Principal Investigator

First Name: Geoffrey
Last Name: Mospan
Degree: Pharm.D.
Primary Affiliation: Wingate University School of Pharmacy
E-mail: g.mospan@wingate.edu
Phone number: 828-697-0105
Address: 220 Fifth Ave East

City: Hendersonville
State or Province: NC
Zip or Postal Code: 28792
Country: USA

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General Information

Key Personnel (in addition to PI): **First Name:** Kurt
Last name: Wargo
Degree: Pharm.D.
Primary Affiliation: Wingate University School of Pharmacy

Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

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Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.
Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

Associated Trial(s): NCT00210886 - A Multicenter, Double-blind, Randomized Study to Compare the Efficacy and Safety of Levofloxacin 750 mg Once Daily for Five Days Versus Ciprofloxacin Twice Daily for Ten Days in the Treatment of Complicated Urinary Tract Infection and Acu
What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Comparison of 5-Day Course of Levofloxacin vs 10-Day Course of Ciprofloxacin Therapy in Males with Urinary Tract Infection

Narrative Summary:
Infections of the urinary tract caused by bacteria are a common occurrence in clinical practice. Although more common in females, it also develops in male patients. Historically, clinical trials have studied only female patients in determining the optimal antibiotic choice, dose, and duration of therapy. Traditionally, antibiotics are given to men for more days than a female would receive (7-14 days), although this has not been formally studied in a clinical trial. If male patients do not need a longer course of antibiotic therapy compared to females, then the male patient (and healthcare system) would save on the cost of the antibiotic and reduce potential side effects of the antibiotic.

Scientific Abstract:
Background: Urinary tract infections (UTIs) in men are deemed complicated and subject to longer treatment durations by clinicians. The study being analyzed grouped male and female patients together in the data analysis, therefore, it is unknown whether males can also be successfully treated for a UTI with a 5-day course of levofloxacin therapy.
Objective: The objective of this study is to analyze the efficacy of a 5-day course of levofloxacin compared to a 10-day course of ciprofloxacin for male subjects with urinary tract infections
Study Design: The current investigators will be performing a sub-group analysis with the requested study. Particularly, this current study will be analyzing the efficacy of 5-day levofloxacin therapy in male patients with complicated urinary tract infections.
Participants: Those included in the original study. The current study will exclude patients with acute pyelonephritis and all female patients.
Main Outcome Measure(s):
Primary outcome: Microbiologic eradication rates at post-therapy in the modified intent to treat and microbiologically evaluable groups.
Secondary outcomes: Clinical success at post-therapy; clinical success and microbiologic eradication at end of blinded therapy and post-study.
Statistical Analysis: Post-hoc subgroup analysis comparing males in the levofloxacin group to males in the ciprofloxacin group. Results for main outcome measures reported as cure rates and tested with Chi-squared test (nominal, nonparametric data). Logistic regression will be utilized to determine variables that may have impacted cure rate.

Brief Project Background and Statement of Project Significance:
Clinical trials demonstrating efficacy of antimicrobials in urinary tract infections have typically enrolled a majority of female patients. In trials for UTIs when male patients are included, they are typically the minority gender and grouped with female patients in the data analysis. 2 As a result, recommendations for male patients with UTIs are extrapolated from trials performed with predominately female patients. Furthermore, the Infectious Diseases Society of America provided a cystitis and pyelonephritis guideline for females only. 3 Urinary tract infections in males have been deemed complicated by definition. The current recommendations are to treat for 7 to 14 days, although the optimal duration has not been studied prospectively. 4 A retrospective analysis showed a shorter duration treatment (< 7 days) was not associated with an increase in early or late recurrence when compared to longer duration of treatment (>7 days) in male patients. 4 Given its' convenient once daily dosing and excellent penetration into the urinary tract, levofloxacin is a popular choice for treating urinary tract infections.
A higher dose, shorter course of levofloxacin therapy has been shown to be non-inferior to longer courses of levofloxacin therapy in other disease states.5,6 Increasing the dose of levofloxacin optimizes the pharmacodynamic parameters of maximum concentration and area under the curve. These parameters are likely the determinants for efficacy of levofloxacin. Moreover, less days of antimicrobial therapy may reduce the development of resistant bacteria.5 This dosing strategy was analyzed again in a multicenter, double-blind, randomized, noninferiority study comparing levofloxacin 750 mg once-daily for five days to ciprofloxacin 400mg IV/500 mg PO twice-daily for ten days in the treatment of complicated urinary tract infections and acute pyelonephritis.1 This study showed the microbiologic eradication rates in the short course of levofloxacin was non-inferior to ciprofloxacin in the modified intent-to-treat (95% CI, -6.3 to 6.3) and microbiologically evaluable (95% CI, -2.5 to 8.9) groups. Clinical success rates were also similar between both antimicrobials in the modified intent-to-treat and microbiologically evaluable groups.
Although this clinical trial showed a shorter course levofloxacin was non-inferior to ciprofloxacin in UTIs, female and male subjects were combined in the data analysis. A subgroup analysis of this study would provide cure rates for male patients with UTI which is otherwise scarce in the literature. Moreover, if cure rates are still high in male subjects, a five day course of levofloxacin would result in decreased costs, antimicrobial exposure, selection of

