COMIRB Protocol

COLORADO MULTIPLE INSTITUTIONAL REVIEW BOARD
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Protocol #:	**16-1355**
Project Title:	**Evaluation of intravenous and intraperitoneal pharmacokinetics of dalbavancin in peritoneal dialysis patients**
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I. **Hypotheses and Specific Aims**:

Hypothesis:

Dalbavancin maintains adequate plasma and peritoneal fluid concentrations for 2 weeks after a single 1500 mg dose when administered intravenously or intraperitoneally, making it a viable and convenient option for treating peritoneal dialysis patients with peritonitis

Specific Aims:

1. Determine dalbavancin plasma pharmacokinetics in peritoneal dialysis patients after intravenous and intraperitoneal administration
2. Determine dalbavancin peritoneal fluid pharmacokinetics in peritoneal dialysis patients after intravenous and intraperitoneal administration
3. Evaluate patients for any adverse effects potentially associated with intraperitoneal administration of dalbavancin

II. **Background and Significance**:

Every year in the United States approximately 110,000-115,000 patients are newly diagnosed with end-stage renal disease (ESRD) and begin treatment with renal replacement therapy. Nearly 10,000 of these patients are started on peritoneal dialysis (PD).[1] The use of home dialysis has increased significantly (35% increase) in the last decade, with 95% of home dialysis patients undergoing PD.[1] Infectious peritonitis is a leading major morbidity associated with PD, and it accounts for approximately 18% of infection-related mortality in PD patients. Severe or prolonged peritonitis can lead to peritoneal membrane failure, ultimately causing technical failure of PD and requiring transition to traditional hemodialysis methodologies. Rapid and effective treatment of peritonitis is required to reduce inflammation and preserve peritoneal membrane function.[2] The current standard of care involves empiric antibiotics covering gram positive organisms as staphylococcus aureus, coagulase negative staphylococcus and enterococcus are common infecting pathogens.[2] Vancomycin is commonly employed at most institutions as there is a risk of MRSA infections in this patient population. Addition of a second drug for gram negative bacteria coverage is recommended until culture and sensitivity results are available. Intravenous or intraperitoneal administration of antibiotics can be utilized; however, guidelines recommend the intraperitoneal administration of antibiotics with a dwell time of at least 6 hours because it provides instant, high, and sustained concentrations of the antibiotic in the peritoneal fluid.[2] Although vancomycin covers the majority of gram positive organisms that cause peritonitis, its use can be cumbersome in PD patients. Plasma vancomycin drug concentration monitoring must occur to evaluate for vancomycin accumulation. Additionally, vancomycin must be re-administered every 3-5 days in order to maintain steady-state trough concentrations around 15 mcg/ml.[2] Similarly to vancomycin, dalbavancin interferes with cell wall synthesis. This is done through binding of the D-alanyl-D-alanine terminus of the cell wall peptidoglycan.[3] Dalbavancin has been shown to rapidly reach therapeutic systemic concentrations and to have an extended half-life of ~8.5 days.[4-8] Dalbavancin has been shown safe and effective with a treatment doses of 1500 mg once or 1000 mg followed by a 500 mg dose on day 7.[9-11] Dalbavancin pharmacokinetics were evaluated in patients who had hepatic or renal impairment. This study showed compared to healthy subjects dalbavancin exposure was not increased in mild renal impairment, exposure was ~50% higher in moderate renal impairment, 100% higher in severe renal impairment, and not significantly different in end stage renal disease

patients undergoing dialysis.[12] Based on this data only patients with severe renal dysfunction, <30 mL/min, and not on hemodialysis should have their dalbavancin dose reduced.[3]

We believe that dalbavancin offers a unique option for PD patients with peritonitis, because it has excellent gram positive bacteria coverage, is administered in a single dose option, does not require dose adjustment in renal dysfunction on dialysis, and there is no need for routine plasma concentration monitoring. For these reasons, we intend to study the pharmacokinetics of dalbavancin when administered intravenously and intraperitoneally in PD patients.

