Review Article

Outline of Meropenem-Vaborbactam for the Treatment of Carbapenem-Resistant Enterobacteriaceae

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ABSTRACT

Meropenem-vaborbactam is a fixed combination drug that combines vaborbactam, a beta-lactamase inhibitor for cyclic boronic acid, with meropenem, a carbapenem class -lactam antibiotic, which was licensed in the US in 1996 under NDA 50,706. Vaborbactam inhibits bacterial beta-lactamases, despite not having any antibiotic activity of its own, to restore the activity of meropenem when beta-lactamases are present. The purpose of the meropenem-vaborbactam combo medication is to address the major antimicrobial resistance threat brought on by KPC-producing CRE. The study's goal is to describe the use of meropenem-vaborbactam for the treatment of carbapenem-resistant Enterobacteriaceae.

Keywords: Meropenem-vaborbactam, treatment, carbapenem-resistant Enterobacteriaceae.

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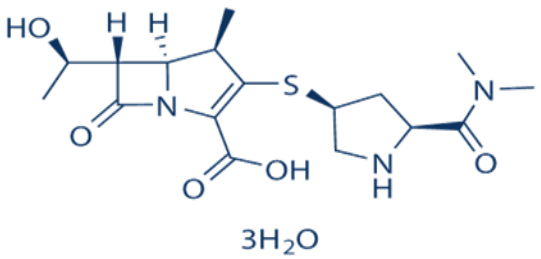
INTRODUCTION

The first carbapenem-β-lactamase inhibitor combination to be approved in the USA for the treatment of complex urinary tract infections (UTI), including acute pyelonephritis (APN), is meropenem-vaborbactam.[1] Meropenem, a carbapenem, and vaborbactam, a new-lactamase inhibitor based on a cyclic boronic acid, are combined in this novel antibiotic as a fixed-dose combination[8,10]. Meropenem and vaborbactam together have demonstrated strong efficacy in many In-vitro studies against MDRO, including CRE that produces KPC.[5,6,8,10]

Meropenem and vaborbactam is a combination product that contains meropenem, a synthetic panel antibacterial drug, and vaborbactam, a cyclic boronic acid beta-lactamase inhibitor[2]. The carbapenem class of β-lactam antibacterial includes the meropenem component of meropenem-vaborbactam. Meropenem inhibits the formation of cell walls, which has a bactericidal effect. Meropenem is resistant to hydrolysis by the majority of beta-lactamases, except those that hydrolyse carbapenem. These include penicillinases and cephalosporinases produced by gram-negative and gram-positive bacteria. The vaborbactam component is a non-beta-lactam, a Class A serine carbapenemase inhibitor with particularly high in vitro activity against Klebsiella pneumonia carbapenemase, KPC. Vaborbactam guards against the degradation of meropenem by KPC and associated beta-lactamases by blocking them.[1] Vaborbactam is a broad-spectrum inhibitor of diverse class A and class C beta-lactamases with potent inhibitory activity against KPC and other class carbapenemases. [9]

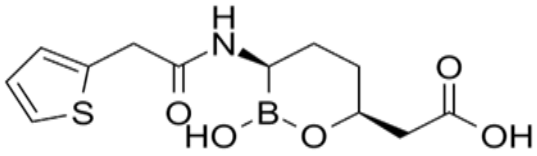
Structure

Meropenem has a molecular weight of 437.52 and is available as a trihydrate. It is a white to light yellow crystalline powder. Meropenem trihydrate's chemical name is (4R, 5S, 6S) -3 [[(3S, 5S) -5-(dimethyl carbamoyl)-3-pyrrolidinyl] thio] -6-[(1R)-1-hydroxyethyl] -4-methyl -7-oxo1-azabicyclo [3.2.0] hept-2-ene-2-carboxylic acid, trihydrate. Meropenem trihydrate with the empirical formula C17H25N3O5S.3H2O and the following chemical makeup[2]:



Structure of Meropenem Trihydrate

Vaborbactam has a molecular weight of 297.14, and it is a white to off-white powder. Vaborbactam is known chemically as (3R,6S) -2-hydroxy-3-[[2-(2-thienyl)acetyl] amino] 1,2-oxaborinane-6-acetic acid. The chemical structure of this substance is C12H16BNO5S, and its empirical formula is[2]:



Structure of Vaborbactam

Pharmacokinetics

When given as a single, 3-hour intravenous infusion, the pharmacokinetics (Cmax and AUC) of meropenem and vaborbactam (1 g to 2 g for meropenem and 0.25 g to 2 g for vaborbactam) are linear across the dose range examined. Following several IV infusions given every 8 hours for seven days in subjects with appropriate renal function, there is no buildup of meropenem or vaborbactam. [1]

Absorption: After oral dosing, meropenem and vaborbactam shouldn't be expected to be absorbed systemically. [1]

Distribution: About 2% of plasma proteins are bound by meropenem. Approximately 33% of vaborbactam's plasma protein binding is to plasma. The steady-state volumes of distribution of meropenem and vaborbactam in patients were 20.2 L and 18.6 L, respectively. [2]

Elimination: Meropenem's clearance after numerous doses in healthy persons is 15.1 L/h, while vaborbactam's clearance is 10.9 L/h. Meropenem and vaborbactam have t1/2s of 1.22 hours and 1.68 hours, respectively. [2]

Metabolism: Meropenem's beta-lactam ring hydrolysis (meropenem open lactam), which represents 22% of a dosage removed in the urine, is a minor mechanism of meropenem elimination. There is no metabolism with vaborbactam[2].

