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In vivo efficacy of WCK 6777 (ertapenem/zidebactam) against carbapenemase-producing *Klebsiella pneumoniae* in the neutropenic murine pneumonia model

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Objectives: Ertapenem has proven to be an effective antimicrobial; however, increasing enzyme-mediated resistance has been noted. Combination with zidebactam, a β-lactam enhancer, is restorative. Human-simulated regimens (HSRs) of ertapenem and zidebactam alone and in combination (WCK 6777; 2 g/2 g q24h) were assessed for efficacy against carbapenemase-producing *Klebsiella pneumoniae* (CP-KP) in the pneumonia model.

Methods: Infected ICR mice were rendered neutropenic and exposed to various doses of ertapenem and zidebactam alone and in combination to develop the HSRs that were subsequently confirmed in additional pharmacokinetic studies. Twenty-one CP-KP (KPC or OXA-48-like producers) with WCK 6777 MICs of 1–8 mg/L were utilized. Mice were treated for 24 h with saline or HSRs of ertapenem, zidebactam and WCK 6777. Efficacy was defined as change in mean lung bacterial density relative to 0 h.

Results: Confirmatory pharmacokinetic analysis showed agreement between predicted human exposures (% $fT_{>MIC}$) and those achieved *in vivo* for all three HSRs. The 0 h bacterial density across all isolates was 6.69 ± 0.31 $\log_{10}$ cfu/lungs. At 24 h, densities increased by 2.57 ± 0.50, 2.2 ± 0.60 and 2.05 ± 0.71 $\log_{10}$ cfu/lungs in the 24 h control, ertapenem HSR and zidebactam HSR groups, respectively. Overall, 18/21 of the isolates exposed to the WCK 6777 HSR displayed a killing profile that exceeded the translational benchmark for efficacy of a 1 $\log_{10}$ cfu reduction. Among the remaining three isolates, two displayed ∼0.5 $\log_{10}$ kill and stasis was observed in the third.

Conclusions: Human-simulated exposures of WCK 6777 demonstrated potent *in vivo* activity against CP-KP, including those with WCK 6777 MICs up to 8 mg/L.

Introduction

Outpatient parenteral antimicrobial therapy (OPAT) is an increasingly utilized treatment strategy to reduce the duration of hospitalization and improve patient satisfaction while maintaining the prerequisite IV exposure profile.[1] Ertapenem, a parenteral carbapenem approved for intra-abdominal infections, community-acquired pneumonia, acute pelvic infections, complicated urinary tract infections and complicated skin and soft-tissue infections, is well-suited to OPAT due to its once-daily regimen and safety profile.[2–4] Ertapenem is typically characterized by broad-spectrum activity against both Gram-positive and Gram-negative anaerobes and aerobes, but has limited activity against *Enterococcus* and *Pseudomonas* spp.; however, the increasing rate of enzyme-mediated resistance, especially among Enterobacterales, threatens to reduce its viability as a therapeutic option.[5] While the reduced potency of ertapenem among the Enterobacterales has historically been attributed to a combination of AmpC β-lactamases, ESBLs and porin loss, the recent proliferation of carbapenemases further challenges the clinical utility of the compound.[6] Recently, a promising approach to addressing β-lactamase-mediated as well as non-enzymatic resistance through a combination with a β-lactam enhancer has been reported. This approach obviates the need for β-lactamase inhibition, as has been demonstrated through cefepime/zidebactam's *in vivo* activity against *Acinetobacter baumannii* expressing OXA carbapenemases, despite zidebactam not being an inhibitor of these enzymes.

Zidebactam, a non-β-lactam bicyclo-acyl hydrazide that demonstrates a high affinity for PBP2 in Gram-negative bacteria, also inhibits Ambler class A and C enzymes.[7,8] The success of the combination of cefepime with zidebactam (WCK 5222), shown to have potent *in vivo* activity against *Pseudomonas aeruginosa*, *A. baumannii* and Enterobacterales through mouse regimens simulating a human q8h dosing regimen, encouraged us to investigate the combination of zidebactam with ertapenem employing a human q24h simulated regimen.[9,10]

The present study developed human-simulated regimens (HSRs) approximating the plasma exposures of ertapenem and zidebactam alone and in combination (WCK 6777) to assess the *in vivo* potency of each regimen against carbapenemase-producing *Klebsiella pneumoniae* in the neutropenic murine pneumonia model.