III. Preliminary Studies/Progress Report:

Dr. Teitelbaum follows 35-40 patients undergoing peritoneal dialysis within his clinic. Approximately 95% of the patients followed in his clinic meet inclusion and exclusion criteria.

IV. Research Methods

A. Outcome Measure(s):

The primary endpoints for the study are to (1) determine dalbavancin plasma pharmacokinetics in peritoneal dialysis patients after intravenous and intraperitoneal administration and (2) determin dalbavancin peritoneal fluid pharmacokinetics in peritoneal dialysis patients after intravenous and intraperitoneal administration.
Secondary endpoint is to evaluate patients for any adverse effects potentially associated with intraperitoneal administration of dalbavancin.

B. Description of Population to be Enrolled:

Inclusion criteria:

- Age ≥18 to ≤89 years of age
- Actively receiving chronic peritoneal dialysis (receiving peritoneal dialysis treatments ≥3 times per week for ≥3 months)
- Ability and willingness to provide written informed consent before the first trial ready activity

Exclusion criteria:

- Patients currently receiving antimicrobial therapy or have received antibiotic therapy within 14 days prior to study
- Patients with known hypersensitivity reactions to dalbavancin or other glycopeptides
- Age <18 years old or >89 years old
- Prisoners
- Pregnant or breastfeeding women
- Decisionally challenged patients: Incompetent to consent, cognitively impaired (e.g. psychiatric disorder), altered decisional capacity due to the environment or situation (e.g. stress).
    - This will be evaluated based on previous medical history given from the patient and chart review
    - If altered decisional capacity is suspected due to environment or situation follow up questions will be asked by clinic personnel not involved with the study or direct care of the patient
- Patients with active peritonitis
- Temperature >38ºC or <36ºC
- Significant abdominal tenderness
- Child-Pugh class B, or C

C. Study Design and Research Methods

This study is an open label, cross-over study, evaluating the plasma and peritoneal fluid pharmacokinetics of dalbavancin after either intravenous or intraperitoneal administration. The

patients will be randomly assigned to receive dalbavancin either intravenously or intraperitoneally on study visit 1. The patients will receive the alternate administration technique following the washout period at visit 4. Patients will be administered dalbavancin either intravenously or intraperitoneally on study day 0. Pharmacokinetic analysis will be conducted on days 0, 7, and 14. Following the wash out period of 45 days or greater, the same 10 patients will cross-over and then be administered dalbavancin via the alternate administration technique received in visit 1 on study day 0. Pharmacokinetic analysis will be conducted again on days 0, 7, and 14. (see Appendix 1)

Sample Size:
Ten (n=10) patients will be evaluated in this pharmacokinetic evaluation. Since this is a descriptive pharmacokinetic study a sample size calculation was not performed

Plasma and peritoneal fluid sampling:
Dalbavancin will be administered on study day 0. On the intravenous administration day dalbavancin will be administered as a 30-minute IV infusion. On the intraperitoneal administration day, dalbavancin will be administered in the peritoneal dialysis fluid with a 6 hour dwell time. On day 0, patients will undergo plasma and peritoneal fluid pharmacokinetic sampling for determination of dalbavancin concentrations at time zero, 1 hour, 2 hours, 3 hours, 4 hours, 6 hours, at time of volume exchange. Patients will be given a specimen collection cup and asked to collect ~30 ml of peritoneal dialysate following scheduled nocturnal dwell approximately 24 hours following the administration of dalbavancin administration. Patients will report for a single PK measurement on study days 7 and 14. (18 total plasma and 18 total peritoneal fluid samples per patient). Blood samples will be drawn from a peripherally inserted intravenous catheter. Peritoneal fluid samples will be drawn from the already placed peritoneal dialysis catheter. Blood samples will be immediately centrifuged at 3000g and plasma and peritoneal fluid samples will be stored at -80°C until analysis.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

