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Physical Compatibility of Cefazolin and Select Crystalloid Intravenous Fluids

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ABSTRACT

Background: Patient care may necessitate concomitant administration of cefazolin with intravenous (IV) fluids. Data is limited for cefazolin with 0.45% sodium chloride (NaCl) and Lactated Ringer's (LR).

Objective: To determine the physical compatibility of cefazolin with 0.45% NaCl and LR admixtures over 24 hours.

Methods: Cefazolin 20 mg/mL admixtures were prepared in a 1:1 ratio with 0.45% NaCl or LR and examined at baseline, 1, 5, 8, and 24 hours. A demonstrable change was an alteration in visual appearance, absorbance (> 0.010 units), and pH (> 0.1 unit).

Results: Visual and absorbance assessments found no demonstrable changes for the admixtures. Both admixtures had demonstrable pH changes at hour 24. The average readings for 0.45% NaCl admixture did not have demonstrable changes until the 24-hour reading.

Conclusions: The 0.45% NaCl and LR admixtures were physically compatible for up to 8 hours. Further studies may be warranted to determine their chemical stability.

INTRODUCTION

Patients often require intravenous (IV) fluid therapy to prevent or correct problems with their fluid and electrolytes [1]. Crystalloid fluids are frequently used for patient fluid resuscitation [2]. These fluids may include 0.45% sodium chloride (NaCl) and Lactated Ringer's for injection (LR) [3,4]. In addition to IV fluid administration, patients often require concomitant antimicrobial therapy. Cefazolin, a first-generation IV cephalosporin antimicrobial agent, is indicated for various infections, including bacteremia and perioperative prophylaxis [5]. Depending on the indication and a patient's kidney function cefazolin may be administered up to four times a day increasing the likelihood that it will be concomitantly administered with IV fluids through a Y-site [6]. To establish safe practices and optimize drug efficacy, knowledge of concomitant administration of drugs in IV fluids is key information for patient care. Currently, limited physical compatibility data is available for cefazolin with 0.45% NaCl or LR. Previous studies have been conducted to determine the compatibility of cefazolin and LR, but the study was limited in its duration and evaluation methods [7]. To ensure safe and effective therapy, the physical compatibility of cefazolin with 0.45% NaCl and LR was investigated.

METHODS

Preparation of Admixtures

This study was conducted using aseptic technique and previously validated methods [8-10]. Cefazolin sodium 20mg/mL was available as a premixed solution in 4 grams of dextrose hydrous with a total volume of 100 mL (Baxter, Deerfield, IL). The IV fluids 0.45% NaCl and LR for injection were supplied as a 1000 mL IV bag (Baxter, Deerfield, IL). Cefazolin with 0.45% NaCl admixture was prepared by transferring 75 mL of cefazolin sodium with a 5-micron filter needle (Baxter, Deerfield IL) to an empty ethylene vinyl acetate Exactamix™ 250mL bag (Baxter, Deerfield IL) followed by 75 mL of 0.45% NaCl (Baxter, Deerfield IL) and then gently mixed. The admixture was then immediately transferred to polystyrene tubes (Fisherbrand, Waltham, MA) and polystyrene cuvettes (Fisher Brand, Ottawa, Ontario, Canada) for each time point measurement. Test tubes were covered with a screwcap and cuvettes were covered with parafilm. This process was repeated for the cefazolin with LR admixture with 75 mL of both cefazolin sodium (Baxter, Deerfield, IL) and LR (Baxter, Deerfield, IL). Admixtures samples in test tubes and cuvettes were prepared in triplicate. To mimic typical preparation and administration conditions, the admixtures were prepared, handled, and stored in a laminar flow hood at room temperature ranging from 21.7 to 22.0 ^{o}C under ambient light with relative humidity ranging from 13-35%.

Evaluation of Admixtures

All admixtures were evaluated by visual observation, spectrophotometric absorbance, and pH measurements at baseline, 1, 5, 8, and 24 hours after mixing. The visual observations were conducted against a black-and-white background by the same study evaluator. The observations were categorized into five categories. The categories were no evidence of precipitation (0), trace evidence of precipitation (1), slight haze (2), medium haze (3), and dense haze (4). For visual comparison, a positive control was prepared by mixing equal volumes of sodium phosphate and calcium gluconate. The negative controls were either 0.45% NaCl and LR when compared with respective admixtures. If a change was observed, a second observer reviewed the findings. A demonstrable change was defined as any change in visual appearance.

The absorbance of the admixtures was measured using a Genesys 10s UV-Visible spectrophotometer (Thermo Scientific, Waltham, MA) at a wavelength of 547 nm, at which the admixture ingredients and the negative controls had 100% transmittance of light. Samples with absorbance values >0.010 units was a demonstrable change.

The pH of each admixture was measured using a Seven Compact benchtop pH meter (Mettler Toledo, Columbus, OH) with an InLab science pH electrode. The pH meter was calibrated using standard pH 4.01, 7.00, and 10.01 buffers every 24 hours during the study duration. A demonstrable change in pH was determined for this study as >0.1.