Methods

Ethics

All murine experiments were conducted in accordance with the National Academy of Sciences-National Research Council. The study protocol (HHC-2019-0114) was approved by the Institutional Animal Care and Use Committee of Hartford Hospital (Assurance #A3185-01).

Bacterial strains

Carbapenemase producers were chosen for study because these organisms are extremely hydrolytic (i.e. have high MICs) and provide enhanced enzymatic degradation as compared with the more moderate effects of AmpC β-lactamases and ESBLs on the phenotypic profile of ertapenem. The phenotypic and genotypic profiles of the 21 clinical *K. pneumoniae* are provided in Table 1. This carbapenemase-producing population of *K. pneumoniae* was highly resistant to the carbapenems, while displaying a wide range of phenotypic profiles, with WCK 6777 MICs ranging from 1 to 8 mg/L determined by broth microdilution at a 1:1 ratio of ertapenem/zidebactam.

Antimicrobial agents

Commercially available ertapenem was used for *in vivo* testing (Par Pharmaceutical, Chestnut Ridge, NY, USA; LOT: S013682). Zidebactam analytical grade standard was provided by Wockhardt Bio AG, Switzerland (LOT: WKP005I18). Ertapenem was reconstituted in 0.9% NaCl. Zidebactam was reconstituted in sterile water and diluted in 0.9% NaCl prior to injection. Doses were administered as 0.1 mL subcutaneous injections.

Murine pneumonia model

Specific-pathogen-free female ICR mice (20–22 g) were obtained from Charles River Laboratories (Wilmington, MA, USA) and were maintained and utilized in accordance with National Research Council recommendations. They were allowed to acclimatize for 48 h and provided food and water *ad libitum*. During acclimatization, animals were housed in groups of six mice at controlled room temperature in HEPA-filtered cages (Innovive, San Diego, CA, USA). Cages were supplemented with nesting material for enrichment purposes. Study rooms were maintained with diurnal cycles (12 h light/12 h dark). Monitoring was conducted at least three times per day for signs of morbidity. Mice were compassionately euthanized and tissues were harvested if found moribund. Mice were rendered transiently neutropenic via intraperitoneal injections of cyclophosphamide at a dose of 250 mg/kg at 4 days and 100 mg/kg at 1 day before inoculation. Three days prior to inoculation, mice received a single intraperitoneal injection of 5 mg/kg uranyl nitrate to achieve a predictable degree of renal impairment to assist with humanizing the target exposures of these renally eliminated compounds. A suspension of bacteria was prepared from a second subculture that was incubated for less than 20 h to yield a concentration of approximately 10^7 cfu/mL in 3% (w/v) mucin. Inoculum density was confirmed by serial dilution. Mice were lightly anaesthetized with vaporized isoflurane (2%–3% v/v in an oxygen carrier) until the respiratory rate decreased upon visual inspection. Pneumonia was induced via intranasal inoculation with 50 μL bacterial suspensions.

Ertapenem and zidebactam human-simulated pharmacokinetic studies

HSRs were developed in the neutropenic murine pneumonia model for ertapenem and zidebactam alone or in combination approximating their plasma pharmacodynamic profiles [i.e. percentage of dosing interval during which unbound plasma drug concentrations were above MIC (% $fT_{>MIC}$)] achieved clinically with 2 g q24h 0.5 h infusion, 2 g q24h 1 h infusion and 2 g/2 g q24h 0.5/1 h infusion regimens, respectively, using previously established pharmacokinetic parameters in mice and man.[11,12] For the purposes of pharmacokinetic/pharmacodynamic simulations, the percentages of protein binding of zidebactam in mouse and human plasma of 12.6% and 4.7%, respectively, were applied.[12] As for ertapenem, the compound displays a non-linear concentration-dependent plasma protein binding profile; the percentage of protein binding ranged from 94.4% to 70.6% at concentrations of 5 to 400 mg/L in human plasma, respectively, and from 95.4% to 80.2% at concentrations of 50 to 200 mg/L in murine plasma, respectively (Methods S1 and S2, and Tables S1 and S2, available as Supplementary data at *JAC* Online). Using the relationships of percentage of protein binding over ertapenem concentrations (Figures S1 and S2), an integrated design was utilized for the construction of the ertapenem HSR based on the bioactive unbound plasma concentrations to account for the variable percentage of protein binding across the plasma concentration profile in humans and mice.

