Modeling & Simulation Exercise to Recommend Dosage Regimens for Patients with End-Stage Renal Disease Receiving Hemodialysis

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Abstract

Objective

End-stage-renal-disease (ESRD) is a condition when kidneys do not adequately excrete wastes via urine to regulate hormones and chemicals in the body, which requires hemodialysis. Due to kidney failure, drug exposure in the body is higher than that of subjects with normal renal function; hence dose adjustment is necessary in ESRD patients. Ceftobiprole [1] is a first broad-spectrum cephalosporin to treat bacterial infections including those caused by methicillin-resistant *Staphylococcus aureus.* This modeling and simulation exercise was performed in order to recommend ceftobiprole dosage regimens for ESRD patients who require hemodialysis thrice a week.

Methods

A final population PK model [2], developed from Phase 1/2/3 subjects, was used to evaluate the PK profiles of a separate ESRD subject study. After model qualification, PK profiles (median and 90 % interval) of various dosage regimens were simulated by superpositioning to account for drug extraction (60% extraction ratio) by hemodialysis. Corresponding % Time-above-MIC (4 µg/mL) as a PK/PD target were calculated. A logistic regression of nausea events with respect to C_{max} was conducted.

Results

The PK model predicted the observed ESRD study PK results well. Three dosage regimens were identified as viable options, considering %T>MIC, probability of causing nausea and patient-convenience. To be conservative, the lower band of 90% prediction interval of PK profiles should yield higher than 50 %T>MIC. The incidences of observed and model-predicted nausea events increased around ceftobiprole concentration of 40 µg/ml. None of the simulated dosage regimen yielded a highest median concentration above 40 µg/ml.

Conclusions

Based on modeling and simulation three dosage regimens may be suitable for patients with ESRD: (1) 250 mg, 1-hr infusion, Q24h, (2) 500mg, 1-hr infusion, Q48h with an additional 250 mg 1-hr infusion on the 7^{th} day, and (3) 500mg, 1-hr infusion, Q48h, twice, followed by 750 mg, 1-hr infusion on the 5^{th} day. Each regimen will achieve > 50% T>MIC over the dosing intervals. Maximum predicted ceftobiprole concentrations do not exceed those that have been observed previously.

Reference

[1] Murthy B, Schmitt-Hoffmann A. Clin. Pharmacokinet. 2008: 47(1):21-33

[2] Kimko H, Murthy B, Xu X, Nandy P, Strauss R, Noel GJ. Antimicrob Agents Chemother. 2009: 53(3):1228-30

Introduction

- End-stage-renal-disease (ESRD) is a condition that occurs when kidney function is not adequate to support life
- Ceftobiprole is the first broad-spectrum cephalosporin to treat bacterial infections including those caused by methicillin-resistant *Staphylococcus aureus* (MRSA).
- Ceftobiprole clearance decreases with decreasing renal function.
- Dosage and interval adjustments have been recommended for patients with moderate and severe renal impairment.
- The PK of ceftobiprole in ESRD subjects undergoing hemodialysis (HD) was evaluated in a Phase 1 study during both dialysis and nondialysis periods

Background: Hemodialysis Extraction

- Hemodialysis effectively removes ceftobiprole and the open-ring metabolite from the systemic circulation.
- For ceftobiprole, the hemodialysis extraction ratio was approximately 0.6 to 0.7
- Based on the dose proportionality over the dosing range and the lack of accumulation of the open-ring metabolite, the available PK data in subjects with renal impairment was sufficient to simulate the plasma concentration-time profile of ceftobiprole after multiple doses under various hemodialysis scenarios.
- With the current dose for patients with severe renal impairment (= 250 mg, q12h), ceftobiprole would accumulate rapidly and result in concentrations higher than necessary to achieve efficacy in ESRD patients requiring hemodialysis