Enrollment and Screening: Study subjects will be contacted an enrolled trough Dr. Teitelbaum's clinic. Initial contact will be made by phone prior to a clinic appointment to discuss initial interest of the patient. Further information and enrollment will take place at a clinic visit or time of the patients choosing. Enrollment will take place in a private room at Dr. Teitelbaum's clinic. Initial baseline and demographic information will be gathered for enrolled patients at the time of enrollment. Safety labs (comprehensive metabolic panel and urine pregnancy test for women of childbearing potential) will be drawn or performed at Dr. Teitelbaum's clinic and will coincide with a scheduled clinic visit closest to study protocol initiation. The comprehensive metabolic panel will be drawn to evaluate Child-Pugh score if there is no comprehensive metabolic panel within the medical record within 30 days of protocol initiation.

Visit 1 and 4: (~8 hours): On visits 1 and 4 the patients will undergo intensive PK sampling. Inclusion and exclusion criteria will be reviewed with the patient at each visit prior to initiation of the protocol. Subjects will be admitted to the CTRC in the morning and a "saline-lock" will be placed. The dalbavancin preparations will be prepared and managed by Dr. Kiser or Dr. Van Matre who are both clinical pharmacists with training in sterile drug preparation. The dalbavancin 1500 mg will either be administered, by CTRC nursing staff, intravenously (as randomly assigned) or into the intraperitoneal space (as randomly assigned) using the patient's existing peritoneal dialysis catheter with the patients currently prescribed dialysate. Following the blood and peritoneal fluid collection at the second dialysis volume exchange, the subjects will be discharged and asked to return at a scheduled time on day 7. Patients will also be given a specimen collection up with instructions to collect approximately 30 ml of peritoneal dialysate following their evening nocturnal dwell. The collected dialysate will be returned to the investigators.

Visit 2, 3, 5, and 6: (~60 minutes): A "saline-lock" will be placed and a single blood and peritoneal fluid sample will be collected at each of these visits. All blood and peritoneal fluid draws will be

completed at the outpatient CTRC. The patient will be discharged and follow up visits will be scheduled for day 14 or next intensive PK sampling visit.

Washout: During the 45 day or greater washout portion of this study the patients will not be asked to come in for any visits. This timeframe, which is greater than 5 half-lives of dalbavancin, is to ensure that all of the medication (dalbavancin) has left the patients' system before administering another dose of the medication.

Laboratory tests: The laboratory tests to be performed as part of this study include pregnancy testing to confirm eligibility and comprehensive metabolic panels if one is not documented within 30 days prior to the initiation of protocol to determine Child-Pugh score. These will be done at an initial screening visit if required to coincide with clinic appointment before visit 1.

Pharmacokinetic Assessments: 4 mL of blood will be collected in a purple top (EDTA) tube and 4 mL of peritoneal fluid in a urine collection cup at pre-dose, and 1, 2, 3, 4, 6, dialysis volume exchange. Blood and peritoneal fluid will be placed in an ice bath to chill until centrifuged. Plasma will be harvested within 30 minutes of each blood sample and will be stored at -80°C until assaying.

Sample Coding and Storage: Study samples will be coded with an indirect identifier and stored in Dr. Kiser's access-controlled laboratory.

Safety Assessments:
All clinical and laboratory adverse events will be graded according to the Common Terminology Criteria for Adverse Events v4.0 as outlined in Appendix 3. All patient reported adverse events will be evaluated. The most common reactions seen with dalbavancin to date are nausea, vomiting, diarrhea, headache, rash, and pruritis. For patients on study protocol following both intravenous and intraperitoneal dalbavancin administration, in the event of grade 2 or higher clinical or laboratory adverse events, these will be reported to the study physician, Dr. Isaac Teitelbaum or the study safety officer Dr. Seth Furgeson within 24 hours and the need for and type of follow-up care will be determined by Dr. Isaac Teitelbaum or Dr. Seth Furgeson (e.g., physician evaluation, follow-up labs, discontinuation of study medication, etc). Subjects will be discontinued from study for any grade 3 or 4 adverse events associated with dalbavancin administration.

