SHORT REPORTS

Stability of Cefepime in pH-Neutral Peritoneal Dialysis Solutions Packaged in Dual-Compartment Bags

Intraperitoneal cefepime is used for the treatment of peritoneal dialysis (PD)-associated peritonitis caused by gram-negative bacteria. The current study investigated the stability of cefepime in a pH-neutral PD solution. A reconstituted solution of cefepime was injected into a total of 9 PD bags and stored at 4°C, 25°C or 37°C for various time points. Cefepime retained more than 90% of its initial concentration for 168, 96, and 12 hours at 4°C, 25°C and 37°C, respectively. No apparent physical precipitation or pH change was observed during the study. This study provides crucial information to healthcare professionals on the physical and chemical stability of cefepime in the pH-neutral solution to help them in preparing such admixtures in advance where required.

Perit Dial Int 2016; 36(4):457–459

www.PDIConnect.com

<http://dx.doi.org/10.3747/pdi.2015.00169>

KEY WORDS: Cefepime; stability; peritoneal dialysis; peritonitis; pH neutral; compatibility.

Peritonitis, typically caused by bacterial infection, is one of the major clinical complications associated with peritoneal dialysis (PD) (1). It is estimated that approximately 20 to 30% of all PD-associated peritonitis is caused by gram-negative organisms (2). The International Society for Peritoneal Dialysis guidelines recommend the use of cefepime (125 mg/L as a maintenance dose) for 21 days when peritonitis is caused by *Pseudomonas aeruginosa*, *Escherichia coli*, *Proteus*, or *Klebsiella* species (3). When used for the treatment of PD-associated peritonitis, cefepime is injected into the PD solution and then administered intraperitoneally to minimize the risk of cefepime-associated systemic toxicities as well as to achieve its high local concentration (1). Among various types of PD solutions, the most frequently used glucose-based PD solutions can alter the structure and functions of the peritoneal membrane as well as cause significant metabolic complications (4). To minimize such complications, newer types of PD solutions have been introduced on the market. One such type is a pH-neutral PD solution present in a dual-compartment bag. The glucose-based acidic solution present in one compartment and the buffer-based basic solution present in another compartment are mixed before use, resulting in a pH-neutral solution. Such a solution, with physiological pH (6.8 – 7.4), causes less peritoneal inflammation and thus helps to preserve peritoneal membrane function (5). Therefore, the newer types

of PD solutions are used in patients with altered structure and functions of the peritoneal membrane as well as in patients with diabetes and cardiovascular abnormalities. As cefepime is preferred to be administered intraperitoneally, failure to know its stability in PD solutions can result in the administration of possible degradation products as well as sub-therapeutic dosing of cefepime. The stability of cefepime in pH-neutral PD solutions has not been investigated so far. Therefore, the aim of this study was to determine the stability of cefepime in a pH-neutral PD solution under 3 different storage conditions at various time points.

MATERIALS AND METHODS

Sample Preparation

Cefepime hydrochloride monohydrate powder for injection (1 g/vial; Cefepime-AFT, Sydney, New South Wales, Australia) was reconstituted with 10 mL of Water for Injection BP to obtain a 100 mg/mL cefepime solution. A suitable volume of the reconstituted solution was injected into the non-glucose compartment (1.25 L) of the 1.5% Balance (Fresenius Medical Care, Sydney, New South Wales, Australia) 2-compartment pH-neutral PD bag (2.5 L) to obtain a final cefepime concentration of 250 mg/L in the non-glucose compartment. After addition of cefepime, each PD bag was shaken for approximately 1 minute to ensure proper mixing. A total of 9 PD bags were prepared and 3 bags were stored at each of 3 different temperatures: 4°C in a domestic refrigerator, 25°C (room temperature) in an incubator, or 37°C (body temperature) in an incubator. Control samples ($n=3$) were also prepared in a similar way except that cefepime was omitted. In clinical practice, immediately before the instillation of PD solution, the glucose solution from one compartment is mixed with the non-glucose solution present in another compartment; then, the mixed solution is warmed on a heating plate to attain the temperature of 37°C. Therefore, immediately prior to the storage of a pH-neutral PD bag at 37°C, the glucose-based solution (1.25 L, pH 3.0, 0 mg/L of cefepime) from the first compartment was mixed with the non-glucose (buffer) solution (1.25 L, pH 8.0, 250 mg/L of cefepime) present in another compartment to obtain a final cefepime concentration of 125 mg/L. An aliquot (1.5 mL) from each PD bag was withdrawn and the concentration of cefepime before (0 hour) and after storage was determined using a stability-indicating high-performance liquid chromatography (HPLC) method (6). All samples stored at 4°C were analyzed at 0, 8, 12, 24, 48, 72, 96, 168, and 336 hours. Samples stored at 25°C were analyzed at 0, 8, 12, 24, 48, 72, 96, and 168 hours,

