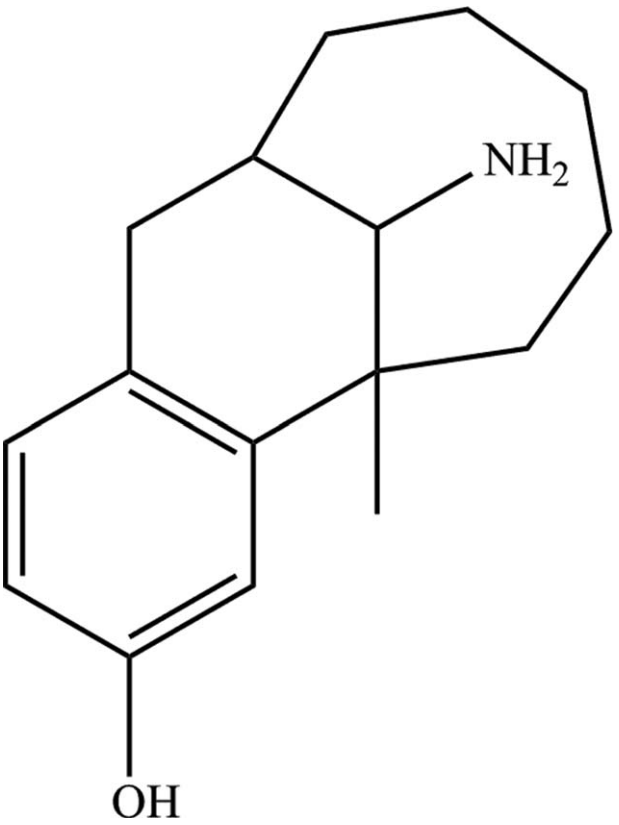

Figure 1. Structures of dezocine.

prefilled polyolefin bags and 100 mL prefilled glass bottles from Kelun Pharmaceutical Co, Ltd (Sichuang, China). This study was approved by the Medical Ethics Committee of the Dongfeng Hospital at the Hubei University of Medicine (MEC-2015–007).

2.2. HPLC Instrumentation and chromatographic conditions

The high-performance liquid chromatography (HPLC) instrumentation (Shimadzu LC-20A, Shimadzu, Kyoto, Japan) consisted of an LC-20AD quaternary pump, a DGU-20A5 degasser unit, an SIL-20AC auto-injector, a CTO-20A column oven, a phenomenex C_{18} column (4.6×150 mm, 5 μm) and an SPD-M20A diode array detector. Data acquisition was carried out using Class VP 7.4 software (Shimadzu, Kyoto, Japan). The mobile phase consisted of a 78:20:2 (v/v/v) mixture of water, acetonitrile, and triethylamine. The pH was adjusted to 3.0 with 85% phosphoric acid. The flow rate was 1.0 mL/min, and the detection wavelength for dezocine was 282 nm. All analyses were performed at ambient room temperature, and the volume of solution injected onto the column was 20 μL.

2.3. Preparation of stock and standard curve solutions

We accurately weighed and transferred 60 mg of the dezocine working standard into a 100 mL volumetric flask. We added approximately 70 mL of HPLC-grade water and sonicated the mixture to dissolve it completely, and we increased the final volume to 100 mL using the same solvent to obtain the final concentration of 0.6 mg/mL of dezocine. The solution was stored at −20°C until use. A 6-point calibration curve was generated using solutions prepared by diluting 0.6 mg/mL dezocine with HPLC-grade water to concentrations of 6.0, 18.0, 60.0, 90.0, 120.0, and 240.0 μg/mL.

2.4. Assay validation

The method was validated for specificity, linearity, precision, and accuracy. The calibration curve was generated using a least-squares regression of the peak area ratio of dezocine and the concentration of each dezocine standard. The precision of the assay was evaluated using intraday and interday validation methods. To determine the intraday variability of the assay, repeated injections (n = 6) of quality control (QC) standards of dezocine at concentrations of 60, 90, and 120 μg/mL were prepared and analyzed. To determine the interday variability, QC samples at 3 concentration levels were analyzed on 6 days. Accuracy was accessed by comparing the predicted concentrations of the QC standards using the standard curve with the theoretical concentrations (60, 90, and 120 μg/mL). The accuracy was calculated by means of the recovery value.

