Absorption, Metabolism, and Excretion of [14C]-Tebipenem Pivoxil Hydrobromide (TBP-PI-HBr) Following a Single Oral Dose in Healthy Male Subjects

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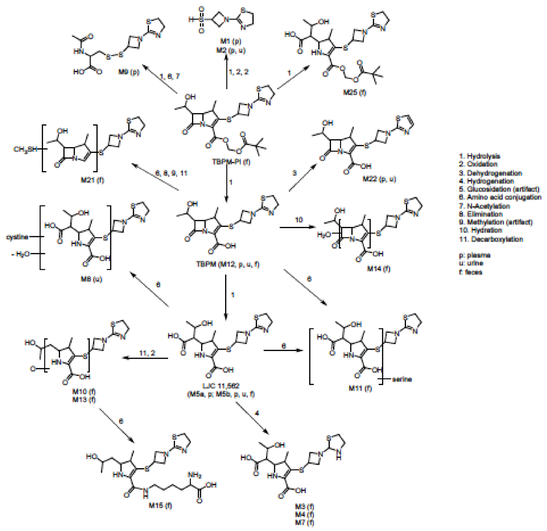
INTRODUCTION

Tebipenem pivoxil hydrobromide (TBP-PI-HBr) is an oral carbapenem with activity against multidrug-resistant gram-negative pathogens (Jain et al, 2018; Arends et al, 2019; Cotroneo et al, 2020; Rubio et al, 2019). TBP-PI-HBr is the prodrug of tebipenem (TBP) with improved absorption and bioavailability after oral administration (Figure 1). TBP-PI-HBr is the first oral carbapenem and is being developed in the U.S. for treating serious infections including complicated urinary tract infections and acute pyelonephritis.

Figure 1. Putative structures of metabolites and proposed biotransformation pathway for TBP



Note: Pathways are proposed based on general knowledge of metabolism and do not imply definitive pathways. Direct experimentation was not performed.

OBJECTIVE

- Evaluate the absorption, metabolism, and excretion of TBP-PI-HBr following administration of a single oral dose of [^{14}C]-TBP-PI-HBr and characterize metabolites present in plasma, urine, and feces.

METHODS

Study Design

- Phase 1, open-label, single-dose study in healthy male subjects.
- Mass balance, metabolite profiles and structures, pharmacokinetics (PK), and safety/tolerability were evaluated.
- Each subject was administered 3 capsules providing the target dose of 600 mg TBP-PI-HBr containing approximately 150 µCi of [^{14}C]-TBP-PI-HBr.
- All subjects fasted overnight for at least 10 hours.

Study Assessments

- Blood samples were collected to determine TBP concentrations, total radioactivity (whole blood and plasma), and metabolite profiling/identification (plasma).
- Urine was collected for TBP concentrations, total radioactivity, and metabolite profiling/identification.
- Feces were collected for total radioactivity and metabolite profiling/identification.

RESULTS

- Eight subjects were enrolled and included in safety and PK analyses.
- Males were aged 23 to 54 years with a BMI of 22.0 and 31.4 kg/m^2.
- Six subjects (75.0%) were white, and 2 subjects (25.0%) were Black or African American.

Pharmacokinetics

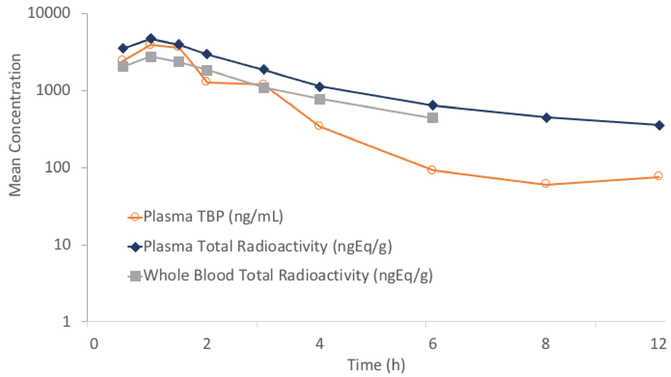
- TBP PK was characterized by rapid absorption in the systemic circulation, with a median T_{max} value of 1.0 hour (range: 0.5 to 1.5 hours) in plasma (Table 1).
- TBP plasma concentrations declined in a biphasic manner (Figure 2).

Table 1. Summary of PK parameters for TBP in plasma and total radioactivity in plasma and whole blood

Parameter	TBP Plasma	Plasma Total Radioactivity	Whole Blood Total Radioactivity
$AUC_{0\text{-}inf}$, (h*ng/mL) [a]	NC	18500 (28.0) [7]	8850 (32.9) [6]
$AUC\%_{extrap}$, (%)	NC	12.1 (22.3) [7]	13.4 (11.0 [6]
$AUC_{0\text{-}last}$, (h*ng/mL) [a]	8340 (25.0) [8]	15500 (28.6) [8]	8570 (35.9 [8]
C_{max}, (ng/mL) [a]	4540 (46.2) [8]	5450 (38.9) [8]	3150 (43.2) [8]
T_{max}, h	1.0 (0.5-1.5) [8]	1.0 (0.5-1.5) [8]	1.0 (0.5-1.5) [8]
T_{last}, h	12 (12-24) [8]	12 (12-24) [8]	8 (6-12) [8]
Half-life, h	NC	5.98 (55.3) [8]	3.52 (54.7) [8]
$AUC_{0\text{-}last}$ plasma TBP/total radioactivity ratio	NA	0.536 (6.3) [8]	NA
$AUC_{0\text{-}inf}$, blood/plasma ratio	NA	NA	0.566 (10.6) [5]
$AUC_{0\text{-}last}$, blood/plasma ratio	NA	NA	0.551 (10.6) [8]