and those stored at 37°C were analyzed at 0, 8, 12, 24, and 48 hours. Baseline samples (0 hour) were kept at room temperature and analyzed within 30 minutes of their preparation. Samples were also assessed for pH (with a pH meter), color change, and evidence of precipitation (visually) immediately after preparation and on each day of analysis. Cefepime was considered chemically stable if it retained more than 90% of its initial concentration.

Sample Preparation for HPLC Analysis

A standard stock solution of cefepime (500 µg/mL) was prepared by dissolving 5 mg of cefepime reference standard (Sigma-Aldrich, Sydney, New South Wales, Australia) in 10 mL of mobile phase. Cefepime calibration standards (25 to 250 µg/mL) were prepared by diluting cefepime stock solution (500 µg/mL) in the mobile phase. A standard curve was generated on each day of analysis by linear regression of the peak area of cefepime against its concentration. An aliquot withdrawn from each PD bag was transferred to a glass auto-sampler vial and then subjected to HPLC analysis. Each sample was analyzed in triplicate.

RESULTS

The mean concentration of cefepime at time 0 (before storage) was found to be 251.2 µg/mL and 125.9 µg/mL in the non-glucose and mixed solution respectively. These initial concentrations were considered as 100%. The percentage of the initial concentration of cefepime remaining after storage at 3 different temperatures is shown in Table 1. Cefepime in the non-glucose solution retained more than 92% of its initial concentration for 168 hours (7 days) at 4°C but lost more than 16% of its initial concentration after 336 hours (14 days). Storage of cefepime in the non-glucose solution at 25°C retained more than 90% of its initial concentration for 96 hours (4 days) but lost more than 10% of its initial concentration after 168 hours (7 days). Cefepime in the mixed solution was found to be stable for up to 12 hours at 37°C. The baseline pH of the cefepime solution in the non-glucose compartment was 8.35 ± 0.44 , whereas the baseline pH of cefepime solution in the mixed solution (after mixing the non-glucose and glucose compartments) was 7.13 ± 0.58 . The pH of cefepime solution remained essentially unchanged for 336 hours, 168 hours, and 72 hours when stored at 4, 25 and 37°C, respectively. No precipitation or color changes were observed under any of the tested storage conditions.

DISCUSSION

This is the first study that investigated the stability of cefepime in a pH-neutral PD solution. The recommended duration of intraperitoneal cefepime for the directed treatment of gram-negative peritonitis is 21 days. Ideally, cefepime should be admixed with the PD solution just before its intraperitoneal administration. However, many patients are unable to self-load

TABLE 1
Percentage of Cefepime Remaining in the pH-neutral PD Solution Before and After Storage at Different Temperatures for Various Time Intervals

Time (hours)	% of initial concentration of cefepime remaining		
	4°C	25°C	37°C
0	100.0±2.5	100.0±2.5	100.0±1.2
8	98.9±1.6	98.9±1.7	96.3±2.1
12	99.3±2.7	95.6±1.5	92.1±0.5
24	97.1±3.4	95.8±2.2	89.8±2.8
48	97.8±1.5	93.7±0.9	83.4±1.5
72	95.2±0.7	93.2±1.2	—
96	95.8±3.2	91.7±1.8	—
168	92.7±1.8	86.7±0.8	—
336	84.3±1.5	—	—