Once the HSRs were established, the plasma profile of each was reconfirmed in additional studies. For each pharmacokinetic study, 48 mice were inoculated and randomized into eight groups of 6 mice each. Two hours after inoculation, mice received the HSR of ertapenem, zidebactam or WCK 6777. At each of eight timepoints, six mice were euthanized by CO_2 exposure and cervical dislocation, and blood was collected via cardiac puncture. The blood was collected into lithium heparin tubes and centrifuged, and plasma was then mixed with an equal volume of 0.1 M MES and stored at −80°C until assayed. Ertapenem and zidebactam concentrations in plasma were determined using a validated LC/MS-MS by the sponsor (Method S3).

Pharmacodynamic studies

Animals were prepared as described above; 30 mice were allocated per isolate. Six were euthanized 2 h after inoculation before receiving any antimicrobial agents to determine initial bacterial load (0 h) and the remaining mice were randomized into the following groups: saline, ertapenem monotherapy HSR, zidebactam monotherapy HSR and WCK 6777 combination HSR. The control mice that received saline were dosed according to the ertapenem monotherapy HSR, as this regimen had the most frequent dosing. After 24 h, the mice in all groups were euthanized, lungs were harvested, homogenized and plated on blood agar and the bacterial load was quantitatively assessed after incubation. Bacterial density changes in the treatment groups were determined relative to 0 h controls and the translational benchmark for efficacy, a 1 $\log_{10}$ cfu reduction, was applied to assess the potential clinical utility of each regimen.[13–15]

In addition, efficacy was also assessed by constructing 95% CIs for the achievable WCK 6777 log kill for each isolate where intervals containing 0 defined stasis, those containing 1 defined 1 log kill and those having an upper boundary of the CI below −1 signified >1 log kill.

Table 1. Identified β-lactamases and associated MICs of ertapenem, zidebactam, meropenem and the ertapenem/zidebactam combination (WCK 6777) for *K. pneumoniae* test isolates

		MIC (mg/L)			
Isolate ID#	β-Lactamases	WCK 6777	ertapenem	zidebactam	meropenem
KP 930	OXA-181, CTXM group 1, CMY, SHV	1	128	1	32
KP 914	KPC, ESBL	2	>128	64	128
KP 915	KPC, ESBL	2	>128	4	128
KP 916	KPC, ESBL	2	>128	>128	128
KP 917	KPC, ESBL	2	>128	2	128
KP 921	KPC, ESBL	2	>128	>128	128
KP 932	OXA-48/181	2	128	>128	32
KP 934	SHV, TEM, OXA-48/181, OXA-4, NDM, CTXM group 1	2	>128	2	128
KP 937	TEM, OXA-48/181, NDM, CTXM group 1	2	>128	>128	128
KP 940	SHV, TEM, OXA-48/181, CTXM group 1, OXA-1	2	>128	>128	64
KP 919	KPC, ESBL	4	>128	4	>128
KP 923	KPC, ESBL	4	>128	>128	>128
KP 925	KPC, ESBL	4	>128	>128	>128
KP 927	KPC, ESBL	4	>128	64	>128
KP 941	OXA-48/181, TEM	4	128	128	32
KP 942	SHV, TEM, OXA-48/181, OXA-1	4	128	>128	32
KP 943	OXA 48/181, SHV, TEM, NDM	4	128	4	64
KP 928	KPC, TEM	8	>128	>128	>128
KP 929	KPC, ESBL	8	>128	>128	>128
KP 944	SHV, TEM, OXA-48/181, NDM, CTXM group 1, OXA-1	8	>128	128	>128
KP 945	SHV, TEM, OXA-48/181, NDM, CTXM group 1	8	>128	>128	128

Identified β-lactamases include cefotaximase (CTXM), cephamycinase (CMY), extended-spectrum β-lactamase (ESBL), *Klebsiella pneumoniae* carbapenemase (KPC), New Delhi metallo-β-lactamase (NDM), oxacillinase (OXA), sulfhydryl variant (SHV) and Temoneira (TEM) β-lactamases.

