Pharmacodynamics of Ceftriaxone versus Cefazolin and Alternatives as Out–Patient Parenteral Antimicrobial Therapy for Methicillin-Susceptible Staphylococcus aureus Infections

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BACKGROUND

Due to convenient dosing, ceftriaxone is often used as OPAT even when broad-spectrum therapy is not required [eg, methicillin-susceptible S. aureus (MSSA) infections]. Once-daily dosing along with high “susceptibility” rates may even lead to the selection of ceftriaxone for treating presumed or actual MSSA infections in hospitalized patients.

Since antimicrobial pharmacodynamics (PDs) are dependent on actual MIC distributions, the activity of cefazolin may be compromised compared with other options such as ceftriaxone. As OPAT, however, cefazolin presents less convenient, twice-daily dosing.

GOAL: To use an integrated pharmacokinetic (PK)-PD analysis to evaluate cefazolin and alternatives as OPAT for MSSA infections.

METHODS

Monte Carlo simulations (MCSs) were used to create cohorts of 5,000 study subjects using SYSTAT® (v12). Ceftriaxone and cefazolin,2,4 and if contradicted, alternatives including vancomycin,2 daptomycin,2 and linezolid2 were tested using published PK models to simulate free (f) plasma concentration profiles in a relevant patient population (75 ≥ 10 kg, Cl, 50–100 mL/min/2).

Robust MIC distributions were based on data from 6,490 MSSA isolates collected from patients in 13 Canadian hospitals from 2007 to 2015. PD targets for cefazolin and ceftriaxone were ≥50%<sub>T</sub><sub>%</sub> (bacteriostatic), >75%<sub>T</sub><sub>%</sub> (1–2 log kill), and >100%<sub>T</sub><sub>%</sub> (bactericidal) based on literature values and previous in vitro PD modeling studies.6

PD targets for vancomycin, daptomycin, and linezolid were an AUC<sub>0-24h</sub>/MIC >800, >800 and >800, respectively.

Predicted target attainment (TA) for each MIC was calculated as the fraction of 5,000 simulated subjects achieving target. Cumulative target attainment (CTA) was determined by multiplying the PTA at each MIC by the fraction of isolates at that MIC, and then adding the values.

CTA was considered optimal when the PD target was achieved in at least 90% of simulated subjects.

RESULTS

The subject body weights and PK parameters generated by MCS are detailed in Figure 1 and Table 1, respectively. The MIC distribution of MSSA isolates is described in Table 2.

Cefazolin 2 g q24h attained PD targets for bacteriostatic, 1–2 log kill and bactericidal activity in 86%, 49%, and 17% of cases, respectively. (Figure 2) Cefazolin 1 g q24h reached these targets in 92%, 78%, and 57%, respectively. (Figure 3) As such, cefazolin 2 g once-daily did not even achieve optimal target attainment for bacteriostatic therapy. Although cefazolin 1 g twice-daily reached optimal target attainment for bacteriostasis, it was still inadequate for bacterial kill.

Cefazolin 2 g q24h attained PD targets for bacteriocidal, 1–2 log kill and bactericidal activity in 96%, 50%, and 15% of cases, respectively. (Figure 2) Cefazolin 1 g q24h reached these targets in 100%, 100%, and 97%, respectively. (Figure 3) Hence cefazolin 2 g once-daily achieved optimal target attainment for bacteriocidosis, and cefazolin 2 g twice-daily was optimal for bacteriostatic therapy.

The influence of renal function on the PDs of cefazolin and ceftriaxone is depicted in Figure 4.

Of the alternatives, vancomycin 1 g q24h (2 g/day) and 1 g q8h (3 g/day) attained AUC<sub>0-24h</sub>/MIC >800 in 81% and 100% of simulated subjects, respectively. Daptomycin 4 and 8 mg/kg q24h achieved AUC<sub>0-24h</sub>/MIC >800 in 96% and 100% of cases, respectively, whereas linezolid 600 mg q24h reached AUC<sub>0-24h</sub>/MIC >800 in 77%.

CONCLUSIONS

Although convenient, once-daily cefazolin has poor PD activity against MSSA and exposes patients to unnecessary broad-spectrum antibiotic therapy.

Once-daily cefazolin was inadequate even for bacteriostasis, and was actually inferior to once–daily cefazolin. (Figure 2)

Twice-daily cefazolin achieved optimal PD targets even for bacteriocidical therapy, offering a more convenient option than the traditional thrice–daily dosing. (Figure 2)

Since renal function influences the PD activity of cefazolin, Figure 4 Cl<sub>e</sub> should be considered in selecting appropriate dosing (eg, once–daily or twice–daily) or if strategies such as adding probenecid would be beneficial.

Of the alternatives, optimal PD targets could be achieved with vancomycin and daptomycin but not with linezolid.

REFERENCES: