REVIEW

Sulbactam-containing β-lactamase inhibitor combinations

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ABSTRACT

Sulbactam irreversibly inhibits the hydrolytic activity of β-lactamases. This compound is commercially available in combination with either ampicillin or cefoperazone. In each instance, the activity of the partner antibiotic against β-lactamase-producing bacteria is restored. One of the particular advantages of using sulbactam-containing combinations is that sulbactam itself has inherent activity against some *Acinetobacter baumannii*. Sulbactam combinations have not demonstrated strong selective pressures for extended-spectrum β-lactamase-producing Enterobacteriaceae and vancomycin-resistant enterococci. In contrast to clavulanate, sulbactam does not induce class I (Ampc) chromosomal β-lactamases in Enterobacteriaceae.

Keywords Ampicillin, β-lactamase inhibitors, cefoperazone, sulbactam

INTRODUCTION

β-Lactamase inhibitors are themselves β-lactam antibiotics, usually with minimal or no antibacterial activity. When combined with certain β-lactam antibiotics, they augment the potency of these against β-lactamase-producing bacteria. Three β-lactamase inhibitors (sulbactam, clavulanate and tazobactam) are commercially available. Sulbactam is combined with either ampicillin or cefoperazone and this review briefly outlines the in-vitro and clinical characteristics of these combinations.

CHEMICAL STRUCTURE AND RELATED ACTIVITY

Sulbactam is chemically a penicillanic acid sulphone and shows particular activity against class A enzymes. However, compared with clavulanate and tazobactam, sulbactam is a less potent inhibitor of this class, particularly for SHV-1 [1]. Against class C β-lactamases, sulbactam is more potent than clavulanate, whereas activity against class D enzymes is less potent than against class A β-lactamases. Similarly, OXA-type enzymes are not as well inhibited by sulbactam as TEM-1 and other clinically used inhibitors.

In general, β-lactamase inhibitors have negligible antimicrobial activity themselves, but restore antimicrobial activity to other β-lactams when used in combination. However, sulbactam is exceptional in that it has intrinsic activity against *Acinetobacter* spp. [2,3] and *Bacteroides fragilis*. High-affinity binding to penicillin-binding protein 2 of these organisms is responsible for this activity [2].

Paradoxically, β-lactamase inhibitors, particularly clavulanate, may induce production of β-lactamases in some Gram-negative bacteria, causing autagonism of their partner β-lactamases [4]. No such activity has been described with sulbactam [5].

IN-VITRO ACTIVITY

Early studies reported that more than 90% of strains, among a variety of organisms, were inhibited at ≤4 mg/L with a fixed ratio (1:2) of sulbactam and ampicillin [6]. These included methicillin-susceptible *Staphylococcus aureus*,

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Staphylococcus epidermidis, *B. fragilis*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Escherichia coli*, *Klebsiella pneumoniae* and *Proteus* spp. However, recent trials have indicated increasing resistance to sulbactam–ampicillin. In a study with a total of 3134 aerobic and facultative Gram-negative bacilli, sulbactam–ampicillin was the least active agent among the 12 antibiotics tested against *E. coli* and *Klebsiella* spp., with susceptibility rates of 56% and 73%, respectively [7]. Extended-spectrum β-lactamases (ESBLs) were detected in 7% of *E. coli* and 13% of *Klebsiella* spp. isolates.

In the absence of CLSI criteria, in-vitro studies have used cefoperazone breakpoints for reporting the susceptibility results for sulbactam–cefoperazone. Thus, resistance was defined as ≥64 mg/L with a fixed ratio (2:1) of cefoperazone and sulbactam (the latter was used at 8 mg/L), intermediate susceptibility as 32/16 mg/L and susceptibility as <16/8 mg/L [8]. Studies with large numbers of Gram-positive and -negative strains revealed susceptibility in methicillin-susceptible *Staphylococcus aureus*, Enterobacteriaceae, anaerobic bacteria, including *B. fragilis*, and various non-fermenters, including *Pseudomonas aeruginosa* and *Acinetobacter* spp. [9]. Higher MIC values were reported for ESBL-producing strains [10].

Substantial in-vitro susceptibility to both sulbactam combinations has been shown in *Acinetobacter* spp., including carbapenem-resistant strains [11]; however, increasing resistance has also been reported. A recent trial from Turkey reported results concerning 1196 Gram-negative clinical isolates, mostly cultured from blood ($n = 323$), urine ($n = 548$) and respiratory secretions ($n = 152$). Susceptibility to sulbactam–cefoperazone, piperacillin–tazobactam, imipenem, ceftriaxone, ceftazidime and cefepime was determined by Etest in *E. coli* ($n = 457$, 26% ESBL-positive), *K. pneumoniae* (390, 32% ESBL-positive),

P. aeruginosa (194) and *Acinetobacter baumannii* (155). Resistance in these isolates to sulbactam–cefoperazone was 6%, 17.7%, 27.9% and 41.3%, respectively. Sulbactam–cefoperazone was the most active drug against *A. baumannii* and the second most active, only after imipenem, against *E. coli* and *K. pneumoniae*; it was the third most active drug against *P. aeruginosa*, after imipenem and piperacillin–tazobactam.