Results

Validation of the HSRs of ertapenem and zidebactam

Human-simulated exposures of ertapenem in the monotherapy and WCK 6777 combination regimens were achieved with the administration of 15 sequential doses ranging from 85 to 5 mg/kg over the 24 h dosing period (Table S3). Zidebactam human-simulated exposures in the monotherapy and WCK 6777 combination regimens were achieved with the administration of two doses (Table S4). As displayed in Figures 1 and 2, the pharmacokinetic profiles of ertapenem and zidebactam both alone and in combination produced the targeted human exposures. Exposures were determined for ertapenem and zidebactam independently and in combination and were largely in agreement, indicating that there is no evidence of pharmacokinetic interaction between ertapenem and zidebactam. Table 2 shows the pharmacodynamic and pharmacokinetic profiles of ertapenem and zidebactam achieved with the HSRs.

In vivo efficacy of the HSRs of ertapenem, zidebactam and WCK 6777

Mean 0 h bacterial density across all isolates was 6.69 ± 0.31 $\log_{10}$ cfu/lungs. By 24 h, mean densities had changed relative to 0 h by 2.57 ± 0.50, 2.2 ± 0.60 and 2.05 ± 0.71 $\log_{10}$ cfu/lungs in the 24 h control, ertapenem and zidebactam groups, respectively, indicating good *in vivo* growth of the isolates and

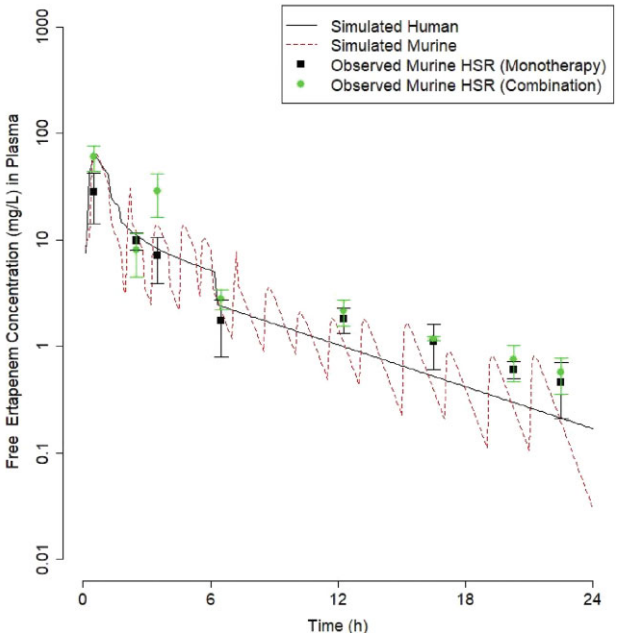

Figure 1. Free concentration–time profiles of ertapenem human-simulated exposures when administered alone and in combination with the zidebactam human-simulated regimen. Observed concentrations are displayed as means ± SD.

limited antibacterial activity in the treated animals (Figure 3). In contrast, the WCK 6777 HSR regimen produced kill in 20 of 21 isolates tested, producing a change in bacterial density ranging from 0.11 ± 0.48 to -3.05 ± 0.71 $\log_{10}$ cfu/lungs (Figure 3). Of the 21 isolates with WCK 6777 MICs up to 8 mg/L, 18 (86%) displayed a killing profile that exceeded the translational benchmark for efficacy of a 1 $\log_{10}$ cfu reduction. Among the remaining three isolates, two displayed less than the prerequisite 1 $\log_{10}$ kill and stasis was observed in the third. Given that the static result for KP 932 was discordant from all other isolates that were tested, the experiment for this isolate was repeated and the result was confirmed. When considering efficacy as assessed by the 95% CIs, a similar assessment of efficacy was observed for WCK 6777, as 18 isolates displayed ≥1 log kill and 3 isolates (KP 914, 916 and 932) were defined as producing stasis (Table S5). Overall, the *in vivo* efficacy of WCK 6777 in these highly resistant carbapenemase-producing *K. pneumoniae* was consistently observed over the MIC range of 1 to 8 mg/L, thus the variable degrees of bacterial killing in several isolates did not appear to be related to overt pharmacodynamic insufficiency, but rather the intrinsic complexity of these organisms, which is poorly defined by their phenotypic profiles.

