Texas Tech University Health Sciences Center

PROJECT SUMMARY

Study Title: Pharmacokinetics of ceftolozane/tazobactam in patients with burns

Sponsor/Funding Source: Merck Investigator Studies Program

Purpose:

1. To describe the pharmacokinetics of ceftolozane and tazobactam (volume of distribution, plasma clearance, urine clearance) in patients with burns.
2. To determine the probability of target attainment for ceftolozane for individual MIC values ranging from 0.5 to 16 mg/L.
3. To determine the cumulative fraction of response using the MIC distributions of Enterobacteriaceae and Pseudomonas aeruginosa from US hospitals (Farrell et al, PMID: 24100499).

Hypothesis:

1. Using a descriptive analysis, we expect to observe that patients with burns will have increased ceftolozane and tazobactam (volume of distribution, plasma clearance, urine clearance) after treatment with a single dose of 2 grams/1 gram of ceftolozane and tazobactam administered intravenously.
2. We will describe the probability of target attainment for patients with burns using a doubling of MIC values from 0.5 to 16 mg/L.
3. We will describe the cumulative fraction of response in patients with burns using the MIC distributions of Enterobacteriaceae and Pseudomonas aeruginosa from US hospitals.

Background:

Patients with burns are at an increased risk of bacterial infections compared to patients without burns. Patients with significant burns can have altered physiology including increased cardiac output, increased blood flow to the kidneys and liver, and decreased albumin production. These changes can result in decreased drug concentrations from the increased volume of distribution and increased systemic clearance.

However, clinicians do not know the optimal dosing regimens of antimicrobials to use in these patients with burns. This lack of knowledge is due, in large part, to the USA Food and Drug Administration failing to require patients with burns to be included in all phases (I-IV) of drug development.

Pharmacokinetic data specifically comparing the impact of burns on ceftolozane administered with tazobactam are not available. Previous data with piperacillin/tazobactam suggest that the tazobactam Cmax is decreased more significantly than piperacillin, which could mean that the co-administered beta-lactam does not have sufficient protection from the beta-lactamase inhibitor. This study will help clinicians be able to know what, if any, dosage adjustment is needed for the co-administration of these agents in patients with burns.

Concise Summary of Project:

A single dose pharmacokinetic study of ceftolozane and tazobactam will be conducted in patients with burns at the Timothy J. Harnar Burn Center at University Medical Center, Lubbock, TX. The Burn Center includes 15 beds with 6 of those intensive care unit beds. The Burn Center meets the criteria of the American Burn Association's Burn Center Verification/Consultation Program and has maintained Burn Center Verification status since 1993. A total of 12 adults aged 18 to 80 years with >/= 20% percent total body surface area burned will be required to complete the study. A single intravenous dose of ceftolozane and tazobactam of 2 grams/1 gram will be administered over 60 minutes and whole blood will be obtained predose and at 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, and 24 hours following the start of infusion. Urine samples (5 ml) will be collected from a urine collection bag (if the patient has urinated) at the following timepoints: 0-0.5, 0.5-1, 1-2, 2-4, 4-8, 8-12, and 12-24 hours for analysis of ceftolozane and tazobactam content. Urine collected during each time period will be measured to determine urine volume for urine clearance calculations. The volume of urine in the urine over the entire 24 hour period and an aliquot sent for analysis of urine creatinine content to determine the patient's 24 hour creatinine clearance.

Drug procurement: Texas Tech University Health Sciences Center Lubbock Pharmacy has agreed to purchase the ceftolozane/tazobactam required for the study with funds provided by the study budget. University Medical Center Investigational Drug Service has agreed to store, dispense and maintain product accountability records for the ceftolozane/tazobactam required for the study.

Study drug preparation:
In order to prepare a 3 g dose of ceftolozane/tazobactam: Constitute each vial (2 vials required for 3 g dose) with 10 mL of sterile water for injection or 0.9% Sodium Chloride for Injection, USP and gently shake to dissolve. Then withdraw the entire contents (approximately 11.4 mL) of each reconstituted vial using a syringe and add to an infusion bag containing 100 mL of 0.9% Sodium Chloride for Injection or 5% Dextrose Injection, USP.

Sample preparation and analysis: Plasma will be separated from whole blood samples. Plasma and urine samples will be stored at -70 C until batch shipped to the Center for Pharmacology and Experimental Therapeutics for analyses of ceftolozane and tazobactam content using a LC-MS/MS method that will be developed and validated. The respective concentrations versus time will be plotted and the best fit model will be selected to calculate pharmacokinetic estimates using Phoenix WinNonlin (Pharsight Corporation). Results will be presented using descriptive statistics.