Objective

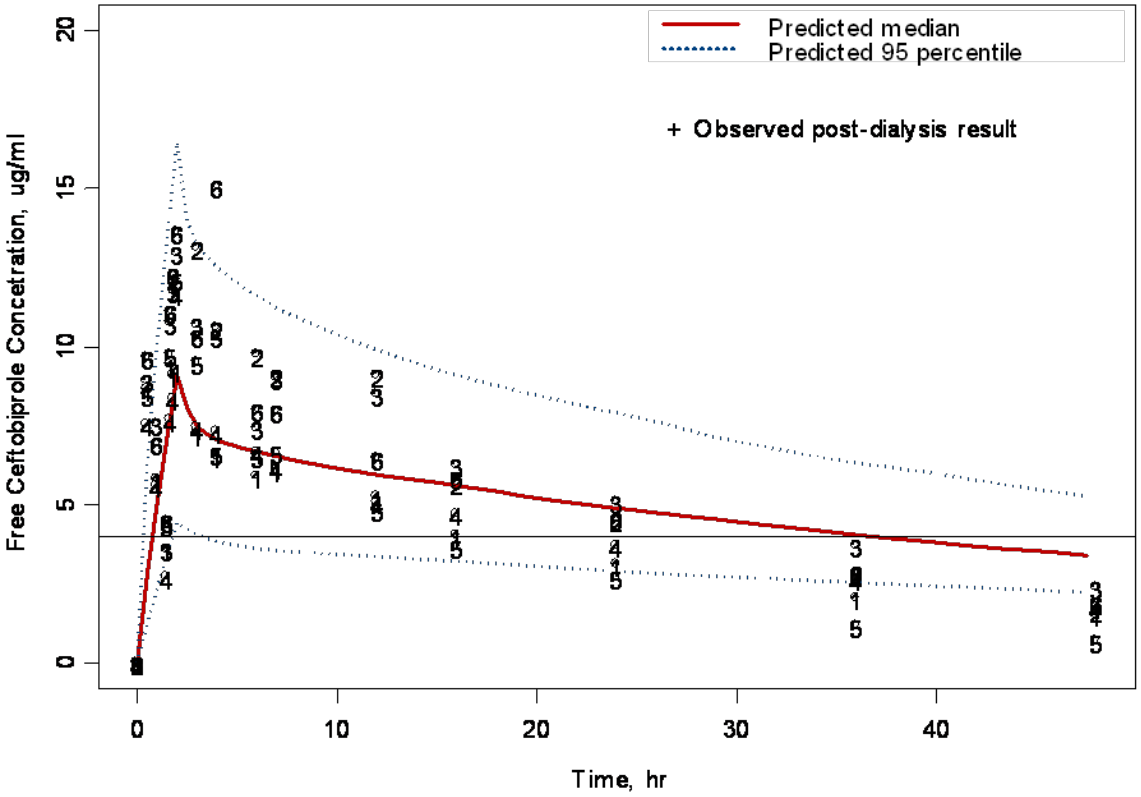
- To recommend dosage regimens for ESRD patients undergoing intermittent hemodialysis based on modeling & simulation exercise
  - Simulate PK profiles of various dosage regimens to meet PK/PD targets of %T>MIC (4 µg/mL) of 50% and 30% during the dosing interval.
  - Ensure these PK/PD targets were met over the last 24 hours of the dosing interval.
  - Evaluate incidences of adverse drug reactions to support safety of the recommended regimens.

Methods

- The previously developed population PK model[2] and covariate (sex, body weight) distributions of complicated skin and skin structure infection (cSSSI) and actual ceftobiprole concentration data from patients with ESRD who participated in a Phase 1 hemodialysis study were used in the simulation.
- 60% reduction in ceftobiprole concentrations after 4 hours of dialysis
- CL_{CR} arbitrarily fixed to 10 mL/min
- 500 virtual ESRD patients were simulated
- Identified doses to yield PK profiles with 90 % prediction intervals to have free ceftobiprole concentrations > 4 µg/mL and %T>MIC of 50%.
- Safety of the simulated dosing regimens was explored by evaluating the most common adverse drug reaction and ceftobiprole exposure (C_{max}) across clinical studies
- Modeling was done to 14 days (336 hours) to provide adequate information to evaluate 14 days of ceftobiprole treatment. The model suggests simulations beyond this are not necessary because steady-state was achieved.

