# Pharmacokinetic Study of Cefazolin in Short Daily Hemodialysis

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## BACKGROUND

- Short daily hemodialysis (SDHD) involves 2 hours of dialysis, 6 days of the week
  - SDHD has been associated with decreased cardiovascular risk, improved quality of life, and a trend towards prolonged survival
- Infection is a leading cause of morbidity and mortality in dialysis patients
  - Gram-positive organisms are the leading cause of infection in hemodialysis patients
- Little is known about the pharmacokinetics and optimal dosing of cefazolin in SDHD

## OBJECTIVES

**Primary Objective:**

- Determine clearance of cefazolin by SDHD

**Secondary Objectives:**

- Characterize other pharmacokinetic parameters
- Determine if current dosing regimens provide serum drug concentrations above target MICs

## METHODS

**Study Design**

- Prospective, observational, single-centre study

**SDHD Dosing and Timing**

- Blood flow rates 350 mL/min
- Dialysate flow rates 800 mL/min
- F80A dialyzers
- 6 days per week
- 2 hours per treatment

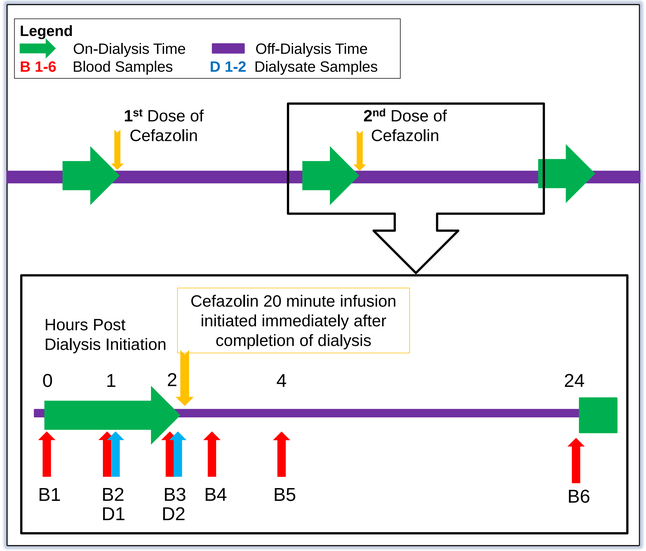
**Sample Collection and Analysis**

- Samples were analyzed using high performance liquid chromatography (HPLC)

## METHODS

**Sample Collection and Analysis**

- Six blood samples and two dialysate samples per patient were drawn over a 24 hour period




## RESULTS

- Five patients enrolled and completed the study. Baseline demographics are shown in Table 1

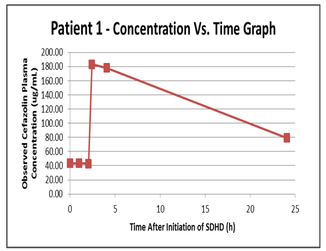
**Table 1: Baseline Characteristics**

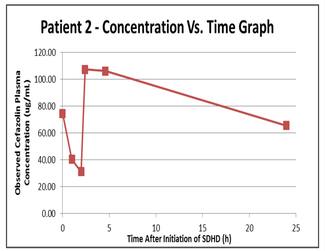
| | Patient 1 | Patient 2 | Patient 3 | Patient 4 | Patient 5 |
|---|---|---|---|---|---|
| **Age (years)** | 62 | 61 | 72 | 85 | 56 |
| **Gender** | M | M | M | F | M |
| **Weight (kg)** | 96.4 | 70.4 | 60.8 | 40.5 | 137.5 |
| **Cause of ERSD** | DM2 Contrast dye | DM2 | DM2 HTN | DM2 HTN | DM2 |
| **Vintage of dialysis** | 2 months | 16 months | 10 years | 5 months | 30 years |
| **Residual renal function* (mL/min)** | 7.11 | 7.59 | 0.55 | 5.62 | Anuric |

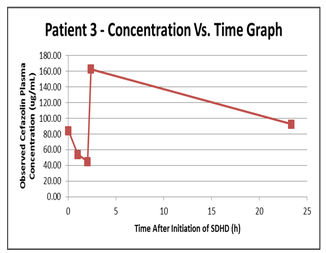
DM2 = Type 2 Diabetes Mellitus, HTN = Hypertension, * Calculated by 24 hour urine collection

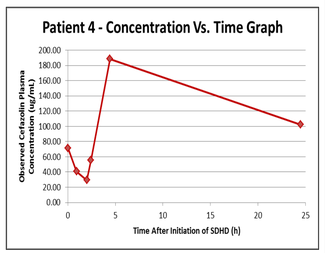
- Pharmacokinetic parameters were calculated using a one-compartment model. See Table 2
- **No** adverse events were reported