Study Procedures:

The study will require 1 dose of ceftolozane/tazobactam in the Burn Center and 24 hours of blood draws (49 mL of blood being drawn)

Screening Procedures
1. Study staff will screen patients in the Burn Center. Study staff will approach the primary physician of eligible patients to gain permission to discuss the study with the patients or the caregiver with power of attorney.

2. Study personnel will provide the patient or caregiver with additional information about the study and provide the patient or caregiver the opportunity to ask any questions. The patient or caregiver will then be asked if they are willing to provide informed consent.

Procedures and Evaluation during the Research

1. At the start of the study, the patient will have an intravenous line inserted if two intravenous lines are not already available for use by study staff.
2. All patients will receive a single 2 grams/1 gram intravenous dose of ceftolozane and tazobactam.
3. Each patient will then have 3 ml of blood drawn 13 times, at t=0h (pre-dose), 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24 hours following the start of the intravenous infusion of the study medication, plus 10 mL at 24 hours post-dose to assess the patient's general health (complete metabolic panel and complete blood count).Labels on blood samples will not contain patient name, but a randomly generated patient identification number.
4. The blood is spun down for plasma separation, and the plasma stored in the Clinical Research Institute at 70°C until shipped to the Center for Pharmacology and Experimental Therapeutics for measurement of ceftolozane and tazobactam concentration using LC/MS/MS methods. A LC-MS/MS analytical method will be developed and validated for determination of plasma ceftolozane and tazobactam content at the Texas Tech University Health Sciences Center's Clinical Pharmacology & Experimental Therapeutics Center. The Center for Pharmacology and Experimental Therapeutics will not be involved with any procedures regarding patient contact. The Center for Pharmacology and Experimental Therapeutics' association in the study is solely for data acquisition from plasma samples.
5. Urine samples (5 ml) will be collected from a urine collection bag (if the patient has urinated) at the following time periods: 0-0.5, 0.5-1, 1-2, 2-4, 4-8, 8-12, and 12-24 hours for analysis of ceftolozane and tazobactam content.
6. The volume of urine in the urine collection bag will be documented and an aliquot sent for analysis of urine creatinine content to determine the patient's 24 hour creatinine clearance.
7. During the study and at the end of the procedure the patient will be monitored to assess for possible adverse events. The medical chart will also be reviewed for any adverse events that occur during the study period.
8. The patient is discharged from the study after the 24 hour blood draw.

Follow-up: There will be no follow up since the patients will not receive ceftolozane and tazobactam for therapeutic purposes, but solely for the purpose of the pharmacokinetic study.

Criteria for Inclusion of Subjects:

(1) Male and female subjects, ages 18-80 years, of all racial and ethnic origins.
(2) Non-English Spanish speakers will be included in the study.
(3) We are recruiting 12 patients with thermal burn injuries (percent total body surface area burned >/= 20%).
    (a) Patients will be at least five days, but no more than 14 days, from the date of the burn injury.
(4) Patients will have 2 intravenous lines (central venous and/or arterial line access)-or be willing to have 2 IV lines inserted.

Criteria for Exclusion of Subjects:

(1) Pregnant or nursing or unwilling to use a reliable contraception method during the study. The effects of ceftolozane and tazobactam on pregnancy are unknown. In addition, the metabolic changes that accompany pregnancy may alter the concentration-time profile of ceftolozane and tazobactam, so that the pregnancy and post-partum state would be a confounding variable.
(2) Abnormal liver function tests: transaminases >10 times upper limit of normal, Alkaline phosphatase >5 times upper limit of normal, total bilirubin >5 times upper limit of normal.
(3) History of allergies to beta-lactam antibiotics.
(4) Patients unwilling to comply with study procedures.
(5) Current or previous participation within 28 days of enrollment in another research study that involves the use of medication, contrast, or any other compound that may alter blood count and/or blood chemistry (liver function, kidney function or electrolyte balance), unless waved by principal investigator (PI).
(6) Donation of 450mL (one unit) of blood or more within 8 weeks (56 days) prior to study enrollment, unless waved by PI.
(7) Creatinine clearance < 30 ml/min as estimated by the Cockcroft-Gault equation.
(8) Patients who are receiving piperazillin/tazobactam or have received piperacillin/tazobactam within the past 48 hours.
(9) Patients who are receiving vasopressors.
(10) Patients with admission total body weight < 60 kg or > 130 kg.

Sources of Research Material:

Pregnancy status (urine sample), medication allergies (patient interview or medical record), comorbid conditions (medical record), height and weight (medical record or directly measured), complete metabolic panel review (medical record), complete blood count (medical record), vital signs (temperature, respiratory rate, and heart rate assessed by review of the medical record), drug and creatinine concentrations (urine and blood samples), adverse events (patient interview and study staff). All data will be obtained specifically for research purposes.

Recruitment Methods and Consenting Process:

(1) Study staff will screen patients in the Burn Center. Study staff will approach the primary physician of eligible patients to gain permission to discuss the study with the patients or the caregiver with power of attorney.
(2) Study personnel will provide the patient or caregiver with additional information about the study and provide the patient or caregiver the opportunity to ask any questions. The patient or caregiver will then be asked if they are willing to provide informed consent. Each potential patient for the study will be informed, as reflected in the consent form, that they do not have to take part in the study if they do not want to, that they can ask to be removed from the study at any time without any consequences of their medical care. No vulnerable populations will be recruited. Patients will also be informed of their information privacy rights and be asked to sign a HIPAA authorization before participating in the study.

The patient will receive a signed copy of both the informed consent and the HIPAA authorization. Informed consent will be documented in a note in the patient's research chart.

(3) Twelve patients with burns will be asked to participate in the study.

Potential Risks:

Intravenous catheter related potential risks:

Sites where intravenous catheter is inserted may develop phlebitis and thrombophlebitis. In addition, some catheters may become infected, although this is rare if catheter is placed for 24h or less. Risks associated with having an intravenous catheter include minimal discomfort and/or bruising. Infection, excess bleeding, clotting, and/or fainting also are possible. Some known discomforts that can be associated with the blood drawing procedures are pain, burning, or the development of a bruise at the site where the intravenous catheter is placed.

Risks of Blood Drawing
A total of 49 ml (9.8 teaspoonfuls) of blood will be obtained over the over the 24 hour study period. Risks associated with drawing blood include minimal discomfort and/or bruising. Infection, excess bleeding, clotting, and/or fainting also are possible.

Loss of confidentiality: Social and psychological distress could arise from a patient's confidential information being lost or misused.

Ceftolozane and tazobactam related adverse events: Ceftolozane and tazobactam has been studied in clinical trials in 1,015 patients. Only 20 of the 1,015 patients (2.0%) required treatment discontinuation due to adverse events in clinical studies. Most of the studies have documented adverse events in the setting of daily doses over more than a single day, so that it is expected that adverse events will be less with a single dose infusion. However, based on the package insert, there are still potential risks.

Occasional events reported > 10% of subjects:
None

Infrequent events reported in 5-10% of subjects:
Nausea, headache, diarrhea, and pyrexia

Rare events reported in 1-5% of subjects:
Constipation, insomnia, vomiting, hypokalemia, ALT/AST increased, anemia, thrombocytosis, abdominal pain, anxiety, dizziness, hypotension, atrial fibrillation, and rash.

Serious but rare events reported in <1% of subjects:
Tachycardia, angina pectoris, ileus, gastritis, abdominal distension, ileus paralytic, infusion site reactions, candidiasis, oropharyngeal, fungal urinary tract infection, increased GGT, increased serum alkaline phosphatase, positive Coombs test, hyperglycemia, hypomagnesemia, hypophosphatemia, ischemic stroke, renal impairment, renal failure, dyspnea, venous thrombosis

PREGNANCY: The effect of ceftolozane and tazobactam on the fetus is unknown.

Risks to Sperm, Embryo, Fetus or Breast-fed Infant

Men: Being in this research may damage their sperm, which could cause harm to a child that they may father while on this study. Any males taking part in this study who are sexually active must agree to use a medically-acceptable form of birth control. Medically-acceptable forms of birth control include:

(1) surgical sterilization (vasectomy), or
(2) a condom used with a spermicide (a substance that kills sperm).

If their spouse or partner thinks she is pregnant during the study or within 28 days after they have stopped taking study drug, they will be advised to tell the study doctor immediately. If their spouse or partner becomes pregnant, she will be asked to sign a release of information form to allow the study doctor to contact her obstetrician to collect updates on the progress of the pregnancy and its outcome. The study doctor will make this information available to the study sponsor for safety monitoring follow-up.

Women: If females are part of this study while pregnant or breast-feeding an infant, it is possible that they may expose the unborn child or infant to risks. For that reason, pregnant and breast-feeding women cannot participate in the study. If a female participant can become pregnant, a urine pregnancy test will be done, and it must be negative before she participates in this study. Females who are sexually active willing to take part in this study and any person that they have sex with must use medically-acceptable birth control (contraceptives) during the study. Medically-acceptable birth control (contraceptives) includes:

(1) surgical sterilization (such as hysterectomy or “tubes tied”),

(2) approved hormonal contraceptives (such as birth control pills, patch or ring; Depo-Provera, Depo-Lupron, Implanon),

(3) barrier methods (such as condom or diaphragm) used with a spermicide (a substance that kills sperm), or

(4) an intrauterine device (IUD).

Females will be advised to tell the researchers immediately if they become pregnant during this study.

If females become pregnant within 28 days after they have stopped taking study drug, we will ask that they contact their study doctor for safety monitoring. In either case, we’ll ask to make their obstetrician aware of their study participation. The study doctor will ask females and their obstetricians to provide updates on the progress of the pregnancy and its outcome. The study doctor will make this information available to the study sponsor for safety monitoring follow-up.

As with any drug there may be unusual, unexpected, or previously unreported side effects that may occur with this study medication. Study participants could also have an allergic reaction to the drug.

Some new problems or side effects could happen. Study participants or their legally acceptable representatives will be told of any changes in the way the study is done. Study

participants will be told of any new risks or side effects. This information may affect their decision about continuing in the study.

Other Risks
There may possibly be other side effects that are unknown at this time. If study participants are concerned about other, unknown side effects, the researchers will be available to discuss any questions and concerns.

Subject Safety and Data Monitoring.

Type of Research Data or Events to be Monitored:

Study accruals, protocol deviations, protocol violations, unanticipated problems, adverse events. An unanticipated event will be defined as any AE that is serious and rare in the absence of drug treatment, or a known adverse event of ceftolozane or tazobactam that occurs at higher frequencies than those described in the product brochure and the ceftolozane and tazobactam related adverse events section above.

Methods and Frequency of Analysis:

Weekly conference call/team meeting with study staff to discuss routine issues. Adverse events will be assessed on a case by case basis as they occur and aggregately at the weekly team meeting. Serious adverse events will be reported to the Texas Tech University Health Sciences Center IRB within 24h of them having occurred. A final safety report, including line listing of AE as well as frequencies of such AE shall be provided to the Texas Tech University Health Sciences Center IRB once enrollment has been completed.

Person(s) Responsible for Data Monitoring:

John Griswold, MD and Ronald Hall, PharmD

Reporting Unanticipated Problems, Adverse Events, Protocol Deviations and Protocol Violations:

Detailed reports will be sent to the Texas Tech University Health Sciences Center IRB within 24 hours of any unanticipated adverse event, serious adverse event, and protocol violation. In terms of adverse events, the action taken to treat the adverse events as well as outcome will also be reported. In addition, a safety report, including line listing of AE as well as frequencies of such AE shall be provided to the Texas Tech University Health Sciences Center IRB after the completed enrolment of 12 volunteers, as described above.

Stopping Rules:

Not applicable to this study.

Procedures and Time Frames for Communicating Outcomes:

1. Serious AE and unanticipated AE will be reported to the Texas Tech University Health Sciences IRB within 24 hours.
2. A final report on safety will be provided to the IRB and sponsor after recruitment of the 12 patients.
3. Final reports to sponsor will be made after last patient is recruited and after drug concentrations have been determined and mathematically analyzed. This is anticipated to be 60 days after recruitment of the last patient.

Precautions for Maintaining Data Integrity

a. All data shall be coded based on a random generated number.
b. The source documents/medical record shall be completed immediately after each procedure, dated and timed.
c. To ensure compliance with the study protocol, GCP guidelines, and TTUHSC Human Research Protection Program research policies and procedures during the conduct of the study, as well as quality data, a monitor in the Clinical Research Institute will conduct the monitoring of the study. The first monitoring visit will be conducted within one week after the first subject has been enrolled into the study. The succeeding monitoring visits will be scheduled periodically, but no less than every 2 months when there is an active study participant, at a mutually agreed timeframe by the PI and study monitor. All data collected will be 100% source document verified. The study monitor may inspect and audit all study documents, i.e. data collection forms, questionnaires, drug accountability, and medical records within the applicable confidentiality regulations.
d. The subject's data file will be secured and locked in the Clinical Research Institute where only research personnel have access.

Blood draws and access for blood draws: The blood draws are limited to 49 ml over a 24 hour period for blood concentrations and assessment of general health.

Review of Adverse Events: All adverse events will be reported to the Texas Tech University Health Sciences Center IRB. In addition, an independent reviewer will review all adverse events for each week.

