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TITLE: Use of Colistin Serum Concentrations After Intravenous Administration of Colistimethate Sodium to Determine Pharmacokinetic and Pharmacodynamic Relationships

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14. ABSTRACT Purpose: To define the pharmacokinetics of colistin after colistimethate sodium infusion and use clinical and microbiological data to explore pharmacodynamic relationships between colistin plasma levels, clinical and microbiological outcomes and drug-related toxicities. Research Design: Multi-center, prospective, open-label, un-controlled observational study. Methodology/Technical Approach: Five plasma samples from 60 patients ≥ 18 years of age receiving colistimethate sodium will be collected, frozen and shipped to Ordway Research Institute where they will be analyzed using a liquid chromatography/mass spectrometry/mass spectrometry system to determine free and protein bound levels of colistin A and colistin B. This data will be used to generate pharmacokinetic models. Additionally, clinical data (to include Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE) score, lab values) of enrolled patients, and results of susceptibility testing on Gram negative bacterial isolates will be collected. The pharmacokinetic, clinical and microbiological data will be analyzed using Monte Carlo population modeling to explore pharmacodynamic relationships between plasma levels of colistin and clinical outcomes, microbiological outcomes and drug toxicities. This project is approved, but we will be unable to complete it as our collaborating lab, Ordway Research has closed and our local use of colistin has dropped to the point that we would be unable to achieve our enrollment goals.					
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Introduction:

Multi-drug resistant Gram negative organisms, especially *Acinetobacter baumannii* complex, have been among the most frequent pathogens identified in several published articles related to trauma related infections from the Global War on Terror in both the United States(1-3) as well as other allied countries(4,5). Some of these pathogens are resistant to the most commonly used antimicrobials and have required the use of intravenous colistin for treatment (6-8).

The pharmacokinetics and pharmacodynamics of colistin are not well defined and the optimal dose and administration interval to maximize clinical benefit while minimizing its serious toxicities are not well understood.

This project was designed to evaluate the pharmacokinetics of colistin and study the pharmacodynamic relationship using Monte Carlo mathematical modeling.

However, due to reasons outlined below, we will be unable to complete this protocol.

Body:

The original statement of work is detailed below. As of our last annual review were awaiting second level approval from the MRMC Human Resources Protection Office (HRPO). That was achieved and task 1 listed in the statement of work below has been achieved. However, the remainder of the original tasks outlined in the original statement of work were not achieved due to the following issues:

- 1) Loss of collaborator. In May of this year we were informed that our collaborating organization, Ordway Research Institute was in bankruptcy. There was hope at that time that our collaborating scientist, Dr George Drusano would be still be able to analyze the blood specimens and perform the statistical analysis once he had found a new place of employment. It has become clear that this will not be the case.
- 2) Decrease in Multi-drug resistant organisms which would require colistin use. In the past year, our hospitals have noted a continued decline in the number of patients who had an organism which would require colistin use.
- 3) Change in microbial resistance. Colistin was one of the few options available for multi-drug resistant organisms, namely *Acinetobacter baumannii*. More recently, there have been an increasing percentage of what few patients we do have with this organism who have colistin resistance and thus cannot be given this drug/enrolled in this study
- 4) Changing practice patterns. There has been a trend in the National Capital Area military treatment facilities towards the use of minocycline for multi-drug resistant *Acinetobacter baumannii* as opposed to colistin, further decreasing the potential pool for enrollment.

As a result of these issues, we will be unable to complete this study.

Task 1. Approval of Study protocol (month 1-3).

- a) Submission of initial protocol to the infectious diseases clinical research program.--Done
- b) Submission of Intramural Proposal for funding (month 1-2)--Done.
- c) Scientific review of proposal (month 1)--Done.
- d) Revision of protocol as warranted (month 1)--Done.
- e) Institutional review board evaluation of proposal (month 2)--Done.
- f) Revision of protocol as warranted (month 2-3)--Done.
- g) Final approval and starting of project (month 3).

Task 2. Enrolling of patients with initial data collection (months 3-33).

- a) Enrolling a total of 50-60 patients from three sites, NNMC, WRAMC, SAMMC who are to receive IV colistin therapy (months 3-33).

Task 3. Collection and processing of blood samples from enrolled patients(months 3-33).

- a) Collection of 5 blood samples from enrolled patients while receiving colistin therapy with special attention paid to precise recording of times to optimize data integrity(month 3-33).
- b) Processing of collected samples. Blood that is drawn will need to be centrifuged, have serum poured off into separate specimen container with no identifying information on it (months 3-33).
- c) Freezing and storing of collected blood specimens until they can be batched and shipped to Ordway Research Institute for processing (months 3-33).

Task 4. Collection of clinical and microbiologic data (months 3-57).

- a) Collection of clinical data (vitals, labs, etc) on enrolled patients (months 3-33).
- b) Collection of disease specific outcome and toxicity data (months 3-57).
- c) Collection of all bacterial specimens of interest on enrolled patients from seven days prior to initiation of colistin therapy until 30 days after its conclusion (months 3-34).

- d) Collection of hospital laboratory determined susceptibility patterns for bacterial specimens of interest (months 3-34).
- e) Evaluating bacterial specimens for minimum inhibitory concentration using broth micro-dilution method (months 34-35).

Task 5. Measuring colistin serum levels, modeling pharmacokinetic (PK) data and determining pharmacodynamic (PD) relationships (months 3-36).

- a) Measuring of colistin serum levels. Samples will be sent to Ordway Research Institute, where levels will be measured using LC-MS/MS. This will be done in-kind (months 3-34).
- b) Modeling of pharmacokinetic data. Serum colistin measurements will be used to find pharmacokinetic properties of colistin with the assistance of collaborator, George Drusano, M.D. (months 3-34).
- c) Determination of pharmacodynamic relationships. Using collected clinical outcome and toxicity data and the information of pharmacokinetics from measuring colistin levels, Dr. Drusano will use Monte Carlo mathematical modeling to determine pharmacodynamic relationships (months 33-57).

Task 6. Presentation and publication of findings (months 18-60).

- a) Presentation of preliminary pharmacokinetic data. With the first twenty-three patients, we will have a sufficiently large sample to present pharmacokinetic data at scientific meetings as this will represent one of the largest sample sizes of PK data yet presented/published (months 18-33).
- b) Presentation/publication of preliminary pharmacodynamic data. With collected clinical and PK data, interval analysis for determinations of PD relationships will be performed (months 27-40).
- c) Final presentation/publication of results. After full follow up of all patients (patients with osteomyelitis will require 2 year follow-up) and evaluation of results, presentation/publication of findings (months 57-60).

Key Research Accomplishments:

Due to issues outlined above, this study will be closed before beginning enrollment.

Reportable Outcomes:

None

Conclusion:

The aims of this project were to gain insight into how best to utilize the antimicrobial colistin to optimize infection outcomes while minimizing toxicity. However, given loss of collaborating organization, change in practice patterns and changing antimicrobial patterns in infections, as well as resistance, we will be unable to complete this study. We have informed our contact at the Military Infectious Diseases Research Program of this issue. As the decision to close the protocol is has occurred immediately prior to this submission deadline, additional paperwork will follow.

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Iraqi and Enduring Freedom. *J Trauma*. 2009; 66: S138 –S144.

Appendices:

None