Effect of Age and Sex on the Pharmacokinetics and Safety of Avibactam in Healthy Volunteers

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ABSTRACT

Purpose: Avibactam is a novel non–β-lactam β-lactamase inhibitor currently being assessed in combination with ceftazidime, ceftaroline fosamil, and aztreonam. The objectives of this study were to investigate the pharmacokinetics, safety, and tolerability of avibactam in healthy young (aged 18–45 years) and elderly (aged ≥65 years) volunteers of both sexes.

Methods: This was a Phase I, open-label study in which healthy volunteers aged ≥18 years were enrolled into 4 cohorts: young male, young female, elderly male, and elderly female (n = 8 in each group). Subjects were excluded if they had any condition requiring regular medication or any other relevant conditions. All subjects received a single dose of avibactam 500 mg/100 mL given intravenously over 30 minutes. Pharmacokinetic measurements included C_{max}, T_{max}, $AUC_{0-\infty}$, plasma clearance, and $t_{½}$.

Findings: Within the two age categories the mean age across male and female subjects was well matched. The majority of subjects in the young cohort were black (≥62.5%), whilst the majority of those in the elderly cohorts were white (≥75%). Mean avibactam plasma clearance was similar between the young male, young female, and elderly male cohorts (10.16, 10.34, and 9.82 L/h, respectively), and slightly lower in elderly women (7.98 L/h). Mean C_{max} was similar in young male, young female, and elderly female subjects (33.8, 36.9, and 38.4 μg/mL) but lower in elderly male subjects (26.5 μg/mL). Point estimates comparing the ratio of C_{max} in male and female subjects over all age groups suggested that C_{max} values were 18% lower (90% CI, 30%–5% lower) in male subjects compared with female subjects. Mean $AUC_{0-\infty}$ data were similar between the young male, young female, and elderly male cohorts (49.86, 49.75, and 52.40 μg · h/mL) but higher in elderly women (66.23 μg · h/mL). Point estimates comparing the ratio of $AUC_{0-\infty}$ in elderly and young subjects across both sexes suggested that $AUC_{0-\infty}$ values were 17% higher (90% CI, 5%–31%) in elderly subjects compared with young subjects. The $t_{½}$ was slightly longer for elderly subjects compared with younger subjects. The most common adverse event was administration/venipuncture site bruising (6 events); all adverse events were mild.

Implications: No notable differences in pharmacokinetics were observed between the male and female cohorts. The generalizability of the study is limited due to its small sample size. However, the small differences observed between the young and elderly cohorts are not sufficient to warrant dosing adjustments based on age. (*Clin Ther*. 2015;▮:▮▮▮–▮▮▮)

Key words: age, avibactam, pharmacokinetics, sex.

INTRODUCTION

Gram-negative pathogens are responsible for a large proportion of nosocomial infections,[1] as well as those acquired in the community. Gram-negative organisms have developed highly efficient mechanisms for antibiotic drug resistance,[2] with the production of extended-spectrum β-lactamases (ESBLs) being one of the most common. Carbapenems are currently used in the first-line treatment of serious infections caused by Gram-negative pathogens likely to produce ESBLs. However, resistance to these β-lactam antibiotics has been demonstrated, mediated by the production of carbapenemases such as *Klebsiella pneumoniae* carbapenemase.[3] Widespread use

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of carbapenems may lead to increased resistance in the future.

Avibactam is a novel non–β-lactam β-lactamase inhibitor with in vitro activity against Ambler class A, C, and some class D β-lactamases, including *K pneumoniae* carbapenemase, AmpC, and ESBLs.[4–6] Furthermore, avibactam is devoid of AmpC induction potential.[7] The drug forms a stable covalent adduct with these β-lactamases, resulting in inactivation,[8] which gives avibactam the potential to be used in combination with β-lactam antibiotics to restore their activity against pathogen-resistant strains. Avibactam is currently in clinical development in combination with ceftazidime for the treatment of complicated intra-abdominal and urinary tract infections and nosocomial pneumonia, and 2 Phase II studies have already been published (NCT00752219 and NCT00690378).[9,10] Avibactam is also being assessed in combination with ceftaroline fosamil[5] and other β-lactams (eg, aztreonam).[11]

The safety, tolerability, pharmacokinetics, and pharmacodynamics of single, ascending intravenous doses of avibactam (as 30-minute infusions) have previously been studied in healthy young adult male subjects.[12] Avibactam was administered either as a single agent (50–2000 mg) or as ceftazidime-avibactam combinations in a 4:1 dose ratio (1000:250 mg and 2000:500 mg). Avibactam, at doses up to 2000 mg, was well tolerated in this population, both systemically and locally, and drug exposure seemed to be proportional to dose. Avibactam is excreted largely unchanged in the urine.[13] Because the pharmacokinetics and safety of medications may vary between male and female subjects, as well as between younger and older subjects,[14,15] further investigation of avibactam pharmacokinetics was required for these different subgroups before advancing the ceftazidime-avibactam combination into clinical Phase II.

The objective of the present study was to investigate the pharmacokinetics, safety, and tolerability of a single dose of avibactam in healthy young and elderly male and female volunteers. The dose of avibactam selected for investigation was based on the highest dose of avibactam planned for use in future therapeutic studies.

SUBJECTS AND METHODS

This was a Phase I, open-label study (sponsor protocol number, NXL104-1004) conducted in healthy volunteers at a single center in the United States between February and October 2008. The study protocol was approved by an institutional review board (Chesapeake Research Review, Inc, Columbia, Maryland), and the study was conducted in accordance with Good Clinical Practice and sponsor standard operating procedures, which conform to the ethical principles of the Declaration of Helsinki. All subjects provided written informed consent.

Subjects

Male and female volunteers were eligible for inclusion if they were aged ≥18 years, in good health, had a body mass index 18 to 28 kg/m^2 for young subjects (18–45 years) or 18 to 30 kg/m^2 for elderly subjects (≥65 years), and systolic and diastolic blood pressures and heart rate were within the normal, age-related ranges. Subjects were excluded if they had any condition requiring regular medication (unless approved by the sponsor); used any other over-the-counter or prescription medication within 14 days of study start; had a QTc interval ≥420 milliseconds (>450 milliseconds in elderly subjects) or a pronounced sinus bradycardia (<40 beats/min), hypokalemia (<3.5 mEq/L), or family history of long QT syndrome, unexplained sudden death, sick sinus syndrome, or any clinically relevant cardiovascular disease; presence or sequelae of gastrointestinal, liver or kidney disease, or other conditions known to interfere with the distribution, metabolism, or excretion of drugs; evidence of HIV or hepatitis C infection; hematologic abnormalities (including white blood cell counts <3500/mm^3, an absolute neutrophil count <1500/mm^3, or a platelet count <100,000/mm^3); creatinine >2 mg/dL; or evidence or history of drug abuse. Subjects were also excluded if they were a smoker of >5 cigarettes per day, a heavy caffeine drinker of >5 cups of coffee a day (or equivalent in xanthine-containing beverages), or whose intake of alcohol exceeded 2 units per day (or who were unwilling to stop alcohol consumption for the duration of the study). Male subjects had to be willing to abstain from sexual intercourse or use a condom/spermicide for the duration of the study and for at least 90 days afterward. Female subjects of childbearing potential had to be willing to use double-barrier methods of birth control.

The volunteers were recruited into 1 of 4 cohorts: young male subjects (aged 18–45 years), young female subjects (aged 18–45 years), elderly male subjects (aged