MEDICAL COLLEGE OF WISCONSIN SCHOOL OF PHARMACY STUDENT WRITING CLUB:

Tebipenem Pivoxil Hydrobromide: Review of a New Oral Carbapenem in Development

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Since the 1985 approval of the first carbapenem antibiotic, imipenem, carbapenems have played an important role in the treatment of serious bacterial infections. Compared to other β-lactam antibiotics, carbapenems have the most broad-spectrum *in vitro* activity against gram-negative bacteria, including those that express extended-spectrum β-lactamases (ESBLs).[1] Guidelines from the Infectious Diseases Society of America for gram-negative bacterial infections published in 2020 considered carbapenems the preferred antibiotic class to treat infections caused by ESBL-producing bacteria outside of the urinary tract.[2] All of the currently approved carbapenems in the United States (U.S.) are available only in an intravenous dosage form. This can pose a challenge for patients who require treatment with a carbapenem in the outpatient setting, due to the need for a central intravenous line, coordination of outpatient infusion services, and limited stability of many carbapenems after reconstitution.[3] An oral carbapenem would thus provide a welcome alternative for the treatment of outpatients with challenging infections.

Tebipenem pivoxil is an oral prodrug of tebipenem, representing the first orally bioavailable carbapenem. Tebipenem pivoxil was approved in Japan to treat bacterial infections in pediatric patients in 2009.[4] Clinical trials and post-marketing surveillance studies demonstrated tebipenem's efficacy and safety for pediatric community-acquired pneumonia and upper respiratory tract and otolaryngologic infections.[5,6] The efficacy and safety of tebipenem is currently being investigated in the U.S. in adult patients with complicated urinary tract infection (cUTI) and acute pyelonephritis (AP).[7,8]

Carbapenem Market Analysis

There are no oral carbapenems currently marketed in the U.S. Faropenem, an oral penem antibiotic with structural similarities to carbapenems that is available in India and China, was rejected by the U.S. Food and Drug Administration (FDA) in 2006 due to inadequately designed clinical trials and lack of quality evidence.[9,10] Another oral penem, sulopenem etzadroxil, was recently submitted to the FDA for review as a combination product with probenecid in December 2020.[11] The expected clinical indication is uncomplicated urinary tract infection (uUTI), based on the results of the SURE-1 trial, which demonstrated sulopenem superiority over ciprofloxacin for the treatment of adult women with uUTI caused by fluoroquinolone non-susceptible pathogens.[12] Tebipenem pivoxil hydrobromide (TBPM-PI-HBr) is also in the pipeline for approval in the U.S., having obtained the Qualified Infectious Disease Product (QIDP) and Fast Track designations from the FDA.[13] TBPM-PI-HBr is expected to be submitted for the indications of cUTI and AP in the second quarter of 2021.[14]

Medicinal Chemistry and Mechanism of Action

Like other marketed carbapenems, tebipenem has a carbapenem nucleus with the 1-β-methyl group in C1, rendering it stable against chemical degradation and hydrolysis by dehydropeptidase-I.[15] However, tebipenem is unique in structure due to the bicyclic azetidine, thiazole side chain attached to the sulfur in C2 (Figure 1).[16,17] Another unique feature is the addition of a pivaloyloxymethyl moiety to the carboxylic acid, turning this agent into an orally bioavailable prodrug referred to as tebipenem pivoxil.[18] The version of this drug in the FDA approval process is formulated as a hydrobromide salt.[17]

All β-lactam antibiotics, including carbapenems, exhibit bactericidal activity by binding to the penicillin-binding protein (PBP) in gram-positive and gram-negative bacteria.[16] When the carbapenem binds to the PBP, it prevents the bacteria from forming the peptidoglycan strands' cross-linking, thus disrupting the integrity of the bacterial cell wall.[1] The peptidoglycan layer in gram-positive bacteria is the outermost layer; therefore, carbapenems have direct access to the PBP. In gram-negative bacteria, the peptidoglycan layer is surrounded by an outer membrane composed of lipopolysaccharides, proteins, and phospholipids. Hydrophilic antibiotics need the help of integral membrane proteins known as porins to cross the outer membrane to reach the periplasmic space where the peptidoglycan layer is located.[19]