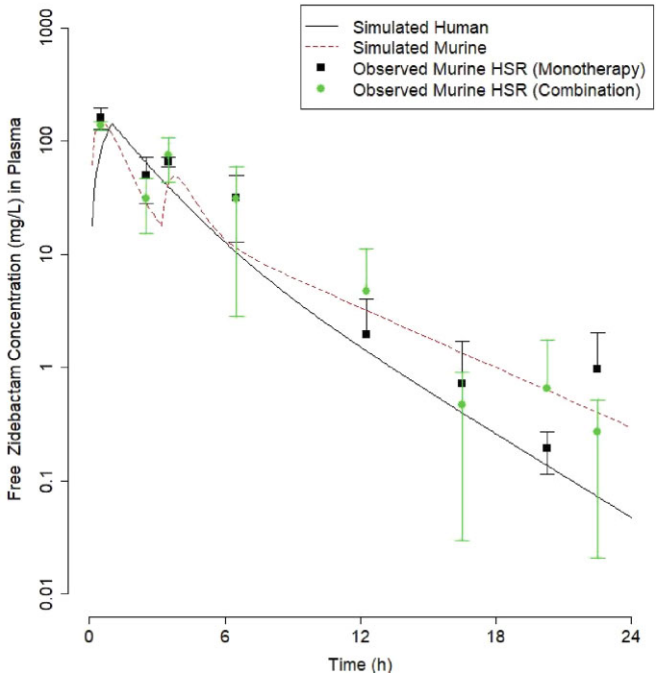

Figure 2. Free concentration–time profiles of zidebactam human-simulated exposures when administered alone and in combination with the ertapenem human-simulated regimen. Observed concentrations are displayed as means ± SD.

Discussion

Over the last 20 years, ertapenem has demonstrated good clinical and microbiological outcomes in the treatment of a wide range of infections due to Enterobacterales. Its once-daily regimen and tolerability have rendered it a popular choice for the management of both the hospitalized population as well as those suitable for transition to home receiving OPAT. While its narrow Gram-negative spectrum has minimized the collateral damage in *P. aeruginosa* associated with broader-spectrum agents like meropenem, the evolution of both non-carbapenemases (i.e. AmpC β-lactamases, ESBLs and porin loss) and carbapenemase-based resistance mechanisms have substantially eroded the *in vitro* potency of ertapenem against Enterbacterales.[16,17]

In the current study, the combination of ertapenem/zidebactam at a 1:1 ratio markedly reduced the MICs of this enzyme-replete, highly carbapenem-resistant population of Enterobacterales to 1 to 8 mg/L, a phenotypic profile that appears to be a suitable target range for *in vivo* efficacy if sufficient doses are utilized.

The pharmacokinetic/pharmacodynamic-supported ertapenem/zidebactam dose of 2 g/2 g q24h is expected to be safe, as higher ertapenem doses of 2 g were well-tolerated with minimal adverse events of nausea and headache, which were linked to a shorter 30 min infusion time.[18] Moreover, the safety of zidebactam in man has also been established.[19] Use of a higher and yet safe ertapenem dose of 2 g would help maximize the therapeutic potential of WCK 6777.

To support the clinical development programme of WCK 6777 we conducted the current study utilizing the translational murine lung model with human-simulated plasma exposures of ertapenem and zidebactam alone and in combination. Growth of these highly resistant *Klebsiella* in this murine model over the 24 h study period in the control groups confirms effective inoculation and the consistent establishment of infection in the lungs. The

Table 2. Comparative $\%fT_{>MIC}$, $fAUC_{0-24h}$ and fC_{max} profiles of ertapenem and zidebactam 2 g q24h in man and the human-simulated regimens in mice

	$\%fT_{>MIC}$ for MIC (mg/L)								
	0.25	0.5	1	2	4	8	16	$fAUC_{0-24h}$	fC_{max}
Ertapenem									
man	89%	70%	51%	32%	25%	15%	6%	97	42
mouse	86%	73%	55%	35%	20%	18%	5%	108	46
Zidebactam									
man	75%	65%	55%	46%	37%	30%	23%	369	142
mouse	75%	63%	54%	46%	37%	28%	23%	378	148

