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LETTER TO THE EDITOR

Cefoxitin Continuous Infusion for Lung Infection Caused by the *Mycobacterium abscessus* Group

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The *Mycobacterium abscessus* group is an increasingly recognized cause of antibiotic-resistant lung infection (1–3). The efficacy of available antibiotics must be optimized. Continuous infusion of active β-lactam agents has the potential to maximize the time blood antibiotic concentrations exceed the MIC of infecting strains (T>MIC) (4, 5). We conducted a pilot study to evaluate the steady-state concentration (C_{ss}) of cefoxitin in blood.

Cefoxitin is an intravenous β-lactam antibiotic used in combination regimens for *M. abscessus* therapy, with recommended doses "up to 12 g/day" (6). Our standard practice has been to give 2 g twice a day (BID) to three times a day (TID) for ≥2 months (3). More-frequent intermittent dosing is often impractical, and higher doses cause toxicity (2). Of note, the breakpoint for cefoxitin "susceptibility" is ≤16 μg/ml (7), and MICs for clinical specimens are often higher. Doses required to achieve T>MIC via continuous infusion may be larger than expected.

Cefoxitin has a half-life of 40 to 60 min when given to persons with normal renal function (8), and a 2-g bolus given to healthy adults produces a mean maximum serum concentration of 244 μg/ml and a mean area under the serum concentration-time curve (0 to ∞) of 129 h · μg/ml (9). The time corresponding to a greater than "susceptible" MIC is approximately 3 h per dose. Extrapolating from pharmacokinetic data from bolus infusion in healthy volunteers, the C_{ss} average of 2 g cefoxitin given over 8 h (or 6 g over 24 h) is expected to be approximately 16 μg/ml. C_{ss} should be achieved within 5 half-lives (5 h).

We gave three female, non-cystic fibrosis *M. abscessus* patients aged 64 to 76 years a single 2-g dose of cefoxitin over 8 h. This was not a therapeutic trial. In order to minimize excess risk to participants, we did not increase the study dose beyond what was prescribed for treatment. Each participant had a calculated creatinine clearance ≥ 45 ml/min (Cockcroft-Gault). Blood was drawn hourly. Cefoxitin levels were measured using high-performance liquid chromatography. Individual patient data were fit to a one-compartment intravenous infusion model using the following formula: $C_t = C_{ss} \times (1\text{-}e^{-k \times t})$, where C_t is the concentration at time t, C_{ss} is the average steady-state concentration, and k is the elimination rate constant (10). All patients gave informed consent. The study was Institutional Review Board (IRB) approved.

Individual patient data and cefoxitin concentration-time curves are plotted in Fig. 1. Graphically, the model fit, and curves plateaued during infusion, indicating that C_{ss} was achieved. The median C_{ss} was 13 μg/ml (range, 11 to 22 μg/ml). One patient achieved a C_{ss} > 16 μg/ml. There were no side effects related to the study dose.

For continuous infusion of cefoxitin to be effective, C_{ss} must be >MIC. MICs for isolates in this study were ≤16 μg/ml. However, the MIC for 72% of 44 isolates from other patients at our institution was ≥32 μg/ml. Our data suggest that in future studies of cefoxitin continuous infusion, the dose will need to be greater than 6 g in 24 h. Higher MICs can be targeted by increasing the dose rate proportionally to the increase in MIC (assuming linear pharmacokinetics). Higher doses may be accompanied by toxicity (2).

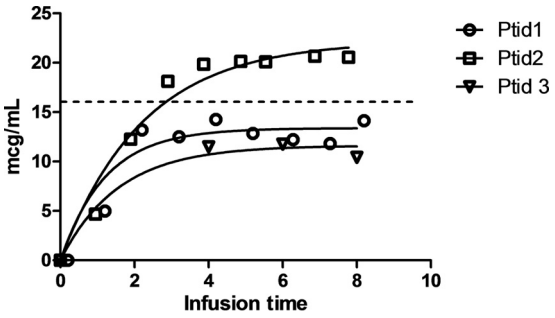

FIG 1 Serum cefoxitin concentration during an infusion of 2 g over 8 h. Individual data were fit to a one-compartment intravenous infusion model to estimate the steady-state concentration (C_{ss}) (10). Ptid1 was a 64-year-old female with estimated creatinine clearance (Cr_{Cl}) = 56.4 ml/min: C_{ss}, 13.37 μg/ml (95% confidence interval [CI], 11.47 to 15.28 μg/ml). Ptid2 was a 68-year-old female with Cr_{Cl} = 47.0 ml/min: C_{ss}, 22.21 μg/ml (95% CI, 19.02 to 25.40 μg/ml). Ptid3 was a 79-year-old female with Cr_{Cl} = 47.1 ml/min: C_{ss}, 11.27 μg/ml (95% CI, 8.80 to 13.75 μg/ml). Ptid3 completed only 4 blood draws. The dashed line at 16 μg/ml represents the MIC breakpoint for cefoxitin susceptibility (7).

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