Risks of Procedures:

<u>Side effects of dalbavancin include</u>:

Most Common
- Nausea (5.5%)
- Vomiting (2.8%)
- Diarrhea (4.4%)
- Headache (2.7%)
- Rash (2.7%)
- Pruritus (2.1%)

Less Common (Less than 2% of patients)
- Anemia, hemorrhagic anemia, leucopenia, neutropenia, thrombocytopenia, petechiae, eosinophilia, thrombocytosis, gastrointestinal hemorrhage, melena, hematochezia, abdominal pain, infusion-related reactions, hepatotoxicity, anaphylactic reaction, *Clostridium difficile* colitis, oral candidiasis, vulvovaginal mycotic infection, hepatic transaminases increased, blood alkaline phosphatase increased, international normalized

ratio increased, blood lactate dehydrogenase increased, gammaglutamyl transferase increased, hypoglycemia, dizziness, bronchospasm, flushing, phlebitis, wound hemorrhage, spontaneous hematoma

It is not expected that patients will have all of these side effects. Other side effects may occur that were not seen before. Side effects are usually temporary and manageable. However, it is possible that these side effects could be serious or fatal.

Risk of development of drug-resistant bacteria

Receiving dalbavancin in the absence of a proven or strongly suspected bacterial infection increases the risk of the development of drug-resistant bacteria. Currently there are no reported cases of dalbavancin resistance reported within the literature. Dalbavancin also shows extremely high potency against medically important *Staphylococcal* and *Streptococcal* species, including methicillin resistant *Staphylococcus* aureus.[13-15]To date in vitro dalbavancin resistance has not been induced but possible mutations have increased the minimum inhibitory concentration.[16,17] This has not been seen clinically, and we will maximize the minimum inhibitory concentration to area under the curve ratio, utilizing the 1500 mg dosing strategy.

Risk of Blood Draw

During the two long study visits a hollow needle/plastic tube will be placed in each patient's arm for taking blood samples and will be left in arm until the last blood draw. There may be some minor discomfort associated with the needle/plastic tube taped to arm. In about 1 in 10 cases, a small amount of bleeding under the skin will produce a bruise. The risk of a blood clot forming in the vein is about one in 100, while the risk of infection or significant blood loss is one in 1000.

E. Potential Scientific Problems:

We have given careful consideration to potential obstacles in conducting this study and how we will address them. *Recruitment*. Subjects will be recruited through current clinical relationships through Dr. Isaac Teitelbaum's clinical practice at the University of Colorado Hospital. Dr. Teitelbaum is responsible for the management of a significant number of patients requiring peritoneal dialysis through his clinic. *Retention*. Subject compensation is distributed over the course of the study to encourage continued participation. *Generalizability to peritoneal dialysis patients with peritonitis*. This study must be performed in non-infected volunteers as the dalbavancin pharmacokinetic profile and therapeutic efficacy for the treatment of peritonitis is not currently established. Also it is unclear if the pharmacokinetics of dalbavancin in non-infected volunteers undergoing peritoneal dialysis would be the same as patients undergoing peritoneal dialysis with active peritonitis. The pharmacokinetic profiles between non-infected volunteers and patients with acute bacterial skin and skin structure infections were previously found to be similar.

F. Data Analysis Plan:

Dalbavancin concentration measurements:

Dalbavancin concentration analysis will be performed utilizing a LC with MS/MS utilizing a previously published method[18] at the Medicinal Chemistry Core, run by Dr. Michael Wempe, part of the University of Colorado Center for Translational Pharmacokinetics and Pharmacogenomics. The center laboratory is a Clinical Laboratory Improvements Amendments (CLIA) certified laboratory. Dr. Kiser is a member of this center and will oversee all data processing and analysis.

