

# Temperature Stability And Antibacterial Activity Of Cefepime (CFP) During Continuous Infusion (CI) Administration

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## Abstract

**Background:** Time above MIC (T>MIC) is the pharmacodynamic parameter that best correlates with bacterial killing for CFP. CFP via CI achieves T>MIC throughout the dosing interval. The purpose of this study is to determine whether CFP exhibits sufficient stability and antibacterial (ABX) activity to be given by 24-hour CI using portable infusion pumps (PIP).

**Methods:** The stability of CFP in D5W solns. was determined in ten replicates for a simulated CI using a PIP (Microject 30, Sorensen Medical) worn over a period of 24-36 hours. The temp. in the bags were measured every ½ hr using a device placed adjacent to the drug-reservoir. CFP concs. were measured by HPLC. Mass spectrometry (MS) was used to identify the major degradation products by comparing mass ions signatures of fresh with degraded solns. The ABX activity of the CFP solns. were measured by comparing the MICs and MBCs of fresh and degraded solns against a reference strain of *P. aeruginosa* according to NCCLS. The degradation rate was determined at various temp. in duplicate: 1, 21, 37 and 55°C, which gave the Arrhenius plot that was used to indicate the clinical stability.

**Results:** CFP stability at 24 hours following CI was 94.3±1.0%. The mean infusion bag temp. was 22.6±1.5°C. CFP is stable for 15 d in refrigerator and 10 hrs at 37°C. CFP degradation rate was first order, thus independent of conc. MS data indicates that degradation includes cleavage of the R2 side chain and opening of the β-lactam ring. ABX activity appeared to correlate with intact CFP remaining in soln. ( $r^2>0.74$ ,  $p<0.001$ ). The Arrhenius plot was linear between 1-55°C ( $r^2=0.99$ ), and showed that the average temperature in the bag should not exceed 29°C in order to maintain 90% stability at 24 hours.

**Conclusion:** The study showed that the stability of CFP supports CI. A cold pack is necessary if the average temperature in the drug soln exceeds 29.1°C. Solns. of CFP should be stored in a refrigerator if not used right away, and in a freezer if not used within 7 days.

## Introduction

- Time above the MIC best correlates with the in vivo antibacterial effect of beta-lactams[1]
- Continuous infusion administration (CI) of beta lactams can achieve T>MIC for 100% of the dosing interval, thereby optimizing dosing.
- Potential advantages of CI include
  - Similar efficacy at a reduced dose [2-6]
  - Facilitate outpatient management through the use of portable infusion pumps (PIP)

### Stability

- CI administration requires the drug solution to be stable throughout the administration time.
  - Clinical stability is defined as 90% of initial parent drug concentration in solution after 24 hours.
  - Cefepime stability is depending on temperature.
- Current data indicates that cefepime is stable for 24 hours at room temperature[7], but data is conflicting at higher temps. [8]
- The temperature and stability of cefepime during CI using a motorized PIP is unknown.

### Study Goal and Objectives

- Goal: Determine if cefepime stability supports CI using a motorized PIP.
- Objectives:

- Determine the temperature variation and its influence on drug stability of cefepime during simulated CI, and stability during storage at varying temperatures.
- Identify the major degradation products of cefepime
- Characterize the antibacterial activity of the degradation products

## Methods

### Stability during continuous infusion

- Simulated patient condition:
  - A motorized PIP (Microject 30, Sorensen Medical, West Jordan, UT) and an infusion bag containing cefepime were placed inside individual pouches contained on a belt by three individuals for 24-36 hours.
- Drug concentrations within each infusion bag ranged from 2-6g/250mL.
- Seven samples were obtained at various time points and analyzed with HPLC for Cefepime content.
- An electronic temperature detector (TempTrace®, Dickson.) was placed adjacent to the drug reservoir to measure the temperature every 30 minutes during administration.

### Stability During Storage

- To simulate an in home-treatment situation, drug reservoirs were stored for one or two weeks in a freezer as well as in a refrigerator before CI administration.
- An Arrhenius plot was constructed for temperatures ranging from 4° to 55°C to provide information about the clinical stability of cefepime at different temperatures.

### Degradation Rate and Products

- Rate of degradation of cefepime over the complete concentration range (100% → 0%) was determined by exposing drug to a 37°C water bath for six days.
  - Samples were taken twice a day for 6 days.
  - Since the degradation rate is pH dependent, pH was measured for each sample.
- Mass spectrometry was used to identify the major degradation products.
  - Mass ion signatures from a fresh solution, 5%, 20%, 45% and a completely degraded cefepime solution, were used to identify the degradation products.
  - By following the degradation and comparing the mass changes in the samples with previous studies done on degradation of ceftazidime the major degradation products were identified.

### Antibacterial Activity

- The antibacterial activity for six solutions of cefepime containing 100%-12% active cefepime, and varying concentrations of cefepime degradation products were measured by determination of both MICs and MBCs.
- Antibacterial activity of cefepime solutions were determined against a reference strain of *P. aeruginosa* (ATCC 27853) using NCCLS methodology.
- The measured MICs were plotted against cefepime concentration remaining to determine if a relationship exists between observed MIC and percent cefepime remaining after degradation.

## Results

### Stability During CI

- The stability of cefepime after 24 hours CI for 8 replicates of 6g/250 mL was 94.2±1.1%
- Stability for the 2g/250mL and 4g/250mL were 95.0% and 92.4% respectively
- The stability after 30 hours simulated CI was 92.2±3.5%
- Cefepime solutions administered over 24 hours were significantly above the stability limit of 90% ( $p<0.0001$ ).