RESULTS

The visual assessment for all admixtures were clear and colorless with no haze or precipitation throughout the 24-hour observation period. There were no demonstrable changes in spectrophotometer readings for any admixture during this study. The pH readings for the cefazolin 0.45% NaCl and LR admixtures remained stable until hour 24, when a demonstrable change was observed. The results can be found in Table 1.

Table 1: Cefazolin Admixtures-Visual, Absorbance, and pH

Cefazolin w/ 0.45% NaCl*‡					
Time (hour)	0	1	5	8	24
Visual					
Sample A	0	0	0	0	0
Sample B	0	0	0	0	0
Sample C	0	0	0	0	0
Average ± SD	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Absorbance					
Sample A	0.000	0.000	0.000	0.001	0.001
Sample B	0.000	0.000	0.001	0.000	0.000
Sample C	0.000	0.000	0.000	0.000	0.000
Average ± SD	0.000 ± 0.000	0.000 ± 0.000	0.000 ± 0.001	0.000 ± 0.001	0.000 ± 0.001
pH					
Sample A	5.69	5.60	5.55	5.65	5.84
Sample B	5.69	5.58	5.56	5.58	5.77
Sample C	5.57	5.55	5.52	5.52	5.79
Average ± SD	5.65 ± 0.07	5.58 ± 0.03	5.54 ± 0.02	5.58 ± 0.07	5.8 ± 0.04
Cefazolin w/ Lactated Ringer's Solution*ǂ					
Time (hour)	0	1	5	8	24
Visual					
Sample A	0	0	0	0	0
Sample B	0	0	0	0	0
Sample C	0	0	0	0	0
Average ± SD	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0
Absorbance					
Sample A	0.000	0.000	0.000	0.001	0.001
Sample B	0.000	0.000	0.000	0.000	0.002
Sample C	0.000	0.001	0.000	0.000	0.002
Average ± SD	0.000 ± 0.000	0.000 ± 0.001	0.000 ± 0.000	0.000 ± 0.001	0.002 ± 0.001
pH					
Sample A	5.86	5.90	5.86	5.90	6.08
Sample B	5.83	5.81	5.84	5.86	6.01
Sample C	5.80	5.80	5.80	5.84	6.01
Average ± SD	5.85 ± 0.02	5.84 ± 0.06	5.83 ± 0.03	5.87 ± 0.03	6.03 ± 0.04

* Cefazolin sodium, 2g/100 mL, Baxter, Deerfield, IL. Lot numbers LD160315 and LD160452

‡ 0.45% Sodium Chloride USP, 1000 mL, Baxter, Deerfield, IL. Lot number Y4021187

ǂ Lactated Ringer's Injection USP, 1000 mL, Baxter, Deerfield, IL. Lot number Y406901

DISCUSSION

Vallee et al. studied the compatibility of LR and cefazolin over 4 hours utilizing visual evaluation and light obscuration particle counting [7]. The study concluded that cefazolin was physically compatible with LR when administered through a Y-site. In contrast, the results of this trial suggest cefazolin and LR are physically compatible for 8 hours.

Overall, the pH was maintained within the normal pH range of 0.45% NaCl until the 24-hour period when sustained demonstrable changes were documented. There was one cefazolin 0.45% NaCl sample that had a demonstrable pH change at hour one, but the average of all samples did not show consistent changes. The evaluation of pH is important when determining physical compatibility as pH is a critical factor affecting the stability of a product. A change in pH can impact the solubility of a molecule, which may determine the stability of medications, the biological tolerability of the formulation, and the activity of the molecule [11]. When a drug

product is placed in a compounded preparation, such as an IV admixture, the overall pH may be altered to be within the range for faster degradation. Drug degradation can often occur by hydrolysis, a reaction of a molecule with water resulting in the cleavage of a chemical bond within that molecule [12]. The pH-rate profile for cefazolin showed a degradation minimum between pH 5.5 and 6.5 [13]. The pH- rate profile determines the pH at which the drug is most susceptible to degradation [12]. The cefazolin and 0.45% NaCl admixtures average pH at baseline was 5.65 and the cefazolin and LR admixtures average pH at baseline was 5.84. These values are within the range of increased degradation. It is plausible that the degradation occurred due to hydrolysis of the ester and amide functional groups present in cefazolin [13]. The delay in pH changes for cefazolin with LR admixtures may be explained due to the buffer qualities of LR, which contains 6 g/L sodium chloride, 3.1 g/L sodium lactate, and 0.3 g/L potassium chloride. LR is considered a balanced or buffered crystalloid fluid because it has fewer effects on acid–base balance [14].

A limitation of this study was that the admixtures were not evaluated hourly, so it cannot be determined at what time after 8 hours a demonstrable pH change occurred.

CONCLUSION

The cefazolin sodium LR admixture was physically compatible for up to 8 hours. In contrast, cefazolin sodium combined with 0.45% NaCl, had fluctuations in one pH sample, but the average readings did not have demonstrable changes until the 24-hour reading, indicating physical compatibility up to 8 hours. Further studies may be warranted to determine the chemical stability of these admixtures.

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