2.5. Accelerated degradation of dezocine

The degradation products were produced in acidic, basic, and oxidative conditions. The experiments were carried out as follows: solutions of dezocine 0.5 mg/mL in water were respectively prepared by mixing (v/v) with 1 N hydrochloric acid, 1 N sodium hydroxide, and 3% hydrogen peroxide, then vortexed and incubated for 4 hours at 60°C. The samples were cooled to room temperature and the pH readjusted with hydrochloric acid or sodium hydroxide. The samples were then adjusted with water to final concentrations of 100 μg/mL and filtered, and 20 μL of each sample was injected onto the column. The chromatograms obtained for the degraded preparations were compared with a chromatogram obtained from the standard curve to determine any changes in concentration, retention time, and peak shape.

2.6. Preparation of dezocine solutions

Dezocine solutions (0.3, 0.45, and 0.6 mg/mL) were prepared by removing 6, 9, and 12 mL of 0.9% sodium chloride injection, respectively, from the 100 mL polyolefin bags or glass bottles and injecting 6, 9, and 12 mL of 5 mg/mL dezocine, respectively. The solutions were prepared in triplicate for each storage condition and container type. To ensure a homogeneous mixture, the contents of each polyolefin bag or glass bottle were manually mixed upon preparation and before each sample were removed. All formulations and sampling were conducted by a single pharmacist using aseptic conditions in laminar flow hoods and kept in the dark at refrigeration (4 ± 0.5°C) and at room temperature (25 ± 0.5°C).

2.7. Stability of dezocine solutions

The stability of the dezocine solutions was assessed by examination of the appearance, pH, and drug concentration. Five-milliliter samples from each polyolefin bags or glass bottles were removed initially and at predetermined times (0, 3, 7, 10, and 14 days at 4°C; 0, 4, 24, 48, and 72 hours at 25°C). At the specified times, the physical characteristics of the solutions such as color, cloudiness, precipitation, and gas production were evaluated. The pH values of the mixture were also determined using a PHS-3c pH meter (Leici Instrument Co, Shanghai, China). Then, all samples were transferred into glass vials and stored at −20°C; thereafter, samples were removed in sets, warmed to room temperature,

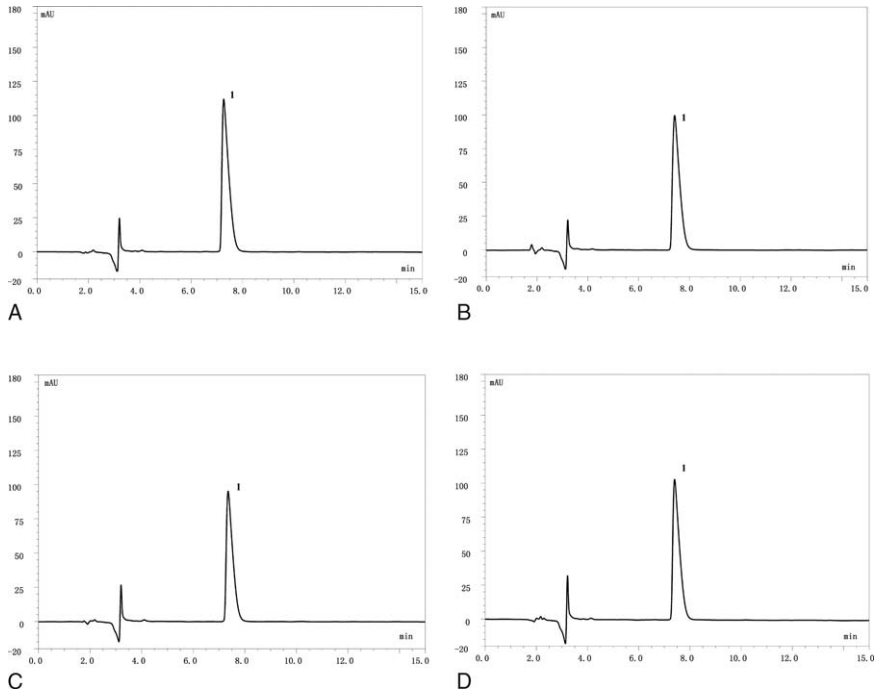

Figure 2. HPLC chromatograms of dezocine following degradation testing. (A) Fresh sample of dezocine at time 0. (B) An acidified dezocine sample after heating at 60°C for 5 h. (C) An alkaline-degraded dezocine sample after heating at 60°C for 5 h. (D) An oxidized dezocine sample after 5 h at room temperature. Retention time was 7.4 min for dezocine (peak 1). The other peaks were for degradation products. HPLC = high-performance liquid chromatography, mAU, milli-absorbance unit.

mixed, sampled, and analyzed. In the concentrations analysis, samples were diluted 1:4 in water before injection into the HPLC system. Samples from each bag and bottle were analyzed in triplicate (total n = 3). The initial concentration of dezocine was defined as 100%, and subsequent sample concentrations for the drug in the mixtures were reported as the percentage of the initial concentration. The mixtures were considered chemically stable if they retained 90% or more of the initial concentration.

