Stability Study of Temocillin for Outpatient Parenteral Antimicrobial Therapy

Beatriz Fernández-Rubio[1]*, Laura Herrera-Hidalgo[1,2], María Victoria Gil-Navarro[1,2,3], Luis E López-Cortés[3,4], Jesús Rodríguez-Baño[4], Rafael Luque-Márquez[2], Arístides de Alarcón[2], Sonia Luque-Pardos[5], Aurora Fernández-Polo[6], José María Gutiérrez-Urbón[7], Alicia Gutiérrez-Valencia[2]

[1] Unidad de Gestión Clínica de Farmacia, Hospital Universitario Virgen del Rocío/Instituto de Biomedicina de Sevilla (IBiS), Seville, Spain.
[2] Unidad de Gestión Clinica de Enfermedades Infecciosas, Microbiología y Medicina Preventiva, Hospital Universitario Virgen del Rocío/Instituto de Biomedicina de Sevilla (IBiS), Seville, Spain.
[3] Centro de Investigación en Red de Enfermedades Infecciosas (CIBERINFEC), Instituto de Salud Carlos III, Madrid, Spain.
[4] Infectious Diseases and Microbiology Clinical Unit, University Hospital Virgen Macarena; Departament of Medicine, School of Medicine, University of Sevilla; and Biomedicine Institute of Sevilla (IBiS)/CSIC, Seville, Spain.
[5]Unidad de Gestión Clínica de Farmacia, Hospital del Mar, Barcelona, Spain.
[6] Unidad de Gestión Clínica de Farmacia, Hospital Universitari Vall d'Hebron, Barcelona, Spain.
[7] Unidad de Gestión Clínica de Farmacia, Complexo Hospitalario Universitario de A Coruña, A Coruña, Spain.

* Corresponding author: Beatriz Fernández-Rubio. Avenida Manuel, Siurot, s/n. 41013, Sevilla (España).
beatrizfernandezrub@gmail.com +34646408880

ABSTRACT

Objective: To evaluate the physical and chemical stability of the antibiotic temocillin at the recommended dose for severe infections and contained in infusion bags or elastomeric devices at different temperatures for its use in Outpatient Parenteral Antimicrobial Therapy (OPAT) programs.

Method: Solutions of temocillin 12 g/L diluted in 0.9% sodium chloride were stored at 4ºC ± 2ºC, 25°C ± 2°C, 32°C ± 2°C and 37°C ± 2°C for 72 h both in polypropylene infusion bags and in polyisoprene elastomeric pumps. Physical and chemical stability were evaluated at 12, 24, 30 48 and 72 h after manufacturing. The solutions were considered stable if color, clearness and pH remained unchanged and if the percentage of intact drug was ≥90%.

Results: There were no observed changes in color or clarity in any of the refrigerated (4°C) samples or in the samples incubated at 25ºC and 32ºC. At 37ºC, an increase in intensity of yellow color was observed at 30, 48 and 72 h in both infusion bags and elastomeric pumps samples. All samples remained within the pH range 6.84–6.06. At 4ºC, 25ºC and 32°C ± 2°C, temocillin attained the stability criteria of ≥90% of the original concentration for the whole experiment in both devices. At 37ºC, temocillin was stable for 24 h but its

concentration dropped below 90% from that time point both in the infusion bags and in the elastomeric pumps.
Conclusions: According to the data provided in this stability study, temocillin administrated by continuous infusion would be an appropriate candidate for the treatment of patients that can be discharge to complete therapy in an OPAT program.

KEYWORDS

Temocillin; Stability; Outpatient Parenteral Antimicrobial Therapy; Temperatures; Elastomeric devices; Infusion bags.

INTRODUCTION

Temocillin is a semi-synthetic β-lactam antibiotic, a 6-α-methoxy derivative of ticarcillin. The methoxy group on the nucleus of the drug confers unusual stability against a wide range of β-lactamases, particularly extended-spectrum β-lactamases (ESBLs) and Amp-C inducible β-lactamases in *Enterobacterales*. It has no activity against Gram-positive bacteria, anaerobes or *Pseudomonas aeruginosa*[1]. Given its narrow spectrum of activity, temocillin offers a carbapemem-sparing option, so it has become an interesting alternative to highly resistant *Enterobacterales* infections[2,3].