Values are geometric mean (% coefficient of variation) [number]; T_{max} and T_{last} are median (min-max [n].
[a] Units for total radioactivity of AUC and C_{max} are h*ngEq/g and ngEq/g, respectively
NC: not calculated, NA: not applicable

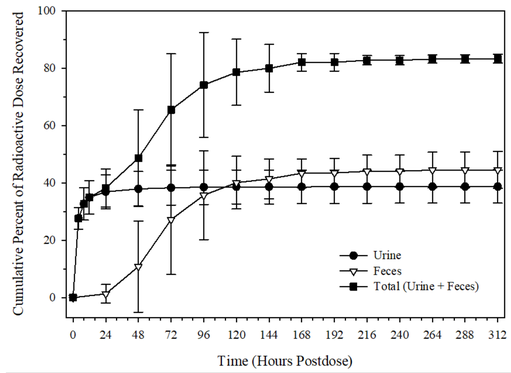
Figure 2. Arithmetic mean plasma concentrations (semi-log) of TBP and total radioactivity in plas



Total Radioactivity PK and Mass Balance

- C_{max} of total radioactivity in plasma and whole blood was reached with a T_{max} of 1.0 hour (Table 1).
- Levels of total radioactivity in plasma declined in a biphasic manner, with a geometric mean $t_{1/2}$ of 6.0 hours (range: 3.2 to 16.6 hours).
- Whole blood total radioactivity declined slightly more rapidly than plasma total radioactivity, with a geometric mean $t_{1/2}$ of 3.5 hours (range: 1.8 to 8.4 hours).
- Geometric mean $AUC_{0\text{-}last}$ plasma TBP/Total Radioactivity Ratio was 0.536, suggesting that metabolites contribute towards the circulating total radioactivity in plasma.
- Geometric mean whole blood/plasma $AUC_{0\text{-}last}$ ratio for total radioactivity was approximately 0.55, indicating a low association of TBP-PI-HBr radioactivity with cellular components.
- The between-subject variability in exposure to TBP in plasma and total radioactivity in plasma and whole blood was moderate to high, based on C_{max} and $AUC_{0\text{-}last}$ with values ranging from 25.0% to 46.2%.
- Mean recovery of radioactivity in urine and feces was 38.7% and 44.6%, respectively (Figure 3).
- 80% of administered radioactivity was recovered in the first 144 hours post dose in urine and feces combined.

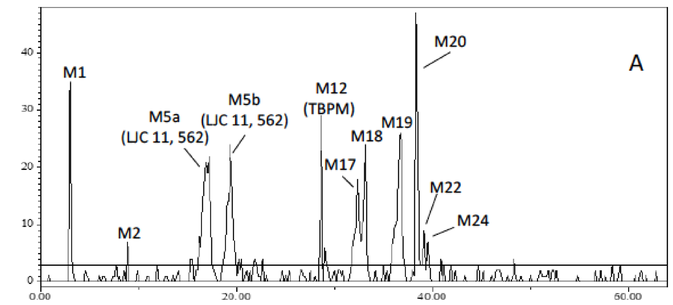
Figure 3. Arithmetic mean (±SD) cumulative percent of radioactive dose recovered in urine and feces at specified intervals after a single 600 mg (150-µCi) oral dose of [^{14}C] TBP-PI-HBr



Metabolite Profiling

- TBP was the major circulating component in plasma (Figure 4).
- An inactive ring open metabolite (LJC 11,562) of TBP was the other major metabolite in plasma (Figure 4).
- In urine, TBP was a major component representing 29.6% of the total radioactive dose.
- In feces, negligible amount of TBP (0.308% of the total radioactive dose) was observed, while LJC 11,562 was the major component and represented 16.6% of the total radioactive dose.
- TBP-PI was not detected in plasma or urine and accounted for only 0.58% of the total radioactive dose in feces.
- Radiochromatogram shows the wide distribution of metabolites in plasma (Figure 4).

Figure 4. Radiochromatogram from analysis of 0.25-6-hour AUC-pooled plasma samples after a single oral dose of [^{14}C]-TBPM-PI-HBr to male human subjects



Safety/Tolerability

- TEAEs were diarrhea in 2 (25%) subjects, ear pain 1 (12.5%), and pollakiuria 1 (12.5%).
- Only diarrhea was related to therapy.
- No deaths, serious adverse events or TEAEs leading to discontinuation occurred.
- No clinically significant abnormalities for clinical laboratory testing, ECG, vital signs or physical examination were reported.

SUMMARY

- TBP-PI-HBr was rapidly converted to TBP and absorbed in the systemic circulation, with a median TBP T_{max} of 1.0 hour in plasma.
- TBP was the main circulating component in plasma followed by its inactive ring open metabolite, LJC 11,562.
- Total radioactivity in both plasma and whole blood decreased rapidly.
- A low association of total radioactivity with cellular components of blood was observed (blood to plasma ratio of 0.551).
- Urine and feces were the main routes for elimination based on radioactivity with a cumulative mean recovery of 80%
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