In Vitro Characterization

Tebipenem has shown broad-spectrum activity against gram-negative and gram-positive bacteria, as expected from this class of β-lactam antibiotics.[20] In surveillance studies, tebipenem had potent activity against a range of *Enterobacterales* species, with a 90% minimum inhibitory concentration (MIC_{90}) value ≤ 1 μg/mL. In general, tebipenem's activity against uropathogens in the *Enterobacterales* family was similar to meropenem and ertapenem, and several-fold more potent than imipenem.[20] The presence of an identified ESBL or AmpC enzyme did not significantly affect the *in vitro* activity of tebipenem against *E. coli*, K. *pneumoniae*, or *P. mirabilis*.[20,21] Tebipenem was less active against non-fermenting gram-negatives including *Acinetobacter*

baumannii, *Stenotrophomonas maltophilia*, and *Pseudomonas aeruginosa*, with an overall spectrum that is similar to ertapenem, which has poor/no activity against these organisms.[22-24]

Tebipenem has *in vitro* activity against methicillin-susceptible *Staphylococcus aureus* (MSSA), but not against methicillin-resistant *Staphylococcus aureus* (MRSA).[23,25] Tebipenem exhibited MIC_{90} >1 µg/mL for *Enterococcus faecalis* and *Enterococcus faecium*.[23,25,26] It should be noted that susceptibility breakpoints for tebipenem have yet to be established. Table 1 summarizes the *in vitro* activity of tebipenem in surveillance studies.

