STABILITY OF THE COMBINATION OF CEFTAZIDIME AND CEPHAZOLIN IN ICODEXTRIN OR PH NEUTRAL PERITONEAL DIALYSIS SOLUTION

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◆ **Introduction:** The objective of this study was to investigate the stability of ceftazidime and cephazolin in a 7.5% icodextrin or pH neutral peritoneal dialysis (PD) solution.

◆ **Methods:** Ceftazidime and cephazolin were injected into either a 7.5% icodextrin or pH neutral PD bag to obtain the concentration of 125 mg/L of each antibiotic. A total of nine 7.5% icodextrin or pH neutral PD bags containing ceftazidime and cephazolin were prepared and stored at 1 of 3 different temperatures: 4°C in a domestic refrigerator; 25°C at room temperature; or 37°C (body temperature) in an incubator. An aliquot was withdrawn immediately before (0 hour) or after 12, 24, 48, 96, 120, 144, 168 and 336 hours of storage. Each sample was analyzed in duplicate for the concentration of ceftazidime and cephazolin using a stability-indicating high-performance liquid chromatography technique. Ceftazidime and cephazolin were considered stable if they retained more than 90% of their initial concentration. Samples were also assessed for pH, colour changes and evidence of precipitation immediately after preparation and on each day of analysis.

◆ **Results:** Ceftazidime and cephazolin in both types of PD solution retained more than 90% of their initial concentration for 168 and 336 hours respectively when stored at 4°C. Both of the antibiotics lost more than 10% of the initial concentration after 24 hours of storage at 25 or 37°C. There was no evidence of precipitation at any time under the tested storage conditions. Change in the pH and color was observed at 25 and 37°C, but not at 4°C.

◆ **Conclusion:** Premixed ceftazidime and cephazolin in a 7.5% icodextrin or pH neutral PD solution is stable for at least 168 hours when refrigerated. This allows the preparation of PD bags in advance, avoiding the necessity for daily preparation. Both the antibiotics are stable for at least 24 hours at 25 and 37°C, permitting storage at room

temperature and pre-warming of PD bags to body temperature prior to its administration.

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KEY WORDS: Ceftazidime; cephazolin; icodextrin; pH neutral; peritoneal dialysis; stability; high-performance liquid chromatography.

Peritonitis is one of the most common complications of peritoneal dialysis (PD), causing significant morbidity and occasional mortality (1). Currently, glucose is a widely used osmotic agent in PD solutions. However, its long-term use is associated with the structural alteration of the peritoneal membrane as well as systemic metabolic and cardiovascular side effects (2–3). To minimize these complications associated with glucose-based PD solutions, newer PD solutions (e.g. Extraneal and Balance) have been introduced. Extraneal PD solution contains icodextrin (a polymer with an average molecular weight of 17,000 Da) as a colloid osmotic agent. Because of its large molecular weight, icodextrin is absorbed less into the systemic circulation and hence, less likely to cause systemic side effects (4). It has been reported that the long-term exposure to a pH neutral Balance PD solution causes less peritoneal inflammation and has a minimal effect on vasoregulation (5–6).

Antibiotics covering both gram-positive and gram-negative organisms are used for the empirical treatment of PD-associated peritonitis. Many PD centers use a first generation cephalosporin, such as cephazolin to cover gram-positive organisms in combination with ceftazidime (a third-generation cephalosporin) to cover gram-negative organisms (7). Although the stability of ceftazidime or cephazolin has been investigated (8), to the best of our knowledge, the stability of the combination of ceftazidime and cephazolin in a 7.5% icodextrin

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or in pH neutral PD solution is currently unknown. Moreover, due to the differences in the composition of PD solutions or container materials, stability of a given drug from one type of container or solution to another type cannot be extrapolated (8). Hence, a better understanding of the stability of these antibiotics in new types of PD solutions can greatly assist clinicians in applying effective treatments for peritonitis. The aim of this study was to investigate the stability of the combination of ceftazidime and cephazolin admixed with either a 7.5% icodextrin or pH neutral PD solution at three different storage temperatures.

