Tebipenem: A Novel Oral Carbapenem

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Abstract
Carbapenems are an important class of drugs very much useful in the therapy of multidrug-resistant gram-negative pathogens. Though these are available for the past 30 years, they can be administered only parenterally, which can reduce the compliance. Tebipenem-pivoxil (TBPM-PI; Orapenem), a prodrug, is the first oral carbapenem. It has been a promising drug in the therapy of drug-resistant respiratory infections and complicated urinary tract infections. It will also be useful in reducing the incidence of central line associated blood stream infections (CLABSI) and improving the rate of treatment completion.

Keywords: Carbapenem, Complicated urinary tract infections, Penicillin-resistant Streptococcus pneumonia, Recurrent respiratory infections.

Introduction
Carbapenems are great drugs for management of multidrug-resistant gram-negative pathogens. They belong to a subclass of beta-lactam antibiotics with broadest spectrum of activity and better beta-lactamase stability. Though these effective drugs are available for over 30 years, treatment of these infections is challenging as majority of available carbapenems can be administered only parenterally, hence compliance becomes jeopardized. Tebipenem-pivoxil (TBPM-PI; Orapenem), a prodrug, is the first oral carbapenem. It was first developed by Pfizer Inc. (New York, NY, USA).1 It is approved in Japan for use in children in 2009 and is currently marketed only in Japan (Meiji Seika Pharma Co., Ltd, “Meiji”) as a granule formulation (Orapenem Fine Granules 10%) for pediatric use. In complicated serious resistant gram-negative infections, this provides an option for oral step down.2

Chemistry
The first carbapenem structure, thienamycin, which is a natural product derived from Streptomyces cattleya, was isolated in 1976. Subsequently, parenteral carbapenem agents, such as imipenem, panipenem, meropenem, and biapenem, were developed based on this parent compound for the treatment of severe bacterial infections.3

In TBPM-PI, tebipenem (TBPM;SPR859) is the active moiety.2 This is esterified to TBPM-PI by adding the pivaloyloxymethyl group to carboxylic acid at the C-2 position (Fig. 1).4 This prodrug with pivaloyloxymethyl ester has a higher absorption rate when compared to other prodrugs of beta-lactam antibiotics and gets quickly hydrolyzed to the active antimicrobial agent.5

Mechanism of Action
Tebipenem passes though the outer membrane into the periplasmic space like other beta-lactam antibiotics. The penicillin-binding proteins (PBPs) are inhibited after acylation of tebipenem in the periplasmic space. Thus, the formation of cell wall peptidoglycan is catalyzed and thus weakens the peptidoglycan, which results in lysis of the bacterial cell.
In *S. pneumoniae*, the C-2 side chain of tebipenem formed key hydrophobic interactions with PBPs 2X and 1A, which are the key conserved residues in the PBPs in *Streptococcus pneumoniae*. The binding affinity to *Haemophilus influenzae* PBPs is also high.5

**Spectrum of Activity**

It has broad spectrum in vitro and in vivo activity against gram-negative and gram-positive pathogens, including resistant bugs like extended spectrum β-lactamases (ESBL)-producing Enterobacteriaceae and strains resistant to fluoroquinolones and trimethoprim sulfamethoxazole.5 The antibacterial activity of TBPM-PI is more efficacious than other carbapenems against infections caused by penicillin-resistant *Streptococcus pneumoniae* (PRSP), macrolide-resistant *Streptococcus pneumoniae* (MRSP) and *Haemophilus influenzae* (Hib), and B-lactamase-nonproducing ampicillin-resistant *H. influenzae* (BLNAR).1, 6 The bactericidal activity of tebipenem against *S. pneumoniae* and *H. influenzae* is comparable to that of levofloxacin and cefditoren.7

Gram-positive organisms like methicillin-susceptible *Staphylococcus aureus*, methicillin-susceptible *Staphylococcus epidermidis*, *Streptococcus pneumonia* including PRSP isolates, and *Streptococcus pyogenes* (MIC50/90 ≤ 0.063 μg/mL) are susceptible to tebipenem (Table 1).2, 5

