Cefepime / Sulbactam as an Enhanced Antimicrobial Combination Therapy for the Treatment of Multi-drug Resistant Gram-negative Infections.

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Running Head: Cefepime / sulbactam combination therapy

Abstract

Background: β-lactam / β-lactamase inhibitors (BL / BLI) are widely used for the treatment of Gram-negative infections. Cefepime has not been widely studied in combination with BLIs. Sulbactam, with dual BL / BLI activity has been partnered with very few β-lactams. We investigated the potential of cefepime / sulbactam as an un-orthodox BL / BLI inhibitor against MDR Gram-negative bacteria.

Methods: *in-vitro* activity of cefepime and sulbactam (1:1, 1:2 and 2:1) was assessed against 157 strains. Monte Carlo simulation was used to predict the probability of target attainment with a number of simulated cefepime combination regimens, modelled across putative cefepime / sulbactam breakpoints (≤16 / ≤0.25 mg/L).

Results: Cefepime / sulbactam was more active (MIC_{50} / MIC_{90} 8/8 – 64/128 mg/L) compared to either drug alone (MIC_{50} / MIC_{90} 128 – >256 mg/L). Activity was enhanced when sulbactam was added at 1:1 or 1:2 ($p < 0.05$). Reduction in MIC was most notable against *A. baumannii* and *Enterobacteriales* (MIC 8/8 – 32/64). PK / PD modelling highlighted up to 48% % of all isolates, and 73 % of carbapenem resistant *A. baumannii* with MIC of ≤16 / ≤8 mg/L, may be treatable with high-dose fixed drug (1:1 or 1:2) combinations of cefepime / sulbactam.

Conclusion: Cefepime / sulbactam (1:1 or 1:2) displays enhanced *in-vitro* activity versus MDR Gram-negative pathogens. It could be a potential alternative to existing BL / BLI inhibitor combinations for isolates with a cefepime / sulbactam MIC 16-8 mg/L either as a definitive treatment or as a carbapenem sparing option.

Introduction

β-lactams (BL) are the most widely used antibiotics in the empirical and targeted treatment of bacterial infections. Efficacy against many Gram-negative pathogens (*Enterobacteriales, Pseudomonas, Acinetobacter*) is increasingly compromised by the emergence and spread of MDR strains that produce β-lactamases. These can confer resistance to one or more penicillin, cephalosporin, monobactam or carbapenem drugs routinely used in clinical practice.[1] A potential solution is to combine β-lactams with β-lactamase inhibitor molecules (BLI). These include β-lactams such as clavulanic acid, tazobactam, sulbactam, and the diazabicyclooctanes avibactam, zidebactam and nacubactam; able to act either as direct or competitive suicide inhibitors of β-lactamase enzymes. Those licensed, and most widely used in the United Kingdom, are fixed dose combinations of amoxicillin / clavulanate (2:1), ticarcillin / clavulanate (15:1), piperacillin / tazobactam (4:1), ceftolozane / tazobactam (2:1), ampicillin / sulbactam (2:1) and ceftazidime / avibactam (4:1). Other BL / BLI combinations such as cefoperozone / sulbactam are available in some regions of the world (South and Southeast Asia). There are also a number of novel combinations in the later stages of clinical development (aztreonam / avibactam, imipenem / relebactam, meropenem / vaborbactam, aztreonam / nacubactam, meropenem / nacubactam).[2,3]

None of the existing BL / BLI combinations have been shown to have reliable activity against all important β-lactam resistant species or provide functional inhibition of all clinically relevant β-lactamases (Supplementary Table 1). Resistance to BL / BLI combinations is further influenced by the permeability (porin), active efflux and target site modifications (PBP) typically found in MDR strains,[4] along with the capacity of the β-lactam component to induce or enhance the production of β-lactamases. With

78 treatment options limited, clinicians are increasingly using un-orthodox BL / BLI
79 combination therapies, often as salvage treatments for MDR infections, especially
80 those with resistance to carbapenems (CRO).[5,6]
81
82 Here, we undertook *in vitro* studies using a collection of contemporary MDR
83 Gram-negative isolates to inform whether cefepime / sulbactam might be a useful
84 combination therapy for development as a treatment for MDR Gram-negative
85 infections.
86