MATERIALS AND METHODS

SAMPLE PREPARATION

Ceftazidime pentahydrate (Glaxo Smith Kline Pty Ltd, Victoria, Australia) or cephazolin sodium (Hospira Pty Ltd, Victoria, Australia) was reconstituted with Water for Injection BP according to the manufacturer's instructions. A suitable volume of the reconstituted solution was injected using a sterile 21 Gauge needle and a 5 mL plastic syringe either into the non-glucose compartment (1.25 L, pH 8.0) of the Balance (Fresenius Medical Care, Sydney, New South Wales, Australia) two-compartment pH neutral balance polyolefin PD bag (2.5 L) or into the Extraneal (Baxter Pty Ltd, New South Wales, Australia) one compartment polyvinyl chloride PD bag (2.0 L) to obtain a concentration of 125 mg/L of each antibiotic.

After addition of each antibiotic solution, the 7.5% icodextrin PD bag or the non-glucose compartment of a pH neutral PD bag was gently shaken for approximately 1 minute to ensure proper mixing. A total of nine 7.5% icodextrin or pH neutral PD bags containing ceftazidime and cephazolin were prepared and stored at 1 of 3 different temperatures: 4°C in a domestic refrigerator; 25°C at room temperature; or 37°C (body temperature) in an incubator. Immediately prior to the storage of a pH neutral PD bag at 37°C, the glucose-based (1.5%) solution (1.25 L, pH 3.0) from one compartment was mixed with the buffer solution present in another compartment. Briefly, the bag was rolled up from one of the upper ends until the middle stream opened. Then the bag was rolled up from the upper edge until the peel seam of the lower triangle was completely opened. Then the solution was thoroughly mixed by gently shaking and inverting the bag for approximately 1 minute. Control samples ($n=3$) were prepared in an identical way except that the ceftazidime and cephazolin were omitted.

An aliquot (1 mL) was withdrawn from each bag at 0, 8, 12, 24, 48, 72, 120, 168 and 336 hours and analyzed

in duplicate for the concentration of ceftazidime and cephazolin using a stability indicating high-performance liquid chromatography (HPLC) assay. Baseline samples (0 hour) were kept at room temperature and subjected to HPLC analysis within 30 minutes of their preparation. Samples were also assessed for pH, color and precipitation immediately after preparation and on each day of analysis.

HPLC ASSAY

The HPLC system consisted of a Prostar 230 solvent delivery module, 335 diode array detector and 410 autosampler (Varian, Victoria, Australia). HPLC was performed using a Kinetex C18 column (150 mm $\times$ 460 mm $\times$ 2.6 μ m) with a 100-Å pore size (Phenomenex, Victoria, Australia). Mobile phase was composed of 0.1% trifluoroacetic acid (TFA) in acetonitrile (A) and 0.1% TFA in water (B). The flow rate was set at 0.8 mL/minute, and the linear gradient for mobile phase A was set as follows: 95 to 70% for initial 11 minutes, 70 to 95% for 1 minute. Then the column was re-equilibrated with 95% of A for 3 minutes. The temperatures of the column and sample compartments were set at 40 and 10°C respectively. The injection volume was 60 μ L and the UV detector was set at 220 nm.

Assay Performance: Calibration solutions containing 0.6, 0.75, 1.5, 3 and 6 μ g/mL of ceftazidime or cephazolin were prepared and used for precision, accuracy and linearity estimations. Intra- and interday (> 5 consecutive days) precision values were investigated using peak areas with repeat analysis ($n=6$) of ceftazidime or cephazolin solution (3 μ g/mL). Accuracy was determined by constructing a calibration graph for the ceftazidime or cephazolin peak area using a linear regression equation. Mean intra- and interday accuracy values for the ceftazidime or cephazolin peak (3 μ g/mL, $n=6$) were determined by the regression equation as follows: (observed concentration - expected concentration)/(expected concentration - 100). Mean intra- and interday retention times were determined based on peak retention time with repeat analysis of 3 μ g/mL ceftazidime or cephazolin solution. The intraday precision of different concentrations of ceftazidime or cephazolin (0.6, 0.75, 1.5, 3 and 6 μ g/mL, $n=6$) was also determined. The linearity of the method was investigated using 1.5, 3 and 6 μ g/mL ceftazidime or cephazolin solution (estimated using correlation coefficient r^2).

Forced Degradation: The stability indicating capability of the developed HPLC method was investigated by subjecting the ceftazidime or cephazolin solution to an

acidic, basic or oxidative stress in capped glass vials. The ceftazidime or cephazolin solution (3 mg/mL) was mixed with an equal volume of 1N hydrochloric acid, 1N sodium hydroxide or 3% of hydrogen peroxide. The solutions were then heated at 50°C for 1 hour. HPLC analysis was performed on both stressed and unstressed samples ($n = 3$) for comparative purposes.

Sample Preparation for HPLC Analysis: A 3 mg/mL stock solution was prepared by diluting cephazolin and ceftazidime powder in Milli-Q water. The samples used for the generation of a standard curve were prepared by diluting a stock solution with Milli-Q water to 0, 0.6, 0.75, 1.5, 3 or 6 µg/mL. A standard curve ($n = 2$) was generated on each day of analysis by linear regression of the peak area of ceftazidime or cephazolin against its concentration. An aliquot (1 mL) withdrawn from each PD bag was diluted with Milli-Q water to a concentration of 2.5 µg/mL and subjected to the HPLC analysis within 30 minutes. To investigate the extent of ceftazidime and cephazolin degradation during HPLC analysis, PD bags ($n = 3$) containing 125 mg/L of each antibiotic were prepared. An aliquot (1 mL) was withdrawn and diluted with Milli-Q water in a glass HPLC vial to obtain a 2.5 µg/mL concentration of ceftazidime and cephazolin. The sample was kept at 10°C in the HPLC sample compartment and analyzed ($n = 2$) immediately and after 6 and 9 hours of storage.

DATA ANALYSIS

The initial concentration of ceftazidime and cephazolin was considered as 100%. The stability of ceftazidime and cephazolin was determined by calculating the percentage of the initial concentration remaining at each time period. Ceftazidime and cephazolin were considered stable if they retained more than 90% of their initial concentration.

RESULTS

HPLC chromatograms of unstressed and stressed ceftazidime and cephazolin are shown in Figure 1. With the unstressed sample, the peak of ceftazidime and cephazolin eluted at 8.5 and 11.0 minutes. Exposure to hydrogen peroxide, sodium hydroxide and hydrochloric acid at 50°C for one hour resulted in the loss of 63, 99 and 8% of ceftazidime and 49, 96 and 9% of cephazolin. More importantly, all the degradation products were completely separated and did not interfere with the peaks of ceftazidime and cephazolin, suggesting the developed HPLC method is suitable for the stability analysis of ceftazidime and cephazolin.

Linearity estimated by correlation coefficient r^2 was greater than 0.999 with each of five different concentrations of ceftazidime or cephazolin (0.6, 0.75, 1.5, 3 and 6 µg/mL) over 5 days. The intra- and interday precision relative standard deviations (RSDs) for the ceftazidime (3 µg/mL) or cephazolin (3 µg/mL) peak were less than 1.2% ($n = 6$) and 1.9% ($n = 6$) respectively. The intra- and interday accuracy RSDs for the ceftazidime or cephazolin peak were less than 2.6 and 2.5% respectively. Intra- and interday retention time RSDs for ceftazidime or cephazolin were less than 0.6% ($n = 6$) and 0.9% ($n = 5$), respectively. The intraday precision RSDs for the ceftazidime or cephazolin peak at the levels of 1.5, 3, and 6 µg/mL ($n = 6$) were less than 1.2%, 1.9%, and 1.7% respectively.

The samples stored at 4, 25 or 37°C for various time intervals were analyzed using HPLC in real time. The HPLC analysis time for each sample was 15 minutes and each time 33 samples were analyzed (6×2 standards, 9×2 samples and 3×1 controls). Therefore, the time between the first and the last analyses was approximately 8.25 hours. The HPLC analysis of 25 µg/mL ceftazidime or cephazolin kept at 10°C showed that neither of the antibiotics underwent degradation for the length of the expected autosampler run.

The concentrations of ceftazidime and cephazolin at time zero (before storage) were found to be 122.5 and 123.8 mg/L and these concentrations were considered as 100%. The percentage of the initial concentrations of ceftazidime and cephazolin remaining before and after storage are shown in Table 1. Both ceftazidime and cephazolin were stable at 4°C for at least 168 hours in either type of PD solutions. Ceftazidime was stable in 7.5% icodextrin and pH neutral PD solutions for up to 24 hours at 25°C. Cephazolin retained more than 90% of its initial concentration in 7.5% icodextrin and pH neutral PD solutions for up to 72 and 24 hours respectively at 25°C. Ceftazidime and cephazolin were stable in both types of PD solutions for at least 24 hours at 37°C. No chromatographic changes were observed between the control samples analyzed before and after storage at 4, 25 or 37°C for up to 336 hours. These results suggested that the 7.5% icodextrin or pH neutral PD solution did not undergo degradation when stored under the tested conditions.