MIC50/MIC90 against MRSA, *E. faecalis*, and *Enterococcus faecium* are 8/16 μg/mL, 0.25/32 μg/mL, and 64/128 μg/mL but much less than that for meropenem, imipenem, and ceftriaxone and cefditoren, hence proving that tebipenem has better action against MRSA, *E. faecalis*, and *E. faecium* but the in vivo action has to be monitored against these bugs despite the better MIC50/MIC90 when compared to other carbapenems.1, 2

Gram-negative organisms including *E. coli*, *Moraxella catarrhalis*, *Klebsiella pneumoniae*, *E. coli*, and *K. pneumoniae* strains expressing either penicillinases or ESBLs, *Proteus mirabilis*, *Proteus vulgaris*, Enterobacteriaceae strains expressing cephalosporinases, *H. influenzae* including ampicillin-resistant isolates, and *Enterobacter aerogenes* are susceptible to tebipenem with MIC90 ≤ 1 μg/mL (Table 2).

Tebipenem shows potent activity against class A (including ESBLs) and class C-lactamase-transformed strains, but not against class B-lactamase (metallo-lactamase)-transformed strains.7 Even *Burkholderia pseudomallei*, a gram-negative pathogen causing melioidosis, is inhibited by tebipenem with minimum inhibitory concentrations (MICs) of 1−2 μg/mL.2 Tebipenem has potent activity against *Neisseria gonorrhoeae*, which is comparable to cefxime that has the most potent activity among oral antibiotics.7

The MIC90 reported for *Acinetobacter baumannii*, *Serratia marcescens*, and *P. aeruginosa* is higher than for meropenem and hence better to avoid tebipenem use for these bugs.1 *Stenotrophomonas maltophilia* and *P. aeruginosa* strains expressing carbapenemases (MICs 50 to >100 μg/mL) are not susceptible to tebipenem.2

Anaerobes including *Peptostreptococcus* spp., *Bacteroides fragilis* (MIC90 ≤ 1 μg/mL), and *Clostridium difficile* (MIC90 = 1 μg/mL) are susceptible to tebipenem.2 It is also effective against *Clostridium perfringens*, *Veillonella* spp., *Prevotella* spp., *Porphyromonas* spp., and *Fusobacterium* spp. (MIC90 ≤ 0.25 μg/mL).7

**Pharmacokinetics and Pharmacodynamics**

The absorption and bioavailability are better with this prodrug form when compared to other carbapenems and has sufficient stability against hDHP-I in its active form.3, 8 From the studies in mice, it is shown that the tablet form has better bioavailability than the granules form.1 After absorption of the prodruk in the

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**Table 1**: Minimum inhibitory concentrations (MICs) of tebipenem pivoxil in comparison with other carbapenems against gram-positive bacteria1

| Strain       | TBPM-PI  | Meropenem | Imipenem and cilastin | Ceftriaxone |
|--------------|----------|-----------|-----------------------|-------------|
| MSSA         | ≤0.125/≤0.125 | ≤0.125/0.25 | ≤0.125/2 | 2/4         |
| MRSA         | 8/16     | 16/32     | 32/128               | >128/>128   |
| MSSE         | ≤0.125/0.5 | ≤0.125/1  | ≤0.125/1 | 1/16        |
| MRSE         | 8/8      | 16/16     | 16/64               | 64/>128     |
| Enterococcus faecalis | 0.25/32 | 2/>128 | 4/>128 | 32/>128 |
| Enterococcus faecium | 64/128 | >128/>128 | >128/>128 | >128/>128 |
| Pyogenic streptococcus | ≤0.125/≤0.125 | ≤0.125/≤0.125 | ≤0.125/≤0.125 | 4/8         |