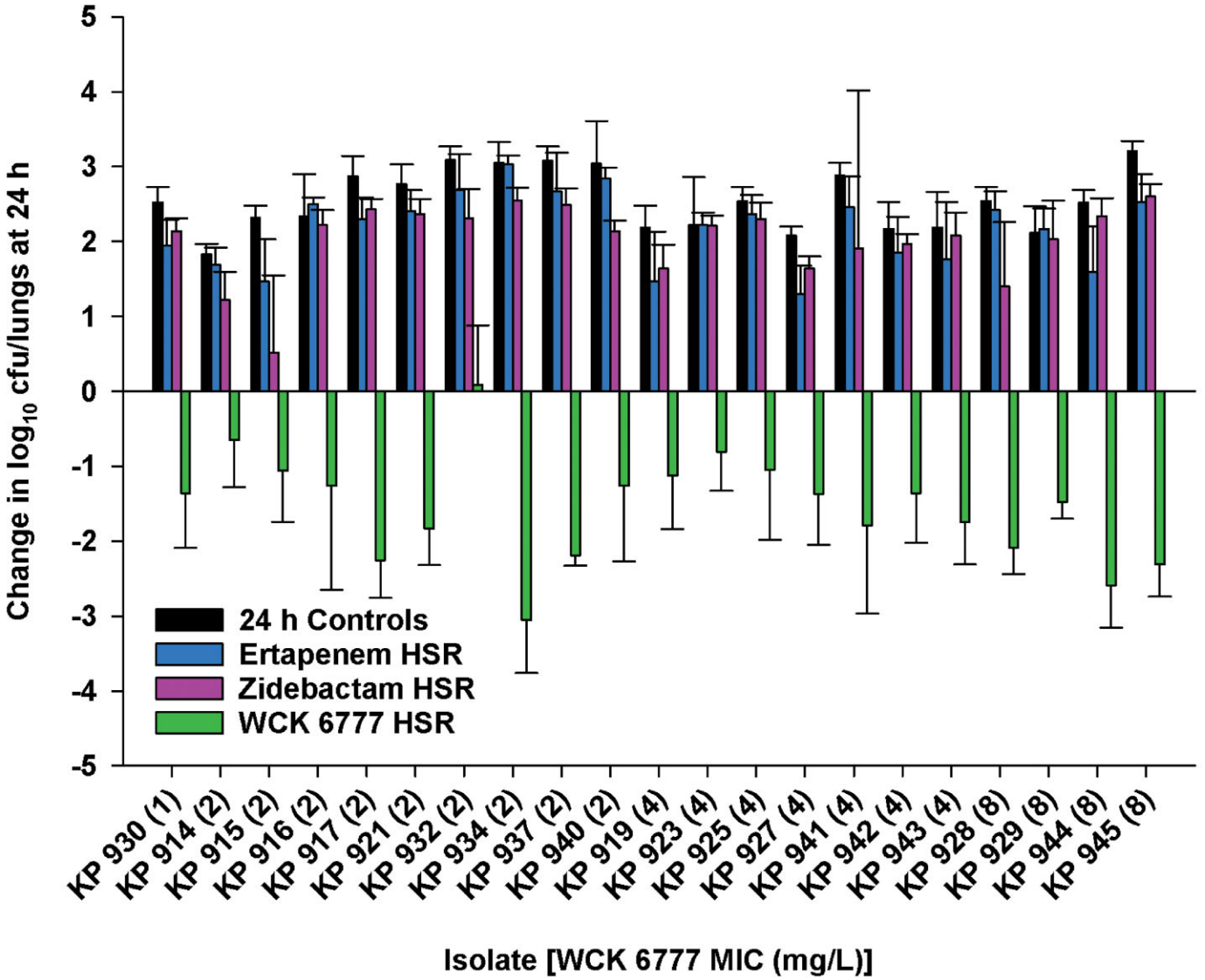

Figure 3. Mean change in $\log_{10}$ cfu/lungs ($\pm$SD) at 24 h from 0 h burden in the murine pneumonia model. Each isolate used in this study is listed in increasing order of the WCK 6777 MIC in mg/L (in parentheses).