PK Model Predicts the ESRD PK Well

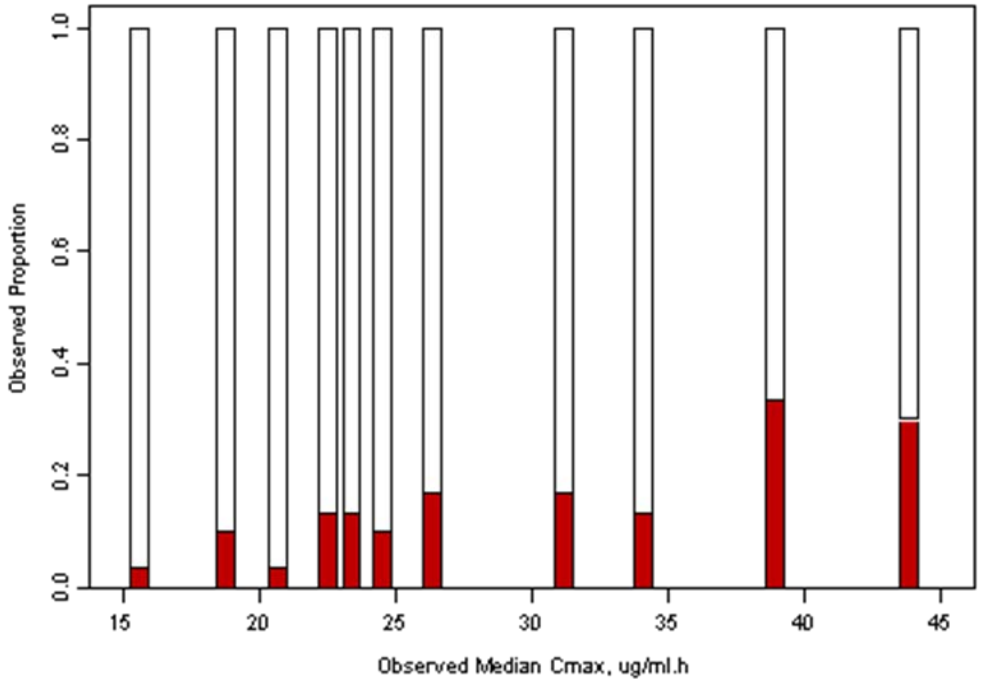
Ceftobiprole given post-dialysis



- The six subjects in an ESRD study appeared to have better CLcr than simulated subjects (i.e., 10 ml/min) and/or more metabolism than assumed in the simulation
- The number of ESRD subjects in the ESRD study is too small to use its CLcr as a good bootstrap sample set.
  - The simulation results may be a slight over prediction of PK