Excretion: Meropenem and vaborbactam are both predominantly eliminated from the body through the kidneys as an unmodified medication in the urine. Within 24 to 48 hours, 40% to 60% of a meropenem dosage is excreted unchanged, and the remaining 25% is retrieved as the open lactam metabolite, which is microbiologically inactive. Approximately 2% of the dosage is lost through feces. For vaborbactam, between 25% and 95% of the dosage is eliminated unchanged in the urine after 24 to 48 hours[1].

Pharmacodynamics

There is a correlation between effectiveness in animal and in vitro models of infection and the period that the unbound plasma concentration of meropenem surpasses the meropenemvaborbactam MIC against the infecting organism. The parameter that determines whether vaborbactam in conjunction with meropenem will be effective in both in vivo and in vitro models of infection is the 24-hour unbound plasma vaborbactam AUC/meropenem-vaborbactam MIC ratio.

RESULTS

Case 1

Efficacy and Safety of Meropenem–Vaborbactam versus Best Available Therapy for the Treatment of Carbapenem-Resistant Enterobacteriaceae Infections in Patients without Prior Antimicrobial Failure: A Post Hoc Analysis.

Study Findings: With very high rates of clinical success and good tolerability, MV was superior to BAT in the subgroup of patients with significant carbapenem-resistant Enterobacteriaceae (CRE) infections but no prior antimicrobial failure.

According to the principles of antimicrobial stewardship, it is still crucial to explicitly define the most suitable group for early, empirical MV coverage. [4]

Case 2

Meropenem-Vaborbactam Resistance Selection, Resistance Prevention, and Molecular Mechanisms in Mutants of KPC-Producing Klebsiella pneumonia

Study Findings: This research aimed to define the selected mutations and determine the doses of both treatments linked to the selection or prevention of single-step mutations that lower sensitivity to the combination. There are 18 strains of Klebsiella pneumonia that produce KPC. Different levels of meropenem sensitivity (MICs, 8 to 512 g/ml) and existing resistance and meropenem-vaborbactam (MICs, 0.06 to 32 g/ml) mechanisms were chosen from recovered isolates from around the world collection. From monitoring studies, highlighting isolates for which MICs were higher dispersion of the meropenem-vaborbactam MIC. Meropenem and vaborobactam at 8 µg/ml each suppressed the drug resistance mutation frequency to <1 $X10^{-8}$ in 77.8% (14/18) of strains, and all strains were inhibited when the meropenem concentration was increased to 16 µg/ml. When mutants were chosen from strains that were OmpK36-proficient or partially functional, they exhibited characteristics linked to previously documented carbapenem resistance pathways, such as inactivation of the ompK36 gene and an increase in the number of copies of the blaKPC gene. The coding area of blaKPC has no known mutations. These findings suggest that the selection of mutants from KPC-producing Klebsiella pneumonia strains with decreased sensitivity to meropenem-vaborbactam is related to previously described mechanisms involving poring mutations and the increase in the copy number of the blaKPC gene, not changes in the KPC enzyme and that this phenomenon can be avoided by the drug concentrations attained with ideal combination dosing. [3]

Case 3

In Vitro Activity of Meropenem-Vaborbactam against Clinical Isolates of KPC-Positive Enterobacteriaceae.

Study Findings: In this investigation, we found that the U.S. FDA's MIC breakpoint for susceptibility, 4 g/ml, caused meropenem-vaborbactam to block 99.0% of KPC-positive

isolates of Enterobacteriaceae. In the present investigation, ceftazidime-avibactam, to which 98.2% of isolates were susceptible, and tigecycline, to which 95.8% of isolates were susceptible, were compared for their in vitro activity to meropenem-vaborbactam. The most current global collection of clinical isolates of KPC-positive Enterobacteriaceae studied showed that meropenem-vaborbactam was a more potent antimicrobial agent in vitro than ceftazidime-avibactam, tigecycline, and all other antimicrobial agents[10].

Case 4

Effect and Safety of Meropenem–Vaborbactam versus Best-Available Therapy in Patients with Carbapenem-Resistant Enterobacteriaceae Infections: The TANGO II Randomized Clinical Trial.

Study Findings: When compared to BAT, monotherapy with meropenem-vaborbactam for CRE infection was linked to higher clinical cure rates, lower mortality rates, and less nephrotoxicity[7].

Case 5

Meropenem-Vaborbactam in the Treatment of Acute Bacterial Infections

Study Findings: The clinical cure rates at end of treatment (EOT) and test of cure (TOC) among the meropenem-vaborbactam group were non-inferior to those of the control group (at EOT, 92.5% versus 89.3%, risk ratio (RR) 1.27, 95% CI 0.64–2.50; at TOC, 86.2% versus 81.7%, RR 1.37, 95% CI 0.62–3.01). Meropenem-vaborbactam was non-inferior to comparators for microbiological eradication at EOT and TOC (at EOT, 93.3% versus 88.3%, RR 1.21, 95% CI 0.74–1.97; at TOC, 66.5% versus 59.9%, RR 1.12, 95% CI 0.97–1.30). In the subgroup of patients with cUTI/APN, meropenem-vaborbactam had a similar overall success rate to the control group at EOT (RR 1.05, 95% CI 1.01–1.09) and TOC (RR 1.05, 95% CI 0.93–1.19) [10].

CONCLUSION

In conclusion, the combination of meropenem-vaborbactam is a potent inhibitor of Enterobacterales with KPC enzymes with very high rates of clinical success and good tolerability compared to other antimicrobial agents.

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