All solutions were clear in appearance during the first 72 hours of the study. However, the samples stored in both types of PD solutions became yellowish in colour after 120 hours at 25°C and 37°C. The baseline pH of the 7.5% icodextrin and pH neutral PD solution admixed with antibiotics was 9.82 ± 0.06 (mean $\pm$ SD) and 5.61 ± 0.08 respectively. The pH of the 7.5% icodextrin and pH

Figure 1 – HPLC chromatogram of ceftazidime and cephalosporin (A), ceftazidime before (B) and after stressing under oxidative, basic or acidic conditions at 50°C for 1 hour (C-E), cephalosporin before (F) and after stressing under oxidative, basic or acidic conditions at 50°C for 1 hour (G-I). Arrows in the left and right panels indicate the expected retention time of cephalosporin and ceftazidime respectively.

TABLE 1
Comparison of Ceftazidime and Cephazolin Remaining in Solution Before and After Storage

Time (hours)	% Initial concentration remaining in 7.5% icodextrin PD solution					
	Ceftazidime			Cephazolin		
	4°C	25°C	37°C	4°C	25°C	37°C
0	100.0±0.3	100.0±1.2	100.0±1.2	100.0±0.9	100.0±0.8	100.0±0.9
12	100.0±0.5	96.2±0.5	94.5±0.8	99.7±0.5	98.9±0.7	97.7±0.5
24	98.5±1.6	94.5±1.8	92.4±1.9	99.2±0.7	97.8±1.8	93.4±1.5
48	97.2±0.9	89.6±0.8	86.7±1.5	98.7±0.4	98.1±0.7	89.2±1.1
72	95.6±0.8	86.1±1.2	78.1±0.5	98.6±0.5	93.7±0.5	81.7±0.8
120	94.2±1.5	84.8±0.8	50.5±1.1	98.9±0.3	89.1±1.1	63.9±0.9
168	93.6±0.7	72.9±1.5	20.3±1.2	98.7±0.7	83.3±1.0	49.5±0.4
336	85.±1.5	50.7±0.8	5.0±1.3	98.8±1.2	76.8±0.8	27.8±0.5

% Initial concentration remaining in pH neutral PD solution						
0	100.0±0.2	100.0±0.2	100.0±1.2	100.0±0.4	100.0±0.5	100.0±0.8
12	101.0±0.1	95.2±0.3	97.5±0.8	100.2±1.5	95.5±0.2	96.6±0.9
24	102.3±1.6	91.3±1.2	96.4±1.9	101.2±1.7	92.4±1.6	91.4±1.2
48	98.2±0.2	82.6±0.9	77.7±1.5	99.1±0.3	88.8±1.1	83.2±1.4
72	98.6±0.7	91.1±1.2	64.1±0.8	99.6±0.4	86.7±1.0	77.7±1.1
120	96.6±0.3	84.8±0.8	40.5±1.1	98.1±1.1	84.2±0.5	53.4±0.7
168	95.8±0.2	68.9±1.5	15.3±1.2	97.9±0.2	81.5±0.9	31.7±0.7
336	89.5±1.5	28.7±0.8	6.0±1.3	96.8±1.1	77.6±0.7	13.9±1.9

Comparison of the percentage of ceftazidime (125 mg/L) and cephazolin (125 mg/L) remaining in the 7.5% icodextrin or pH neutral PD solution before and after storage at 4, 25 and 37°C for various time intervals. Results are presented as mean ± SD. Samples were prepared in triplicate and analyzed in duplicate.

neutral PD solution stored at 4°C remained essentially unchanged for at least 168 hours. After 120 hours of storage at 25 or 37°C, the observed pH of the 7.5% icodextrin and pH neutral PD solution was less than 8.12 ± 0.12 and 5.02 ± 0.08 respectively.