Adverse Effect: Nausea

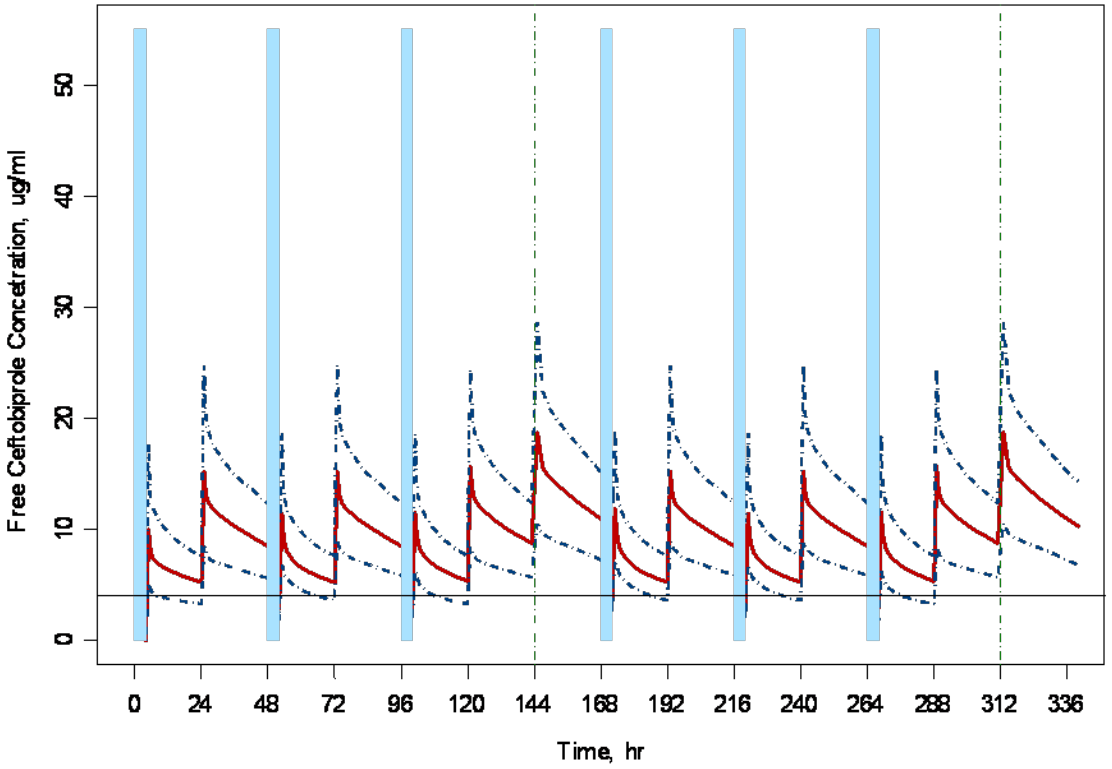
- Nausea, which was most frequently reported ADR, was a candidate adverse event to explore the relationship with respect to ceftobiprole exposure.
- Stacked bar plot showing the proportion of subjects who did or did not experience nausea with a range of C_{max} values.



- 40 μg/mL selected as a benchmark for safety

Simulation: Regimen 1

Once Daily 1-hr Infusions of Ceftobiprole 250 mg to ESRD Patients Receiving Intermittent Hemodialysis on Monday, Wednesday, and Friday