Temocillin is only marketed in a handful of countries such as Belgium, France, Luxembourg and the United Kingdom for its use in urinary tract infections, bloodstream infections and lower respiratory tract infections where susceptible Gram-negative bacilli are highly suspected or confirmed. It is also designated as an orphan drug by both the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) for the treatment of *Burkholderia cepacia* lung infection in cystic fibrosis[4]. The usual dose of temocillin for adults is 4 g daily, but for the treatment of severe infections, a higher dose of 6 g daily is recommended[5]. It can be administrated by slow injection twice or three-times a day, although recent studies have proved that the administration of temocillin as continuous infusion shows superior PK/PD indexes than intermittent infusion[6,7].

Outpatient Parenteral Antimicrobial Therapy (OPAT), defined as alternative programs to conventional hospitalization that allow patients who require intravenous antibiotics to be treated outside hospital, has been shown to be clinically efficient and cost effective[8]. This

healthcare tool provides several advantages, such as the improvement of the quality of life of patients, allowing them to complete treatment in the comfort of their home or another outpatient site. Additionally, it avoids potential exposure to nosocomial pathogens and decreases the expense of hospitalization to complete a prescribed intravenous antibiotic course[9,10]. In this context, the administration of temocillin in OPAT programs is growing, particularly in urinary tract infections caused by resistant Gram negative bacteria[11,12]. However, drug stability should be taken into account, since it may vary with diluent, drug concentration, infusion container material and storage conditions (for example, refrigerated vs room temperature)[13]. Therefore, long-term stability of temocillin needs to be assessed before any extensive implementation in the OPAT setting.

The purpose of the present study was to evaluate the physical and chemical stability of temocillin at the recommended dose for severe infections and contained in infusion bags or elastomeric devices at different temperatures for its use in OPAT programs.

METHODS

Standards and reagents. Temocillin 1 g was donated by Eumedica S.A. (Manage, Belgium). The internal standard cefixime was purchased from by Alsachim (Illkirch, France). Dosi-fuser elastomeric pumps were supplied by Leventon (Barcelona, Spain) and 0.9% sodium chloride (NS) bags were obtained from Baxter Healthcare, Inc. (IL, USA). Liquid chromatography-mass spectrometry (LC-MS) grade (reagent grade, > 98% pure) acetonitrile was obtained from Merck KGaA (Darmstadt, Germany), and formic acid was purchased from Scharlab (Barcelona, Spain). Ammonium formate was obtained from Acros Organics (NJ, USA). Ultrapure water was prepared from a Milli-Q water purification system.

Preparation of solutions. Temocillin vials were reconstituted with water for injection (10 ml per each g of antibiotic), resulting in a concentration of 100 g/liter. The solutions obtained were further diluted in NS in order to get the final concentration, 12 g/l, and they were introduced into the polypropylene infusion bags and into the polyisoprene elastomeric pumps. The concentration results from the dilution of daily dose of temocillin, 6 g, in 500 mL NS. Three different infusion bags and three elastomeric pumps were prepared for each temperature, resulting in 24 devices.

Storage conditions and sample processing. Temocillin stability was tested at 4, 25, 32 and 37ºC. Once initial (0 h) samples were collected, the devices were stored in a fridge or in an air thermostat oven for the duration of the study (72 h). At each analyzed point (0, 12, 24, 30, 48 and 72h), duplicate 1 mL samples were taken from each device and frozen at −80 ºC until the analysis. Before the analysis, samples were diluted in Milli-Q water, vortexed and aliquoted in autosampler vials. Ten microliters of every solution were injected into the LC-MS/MS.

Instrumentation and chromatographic conditions. The analytical system consisted of an Agilent 1290 Infinity liquid chromatograph (Agilent Technologies, CA, USA) coupled to an AB SCIEX API 4000 mass spectrometer operating in electrospray positive-ionization mode. Chromatographic separation was performed using a reversed phase Phenomenex Luna C18 analytical column (5 mcm, 150 x 2.0 mm). The column and auto-sampler tray temperatures were set at 40°C and 4°C, respectively. Monitored transitions were 415.3 → 339.1 (temocillin) and 454.0 → 285.0 (cefixime, internal standard) *m/z*. A binary pump was used to deliver the mobile phases consisting of 0.1% formic acid and 2 mM ammonium formate in Milli-Q water (mobile phase A), and 0.1% formic acid in acetonitrile (MPB). Ten microliters were injected into the column and temocillin was eluted using a gradient elution at a flow rate set at 0.5 mL/min. From 0 to 0.5 minutes, the mobile phase consisted of 100% MPA. From 0.5 until 1.50 minutes, the MPB was increased linearly to 50% followed by a further increase to 95% MPB from 1.50 to 1.51 minutes. From 1.51 to 3.50 minutes, MPB was retained at 95%. At 3.51 minutes, the analytical column was re-equilibrated to the initial conditions. Total run time was 6 minutes. Validation of the method was performed following FDA guidelines, and the results met the acceptance criteria[14].

Physical stability. Precipitation, clarity and color of each infusion bag and elastomeric pump were visually assessed at each sampling time point. For the evaluation of the appearance of the solutions, the data were evaluated based on “no significant change” from the initial time point solution to the hold solutions. The pH (power of hydrogen) of every sample was measured by a stainless electrode pH meter (Hach, DC, USA).

Chemical stability. Drug stability was calculated as the percentage (*P*) of the initial drug remaining in the device at each analyzed time point (*Ct*), in relation to the concentration at the initial time (*C0*) ($P = Ct / C0 \times 100$). Chemical stability was defined as the recovery of

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more than 90% of the initial concentration of temocillin. Data are expressed as mean and 90% confidence interval (CI).

RESULTS

Precipitation, clarity and color. All samples were free of visible particulate matter. There were no observed changes in clarity or color in any of the refrigerated (4°C) samples or in the samples incubated at 25ºC and 32ºC. At 37ºC, an increase in intensity of yellow color was observed at 30h, 48h and 72h in both infusion bags and elastomeric pumps samples.

pH measurements. All samples remained within the pH range 6.84–6.06. Table 1 summaries the change in pH of temocillin samples.

Table 1. Change in pH of temocillin solutions.

Temperature	Device	pH (mean ± 90% CI) (n=6)					
		0h	12h	24h	30h	48h	72h
4 ± 2ºC	Infusion bag	6.84 (±0.09)	6.78 (±0.04)	6.76 (±0.07)	6.80 (±0.03)	6.78 (±0.03)	6.62 (±0.11)
	Elastomeric pump	6.60 (±0.10)	6.76 (±0.08)	6.74 (±0.05)	6.79 (±0.04)	6.82 (±0.06)	6.81 (±0.04)
25 ± 2°C	Infusion bag	6.78 (±0.12)	6.68 (±0.08)	6.49 (±0.07)	6.45 (±0.07)	6.22 (±0.03)	6.06 (±0.01)
	Elastomeric pump	6.73 (±0.9)	6.64 (±0.08)	6.47 (±0.07)	6.51 (±0.03)	6.31 (±0.05)	6.16 (±0.10)
32 ± 2°C	Infusion bag	6.66 (±0.08)	6.49 (±0.13)	6.29 (±0.06)	6.27 (±0.02)	6.16 (±0.05)	6.14 (±0.08)
	Elastomeric pump	6.79 (±0.02)	6.49 (±0.03)	6.40 (±0.10)	6.24 (±0.10)	6.17 (±0.11)	6.22 (±0.07)
37 ± 2°C	Infusion bag	6.73 (0.02)	6.35 (±0.03)	6.30 (±0.04)	6.20 (±0.09)	6.30 (±0.06)	6.40 (±0.13)
	Elastomeric pump	6.56 (±0.05)	6.51 (±0.13)	6.37 (±0.08)	6.44 (±0.07)	6.29 (±0.05)	6.49 (±0.03)

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Drug concentrations. At refrigerated temperature, 25ºC and 32°C ± 2°C, temocillin attained the stability criteria of ≥90% of the original concentration for the whole experiment in both devices. At 37ºC, temocillin was stable for 24 h but its concentration dropped below 90% from that time point both in the infusion bags and in the elastomeric pumps. Percentage and 90% CI of the remaining concentrations that were observed at each analytic time point during 72 h for each storage condition are listed in Table 2.

Table 2. Percentage of temocillin remaining at each analyzed point.

Temperature	Device	Concentration remaining (90% CI) (n=6)				
		12h	24h	30h	48h	72h
4 ± 2ºC	Infusion bag	99.63 (±3.50)	101.61 (±5.05)	102.52 (±5.26)	96.07 (±5.60)	99.80 (±6.59)
	Elastomeric pump	101.31 (±7.39)	103.76 (±6.15)	102.41 (±4.85)	101.31 (±5.92)	108.19 (±3.62)
25 ± 2°C	Infusion bag	103.96 (±3.45)	100.88 (±9.13)	102.23 (±6.16)	101.96 (±8.44)	102.26 (±6.82)
	Elastomeric pump	98.26 (±4.71)	103.48 (±7.17)	98.69 (±7.83)	100.10 (±6.17)	101.39 (±9.06)
32 ± 2°C	Infusion bag	93.28 (±1.77)	101.38 (±6.79)	96.72 (±3.58)	96.40 (±3.83)	106.86 (±4.98)
	Elastomeric pump	103.65 (±6.53)	101.30 (±8.64)	100.34 (±3.66)	96.10 (±2.93)	93.41 (±1.72)
37 ± 2°C	Infusion bag	96.13 (±7.00)	103.09 (±7.93)	83.21 (±7.00)	87.89 (±7.11)	66.77 (±4.27)
	Elastomeric pump	99.17 (±7.21)	107.48 (±2.45)	80.56 (±0.96)	79.07 (±4.00)	59.74 (±3.34)