Pharmacokinetic analysis:

Plasma and peritoneal fluid concentration-time data for dalbavancin will be evaluated using a multi-compartment model in Phoenix WinNonlin (Pharsight corporation). One, two, and three compartment models will be explored. The following PK parameters will be calculated for plasma and dialysate samples: Cmax – measured, Tmax – measured, Cmin – measured. Fraction of intraperitoneal (IP) dose absorbed [(Dose – drug concentration remaining in dialysate at end of

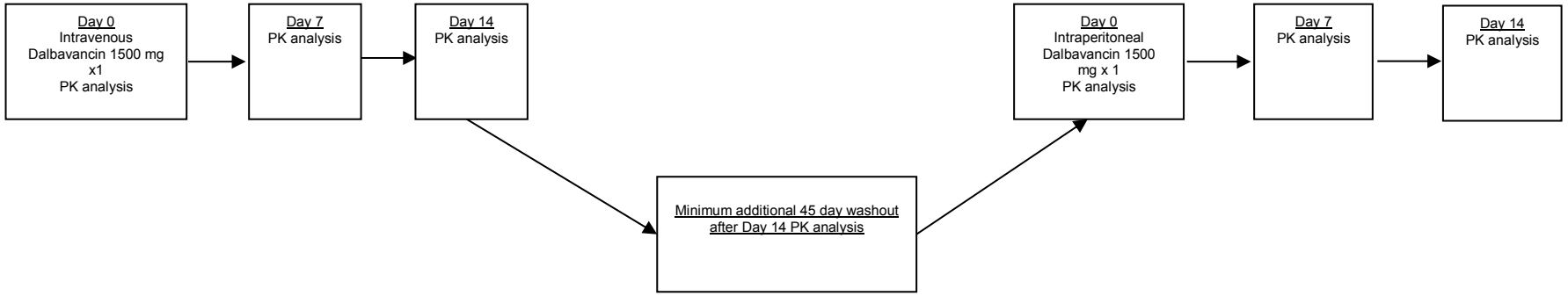
antibiotic dwell)/Dose]. Kel – elimination rate constant. T1/2 – 0.693/Kel. Kpc0-6 – rate constant for distribution of dalbavancin from peritoneal cavity between 0-6 hours. Distribution half-life in the peritoneal cavity between 0-6 hours (t1/2 = ln2/kpc0-6). Clearance systemic = (FxDose)/AUC0-infinity. Clearance peritoneal – dalbavancin concentration in spent dialysate/AUC of peritoneal fluid. Non-dialysis clearance – Cl= Clplasma – Clperitoneal. AUC0-infinity – linear trapezoidal method. AUC0-12 hours – linear trapezoidal method. Volume of distribution for each compartment – Cl/kel; nonsteady state equations will be utilized. The ratio of plasma dalbavancin to dialysate plasma concentration at each time point – Cplasma/Cdialysate and via AUCplasma/AUCdialysate. Given the sample size of 10 patients completing each treatment modality we will be able to calculate means and standard deviations for all included pharmacokinetic parameters. We will incorporate the dalbavancin PK parameters into a nonlinear mixed effects model (NONMEM) or ADAPT II to determine the pharmacokinetics and examine the effects of varying dosing strategies on plasma and peritoneal fluid concentrations.