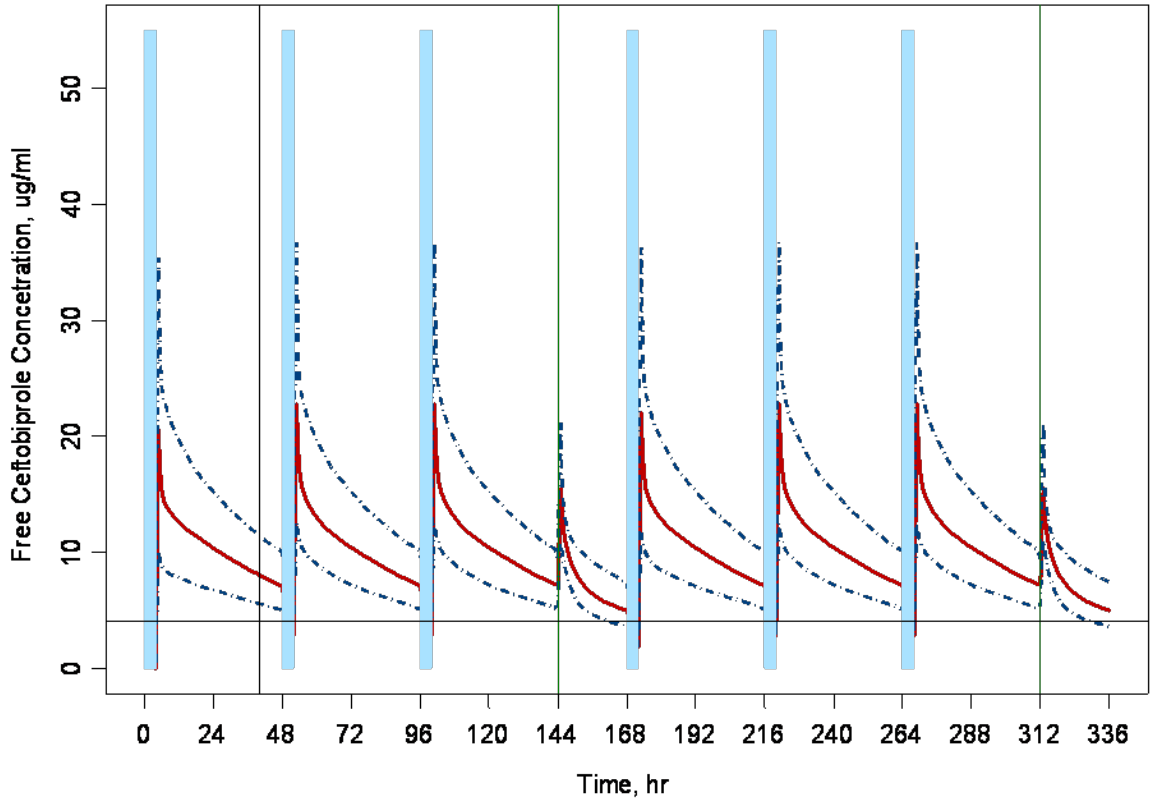


4 ng/ml target

Blue shaded area - 4 hour dialysis period; red line - median; blue dashed line - 90 % interval; green dashed line a week

Simulation: Regimen 2

1-hr Infusions of Ceftobiprole 500 mg on Monday, Wednesday, and Friday After Dialysis with Additional 250 mg dose on Sunday