Materials and Methods

Isolates (n=157) were from the collection held at Queen Mary University London, recovered from routine specimens submitted to Barts Health NHS Trust and associated London hospitals. Species identification was performed by MALDI-Tof mass spectrometry (Bruker, Coventry, UK) with resistance to cephalosporins, carbapenems and monobactams determined by a combination of disc diffusion (ertapenem, imipenem, meropenem), the Microscan WalkAway System (Beckman Coulter, High Wycombe, UK) and Etest (bioMeriueux, Basingstoke UK) interpreted according to current EUCAST / CLSI breakpoints. Genes encoding common class A (KPC, IMI), B (NDM, IMP, VIM) and D (OXA CHDL) β-lactamases were identified using a range of multiplex PCRs and whole genome sequencing methods.[7]

Initial screens for cefepime / sulbactam synergy were performed by double disc diffusion tests using cefepime (30 µg) and ampicillin / sulbactam (10 µg / 10 µg) discs (Oxoid, Basingstoke, UK) placed 10 – 15 mm apart with >3 mm zones of expansion or 'keyhole' effects used to identify synergistic activity. (Figure S1).

Antibiotics (cefepime hydrochloride Lot no. LRA9570, sulbactam Lot no. 3100156) purchased from Sigma-Aldrich (Poole, UK) and Cambridge Bioscience Ltd (Cambridge, UK) were made as stock solutions of 10,000 mg/L in phosphate buffered saline (PBS). MICs of cefepime, sulbactam and cefepime / sulbactam at 2:1, 1:1 and 1:2 ratios were determined by the agar dilution using Muller-Hinton (MH) agar, supplemented with doubling dilutions of cefepime / sulbactam from 0.125 / 0.0625 – 128 / 256 mg/L according to Andrews.[8] Control organisms used in MIC determinations were ATCC 25922 (*Escherichia coli)*, ATCC 27853 (*Pseudomonas*

aeruginosa), ATCC 9633 (*Klebsiella pneumoniae*) and ATCC 19606 (*Acinetobacter baumannii*). Assays were only considered valid if the MIC of controls fell within +/- 1 dilution of the reference MIC.

The MIC distribution of cefepime combined with sulbactam (2:1, 1:1, 1:2) were used to predict the likelihood of therapeutic success with a number of simulated cefepime dosing regimens. Monte-Carlo simulation was performed in R using the linpk package. The cefepime pharmacokinetic (PK) model was taken from Jonckheere et al[9] whereas the sulbactam model was taken from Soto et al.[10] In both cases a 2 compartment model was used and fraction unbound assumed to be 81% for cefepime and 62% for sulbactam. A population of 10,000 adult ICU patients was sampled from a real adult demographic dataset, with a plot of the age, weight and creatinine clearance given in Figure S2.

The PTA was set at 60% time >MIC at steady state for cefepime and sulbactam, with PTA for 1:1, 2:1 and 1:2 ratios compared across 36 possible cefepime / sulbactam dosing regimens (3 – 8g / day) administered either by bolus, extended (EI) or continuous infusion (CI). The proportion of isolates for which the PTA was achieved for both cefepime and sulbactam[11] was compared by species and by the dosing regimen.

Results and Discussion

A total of 157 cephalosporin / carbapenem resistant *E. coli* (n=36), *Klebsiella* spp. (n=49), *A. baumannii* (n=66) and *P. aeruginosa* (n=6) were tested (Table 1). Synergy was observed in cefepime / sulbactam double disc diffusion assays with 73 % of the *E. coli* and 78 % of the *A. baumannii* isolates. Most isolates exhibited high level resistance to both cefepime and sulbactam (MIC_{90} >256 mg/L) alone. The exception was for ESBL producing *E. coli* and *K. pneumoniae*, which retained some susceptibility to cefepime (MIC_{50} ≤ 0.25 – 1 mg/L) and for *A. baumanni*, where an enhanced activity of sulbactam was observed ($MIC_{50/90}$ 16 - ≥256 mg/L). At a ratio of 2:1 the activity of cefepime / sulbactam was improved against ESBL producers ($MIC_{50/90}$ 2/1 – 64/32 mg/L) but had little effect on carbapenem resistant Enterobacteriales ($MIC_{50/90}$ 64/32 - ≥256/128) A stepwise increase in the ratio of sulbactam to cefepime (1:1, 1:2) resulted in a decrease in the cefepime / sulbactam MIC (Figure 1). This was most marked with respect to *A. baumannii* ($MIC_{50/90}$ 8/8 – 32/64 mg/L) and for all isolates with carbapenem resistance ($MIC_{50/90}$ 4/8 – 32/64 mg/L). Activity was most enhanced when sulbactam was added to cefepime at a concentration of 1:1 or 1:2 ($p < 0.05$). Reduction in MIC was then most notable against carbapenem resistant *A. baumannii* and Enterobacteriales isolates harbouring OXA-like carbapenemases (MIC 8/8 – 32/64).

