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Assessment of ceftolozane/tazobactam stability in elastomeric devices and suitability for continuous infusion via outpatient parenteral antimicrobial therapy

Conor Jamieson[1]*, Felicity Drummond[2], Tim Hills[3], Laima Ozolina[4], Mark Gilchrist[5], R. Andrew Seaton [6], Mark Santillo[7], Alan-Shaun Wilkinson[4] and Michael C. Allwood[4]

[1]Pharmacy Department, Sandwell and West Birmingham NHS Trust, Birmingham, UK; [2]British Society for Antimicrobial Chemotherapy (BSAC), Birmingham, UK; [3]Pharmacy Department and OPAT Service, Nottingham University Hospitals NHS Trust, Nottingham, UK; [4]R&D, Biopharma Stability Testing Laboratory Ltd, Nottingham, UK; [5]Department of Pharmacy/Infection, Imperial College Healthcare NHS Trust, London, UK; [6]Department of Infectious Diseases, Queen Elizabeth University Hospital, NHS Greater Glasgow and Clyde, Glasgow, UK; [7]Torbay & South Devon NHS Foundation Trust, Torquay, UK

*Corresponding author. E-mail: conor.jamieson@nhs.net

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Objectives: To investigate the stability of ceftolozane/tazobactam 5 mg/mL and 20 mg/mL solutions for infusion in two elastomeric devices: FOLFusor LV10 (Baxter Healthcare) and Easypump® II (B. Braun Medical Ltd) and determine if an extended shelf life of up to 8 days storage at 2–8°C plus 24 h 'in use' at 32°C was achievable.

Methods: Testing was as per the latest NHS Pharmaceutical Quality Assurance Committee Yellow Cover Document (YCD) requirements. A stability-indicating LC method was used for assessing the stability of solutions of ceftolozane/tazobactam at 5 mg/mL and 20 mg/mL (combined concentration of both actives) respectively, tested in two batches in triplicate ($n = 3$) at five timepoints according to the requirements of the YCD.

Results: Ceftolozane/tazobactam, diluted in 0.9% w/v sodium chloride at 5 mg/mL and 20 mg/mL, degraded during in-use storage at 32°C with <95% remaining after 18 h for some device/concentration combinations and all device/concentration combinations at 24 h, respectively. The data does support extended storage of up to 8 days at 2–8°C plus 12 h at 32°C 'in-use' when using either FOLFusor LV10 or Easypump® II devices and is compliant with YCD.

Conclusions: Solutions of ceftolozane/tazobactam can be administered in outpatient parenteral antimicrobial therapy (OPAT) services following refrigerated storage for up to 8 days, when limited to a 12 h infusion at in-use temperature of 32°C. For UK OPAT services where twice daily dosing is feasible, our data provides another treatment option for challenging infections. In countries where a 10% loss of ceftolozane/tazobactam is acceptable, a 24 h infusion is supported by the data.

Introduction

Ceftolozane/tazobactam (Zerbaxa®, Merck Sharp & Dohme Corp) is a licensed broad-spectrum intravenous antibiotic with activity against multidrug-resistant Gram-negative (MDRGN) pathogens, which are an increasing problem worldwide.[1–3]

Deep-seated and complex infections caused by MDRGN pathogens are increasingly recognized and outpatient parenteral antimicrobial therapy (OPAT) has an important role for those patients who can be safely discharged from the acute care setting where there are limited or no oral treatment options.[4,5]

Antimicrobial elastomeric infusion devices with an acceptably long shelf-life and up to 24 h 'in use' stability offer a convenient method for delivering a continuous infusion of a drug to a patient in an ambulatory or home setting; infusion periods up to 24 h are possible and these devices are frequently employed in many parts of the world to facilitate OPAT delivery and antimicrobial stewardship.[6–10]

In the UK, the stability assessment of antimicrobial agents is dictated by the requirements of the National Health Service (NHS) Yellow Cover Document (YCD)[11] and is relevant to both broad- and narrow-spectrum agents to support antimicrobial stewardship.

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Test agents need to demonstrate acceptable stability in order for use in the NHS.

In this study, we aimed to test the stability of ceftolozane/tazobactam at two clinically relevant concentrations following reconstitution and dilution in 0.9% sodium chloride for use in two different elastomeric devices, in accordance with the requirements of the NHS YCD.[11]

Methods

See the Supplementary data at *JAC-AMR* Online for details of the materials (Table S1) and methods.

Results

A stability-indicating HPLC-diode array detector method was developed and shown to separate all degradation species from the main actives, ceftolozane and tazobactam. Peaks for actives appear at retention times of 2.86 min and 3.7 min, respectively, and were separated from all degradant peaks using a detection wavelength of 210 nm.

Throughout the study all samples remained completely clear and free from any visible particles (>100 microns) in accordance with British Pharmacopoeia (BP) requirements. The colour of the solution remained within the specified range from colourless to slightly yellow.

The YCD limit of 95%–105%[11] was applied to both ceftolozane and tazobactam remaining concentrations as a percentage of the starting concentration as there was no BP monograph available for ceftolozane/tazobactam solutions for injection.