## RESULTS



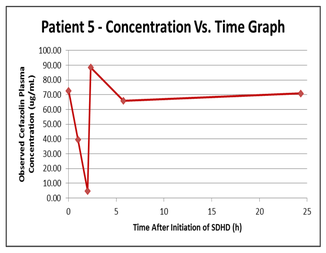




**Figure 1:** Observed plasma cefazolin concentration versus time curves for patient 1-5.

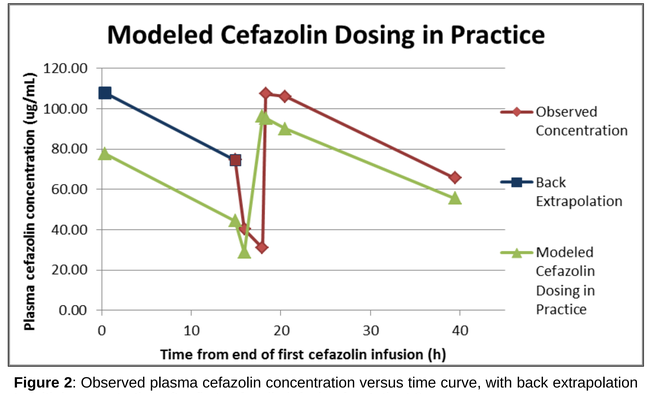



**Figure 2**: Observed plasma cefazolin concentration versus time curve, with back extrapolation to initial concentration after first cefazolin infusion for Patient 2.

Modeled cefazolin dosing in practice implies infusion over the last 20 minutes of dialysis. The following equations were used to determine cefazolin plasma concentrations:

$C_{t'} = (K_0/K_{el\ on}V_d)*(1-e^{-Kel\ on\ *\ t'})$ $\quad C_t = C_0 * e^{-Kel*t}$

$K_0$ = infusion rate

t' = infusion duration

## RESULTS

**Table 2: Pharmacokinetic Parameters**

| | $t_{½\ off}$ | $Cl_{s\ off}$ | $t_{½\ on}$ | $Cl_{s\ on}$ | $V_d$ | End Observed SDHD Conc. | SDHD Removal |
|---|---|---|---|---|---|---|---|
| | (hr) | (mL/min) | (hr) | (mL/min) | (L/Kg) | (ug/mL) | (%) |
| **Patient 1** | 17.2 | 4.8 | 174.2* | 0.5* | 0.08 | 43.1 | -7.6* |
| **Patient 2** | 27.3 | 5.1 | 1.6 | 87.3 | 0.17 | 31.0 | 56.2 |
| **Patient 3** | 25.8 | 3.6 | 2.2 | 41.9 | 0.13 | 44.9 | 34.2 |
| **Patient 4** | 22.7 | 2.6 | 1.6 | 37.7 | 0.13 | 29.3 | 56.2 |
| **Patient 5** | 69.3 | 1.6 | 0.5 | 217.8 | 0.07 | 4.8 | 93.3 |
| **Median** | 25.8 | 3.6 | 1.6 | 41.9 | 0.13 | 31.0 | 56.2 |
| **1st QRT** | 22.7 | 2.6 | 1.6 | 37.7 | 0.08 | 29.3 | 34.2 |
| **3rd QRT** | 27.3 | 4.8 | 2.2 | 87.3 | 0.13 | 43.1 | 56.2 |

*Patient 1 showed essentially no removal during dialysis for unknown reasons. QRT = Quartile.
End Observed SDHD Conc. = Concentration observed immediately after SDHD treatment

## DISCUSSION

**Pharmacokinetic Parameters**

- Small number of patients and variability in the parameters limit the analysis of results
- Further study is required with a larger cohort of patients

**Assess Current Dosing Regimen**

- *Staphylococcus aureus* breakpoint MIC for cefazolin is 4 ug/mL[1]
  - Aim for four to eight times the MIC of the bacteria (i.e. 32 ug/mL)
- All observed and calculated cefazolin plasma concentrations between dialysis sessions were above 32 ug/mL

## CONCLUSION

- Estimated SDHD clearance (41.9 mL/min) is higher than with intermittent hemodialysis (30.9 mL/min) using similar dialyzers
- Current dosing recommendations of cefazolin 1 gram infused over the last 20 minutes of SDHD appear to produce adequate plasma concentrations for bacterial eradication

1. The European Committee on Antimicrobial Susceptibility Testing. Version 3.1, 2013. http://www.eucast.org.