The probability of individualised cefepime / sulbactam dosing regimens to achieve the cefepime / sulbactam PK / PD target of 60 % *f*T > MIC at each ratio are shown in Table 2**.** Up to 48 % of all isolates, and 73 % of carbapenem resistant *A. baumannii* with a cefepime / sulbactam MIC of ≤ 16 / ≤ 8 mg/L were predicted treatable with a high-dose (6-8 g /day) cefepime / sulbactam (1:1 or 1:2) combination. Furthermore, if a cefepime / sulbactam (>1:1) regimen of 8 g / day were adminstered by continuous

(CI) or extended infusion (EI), efficacy against 62 % of the CRO tested is predicted for those with a cefepime / sulbactam MIC of up to 16 / 16 mg/L (Figure S3).

These *in vitro* activity data suggest that cefepime / sulbactam could be developed as a BL / BLI based treatment for some MDR Gram-negative infections. There are a number of reasons to progress it as a preferred combination but also some challenges.

Cefepime monotherapy has been licensed and used for decades in the treatment of bacterial infections. There is a wealth of data on its efficacy, safety and tolerability, including at high doses for the treatment of susceptible Gram-negative infections. As the primary component of a BL / BLI therapy, cefepime also offers some advantages over other cephalosporins (cefoperazone, ceftazidime). Of note, it is stable to hydrolysis by many class C (AmpC) β-lactamases and, carrying a neutral (zwitterionic) charge, is less affected by permeability (porin) and efflux mediated resistance mechanisms.[12] The potential of cefepime is evident from recent studies assessing its activity in combination with tazobactam,[13] en-metazobactam (AAI101),[14] zidebactam,[15] avibactam[16] and nacubactam[17] as BLIs. These all demonstrate *in vitro* activity against MDR Gram-negatives that produce ESBLs and / or carbapenemases comparable to that we have observed with cefepime / sulbactam.

Sulbactam a β-lactam, is licensed and used as a competitive BLI usually in combination with ampicillin or cefoperazone. It also has intrinsic antimicrobial activity, through inhibition of penicillin binding proteins (PBPs) with most affinity for

PBP1a and 2. The ability to inhibit PBP2 makes it particularly active against *A. baumannii,* including those with carbapenem resistance.[18]

Sulbactam is susceptible to hydrolysis by most class A (TEM, SHV, CTX-M, KPC), B (IMP, VIM, NDM) and D (OXA-10, 23, 24, 48) β-lactamases but appears relatively stable to many class C (AmpC-like) enzymes.[18,19] Although the majority of the carbapenem resistant *A. baumannii* we assessed here were positive for $bla_{\text{OXA-23,}}$ we still observed a significant increase in the activity of a cefepime / sulbactam combination. This could in part be due to preferential hydrolysis of sulbactam and preservation of enough cefepime activity able to withstand degradation by *Acinetobacter* ADC cephalosporinases. This contrasts with the activity of cefepime / sulbactam we saw against carbapenem resistant *E. coli* and *K. pneumoniae*, whereby the activity of both cefepime and sulbactam is likely compromised by the co-production of class A (CTX-M, KPC) and B (NDM, VIM) ESBLs and carbapenemases. Subactam has little intrinsic activity against *P. aeruginosa* and did not seem to enhance the activity of high dose cefepime *in-vitro* (Table 2).