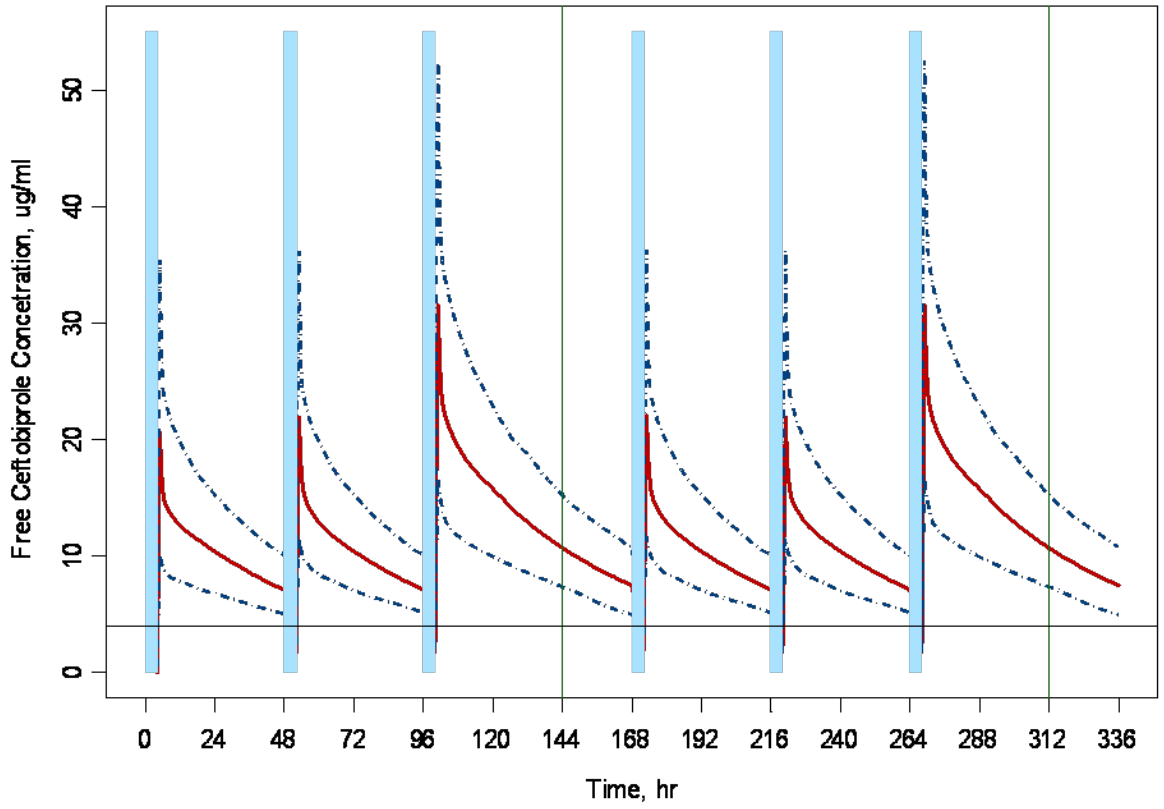


4 ng/ml target

Blue shaded area - 4 hour dialysis period; red line - median; blue dashed line - 90 % interval; green dashed line a week

Simulation: Regimen 3

1-hr Infusions of Ceftobiprole 500 mg on Monday and Wednesday, and 750 mg on Friday



4 ng/ml target

Blue shaded area - 4 hour dialysis period; red line - median; blue dashed line - 90 % interval; green dashed line a week

Technical Note

- Prepare NONMEM dataset for simulation
  - NM q48h sim data 44h only.ssc
  - NM q72h sim data 68h only.ssc
- Run NONMEM to get simulated results
  - Q48h44h.250mg.ctl
  - Q72h68h.250mg.ctl
- Using the simulated 44 and 68 hour PK profiles (4 hour dialysis considered), superpositioning was conduted with S-Plus after reducing the concentration just before dialysis by 60% (=extraction ratio) as the residual cocentrations at the begining of the next dosing

- The residual concentration from a previous dosing after dialysis was assumed to decline using the beta-phase of the 3 compartment PK model
  - This approximation is a conservative approach (i.e., Ceftobiprole is computationally removed faster than actual)
  - It will influence the simulation results little, due to low level of residual after dialysis
- Dose, dosing frequency and infusion duration should be entered appropriately for each simulation scenario

Summary

- All 3 regimens conservatively meet the target %T > MIC required for the treatment of cSSSI due to either gram positive (including MRSA) and or gram negative infections
- Simplified dosing schemes consisting of either one-half of or all of the 500 mg ceftobiprole vial
- Simple and intuitive dosing regimens may reduce dosing errors
- Regimen 1 based on current recommendation for dosing patients with severe renal impairment. But - least convenient since patients must be hospitalized or come into the hemodialysis clinic or infusion center every day, regardless of their dialysis schedule
- Regimens 2 and 3 would be more convenient for patients in that there would be fewer clinic visits.
- Regimen 3 has added advantage of dosing only on dialysis days with no additional visits by the patient.

Summary (cont)

- However, the 500 mg and 750 mg doses have not been studied in patients with severe renal impairment or ESRD undergoing intermittent hemodialysis
- Total weekly exposure (1750 mg) would be half that recommended for patients with severe renal impairment (3500 mg).
- The 90% prediction intervals for C_{max} for these simulations suggest that the maximum ceftobiprole concentrations will not exceed those that have been observed previously

Recommended Ceftobiprole Dosing Regimens For Patients With Varying Degrees of Renal Impairment Including Those Undergoing Hemodialysis

Renal Function	CL_{CR} (mL/min)	Recommended Dose	Weekly Dose (mg)
Normal	> 80	500 mg q8h	10,500
Mild	50 – 79	500 mg q8h	10,500
Moderate	31 – 49	500 mg q12h	7000
Severe	<30	250 mg q12h	3500
Inpatient Dosing in HD	NA	250 mg qd post HD	1750
Outpatient Dosing in HD	NA	500/500/500 + 250 mg 500/500/750 mg	1750

HD: Hemodialysis
HD recommendations are based on modeling & simulation exercise