DISCUSSION

The present study evidences that temocillin, diluted in NS at a standard concentration of 12 g/l, was stable for 3 days at refrigerated temperature (4ºC), room temperature (25ºC) and

high temperature (32ºC), both in infusion bags and elastomeric pumps. At 37ºC, temocillin was stable for 24 hours in the two devices.

Our data is consistent with previous investigations carried out in elastomeric pumps: at refrigerated temperature, Carryn *et al*. proved that temocillin 10 and 20 g/l was stable for 4 weeks diluted in water for injection[15]. Besides, all the solutions remained stable for 24h at room temperature after being removed from the fridge. In the same way, Sime *et al*. showed that temocillin with 0.3% citrate buffer was stable during refrigeration for 14 days in a concentration range from 2.17 g/l to 25 g/l. Subsequent warming to 32ºC maintained the stability for 24 h[16]. At the highest temperature, 37ºC, Loeuille *et al*. gave evidence of the stability of temocillin for 24 h at a concentration of 25 g/l in NS. However, the antibiotic was not stable at any time diluted in dextrose 5% (D5W) under the same conditions[17]. Regarding the stability of temocillin contained in polypropylene syringes, it remained stable for 24 h diluted in different solvents, including NS and D5W, at a concentration of 125 g/l[18].

In spite of the information provided in the above-mentioned studies, the present investigation is the only one that examines and compares the stability of temocillin in the two main containers used in OPAT programs for continuous infusion, polypropylene infusion bags and polyisoprene elastomeric pumps[19,20]. This data is essential, since the composition of the delivery devices can modify the stability of the drug[13]. Furthermore, this study was carried out at four different temperatures, given that temperature is not usually under control at home and it is a parameter closely related to drug degradation[21]. This factor is particularly critical in elastomeric infusers, as they are placed near the body. In this case, some authors recommend using 32ºC for stability studies considering that the elastomeric pump is not implant in the body[22,23]. However, other investigators suggest that the devices can even reach 37ºC in some warm geographical areas[24]. Therefore, we conducted our study at both temperatures, as well as at refrigerated and room temperature. Finally, the concentration was chosen based on the maximum daily dose of temocillin, 6 g, since it is the recommended for complicated infections, which are the main ones treated in the OPAT programs[25]. This dosage was diluted in 500 mL of the most common solvent, NS, because the administration of less volume would produce a higher concentration and, probably, a greater instability.

Some limitations can be found in our study: First of all, we did not identify the degradation products that appeared in the chromatographs, although acid, alkaline and enzymatic degradation of temocillin have been assessed[26]. However, it is not proved that these

products are clinically relevant or toxic[27]. Secondly, the only solvent used in the study was NS, even though other diluents such as water for injection or D5W are also suitable solvents[18]. In the third place, our tests are limited to only one brand of infusion bag and elastomeric pump. Containers from different manufacturers may produce different results and therefore require further testing.

In conclusion, according to the data provided in this stability study, temocillin administrated by continuous infusion could be an excellent choice for the treatment of patients that can be discharge to complete therapy in an OPAT program. In consequence, patients would benefit from a better quality of life and a reduction of the risk of nosocomial acquired infection, especially those patients that need a narrow spectrum alternative to other parenteral anti-Gram-negative agents, such as carbapenems, or patients with cystic fibrosis and *B. cepacia* lung infection.

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CONFLICTS OF INTEREST

L.E.L.-C. has served as a scientific advisor for Angelini, a speaker for Angelini, ViiV, Gilead, and Correvio, and as a trainer for ViiV. A.d.A. has served as a scientific advisor forAngellini, Novartis, Roche, and Cook Medical, a speaker for MSD, Pfizer, Angellini, Novartis, Roche, and ViiV, and as a trainer for MSD and Cook Medical. The remaining authors have no conflict of interest to declare.