The importance of the ratio of BL to sulbactam is evident from studies of cefoperozone / sulbactam, most widely available as a 2:1 formulation. Adjusting the cefoperozone / sulbactam ratio to 1:1 or 1:2 increases the *in-vitro* susceptibility of ESBL producing *E. coli* and carbapenem resistant *A. baumannii* by up to 90 %.[20,21] Furthermore, meta-analysis of clinical studies identifies the importance of higher doses of sulbatam when combined with ampicillin or cefoperazone.[22] This is entirely in keeping with our findings for cefepime / sulbactam in which a 1:1 or 1:2 ratio is optimal. Whether higher ratios (1:3) are likely to be more effective would require synthesis of enzyme kinetic and MIC data on a strain by strain basis.

From the PK / PD modelling analysis, both a 1:1 or 1:2 cefepime / sulbactam therapy would require dosing at the upper range of both drugs to provide useful activity against carbapenem resistant strains. Cefepime has been safely used at 8 g / day and sulbactam at 9 g / 8hrly in the treatment of bloodstream infections and pneumonia.[19] A combined cefepime / sulbactam dosing regimen of 8g / 8g should enable treatment of ESBL and carbapenem resistant isolates with cefepime / sulbactam MIC up to 16 mg / L.

Effective targeted antimicrobial therapy is fundamental in the treatment of Gram-negative sepsis. The increasing prevalence of ESBLs in Enterobacteriales has led to increased empiric use of carbapenems, a strategy that further drives carbapenem resistance. Existing BL / BLI therapies, in the formulations and doses currently used, are increasing shown to be sub-optimal in severe infections as alternatives to carbapenems.[23]

Given the current challenges in antimicrobial drug development it is unlikely that all of the cefepime / BLI therapies currently under investigation will enter widespread clinical use. The data for cefepime / sulbactam suggests it could be most useful to progress as a 1:1 formulation targeting ESBLs and in particular carbapenem resistant *Acinetobacter* infections. It could also be employed as a BL / BLI carbapenem sparing agent which still retains some useful activity against emerging carbapenem resistant strains.

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Transparency Declarations

DWW is a member of the Scientific Committee of ANTRUK and has served on advisory boards for Shionogi and Pfizer. All other authors declare no conflict of interest.

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Table 1. *In-vitro* activity of cefepime (FEP), sulbactam (SUL), FEP / SUL (1:1), FEP / SUL (2:1) and FEP / SUL (1:2) fixed ratio combinations versus multi-drug resistant pathogens.

Isolate	**FEP**		**SUL**		**FEP / SUL (1:1)**		**FEP / SUL (2:1)**		**FEP / SUL (1:2)**	
	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}
Escherichia coli (n=36)	4	>256	32	>256	1 / 1	>256 / 256	8 / 4	128 / 64	0.5 / 1	16 / 32
ESBL +ve (28)	≤0.25	≥256	32	≥256	1-Jan	64 / 64	4-Aug	64 / 32	0.5 / 1	32 / 64
bla$_{CTX-14/15, OXA-1}$										
Carbapenem Resistant (8)	128	≥256	32	≥256	32 / 32	≥256 / 256	64 / 32	≥256 / 128	8-Apr	32 / 64
bla$_{OXA-48, NDM, IMI}$										
Klebsiella spp (n=48)	≥256	≥256	≥256	≥256	32 / 32	≥256 / 256	64 / 32	≥256 / 128	16 / 32	≥128 / 256
ESBL +ve (7)	1	32	≥256	≥256	1 / 1	4/ 4	2/ 2	16 / 8	1/ 2	4/ 8
bla$_{SHV,CTX-14/15, OXA-1}$										
Carbapenem Resistant (42)	≥256	≥256	≥256	≥256	32 / 32	≥256 / 256	64 / 32	≥256 / 128	32 / 84	≥128 / 256
bla$_{NDM, KPC, VIM}$										
Acinetobacter spp (n=66)	128	>256	16	>256	8 / 8	32 / 32	16 / 8	64 / 32	8 / 16	32 / 64
Carbapenem Resistant (59)	≥256	≥256	16	≥256	8-Aug	64 / 64	16 / 8	64 / 32	16-Aug	32 / 64
bla$_{OXA-23}$										
Pseudomonas aeruginosa (n =6)	4	16	≥256	≥256	4 / 4	8 / 8	2 / 1	16 / 8	4 / 8	16 / 32
Carbapenem Resistant (2)	2	2	≥256	≥256	2 / 2	2 / 2	1 / 0.5	1 / 0.5	2 / 4	16 / 32
bla$_{VIM-2}$										
Total (n=157)	128	>256	128	>256	8 / 8	128 / 128	16 / 8	128 / 64	8 / 16	64 / 128

Table 2. Susceptibility of carbapenem resistant strains to simulated cefepime (3 – 8 g / day) / sulbactam (1:1, 1:2, 2:1) dosing regimens. Probability of target attainment (PTA >0.9) for isolates with MIC ≤ 2 – ≤ 16 mg/L.