### Stability During Various Storage Conditions

The cefepime-solution was stable in all 24 hour experiments with the exception of the one following two weeks storage in a refrigerator

See Figure 1

## Results

Figure 1

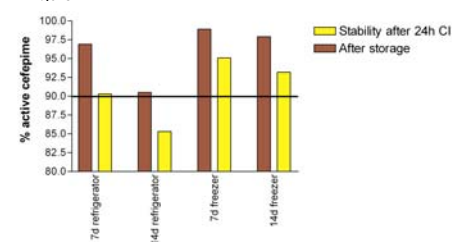


Figure 2

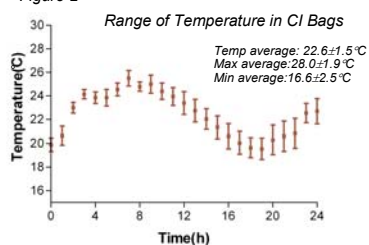
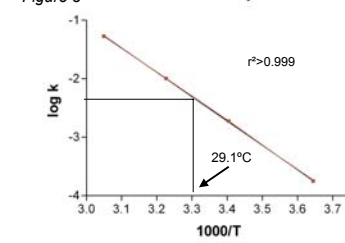
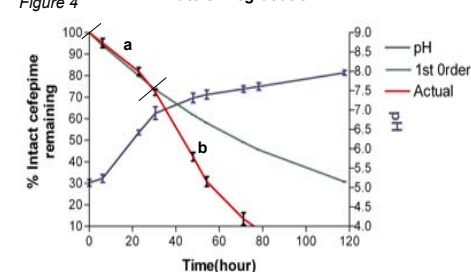


Figure 3



- The plot of log of the degradation rate constant k over the reciprocal of temperature (K) yields a linear relationship ( $r^2>0.999$ )
- The temperature that was calculated to give the stability limit of 90% stability was 29.1°C.
- The stability in refrigerator(4°C) was predicted to be 95.8% after 1 week and 91.8% after 2 weeks, and in freezer(-15°) 99.6% and 99.3%, respectively which compares favorably with the measured data depicted above.

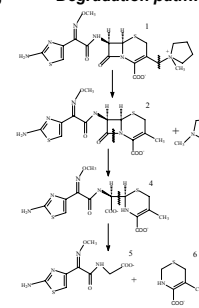
Figure 4



- The complete degradation of cefepime in D5W from the commercial product Maxipime® follows first-order kinetics in the first 25% (a. in figure) of the degradation ( $r^2>0.97$ ).
- Deviation from 1<sup>st</sup> order degradation is due to accumulation of alkaline degradation products that increase the pH, and thereby enhances degradation of cefepime.
  - Cefepime is most stable in the pH range of 4-6(6).
  - Degradation was associated with colorimetric changes: A fresh solution is clear, 10% degradation is pale yellow, 20% degradation is yellow, and 30% and more are orange, and complete degradation has orange/brown color.

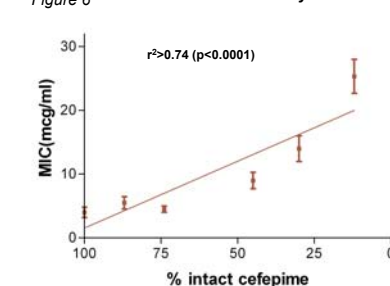
Figure 5

### Degradation pathway



- The degradation of cefepime includes cleavage of R2-side chain(3) and opening of the cephem (2)(β-lactam ring)
- MS analysis indicates that the ring opening occurs before the cleavage of R2-side chain
- Structure 5 is 2-[[2-amino-4-thiazolyl](Z)-methoxyimino]acetyl]amino]acetaldehyde
- Structure 3 is N-methylpyrrolidine

Figure 6



- A linear relationship between intact cefepime and its MIC against the reference strain of *P. aeruginosa*  $r^2>0.74$  ( $p<0.0001$ ), indicating that the degradation products exhibit no antibacterial activity.
- MICs for both fresh solutions and solutions for CI administration after 24 hours were the same at 4 mcg/ml, (breakpoint for susceptibility = 8 mcg/ml).

## Summary

- Cefepime solutions administered over 24 hours were significantly above the stability limit of 90% ( $p<0.0001$ ).
- The stability in refrigerator(4°) was 95.8% after 1 week and 91.8% after 2 weeks. In the freezer(-15°) the stability after one and two weeks were 99.6% and 99.3% respectively.
- The temperature in the drug reservoir was on average 22.6±1.5°C
- Degradation includes cleavage of the R2 side chain and opening of the β-lactam ring
- The degradation products appeared to possess no antibacterial activity

## Conclusion

### Optimal conditions for storage & CI administration

- Cefepime in D5W is stable and maintains antibacterial activity (>90% active) after 24 hours of continuous administration using a motorized portable infusion pump.
- Cefepime solutions must be stored in a refrigerator, if the supply is stored for more than five days before use, it must be kept in a freezer and allowed to thaw in a refrigerator one day before use.
- For patients who will be outside in temperatures exceeding 29°C for any length of time, a cold pouch should be placed adjacent to the drug reservoir to ensure cefepime stability.

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## Acknowledgements

- This study was supported in part by an educational grant from Elan Pharmaceuticals.
- Portable infusion pumps/supplies were provided by a gift from Sorensen Medical, West Jordan, UT