3. Results

3.1. Accelerated degradation and assay validation

Typical chromatograms of dezocine at time 0 and in acidified, alkaline, and oxidized conditions of degradation appear in Figure 2. The chromatogram peaks were symmetric and sharp. The average retention time for dezocine was 7.4 minutes. Under extreme conditions, the degradation peaks were detected with <10% of decomposition compounds and did not interfere with quantification of dezocine. The standard calibration curves of dezocine exhibited good linearity over the range of concentrations tested, with correlation coefficients >0.999. Table 1 summarizes the dezocine assay validation data. As shown in Table 1, the intraday and interday relative standard derivations (RSDs) were <1.7% and <2.4%, respectively, indicating good reproducibility for dezocine. Recovery was within the range of 100 ± 2%, which indicates good accuracy of the developed method.

Table 1

Validation of HPLC method.

Drug	Measured concentrations, μg/mL	Accuracy, %	Precision RSD, %	
			Intraday	Interday
Dezocine	60.0	99.3	1.7	2.4
	90.0	100.8	0.7	1.6
	120.0	100.3	1.3	1.8

HPLC = high-performance liquid chromatography, RSD = relative standard derivation.

3.2. Stability study of dezocine solutions

During the stability study period, no precipitate was visible in any solution, no color changes occurred, no gas was produced, and the pH values remained stable at both 4°C and 25°C when protected from room light. The HPLC analysis showed that, at both storage temperatures, solutions of dezocine at 0.3, 0.45, and 0.6 mg/mL concentration stored in polyolefin bags and glass

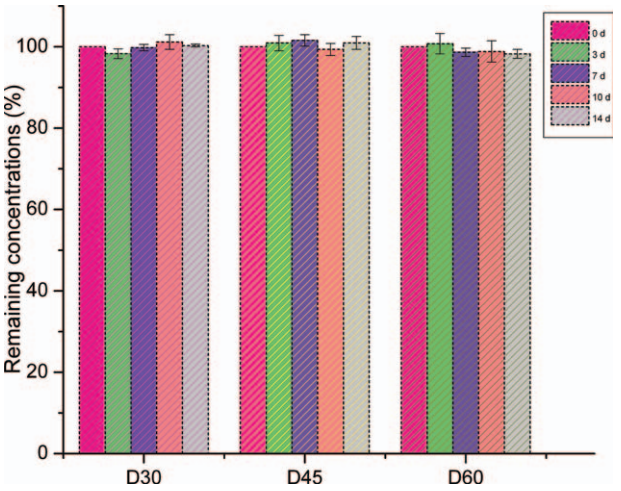

Figure 3. The stability of dezocine based on 3 different concentrations packaged in glass bottles and protected from light over 14 d at 4°C. Error bars represent the standard deviations (n = 3).

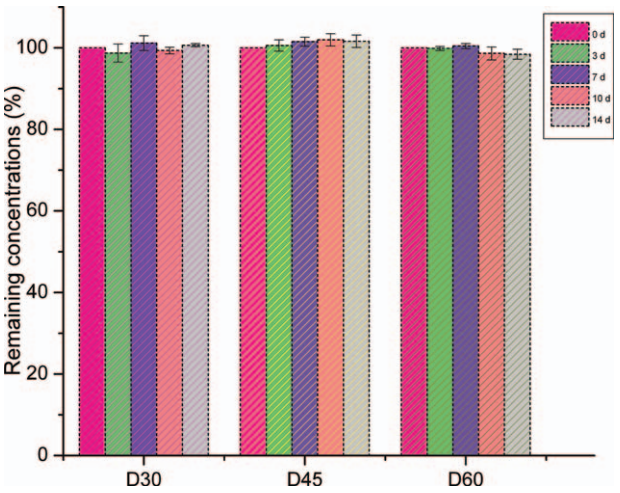

Figure 4. The stability of dezocine based on 3 different concentrations packaged in polyolefin bags and protected from light over 14 d at 4°C. Error bars represent the standard deviations (n=3).

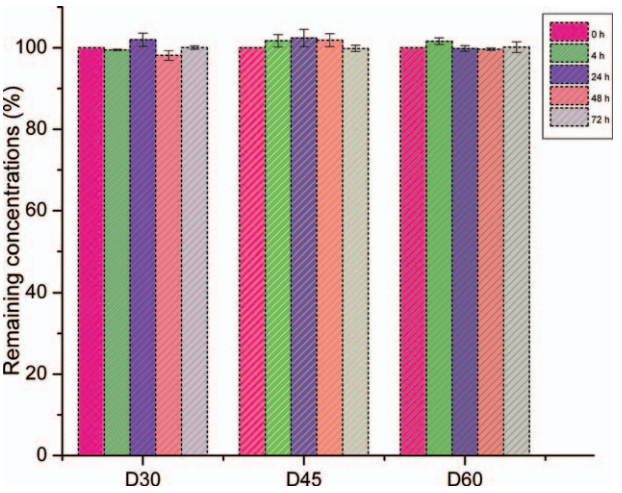

Figure 6. The stability of dezocine based on 3 different concentrations packaged in polyolefin bags and protected from light over 72 h at 25°C. Error bars represent the standard deviations (n=3).

bottles maintained between 97% and 103% of their initial concentrations during the study experiment (Figs. 3–6).

4. Discussion

To the author's knowledge, this is the first reported study of the stability of dezocine in 0.9% sodium chloride for injection stored in polyolefin bags and glass bottles for PCA via iv pump administration. Stability studies may have a variety of aims, including time management and reductions in cost, waste, and workload.[13] At the authors' institution, more than 800 vials of dezocine are used monthly; therefore, extending the expiry date of these analgesia solutions would be beneficial.

In China, dezocine for injection is formulated with lactic acid, sodium chloride, sodium pyrosulfite, and propylene glycol. As shown in Figure 1, dezocine is a weak acid with a pK_a 8.1, and the compound is stable in acidic solutions. To date, there is limited published information regarding the compatibility and stability of dezocine alone or combined with other drugs in solutions for infusion. Hu HX and others[12] studied the effect of different concentrations and time periods of dezocine injection mixed with ketorolac tromethamine prepared in 0.9% sodium chloride solutions. They reported that 0.01 mg/mL dezocine and ketorolac tromethamine at concentrations of 0.01, 0.02, or 0.04 mg/mL in 0.9% sodium chloride for injection was stable for 12 hours when stored at 25°C. In the present study, the pH of the dezocine mixtures was acidic and had a pH ranging from 3.3 to 3.5. No significant modification of the pH was observed during the storage period. No notable changes in color, cloudiness, precipitation, and gas production were observed in solutions after storage at either 4°C or 25°C. The concentrations of dezocine at 3 different dilutions were >97.0% of their initial concentrations after being stored in polyolefin bags or glass bottles at both storage temperatures. This study has demonstrated that dezocine is a fairly stable drug.

In this stability study, the concentrations of dezocine were chosen to reflect the use of the drug by specialized analgesic treatment teams using expert consensus[14] and clinical research[7–11] in order to ensure that the results would have clinical utility. For adult patients in severe postoperative pain, the doses of dezocine for PCA administration ranged widely from 0.6 to 1.0 mg/kg or from 30 to 60 mg of dezocine diluted to 100 mL in 0.9% sodium chloride solutions. A limitation of the study design is that the sterility was not tested; however, the infusion bags and bottles were sterile, and the solutions were prepared in a sterile environment.

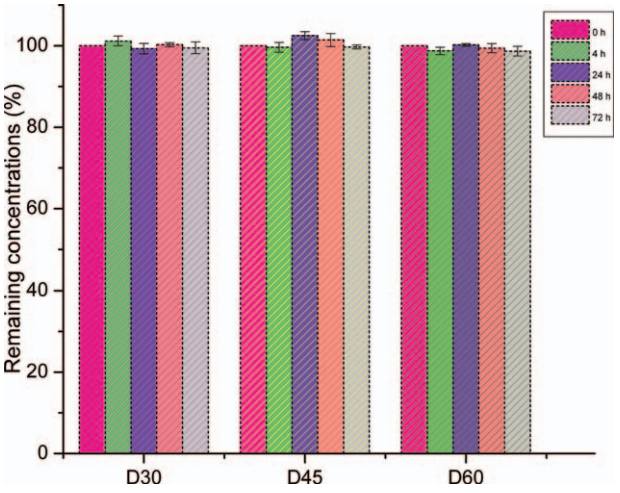

Figure 5. The stability of dezocine based on 3 different concentrations packaged in glass bottles and protected from light over 72 h at 25°C. Error bars represent the standard deviations (n=3).

5. Conclusion

According to serial qualitative, pH, and HPLC analyses, infusion solutions of 0.3, 0.45, or 0.6 mg/mL dezocine in 0.9% sodium chloride for injection were very stable for 72 hours at 25°C and for 14 days at 4°C when packaged in polyolefin bags or glass bottles and protected from light. The satisfactory stability of dezocine in the solutions makes it possible to prepare them in advance by licensed central intravenous additive services, which may be convenient in hospitals.

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