**Table 2**: Minimum inhibitory concentrations (MICs) of tebipenem pivoxil in comparison with other carbapenems against gram-negative bacteria1

| Strain                | Tebipenem Pivoxil | Meropenem | Imipenem and Cilastin | Ceftriaxone |
|-----------------------|-------------------|-----------|-----------------------|-------------|
| *Escherichia coli*    | ≤0.125/1          | ≤0.125/1  | 0.25/1                | 64/>128     |
| *Klebsiella pneumonia* | ≤0.125/0.5      | ≤0.125/1  | 0.5/4                 | 2/>128      |
| *Enterobacter cloacae* | ≤0.125/1         | ≤0.125/2  | 0.25/2                | 128/>128    |
| *Enterobacter aerogenes* | ≤0.125/≤0.125 | ≤0.125/0.25 | 0.5/2            | 0.5/32      |
| *Acinetobacter baumannii* | 16/64   | 32/64     | 64/128               | 128/>128    |
| *S. maltophilia*      | 32/64             | 32/128    | >128/>128            | >128/>128   |
| *Pseudomonas aeruginosa* | 8/64    | 2/32      | 16/128               | 128/>128    |
| *Serratia marcescens* | ≤0.125/16       | ≤0.125/32 | 2/64                 | 8/>128      |
| *H. influenzae*       | ≤0.125/0.25      | ≤0.125/<0.5 | ≤0.125/1            | 2/16        |
| *Proteus mirabilis*   | ≤0.125/≤0.125    | ≤0.125/0.5 | ≤0.125/0.5           | 16/64       |
Tebipenem has a superior bactericidal activity against S. pneumoniae, which was evident by rapid decrease in body temperature and the reduction in leukocyte counts and CRP levels.12 Dose of 6 mg/kg bid has higher efficacy and is useful based on symptoms and severity.14 The 3 day TBPM-PI regimen was shown to cure all cases of bacterial pneumonia in children except in pneumonia caused by MRSA. A 3 day course of TBPM-PI at 6 mg/kg/dose twice daily was very effective in treating pneumonia in those without immunocompromised state or without complications. The short duration of oral therapy improves the compliance, reduces chances of the bacterial resistance, adverse effects, and cost of therapy.12

The recommended dosage for children is 4 mg/kg/dose, 12th hourly, and the dose can be increased to the maximum dose of 6 mg/kg/dose, 12th hourly. In pediatric patients at risk for the aggravation or prolongation of otitis media caused by resistant bacteria, who are less than 2-years-old, who are under group nursing, who have received at least one antibiotic, who are concurrently affected by rhinosinusitis, and who have a history of otitis media, the maximum dose can be considered.9

The break points of 1 μg/mL, 2 μg/mL, and 4 μg/mL are considered for interpretation of susceptible, intermediate, and resistant strains of S. aureus and H. influenzae.2

ADVERSE EFFECTS AND DRUG INTERACTIONS
Despite tebipenem being a broad-spectrum oral antibiotic, it has minimal effect on gut organisms after 5 days of BD dosing. The development of antibiotic-resistant organisms with this drug was minimal.3 Tebipenem-pivoxil is considered to be safe at dosage of 4 mg/kg bid in pediatric patients.15 The common adverse effects associated with tebipenem are watery stools, mushy stools, diarrhea (9.52%), and thrombocytosis.13 No severe or serious adverse drug reactions were seen.14 Carbapenems are known to reduce valproic acid (VPA) concentration in the blood when VPA and injectable carbapenem antibiotics are coadministered. Even tebipenem has similar interaction; the probable mechanism is that tebipenem directly or indirectly promotes the production of valproic acid glucuronic acid conjugates (VPA-Gluc), which are thought to reduce VPA blood concentrations. Hence, coadministration of oral carbapenem antibiotics and VPA should be avoided.15

CONCLUSION
There are strong expectations for TBPM-PI in the treatment of drug-resistant pediatric infections. However, since it is the first oral carbapenem antimicrobial drug, its use should be limited from the viewpoint of preventing the emergence of resistant bacteria. Its indications should be narrowed down to refractory pediatric otitis media, sinusitis, and pneumonia due to drug-resistant bacteria.

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