Stability of Cefazolin in Polyisoprene Elastomeric Infusion Devices

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ABSTRACT

Purpose: The aim was to investigate the stability of cefazolin in elastomeric infusion devices.

Methods: Elastomeric devices (Infusor LV) that contain cefazolin (3 g/240 mL and 6 g/240 mL) were prepared and stored at 4°C for 72 hours and then at 35°C for 12 hours, followed by 25°C for 12 hours. An aliquot was withdrawn at predefined time points and analyzed for the concentration of cefazolin. Samples were also assessed for changes in pH, solution color, and particle content.

Findings: Cefazolin retained acceptable chemical and physical stability over the studied storage period and conditions.

Implications: These findings will allow the administration of cefazolin by the Infusor LV elastomeric device in the outpatient and remote settings. (*Clin Ther*. 2018;▮:▮▮▮–▮▮▮)

Key words: cefazolin, continuous infusion, elastomeric device, high-performance liquid chromatography, infective endocarditis, stability.

INTRODUCTION

Intravenous infusion of cefazolin (6 g/d in 3 divided doses) is commonly used for the treatment of infective endocarditis (IE) caused by methicillin-sensitive *Staphylococcus aureus* or relatively resistant streptococci for a period of 4 to 6 weeks.[1] Once the treatment is commenced, patients may be clinically stable but are often required to be treated either as hospital in-patients or at outpatient infusion settings for the entire duration of their treatment because of the need for daily intravenous administration.[2–4] However, prolonged hospital stays are costly and carry the risk of adverse events, including nosocomial infections.

It would be preferable if patients could complete their antibiotic therapy at home, using elastomeric devices. In fact, guidelines published by the European Society of Cardiology suggest that a large number of patients with IE could be candidates for outpatient intravenous therapy.[4] However, the physicochemical stability of cefazolin in the Infusor LV elastomeric device (Baxter Healthcare, Old Toongabbie, NSW, Australia) is unknown; this device, which allows the continuous infusion of cefazolin over 24 hours, is commonly used by European, Asian, Australian, and New Zealand hospitals. The stability of cefazolin in both the Accufuser (Woo Young Medical, Chungbuk, South Korea) and Easypump LT (B. Braun Medical, Melsungen, Germany) elastomeric devices has been previously reported.[5,6] However, the elastomer membrane of these devices is composed of silicone, whereas in the Infusor LV polyisoprene rubber is used.[7] The stability of pharmaceuticals can vary depending on the composition of the material in which they are stored[8,9]; therefore, the stability of cefazolin reported in the Accufuser cannot be extrapolated to the Infusor LV. The aim of this study was to investigate the stability of cefazolin in Infusor LV elastomeric devices stored at 3 different temperatures for various time points.

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METHODS

Sample Preparation

Cefazolin vial (1 g; AFT Pharmaceuticals, North Ryde, NSW, Australia) was reconstituted with 3 mL of Water for Injection BP to obtain a concentration of 330 mg/mL. An appropriate volume of the reconstituted solution was injected into either 0.9% sodium chloride or 5% dextrose in water (D5W; Baxter Healthcare) to obtain 3 g/240 mL (12.5 mg/mL) or 6 g/240 mL (25 mg/mL) of cefazolin solution. The solution was then carefully transferred into an polyisoprene elastomeric infusion pump (Infusor LV; Baxter Healthcare) as described before.[10,11] A total of 12 elastomeric devices were prepared as follows: 3 pumps contained 3 g of cefazolin in 0.9% sodium chloride, 3 pumps contained 3 g of cefazolin in 5% D5W, 3 pumps contained 6 g of cefazolin in 0.9% sodium chloride, and 3 pumps contained 6g of cefazolin in D5W. Control samples (n = 6) were prepared in a similar way except that cefazolin was omitted.

To simulate clinically relevant conditions,[6] the elastomeric devices were first kept in a refrigerator at 4°C for 72 hours and then stored at 35°C for 12 hours, followed by 25°C for 12 hours. The beginning of the storage of elastomeric device at 35°C started at 72 hours and ended at 84 hours, whereas the beginning of the elastomeric device storage at 25°C started at 84 hours and ended at 96 hours. An aliquot was withdrawn at 0 (baseline), 24, 48, and 72 hours after storage at 4°C. An aliquot was withdrawn at 74, 76, 78, and 84 hours of storage at 35°C. An aliquot was then withdrawn at 86, 88, 90, and 96 hours of storage at 25°C. Each aliquot was then divided into 4 different parts. The first part was used to determine the concentration of cefazolin with the use of a stability-indicating high-performance liquid chromatography (HPLC) assay, the second part was used to determine particle contents with the use of light microscopy, and the third and fourth parts were used to assess color change (visually) and pH, respectively.

Chemical Stability

HPLC was performed with a Dionex UltiMate 3000 UHPLC system (Thermo Fisher Scientific, Sunnyvale, Calif). The HPLC separation of cefazolin was performed with a Kinetex C_{18} 5-μm column (100Å, 50 × 4.6 mm; Phenomenex, Lane Cove, NSW, Australia) as described before.[12] The stability that indicated the nature of the HPLC method was investigated by subjecting the cephazolin solution to acidic, basic, and oxidative stresses. The cephazolin solution (3 mg/mL) was mixed with an equal volume of 1N hydrochloric acid, 1N sodium hydroxide, or 3% hydrogen peroxide. The solutions were then heated at 50°C for 60 minutes. Unstressed and stressed samples were analyzed for comparative purpose.

Physical Stability

Particle Content Analysis

Analysis for particle contents with the use of light microscopy was performed as previously described.[11] Positive control (n = 3) for cefazolin was prepared by mixing 1 mL of 250 mg/mL cefazolin solution with 1 mL of 10 mg/mL sodium chloride. Each sample was analyzed in duplicate.

Visual and pH Analysis

A calibrated pH meter (model 1852 mv; TPS Pyt. Ltd., Springwood, QLD, Australia) was used to measure the pH of each sample. Samples were examined visually for changes in color and evidence of haziness by observing against a white background for any color change and then against a black background with polarized light for the presence of haziness. Each sample was analyzed in duplicate.

Data Analysis

Cefazolin was considered chemically stable if it retained >90% of its initial concentration. Cefazolin was considered physically stable if (1) there were >50 particles larger than 10 μm and >5 particles larger than 25 μm and (2) the pH of cefazolin solution remained at 3.6 or greater. Cefazolin is a weak acid and its pKa is 3.6. If the pH of the cefazolin-containing solution is lower than the pKa of cefazolin, then >50% of cefazolin would be in the unionized form, increasing the risk of precipitation.

RESULTS

Chemical Stability

The concentrations of cefazolin before and after storage in the Infusor LV elastomeric device are shown in Table I. At time zero, the mean concentrations of the 3 g of cefazolin admixed with 240 mL of 0.9% sodium chloride and D5W, were found to be 12.6 and 12.3 mg/mL, respectively, whereas the mean concentrations of the 6 g of cefazolin admixed with 240 mL of 0.9% sodium