Dosing Regimen		**FEP / SUL Target MIC (mg/L)** *f*T > MIC > 60%			***E. coli***			***Klebsiella***			***Acinetobacter***			***Pseudomonas***			**All Isolates**		
					FEP / SUL Ratio			**FEP / SUL Ratio**			**FEP / SUL Ratio**			**FEP / SUL Ratio**			**FEP / SUL Ratio**		
					1:1	**2:1**	**1:2**	**1:1**	**2:1**	**1:2**	**1:1**	**2:1**	**1:2**	**1:1**	**2:1**	**1:2**	**1:1**	**2:1**	**1:2**
		SUL 3g	SUL 1.5 g	SUL 6 g	% Susceptible														
FEP 3g	Bolus	≤2 / ≤0.25	≤2 / ≤0.25	≤2 / ≤0.5	33%	40%	53%	6%	10%	10%	5%	3%	5%	0%	14%	0%	11%	10%	11%
	EI[a]	≤4 / ≤1	≤4 / ≤0.5	≤4 / ≤ 2	53%	43%	73%	17%	12%	17%	9%	6%	8%	14%	43%	0%	21%	15%	24%
	CI[b]	≤4 / ≤2	≤4 / ≤1	≤4 / ≤4	60%	46%	73%	23%	19%	17%	19%	9%	9%	43%	57%	29%	30%	19%	26%
		SUL 4 g	SUL 2 g	SUL 8 g															
FEP 4g	Bolus	≤4 / ≤0.5	≤4 / ≤0.25	≤4 / ≤1	47%	40%	53%	12%	10%	10%	5%	6%	6%	0%	14%	0%	15%	10%	17%
	EI	≤8 / ≤4	≤8 / ≤2	≤8 / ≤8	63%	50%	83%	31%	19%	25%	24%	9%	47%	57%	57%	43%	42%	19%	48%
	CI	≤8 / ≤4	≤8 / ≤2	≤8 / ≤8	63%	50%	83%	31%	19%	25%	24%	9%	47%	57%	57%	43%	42%	19%	48%
		SUL 6g	SUL 3g	SUL 12g															
FEP 6g	Bolus	≤4 / ≤0.5	≤4 / ≤0.5	≤4 / ≤1	47%	43%	53%	12%	12%	10%	5%	6%	6%	0%	43%	0%	15%	15%	17%
	EI	≤8 / ≤2	≤8 / ≤1	≤8 / ≤4	60%	46%	73%	23%	19%	25%	19%	6%	47%	43%	57%	29%	30%	19%	26%
	CI	≤8 / ≤4	≤8 / ≤8	≤8 / ≤8	63%	63%	83%	31%	23%	25%	38%	28%	47%	57%	86%	43%	42%	33%	48%
		SUL 8g	SUL 4g	SUL 16g															
FEP 8g	Bolus	≤8 / ≤1	≤8 / ≤0.5	≤8 / ≤2	53%	43%	73%	16%	15%	17%	9%	6%	47%	14%	43%	29%	21%	15%	27%
	EI	≤16 / ≤8	≤16 / ≤4	≤16 / ≤8	67%	63%	83%	37%	23%	33%	73%	28%	73%	100%	86%	43%	62%	47%	48%
	CI	≤16 / ≤8	≤16 / ≤4	≤16 / ≤16	67%	63%	83%	37%	23%	33%	73%	28%	73%	100%	86%	57%	62%	47%	62%

[a]CI: Continuous Infusion; [b]EI: Extended Infusion

Figure 1: Distribution of cefepime (FEP) MIC versus 157 MDR Gram-negative pathogens combined with sulbactam (SUL) at fixed ratios.