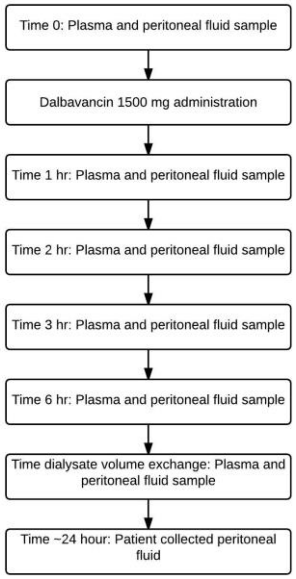
Analysis of pharmacodynamic targets:
Pharmacodynamic parameters will be evaluated in order to determine whether dalbavancin dosing results in initial and steady-state plasma and peritoneal concentrations that are adequate for treatment of infections due to common pathogens (Staph aureus, Coag neg staph, and enterococcus). Monte Carlo simulation (Crystal Ball version 7, Decisioneering, Inc., Denver, CO) will be used in this study to calculate probability of target attainment (PTA) for pharmacodynamic goals. The model randomly applies values for C_{max} and AUC_{0-12} derived from data obtained from the study patients. We will utilize CLSI and EUCAST MIC data for the common gram positive pathogens. We will place these MIC distributions into our Monte Carlo simulation for comparison to dalbavancin plasma concentrations and PK variability. From these studies, MIC frequency distributions will be constructed and used in the Monte Carlo simulations. Ten thousand simulations will be performed at each MIC value and for each of the selected pathogens.

Statistical comparisons of PK/PD findings
Intra-patient pharmacokinetics and pharmacodynamics of dalbavancin will be compared between intravenous and intraperitoneal administration using the paired-test. Given the sample size of 10 patients completing each phase of the study, we will be able to detect a mean difference in area under the curve between the two treatment modalities of 1527 mg·hr/L at a power of 80%. Probability of target obtainment will be compared with the paired t-test. Statistical comparisons will be compared using SAS version 9.3. A p-value < 0.05 will be considered significant.

G. Summarize Knowledge to be Gained:
This study will determine the pharmacokinetic profile of dalbavancin within the plasma and peritoneal fluid following the administration of dalbavancin intravenously and then intraperitonealy in patients undergoing peritoneal dialysis. This study may also identify possible side effects from intraperitoneal administration of dalbavancin. Determining the pharmacokinetic profile and side effect profile of dalbavanicin in patients undergoing peritoneal dialysis may allow for further treatment applications of dalbavanicin including peritonitis.

Appendix 1:


Day 0
Intravenous
Dalbavancin 1500 mg
x1
PK analysis
Day 7
PK analysis
Day 14
PK analysis
Minimum additional 45 day washout
after Day 14 PK analysis
Day 0
Intraperitoneal
Dalbavancin 1500
mg x 1
PK analysis
Day 7
PK analysis
Day 14
PK analysis


Time 0: Plasma and peritoneal fluid sample
Dalbavancin 1500 mg administration
Time 1 hr: Plasma and peritoneal fluid sample
Time 2 hr: Plasma and peritoneal fluid sample
Time 3 hr: Plasma and peritoneal fluid sample
Time 6 hr: Plasma and peritoneal fluid sample
Time dialysate volume exchange: Plasma and peritoneal fluid sample
Time ~24 hour: Patient collected peritoneal fluid

Appendix 2. Schedule of Events

	Blood Volume (mL)	Tube Type	Visit 1	Visit 2	Visit 3	Washout	Visit 4	Visit 5	Visit 6
Duration (days)			1	1	1	At least 45	1	1	1
Consent			x						
CMP	7	Green	x				x		
Urine pregnancy test			x				x		
Study drug administration			x				x		
Intensive Pharmacokinetic Sampling (4 mL for each drug in purple top tubes)	36	Purple	x				x		
Follow up Pharmacokinetic Sampling	4	Purple		x	x				
Clinical Adverse Events Assessed			x	x	x		x	x	x
Blood volume (mLs)[b]			43	4	4		43	4	4

Appendix 3: Adverse drug reaction grading

	Description
Grade 1	Mild ; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL
Grade 3	Sever or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to adverse event
Complete descrition of grading for each system organ class can be found through the U.S. Department of Health and Human Services,National Institutes of Health, and National Cancer Institute at the following web address. https://ctep.cancer.gov/protocoldevelopment/electronic_applications/ctc.htm#ctc_40	

H. References:

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