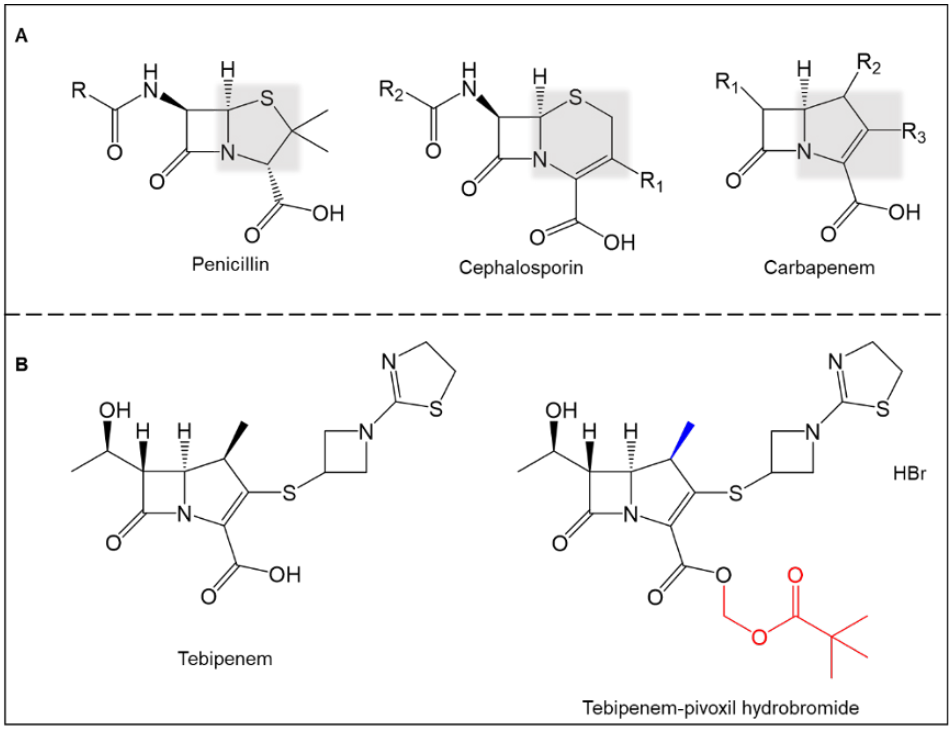
Pharmacokinetics

In contrast to its Japanese counterpart, the formulation of tebipenem being investigated in the U.S. is formulated as a hydrobromide salt to improve its stability.[21,28] Differences in pharmacokinetic parameters between this formulation and the Japanese formulation have not been directly assessed at this time.[21,28] The pharmacokinetics of TBPM-PI-HBr have been studied in healthy subjects in both single- and multiple-dose ascending doses in fed and fasting states. Both immediate-release (IR) and extended-release (ER) formulations of TBPM-PI-HBr were evaluated.[28] Because ER formulations of TBPM-PI-HBr did not result in predictable and sustained plasma concentrations, IR formulations were chosen for the multiple-dose phase of the study and subsequent phase III studies. The data that follow refer specifically to 300 mg or 600 mg IR TBPM-PI-HBr.

Absorption

TBPM-PI-HBr has demonstrated linear increases in plasma exposure following administration in the fasted state across all formulations.[28] Median time to maximum concentration (T_{max}) in serum has been shown to range from 0.5 to 1.3 hours, indicating rapid absorption following oral administration.[21] Administration of TBPM-PI-HBr following a high-fat meal decreased the maximum concentration, but not the area under the concentration-time curve (AUC_{last}), for a 300 mg IR dose. A high-fat meal did not appear to impact the pharmacokinetics of a 600 mg IR dose.[28,29] This suggests that standard dosing of TBPM-PI-HBr can be administered without regard to food.

FIGURE 1. (A) General chemical structures of penicillins, cephalosporins, and carbapenems. (B) *left* – chemical structure of tebipenem (parent drug); *right* – chemical structure of tebipenem pivoxil hydrobromide (pivoxil moiety in red) (methyl group in C1 that prevents degradation by dehydropeptidase-I in blue).



Distribution

The mean volume of distribution of tebipenem at steady-state was 36.5 L for the 300 mg dosing regimen and 31.8 L for the 600 mg regimen.[28] Studies are underway to characterize the distribution of tebipenem in the respiratory tract.[30]

Metabolism and Excretion

Tebipenem is likely excreted mostly in the urine as unchanged drug following either fed or fasted administration.[28] It has a short half-life in patients with normal renal function, ranging from 0.72 to 0.83 hours in multiple-dose studies. No significant accumulation has been shown to occur following the administration of multiple doses in healthy subjects.[28] Studies to characterize the renal clearance of TBPM-PI-HBr in subjects with varying degrees of renal function have been completed but not yet published. The renal route of excretion suggests a potential need for dose modification in individuals with compromised renal function.[28,29]

Pharmacodynamics

In a neutropenic murine thigh infection model, tebipenem demonstrated time-dependent pharmacodynamics (PD), consistent with the other members of the carbapenem class.[29] These studies investigated the magnitude of drug exposure required for stasis with 11 strains of *Enterobacterales* spp., and found that the PD target was best described by the ratio of the free drug area under the concentration-time curve ($fAUC_{0-24}$) to the MIC, corrected for the length of the dosing interval ($fAUC_{0-24}$/MIC*1/tau). This parameter differs from other carbapenem agents, for which the optimal PD index is the amount of time that free concentrations exceed the MIC (*f*T>MIC). The median value for the achievement of stasis in the strains with an every 8 hour dosing interval was $fAUC_{0-24}$/MIC*1/tau= 23, while a $fAUC_{0-24}$/MIC*1/tau greater than 35 was needed for bactericidal effects and suppression of resistance.[29]

TABLE 1. Activity of Tebipenem Against Gram-negative and Gram-positive Pathogens from Surveillance Studies