resistant organisms, and untoward effects of antimicrobials.

Specific Aims of the Project:
To determine if microbiologic eradication rates and clinical success rates were similar among male patients with UTIs treated with 5 days of levofloxacin or 10 days of ciprofloxacin.

What is the purpose of the analysis being proposed? Please select all that apply. New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
The data source used for this study is ClinicalTrials.gov Identifier: NCT00210886; A double-blind, randomized comparison of levofloxacin 750 mg once-daily for five days with ciprofloxacin 400/500 mg twice-daily for 10 days for the treatment of complicated urinary tract infections and acute pyelonephritis.

The proposed study will retain all inclusion and exclusion criteria from the original trial with the following exceptions: only male patients with urinary tract infections will be included. Female patients and all patients with acute pyelonephritis will be excluded.

Main Outcome Measure and how it will be categorized/defined for your study:
The proposed study will retain the same outcomes as the original study, however, only male patients with urinary tract infections will be analyzed:
Primary outcome: Microbiologic eradication rates at post-therapy in the modified intent to treat and microbiologically evaluable groups.
Secondary outcomes: Clinical success at post-therapy; clinical success and microbiologic eradication at end of blinded therapy and post-study.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
Male gender

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
Catheter use (presence of catheter during study), diabetes (as defined in study), age (< 45, 46-64, 65-74, > 75), immunosuppression (as defined in study)

Statistical Analysis Plan:
Post-hoc subgroup analysis comparing males in the levofloxacin group to males in the ciprofloxacin group. Results for main outcome measures reported as cure rates and tested for a difference between the two groups with Chi-squared test (nominal, nonparametric data). Logistic regression will be utilized to determine variables that may have impacted cure rate (catheter use, diabetes, age, immunosuppression).

Project Timeline:
Anticipated Project Start Date: August 1, 2015
Analysis Completion Date: January 1, 2016
Manuscript Draft: February 28, 2016
Manuscript Submission: April 1, 2016
Results Reported to YODA Project: April 1, 2016

Dissemination Plan:
The target audience for the results of this study includes: doctors, pharmacists, nurse practitioners, physician assistants, nurses, microbiologists, and students. The expectation for the manuscript is for publication in a peer-reviewed journal. Examples of suitable journals include: Clinical Infectious Diseases, Annals of Pharmacotherapy, Annals of Internal Medicine, Pharmacotherapy, and American Journal of Health-System Pharmacy.

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1. Peterson J, Kaul S, Khashab M, Fisher AC, Kahn JB. A double-blind, randomized comparison of levofloxacin

750 mg once-daily for five days with ciprofloxacin 400/500 mg twice-daily for 10 days for the treatment of complicated urinary tract infections and acute pyelonephritis. Urology. 2008 Jan;71(1):17-22.
2. Lipskv BA. Urinary tract infections in men. Epidemiology, pathophysiology, diagnosis and treatment. Ann Intern Med. 1989;110: 138-50.
3. Gupta K, Hooton TM, Naber KG, Wullt B, Colgan R, et al. International clinical practice guidelines for the treatment of acute uncomplicated cystitis and pyelonephritis in women: A 2010 update by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases. Clin Infect Dis. 2011 Mar 1;52(5):e103-20.
4. Drekonja D, Rector T, Cutting A, Johnson J. Urinary Tract Infection in Male Veterans: Treatment Patterns and Outcomes. JAMA Intern Med. 2013;173(1):62-68.
5. Dunbar LM,Wunderink RG, Habib MP, et al. High-dose, short-course levofloxacin for community-acquired pneumonia: a new treatment paradigm. Clin Infect Dis 2003; 37:752–60.
6. Poole M, Anon J, Paglia M, Xiang J, Khashab M, Kahn J. A trial of high-dose, short-course levofloxacin for the treatment of acute bacterial sinusitis. Otolaryngol Head Neck Surg. 2006 Jan;134(1):10-7.