Initial cefepime concentration was 125 mg/L. Results are presented as mean ± standard deviation. Samples were prepared in triplicate and analyzed in triplicate. PD = peritoneal dialysis.

antibiotics in their own PD solutions, resulting in subsequent limitations and logistical issues. For example, patients' caregivers are required to travel to hospitals or PD clinics on a daily basis to collect the required drug admixed PD solutions. On the other hand, it may not be feasible for PD nurses to visit patients' homes every day to prepare antibiotics for admixed PD bags. Therefore, hospital pharmacists and PD nurses often refer to the available stability information to prepare antibiotic containing PD solutions in advance in order to provide extra supply to those patients living far away from the hospitals or for those who are unable to self-load antibiotics into their own PD solutions. Cefepime admixed in the non-glucose solution of pH-neutral PD bags is chemically and physically stable for at least 168 hours at 4°C. Hence, cefepime can be added into the non-glucose compartment in advance before storing the PD bags at 4°C, avoiding the necessity for frequent preparation. The PD solution is usually warmed to body temperature prior to instilling into the peritoneal cavity. This both enhances the patient's comfort and assists in the removal of waste products when the dialysate fills the peritoneal cavity. Results of the current study indicated that the pH-neutral PD solution containing cefepime was stable at 37°C for up to 12 hours. Therefore the 2 compartments can be mixed and then warmed to body temperature prior to instillation of PD solution into the peritoneal cavity.

ACKNOWLEDGMENTS

The authors are grateful to Andrew Reynolds and Andrea Whittle (home therapies nurses, Karingal Renal Education Centre, Department of Nephrology, Royal Hobart Hospital, Tasmania, Australia) for providing consumables to prepare antibiotics admixed PD bags.

DISCLOSURES

The authors have no financial conflicts of interest to declare.

Farzana Yousaf,¹
Syed T.R. Zaidi¹
Troy Wanandy^{1,2,3}
Matthew D. Jose^{2,4}
Rahul P. Patel^{1*}

Pharmacy¹
Medicine²
School of Medicine
University of Tasmania, Hobart, Tasmania, Australia
Department of Pharmacy³
Department of Nephrology⁴
Royal Hobart Hospital, Hobart, Tasmania, Australia

*email: Rahul.Patel@utas.edu.au

REFERENCES

1. de Vin F, Rutherford P, Faict D. Intraperitoneal administration of drugs in peritoneal dialysis patients: a review of compatibility and guidance for clinical use. *Perit Dial Int* 2009; 29(1):5–15.
2. Szeto CC, Chow KM. Gram-negative peritonitis—the Achilles heel of peritoneal dialysis? *Perit Dial Int* 2007; 27(Suppl 2):S267–71.
3. Li PK-T, Szeto CC, Piraino B, Bernardini J, Figueiredo AE, Gupta A, *et al*. Peritoneal dialysis-related infections recommendations: 2010 update. *Perit Dial Int* 2010; 30(4):393–423.
4. Lage C, Pischetsrieder M, Aufricht C, Jorres A, Schilling H, Passlick-Deetjen J. First *in vitro* and *in vivo* experiences with Stay-Safe Balance, a pH-neutral solution in a dual-chambered bag. *Perit Dial Int* 2000; 20(Suppl 5):S28–32.
5. Szeto CC, Chow KM, Lam CW, Leung CB, Kwan BC, Chung KY, *et al*. Clinical biocompatibility of a neutral peritoneal dialysis solution with minimal glucose-degradation products—a 1-year randomized control trial. *Nephrol Dial Transplant* 2007; 22(2):552–9.
6. Behin S, Punitha ISR, Krishnan S. Stability studies of cefepime hydrochloride by stability indicating RP-HPLC method. *Int J Pharm Sci Nanotech* 2013; 6(3):2181–6.