Pathogen	MIC_{90} (µg/mL)	Reference
Gram-negative		
Escherichia coli	0.015-0.03	20, 21, 27
Klebsiella pneumoniae	0.03-0.06	20, 21, 27
Proteus mirabilis	0.125-0.25	20, 21, 27
Enterobacter cloacae	0.25-1	23, 27
Enterobacter aerogenes	≤0.125	23, 27
Citrobacter freundii	0.03-0.25	23, 27
Acinetobacter baumannii	64	23
Stenotrophomonas maltophilia	64	23
Pseudomonas aeruginosa	8-64	21, 23
Clostridium difficile	1-2	21, 24
Bacteroides fragilis	0.06	24
Gram-positive		
Staphylococcus aureus- MSSA	0.03-0.125	21, 23
Staphylococcus aureus- MRSA	16	21, 23, 26
Enterococcus faecalis	2-32	21, 23
Enterococcus faecium	128	23

MIC_{90}= minimum inhibitory concentration that encompasses 90% isolates in the sample
MSSA= methicillin-sensitive Staphylococcus aureus
MRSA= methicillin-resistant Staphylococcus aureus

Clinical Data

The phase III randomized clinical trial ADAPT-PO evaluated an all-oral regimen of TBPM-PI-HBr compared to intravenous ertapenem for the treatment of cUTI and AP, with a regimen duration of 7 to 10 days. ADAPT-PO was conducted at more than 100 sites in 15 countries, including the United States, and included 1,372 hospitalized patients.[8] TBPM-PI-HBr was statistically non-inferior to ertapenem, achieving clinical cure in 93.1% of patients compared to 93.6% with ertapenem. Side effects were similar between the groups, with headaches and diarrhea being the most common in approximately 25% of the subjects in both groups. There were three reported cases of *Clostridium difficile* treatment-emergent adverse events, and they all occurred in the IV ertapenem group.[8]

Implications for Practice

The potential FDA approval of TBPM-PI-HBr marks a new milestone in the world of antimicrobial agents with the introduction of an oral carbapenem. While this is expected to expand access to carbapenems in the outpatient setting, its introduction raises important antimicrobial stewardship concerns.

Inpatient antimicrobial stewardship programs routinely implement restriction processes for broad-spectrum antibiotics, including carbapenems. Studies have shown that carbapenem restrictions may decrease institutional rates of carbapenem-resistant *Pseudomonas aeruginosa* and non-pseudomonal gram-negative bacilli.[31-33] It is unlikely that a restriction process overseen by an antimicrobial stewardship team could exist for TBPM-PI-HBr, given the process for oral antibiotic prescribing in most health systems. Mechanisms to limit overutilization of TBPM-PI-HBr could include medication use criteria established by insurance companies or by manufacturer requirements that limit the settings in which TBPM-PI-HBr can be dispensed. Other recently approved oral antibiotics, such as lefamulin and omadacycline, have restricted dispensing to specialty pharmacies or hospital pharmacies. The need for and mechanisms to restrict TBPM-PI-HBr prescribing have yet to be elucidated. A theoretical concern with unchecked use of TBPM-PI-HBr in the community is increased incidence of multidrug-resistant infections in individuals who have used this agent.

The current indication for which TBPM-PI-HBr seeks approval is the treatment of cUTI and AP in adults.[21] It is unknown whether the manufacturer will seek to limit the approval to treatment of pathogens that are resistant to first-line therapies for cUTI. Regardless of the approved indication, the most prudent application of this agent is likely to be reserving it for treatment of patients who cannot receive other oral agents, such as sulfamethoxazole-trimethoprim, cephalosporins, or fluoroquinolones, due to resistance, allergies, or drug-drug and drug-disease contraindications.[21]

Conclusion

TBPM-PI-HBr is a novel, orally bioavailable carbapenem antibiotic. It has been studied in a phase III trial of AP and cUTI and will likely be submitted to the FDA to consider approval for these indications in 2021. Tebipenem may fill a niche role in treating resistant infections in the outpatient setting, with the potential for use in the treatment of challenging infections well beyond its initial FDA-approved indication. Availability of an oral carbapenem, however, will be accompanied by several antimicrobial stewardship concerns. Emerging data will likely better inform clinical decision-making about the role of tebipenem in U.S. practice settings.

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