DISCUSSION

This is the first study that investigated the stability of the combination of ceftazidime and cephazolin in a 7.5% icodextrin or pH neutral PD solution. Although the stability of cephazolin in the pH neutral PD solution has been reported (9), the current study re-assessed its stability in the same solution for three main reasons. Firstly, the previous study did not investigate the stability of cephazolin at body temperature. Understanding the stability of cephazolin at this temperature is important because a PD bag is usually warmed on a heating plate to body temperature (37°C) prior to its instillation. This enhances both the patient's comfort and the removal of waste products when the dialysate fills the peritoneal cavity. Failure to know the stability of cephazolin at body temperature can result in under-dosing or administering

degradation products. Secondly, the stability of cephazolin was not investigated using a stability indicating assay. A non-stability indicating method may not be capable of detecting and separating cephazolin from its degradation products or other interfering products present in the PD fluid. Thirdly, a single cephazolin PD bag was prepared and analyzed for each storage condition. Duplicate analyses of three replicate test samples are considered to be a minimum requirement for stability studies in order to increase confidence in the accuracy of the results (10).

The stability of cephazolin or ceftazidime in different types of PD fluids has been investigated before (11–15). Cephazolin (500 mg/L) is reported to be stable in icodextrin or dextrose PD fluid for at least 336 and 24 hours at 4 and 37°C respectively. Compared to the previously reported stability of cephazolin in icodextrin or dextrose PD solution, the stability of cephazolin in the pH neutral PD solution was found to be similar when stored at 4 or 37°C, but the drug was found to be less stable in the pH neutral PD solution when kept at 25°C. The pH of the non-glucose compartment of the pH neutral PD solution is higher (8.0 to 8.2) than the

dextrose (4.9 to 5.2) containing PD fluid. Cephazolin is more stable at acidic pH (maximum stability at pH 4) than at basic pH (16) and this may explain the difference in the observed stability of cephazolin at 25°C. Also in the current study, the greater stability of cephazolin in the acidic environment was evident from the fact that its degradation was approximately 10 times higher in the presence of 0.5N sodium hydroxide compared to 0.5N hydrochloric acid.

Our results indicated that the 7.5% icodextrin or pH neutral PD solution containing 125 mg/L of ceftazidime and cephazolin can be warmed to body temperature for use in the treatment of peritonitis in adult patients. However, in pediatric patients PD solution from a single bag may be administered for up to 96 hours. Hence, in such conditions patients can be exposed to the degradation products of ceftazidime including pyridine which is known to have toxic effects in humans (8,17).

Anecdotal evidence suggests that in some situations, antibiotics premixed in PD bags are prepared in a batch by nurses at patients' homes towards the end of the week to be used by the patients early in the following week. For practical reasons such bags are often stored at room temperature. Cephazolin was stable for 72 hours in 7.5% icodextrin PD solution and for 24 hours in pH neutral PD solution when stored at 25°C. On the other hand, ceftazidime was stable for 24 hours in either of the PD solutions. For the empirical treatment of peritonitis, ceftazidime and cephazolin are used in combination and, based on our results, we recommend using the antibiotics-admixed 7.5% icodextrin or pH neutral PD solution within 24 hours of storage at 25°C.

Ceftazidime and cephazolin solutions retained more than 90% of the initial concentration in both types of PD solutions for at least 7 days when stored at 4°C. Hence, to ensure prolonged stability, ceftazidime and cephazolin in 7.5% icodextrin or pH neutral PD solution should be stored under refrigeration.

Uncomplicated peritonitis can be managed by intra-peritoneal administration of antibiotics at a patient's home or in an outpatient setting. Hospital pharmacists or PD nurses often refer to the available stability information to prepare antibiotic containing PD solutions in advance in order to provide extra supply to patients living far away from hospitals or for those who are unable to self-load antibiotics into their own PD solutions. This study provides crucial information to healthcare professionals on the stability of ceftazidime and cephazolin in two different types of PD solutions to help make their decisions for preparing such admixtures in advance and storing them under appropriate conditions prior to administration.

CONCLUSION

Premixed ceftazidime and cephazolin in 7.5% icodextrin or pH neutral PD solution is stable for at least 168 hours when stored at 4°C. Therefore, such admixtures may be prepared in advance and stored at 4°C avoiding the necessity for frequent preparation.

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DISCLOSURE

The authors confirm that this article content has no conflict of interest.

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