2 log growth relative to the starting inoculum in mice treated with the ertapenem monotherapy HSR is consistent with its poor activity characterized by MICs of $\geq$128 mg/L and authenticates these isolates as excellent candidates to test the capacity of zidebactam to potentiate ertapenem. While zidebactam has intrinsic *in vitro* activity against some Enterobacterales and *P. aeruginosa* through its PBP2 mechanism, that impact appears to be minimal *in vivo* among the 21 isolates tested, given the roughly 2 log growth in the groups treated with the zidebactam monotherapy HSR. While neither the ertapenem monotherapy HSR nor the zidebactam monotherapy HSR produced antibacterial effects, the WCK 6777 combination resulted in potent *in vivo* activity, as 86% of isolates displayed a killing profile that exceeded the translational benchmark for efficacy of a 1 $\log_{10}$ cfu reduction. Moreover, this *in vivo* potency was observed across different enzymologies involving KPC and OXA-48-like carbapenemases and a WCK 6777 MIC range of 1–8 mg/L. These two carbapenemases offer an interesting opportunity to test the role of zidebactam as a β-lactamase inhibitor as well as a β-lactam enhancer. Against KPC-expressing *K. pneumoniae*, the observed efficacy of WCK 6777 is primarily attributable to the β-lactamase inhibition action of zidebactam, while, against OXA-48-like *K. pneumoniae*, the activity of the combination is solely driven by the β-lactam enhancer mechanism of action, as zidebactam does not inhibit class D and B β-lactamases. It was interesting to note that the bactericidal effect of WCK 6777 was not contingent on the MICs for the pathogen, as the bactericidal effect was observed for the majority of strains with MICs spanning across 1–8 mg/L. Further, the $\%fT_{>MIC}$ of ertapenem in the presence of zidebactam to produce a bactericidal effect was just 18% (versus 30%–40%

reported for ertapenem monotherapy). Thus, the efficacy of WCK 6777 against *K. pneumoniae* with MICs up to 8 mg/L is attributable to a combination of factors involving use of a higher 2 g ertapenem dose and pharmacodynamic gain through reduction in $\%fT_{>MIC}$ of ertapenem requirement (in the presence of zidebactam) for bactericidal effect. Previous studies have described the latter feature of zidebactam in combination with cefepime.

Of particular interest is OXA-48-harbouring KP 932, the isolate for which WCK 6777 produced a classically defined stasis profile, despite having a WCK 6777 MIC of 2 mg/L. As mentioned, the efficacy of WCK 6777 against OXA-48 carbapenemase-expressing isolates is mediated through the β-lactam enhancer effect of zidebactam.[20,21] While other isolates that were tested also bear OXA-48 enzymes, KP 932 is the only isolate for which OXA-48 is the only β-lactamase identified. In the other OXA-48-bearing isolates, zidebactam could be inhibiting other enzymes in order to contribute to kill, while, in KP 932, there is no such opportunity. The lack of a 1 log kill effect could be attributed at least in part to factors intrinsic to the strain in the context of phenotypic limitations to fully comprehending the complexity of infectivity and virulence. Co-expression of other enzymes may also be important in explaining potency against KP 934, 937, 943, 944 and 945, strains bearing the New Delhi metallo-β-lactamase (NDM). All of these isolates also bear other non-metallo-β-lactamases, so it is likely that the restoration of ertapenem activity by zidebactam is achieved through the inhibition of the serine carbapenemases rather than the inhibition of the NDM.[22]

The combination of ertapenem and zidebactam, WCK 6777, resulted in a restoration of *in vitro* potency against a highly resistant, carbapenem-producing population of *K. pneumoniae*. This MIC reduction in the range of 1–8 mg/L allowed human-simulated plasma exposures of the 2 g/2 g q24h regimen to produce an *in vivo* killing profile, which is anticipated to achieve good clinical outcomes based on the translational murine lung model utilized. These data support the continued development of WCK 6777 for organisms displaying a wide range of enzyme-mediated resistance to conventional carbapenems.

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Supplementary data

Methods S1 to S3, Tables S1 to S5 and Figures S1 and S2 are available as Supplementary data at *JAC* Online.

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