MECHANISMS OF RESISTANCE TO INHIBITOR COMBINATIONS

The in-vitro and clinical efficacies of β-lactamase inhibitors have been compromised by the emergence of resistant isolates during the last decade. The mechanisms involved in and responsible for this resistance are multiple. Most bacteria with derepressed class C β-lactamases are resistant to inhibitor combinations. Overproduction of the class A penicillinases TEM-1 and TEM-2, or production of low-affinity enzymes such as inhibitor-resistant TEM and the OXA enzymes, are other mechanisms of resistance. Overproduction of β-lactamases is due to either a point mutation in the promoters for the genes encoding TEM-1 and TEM-2 or to multicopy, plasmid-borne genes [12].

PHARMACOKINETICS

The pharmacokinetic parameters of sulbactam combinations are shown in Tables 1 and 2 [13,14]. Oral absorption of sulbactam is very poor. However, a double-ester prodrug, in combination with ampicillin (sultamicillin), allows up to 68% absorption [15]. Sulbactam is mainly excreted via kidneys, with 75% of the dose being recovered in the urine in the first 8–12 h [13]. Therefore, its clearance is significantly decreased in patients with renal failure. Haemodialysis removes 30% of the given doses of sulbactam–ampicillin, and

	Alone		Combined	
	Ampicillin	**Sulbactam**	**Ampicillin**	**Sulbactam**
C_{max} (μg/h/mL)	27.6	31.8	23.2	30.4
AUC (μg/h/mL)	30.3	29.6	24.7	36.6
$t_{1/2}$ (h)	1.3	0.96	1.00	1.06

Table 1. Pharmacokinetic properties of intravenous sulbactam–ampicillin in healthy adults [13]

C_{max}, maximum serum concentration of the drug; AUC, area under the concentration curve; $t_{1/2}$, serum half-life of the drug.

Table 2. Pharmacokinetic properties of intravenous sulbactam–cefoperazone in healthy adults [14]

	C_{max} (mg/L)	V (L)	AUC (μg/h/mL)	$t_{1.2}$ (h)	CL (mL/min)	CL_R (mL/min)
Cefoperazone (day 7)						
Alone ($n = 14$)	430 ± 44	11 ± 2	690 ± 82	1.8 ± 0.3	73 ± 9	21 ± 4
+ Sulbactam ($n = 14$)	431 ± 57	11 ± 1	679 ± 122	1.8 ± 0.3	76 ± 10	19 ± 3
Sulbactam (day 7)						
Alone ($n = 12$)	91 ± 20	30 ± 8	80 ± 20	1.1 ± 0.1	331 ± 75	296 ± 74
+ Cefoperazone ($n = 14$)	92 ± 17	28 ± 6	85 ± 14	1.1 ± 0.2	301 ± 46[a]	262 ± 52[b]

V, volume of distribution; L, litres; CL, total body clearance; CL_R, renal clearance.
[a]p 0.04 vs. administration alone.
[b]p 0.03 vs. administration alone.

supplemental doses are recommended after dialysis [13]. However, only 4% of cefoperazone is removed with the same intervention, and the main route of excretion for this drug is via the biliary tract. Thus, in patients with a creatinine clearance of <30 mL/min, if sulbactam is given once-daily in combination with cefoperazone, additional doses of cefoperazone alone are required every 12 h. Both sulbactam–ampicillin and sulbactam–cefoperazone penetrate well into tissue. However, cerebrospinal tissue penetration is negligible with sulbactam–cefoperazone and yields only 34% of the serum concentration with sulbactam–ampicillin [13].

CLINICAL USAGE

Parenteral sulbactam–ampicillin has been widely used in cases of community and/or hospital-acquired pneumonia, including those due to aspiration of oropharyngeal secretions, and in several mixed infections, including intra-abdominal infections, diabetic foot infections, brain abscesses, staphylococcal bacteraemia, outpatient sepsis and skin and soft-tissue infections, paediatric infections such as acute epiglottitis, and periorbital cellulitis [16–20]. In neonates, exposure to sulbactam–ampicillin was not significantly associated with colonisation with multidrug-resistant Gram-negative bacteria, including ESBL producers [21].

Oral sulbactam–ampicillin is indicated in less severe infections such as sinusitis, otitis media, urinary tract infections and cellulitis, or as step-down therapy for patients who have improved under parenteral therapy.

Sulbactam–cefoperazone has been used in several nosocomial infections, including mild-to-moderate and severe nosocomial pneumonia, intra-abdominal infections, including biliary sepsis, intra-abdominal abscesses, pelvic inflammatory disease, gynaecological infections, sepsis, infections in burn patients, and infections in febrile neutropenic patients [2,18]. In a prospective controlled clinical trial, treatment with sulbactam–cefoperazone for bacteraemia due to CTX-M-type ESBL-producing *E. coli* was as successful as that with imipenem or ceftazidime [22].

On the other hand, despite in-vitro sensitivity to sulbactam and other β-lactamase inhibitor combinations, high failure rates in patients infected with ESBL-positive bacteria have been reported [23], most probably due to the concurrent presence of other resistance mechanisms in the strains responsible for the infection.

ADVERSE EFFECTS

Both sulbactam combinations have favourable safety profiles and are well-tolerated [2,13]. The addition of sulbactam to either ampicillin or cefoperazone does not compromise the safety of these β-lactam antibiotics.

CONCLUSION

Owing to their in-vitro activity against several aerobic and anaerobic bacteria, and their reliable pharmacokinetic and safety profiles, sulbactam combinations have been widely used for several clinical indications. Among these, infections caused by *Acinetobacter* spp., with or without multidrug-resistant profiles, have become a prominent indication. However, clinical efficacy is doubtful in the case of severe infections caused by ESBL-producing bacteria and, as with the other inhibitors, clinicians should be very cau-

tious in using sulbactam combinations for infections due to these organisms.

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