Precautions to prevent injury. All research personnel who will interact with the patient are trained research staff (coordinators, nurses and physicians) who have privileges to see patients at University Medical Center. All of them have passed the Good Clinical Practice requirements. Drug administration will occur in the presence of one of these trained personnel. In the event of any adverse event, Dr. Griswold or Dr. Dissanaike will be promptly informed and they will make the necessary diagnostic and therapeutic decisions to minimize

injury. All serious adverse events will be reported to the Texas Tech University Health Sciences Center IRB within 24 hours.

Procedures to Maintain Confidentiality:

The information obtained from subjects in this trial will be strictly confidential. Each subject will be assigned a research code number that will be used on all case report forms. The volunteer's medical record will contain a scanned copy of the original signed informed consent document, clinical data and laboratory test results. The research data will be kept behind locked doors in the Clinical Research Institute. This data will only be used for research purposes.

Volunteers will be advised that representatives of the FDA, Sponsor, University Medical Center, and Texas Tech University Health Sciences Center IRB, may review their medical and research records to assure the quality of the information used in the research. Identifiers will be removed from the volunteer's research data before the data is reviewed by any of these groups.

Blood samples collected from the participants will be sent to the Clinical Pharmacology and Experimental Therapeutics Center, which will utilize the following coding system:

Study ID – Blinded Volunteer ID – Sample number	123-745-01
Date	mm/dd/yy
Sample material	blood

Blood samples will be sent to the Clinical Pharmacology and Experimental Therapeutics Center for pharmacokinetic analysis. Study enrollment will not include any participants less than 18 years of age.

All blinded samples will be shipped to and logged into the Center, processed for -80^{0}C storage, and batched for later analyses. Following analyses, residual samples will be retained not more than one year following study conclusion and with approval of the investigator be destroyed earlier (residual samples are kept to allow repeat analyses during the critical peer review process). Residual blinded samples will be stored in a locked -80^{0}C freezer located within Clinical Pharmacology and Experimental Therapeutics Center and only accessible to Center research personnel.

After discharge no data can be traced back to the volunteer's identifiers; however, the volunteer's information will be kept under locked doors and password-protected (electronic records) should he/she agree to be contacted for future research studies. During and after the study, all data is kept locked up in the Clinical Research Institute, and access is restricted only to study personnel.

Publications resulting from the study will not contain volunteer identifiers.

Potential Benefits:

There are no direct benefits to volunteers participating in this study. Patients with burns (including those participating in this study) who receive ceftolozane and tazobactam may benefit in the future from an individualized dosing regimen.

Biostatistics:

Justification for sample size: The sample size requested is based on standard sample sizes of 6-12 patients per group for population pharmacokinetic studies based on FDA guidance.

Pharmacokinetic modeling: Plasma content versus time will be plotted and the best-fit compartmental model will be selected and pharmacokinetic estimates will be calculated using Phoenix WinNonlin. The urinary clearance of ceftolozane and tazobactam will also be calculated using Phoenix WinNonlin.

Primary hypothesis testing: The data will be presented as a descriptive analysis. We will also assess the relationships between pharmacokinetic parameters and 1) percent total body surface area burned and 2) degree of burn using a descriptive analysis.

Pharmacodynamic analysis: We will conduct a 10,000-patient Monte Carlo simulation using Crystal Ball to determine the percent free drug above the MIC (% fT>MIC) to determine the probability of a simulated patient achieving the pharmacodynamic target, otherwise known as the probability of target attainment (PTA). We will use a doubling of MIC values from 0.5 to 16 mg/L. For each analysis, Cl (in liters), Vd, f, and the MIC value will be substituted into the appropriate equations. The result will be 10,000 different estimates of pharmacodynamics exposure for each analysis that are based on the probability distributions.

Values for % fT>MIC will be plotted on a histogram to determine the frequency of simulated patients achieving a % fT>MIC for >/= 40%, >/= 50%, and >/=60% of the dosing interval.

PTAs will also be used to calculate the cumulative fraction of response (CFR) using MIC distributions of *Enterobacteriaceae* and *Pseudomonas aeruginosa* from US hospitals (Farrell et al, PMID: 24100499). The CFR will be calculated using the equation $PTAi*Fi$. The MIC category, from lowest to highest MIC value, is represented by the subscript i. The PTA of each MIC category is $PTAi$. The fraction of the population of microorganisms at each MIC category is denoted as F. A CFR of >/=90% against a bacterial population is considered optimum.

References
1. Zerbaxa prescribing information, Merck & Co., Inc. [Revised 9/2016]
2.aMedical Information letter, Merk & Co., Inc. [Sent 8/2016]