The amount of tazobactam in both devices remained above the YCD 95% limit for acceptability[11] at all measured test timepoints (Tables 1 and 2).

In contrast however, the amount of ceftolozane remaining in both devices was observed to decrease significantly during the 'in-use' period where the devices were kept at 32°C for up to 137 h (Tables 1 and 2). Both elastomeric devices appear to show acceptability with the YCD[11] at the 18 h 'in-use' timepoint at the low concentration (5 mg/mL) but with additional storage at 32°C the amount of ceftolozane reduces to below the 95% limit. At the high concentration (20 mg/mL), the amount of ceftolozane remaining at 18 h is below the 95% limit for the FOLFusor LV10, and on the limit for the Easypump II device. Both concentrations of ceftolozane yielded values below the 95% limit for both devices at the interpolated 24 h timepoint.

No significant changes in pH of the 20 mg/mL (high) and 5 mg/mL (low) ceftolozane/tazobactam solutions were observed during the stability study. All results remained within the ±0.5 unit range for acceptability from the initial value (see Table S2). Particle count results are noted in Tables S3 to S6.

In this study, testing was extended beyond the initial proposed administration period of 24 h. Additional timepoints beyond the acceptance limit helped to improve the robustness of the data compared with the usual approach typically adopted in stability testing studies (Tables 1 and 2).

Discussion

The results of our study show that a 24 h infusion is not possible for ceftolozane/tazobactam based on current YCD criteria but a reduced 12 h administration is supported by the data. The maximum shelf-life that could be assigned was for 8 days refrigerated storage at 2–8°C, followed by a 3 h warm-up and a 12 h administration period at the UK 'in-use' temperature of 32°C.

Table 1. HPLC assay results for concentrations of ceftolozane (COZ) and tazobactam (TAZ) in FOLFusor LV10 (Baxter) devices

	20 mg/mL (COZ + TAZ)		5 mg/mL (COZ + TAZ)	
Timepoint	% Drug remaining	95% CI	% Drug remaining	95% CI
Ceftolozane				
Day 0	100% (13.969 ± 0.010 mg/mL)	–	100% (3.403 ± 0.012 mg/mL)	–
Day 2	99.65	0.18	100.13	0.32
Day 5	99.32	0.23	99.84	0.16
Day 8	99.37	0.10	99.62	0.11
Day 8 + 12 h	96.68	0.38	97.11	0.25
Day 8 + 18 h[a]	94.75	0.10	95.21	0.31
Day 8 + 110 h[a]	74.04	0.20	77.12	0.48
Day 8 + 137 h[a]	68.98	0.17	72.01	0.15
Tazobactam				
Day 0	100% (6.778 ± 0.002 mg/mL)	–	100% (1.656 ± 0.007 mg/mL)	–
Day 2	98.65	0.26	99.37	0.35
Day 5	99.74	0.54	99.73	0.21
Day 8	100.57	0.07	100.57	0.12
Day 8 + 12 h	98.71	0.85	99.26	0.88
Day 8 + 18 h[a]	98.88	0.16	98.35	0.28
Day 8 + 110 h[a]	92.60	0.50	94.52	0.22
Day 8 + 137 h[a]	90.33	0.10	91.39	0.08

[a]Additional timepoints to allow for statistical analysis.

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Table 2. HPLC assay results for concentrations of ceftolozane and tazobactam in Easypump II (B. Braun) devices

	20 mg/mL (COZ + TAZ)		5 mg/mL (COZ + TAZ)	
Timepoint	% Drug remaining	95% CI	% Drug remaining	95% CI
Ceftolozane				
Day 0	100% (14.04 ± 0.06 mg/mL)	–	100% (3.440 ± 0.009 mg/mL)	–
Day 2	99.55	0.19	100.04	0.24
Day 5	99.07	0.16	99.48	0.25
Day 8	99.31	0.26	99.52	0.03
Day 8 + 12 h	96.27	0.31	97.46	0.50
Day 8 + 18 h[a]	95.06	0.35	95.16	0.53
Day 8 + 110 h[a]	75.00	0.58	77.84	0.29
Day 8 + 137 h[a]	70.25	0.49	73.31	0.49
Tazobactam				
Day 0	100% (6.79 ± 0.03 mg/mL)	–	100% (1.672 ± 0.005 mg/mL)	–
Day 2	99.13	0.29	99.63	0.26
Day 5	99.48	0.28	99.80	0.28
Day 8	101.14	0.19	100.94	0.13
Day 8 + 12 h	99.26	0.31	99.84	0.81
Day 8 + 18 h[a]	98.59	0.25	98.31	0.34
Day 8 + 110 h[a]	95.33	0.82	95.71	0.35
Day 8 + 137 h[a]	92.39	0.46	92.77	0.56

[a]Additional timepoints to allow for statistical analysis.

The stability of ceftolozane/tazobactam in elastomeric devices has previously been studied by Terracciano *et al.*[12] and Raby *et al.*,[13] however, those studies do not meet the requirements of the NHS YCD protocol. The testing temperatures for stability assessment by Terracciano *et al.*[12] is not specified and in the work by Raby *et al.*,[13] the stability at 32°C is predicted as being greater than 95% for both actives at 24 h 'in-use' storage but this was not determined experimentally (empirical data was generated for 4°C, 25°C and 37°C).

Some refrigerated storage of filled elastomeric devices is desirable for OPAT services, thus allowing devices to be compounded in controlled aseptic conditions and held in stock. Data from Terracciano *et al.*[12] indicated chemical stability parity between ceftolozane and tazobactam under the conditions studied, with recoveries of more than 93% for ceftolozane and 94% tazobactam following storage at 2–8°C for 10 days in elastomeric pump devices. However, the data presented in this study and that of Raby *et al.*[13] indicates that when ceftolozane/tazobactam is stored at 2–8°C, negligible loss of either active is observed over a period of 7 days. It is notable that at ambient storage both report minimal losses of both actives over a 24 h period.[12,13] The 'in use' temperature for assessing the stability of ceftolozane/tazobactam is a critical differentiator between the study data reported here and previously published data.[12,13] Our study supports modelled data published by Raby *et al.*,[13] which indicates a significant lack of chemical stability for ceftolozane at 'in-use' temperatures above ambient compared with tazobactam, which was not reported by Terracciano *et al.*[12] because ambient storage was the highest storage temperature condition tested in that study.[12] As such, Raby *et al.*[13] is the first study to identify significant challenges in maintaining effective concentrations of ceftolozane when higher 'in-use' temperatures are required for compliance with OPAT. Critically, the Raby *et al.*[13] study used the 90% of initial drug concentration remaining acceptance criterion rather than the NHS YCD acceptance limit of 95%, but also a higher 'in-use' temperature of 37°C, which is also above that stated in the UK YCD requirements.[11]

The current study found that ceftolozane is most stable during refrigerated storage at 2–8°C but then degrades much more quickly than tazobactam during 'in-use' storage at 32°C. Kratzer *et al.*[14] showed that ceftolozane/tazobactam (30 mg/L and 15 mg/L) solutions were stable for up to 24 h at room temperature not protected from light in both 0.9% w/v sodium chloride and 5% glucose as diluent, supporting extended administration for up to 24 h. The Raby *et al.* study[13] has the only data where simulated body temperature had been studied, as required for studies involving elastomeric pump devices as the container, to meet YCD compliance for the UK. There is now data on a range of 'in-use' temperatures assessing ceftolozane/tazobactam stability.

Raby *et al.*[13] shows divergence in the chemical stability data between ceftolozane and tazobactam occurring in the temperature window between 25°C and 32°C which continues up to 37°C. Modelled data suggests 24 h is possible at 32°C with no additional refrigerated storage period.[13] Other studies demonstrated that ceftolozane/tazobactam solutions for injection at clinically relevant concentrations were stable for up to 24 h at room temperature in both 0.9% w/v sodium chloride and 5% glucose as diluent for up to 24 h with a 90% acceptance limit applied.[12,14]

In our study, ceftolozane/tazobactam was not sufficiently stable to meet the 95% limit for compliance with the YCD standards

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at the 'in-use' storage temperature of 32°C for a continuous 24 h infusion. However, literature searches have not identified any toxic degradants of ceftolozane/tazobactam and because continuous infusion of ceftolozane/tazobactam results in target attainment for pharmacokinetic/pharmacodynamic targets,[15] it is feasible that a lower acceptable limit outside of UK standards might allow for this. Given the challenge of MDRGN pathogens currently facing clinical practice, this needs to be properly validated.

Outside of the UK, in territories where a 90% limit is acceptable, and the 32°C testing temperature is not a requirement, lowering the 'in-use' temperature of the stability testing protocol to below 32°C (e.g. 25°C) would likely result in the concentration of ceftolozane/tazobactam remaining above 95% for the required 24 h 'in-use' period, and may also allow for a longer refrigerated shelf-life. Our data shows that a convenient 8 day shelf-life at 2–8°C is possible, followed by infusion at 32°C for 24 h, with the concentrations of both actives remaining above the 90% limit. Our data supports the use of continuous infusions of ceftolozane/tazobactam and will benefit the OPAT community worldwide.

Conclusions

Ceftolozane/tazobactam is insufficiently stable to be infused over 24 h for NHS use in the UK, and infusion must be limited to 12 h to meet the requirements of the YCD. The data supports an extended shelf-life of up to 8 days refrigerated storage at 2–8°C plus 12 h at 32°C, allowing a twice daily infusion in OPAT services. For territories that allow a lower acceptance limit of 90% remaining for actives or a lower 'in-use' temperature in OPAT services, a 24 h infusion may be achievable.

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Transparency declarations

M.G. has participated in an MSD educational antimicrobial podcast series. C.J. and M.G. are Editors of *JAC-Antimicrobial Resistance* but took no part in the handling or peer review of this article. All other authors have none to declare.

Supplementary data

Methods and Tables S1 to S6 are available as Supplementary data at *JAC-AMR* Online.

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