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Monte Carlo simulation of Fluoroquinolone treatment for urinary tract infection caused by *Escherichia coli*: Analysis of Canadian versus U.S isolates

Ahmed Noreddin
Department of Biology
Virginia Commonwealth University
Richmond, Virginia 23220 USA

Faculty Advisor: David Ombengi

Abstract

This study aimed to assess the probability of Ciprofloxacin (Cipro) compared to Gatifloxacin (Gati) and Levofloxacin (Levo) achieving favorable activity for bacterial eradication and prevention of resistance development in *Escherichia coli* (*E.coli*). Cipro 500mg Twice Daily (BID) along with various doses of Gati and Levo were simulated, and target attainment potential was estimated in hospitalized patients. Previously described and validated population pharmacokinetic (PK) models of Cipro, Gati and Levo in hospitalized patients were utilized to simulate Cipro, Gati and Levo PKs. Free-drug Area Under the Concentration (AUC 0-24) was simulated in Plasma (P) using Cipro 500mg BID, Gati 200mg and 400mg Once Daily (OD) as well as Levo 500mg, 750mg and 1000mg OD. *E.coli* susceptibility data were obtained from the North American Urinary Tract Infection Surveillance Study (NAUTICA). The NAUTICA study collected 2000 outpatient urinary isolates (1142 *E.coli*) from all geographic regions in Canada and USA. Use of Monte Carlo Simulation (MCS) allowed for the full variability of susceptibility data and AUC 0-24 data for all patients. In hospitalized patients, Cipro 500mg BID, Gati 400mg OD and Levo 750mg OD showed high probability for target attainment of free $AUC_{0\text{-}24}$/Minimum Inhibitory Concentration (MIC) of 125 or 250 against *E.coli*. Compared to Canada, U.S isolates showed lower probability of achieving a favorable outcome.

Keywords: *Escherichia Coli*, Pharmodynamics, Monte Carlo Simulation

1. Introduction

Urinary tract infections (UTIs) are a significant cause of morbidity. UTI's account for approximately $6 billion in health care costs per year worldwide[1]. 80% of documented cases of uncomplicated UTI's are caused by the gram-negative bacteria *E. coli*[2]. *E. Coli* is a gram-negative rod shaped bacteria that is known to cause diarrhea, sepsis, and UTI[3]. The Infectious Diseases Society of America (IDSA) recommends trimethoprim-sulfamethoxazole as the first line of treatment, with fluoroquinolones (FQs) recommended as the second-line therapy[4,5]. In the United States, prescribing FQs as first-line treatment of UTI's has been trending upwards[6]. Although data is limited, recent studies have suggested that resistance to FQs is also increasing[6].

The FQ's widely used for UTI's are Cipro, Levo, and Gati[6,7]. They are available in both oral and intravenous formulations. This allows physicians flexibility in prescribing these treatments to both hospitalized and outpatient populations[7]. FQs have long elimination half-lives ranging from 4-14 hours, which allows for single and double daily dosing[8]. It however remains unclear which dosage of each of these FQs is most effective, and whether there is a difference between bacterial resistance to FQs in Canadian versus United States isolates of *E. coli*. Various doses of Cipro, Gati, and Levo were simulated, and target attainment potential was estimated in hospitalized patients. These simulations were made using the Monte Carlo program. Monte Carlo Simulation (MCS) is an interpretation of pharmacokinetics and in vitro potency, and is used to determine the reliability of a regimen for the intended patient population and assist clinicians in empirical antimicrobial selection[9]. MCS uses computer software to perform virtual clinical trials. MCS analysis is essentially the use of computer software via simulation platforms to 'expand' the

sample size of a study to provide predictions of the likely result of different therapeutic approaches. These include the altering of drug dose or frequency on the probable outcome of treatment, or more correctly the achievement of therapeutic targets. MCS allows researchers and clinicians to ask the many 'what if?' questions about different dosing regimens and targets in virtual clinical trials without the capital and human cost of conducting the many possible clinical trials in patient populations. From this information, a single definitive multi-center trial could be developed and executed.

2. Methodology

The two contributing factors in target attainment potential are the pharmodyamics of the drug bacteria interaction, and the pharmokinetic model of each FQ. Pharmodynamic parameters of the drug against the bacteria are illustrated using the MIC. *E.coli* susceptibility data obtained from the NAUTICA study. The NAUTICA study collected 1142 *E.coli* outpatient urinary isolates from all geographic regions in Canada and USA[10]. These isolates were tested against each FQ to measure drug potency.

Previously described and validated population pharmokinetic models of Cipro, Gati, and Levo in hospitalized patients were utilized to simulate the pharmacokineticss of each drug[11,12]. Free-drug $AUC_{0\text{-}24}$ was simulated in plasma using Cipro 500mg BID, Gati 200mg and 400mg OD, as well as Levo 500mg, 750mg, and 1000mg OD. [11,12]

2.1. Monte Carlo Simulation

Monte Carlo simulation was used to predict target attainment potential of the 3 fluoroquinolones in patients hospitalized with Urinary Tract Infections[13,14]. The pharmokinetics and susceptibility data (pharmodynamics) were integrated via the Monte Carlo simulation using the Professional Crystal Ball® 2000 program (Decisioneering (UK) Ltd, London, UK). A 10,00 patient simulation was performed to determine the percentage of patients that achieved an $AUC_{0\text{-}24}$/MIC ratio of 125-250 for all fluoroquiolone-dosing schemas evaluated against isolates of *E.coli* from the NAUTICA study.[10, 11,12,13,14]

3. Data

The probability of target attainment varied between each different fluoroquinolone, as well as the dosages for each one.

Table 1. Probability of target attainment (free $AUC_{0\text{-}24}$/MIC of 125 and 250) of Cipro, Gati, and Levo between U.S and Canadian outpatients

	Canada		**U.S**	
	125	250	125	250
Cipro 500mg BID	98.5%	98.4%	93.1%	92.9%
Gati 200mg OD	98.7%	98.4%	95.3%	94.7%
Gati 400mg OD	98.8%	98.7%	95.3%	95.1%
Levo 500mg OD	96.8%	95.9%	91.8%	90.8%
Levo 750mg OD	97.5%	96.4%	93.1%	91.7%
Levo 1000mg OD	98.3%	96.8%	94.0%	93.0%

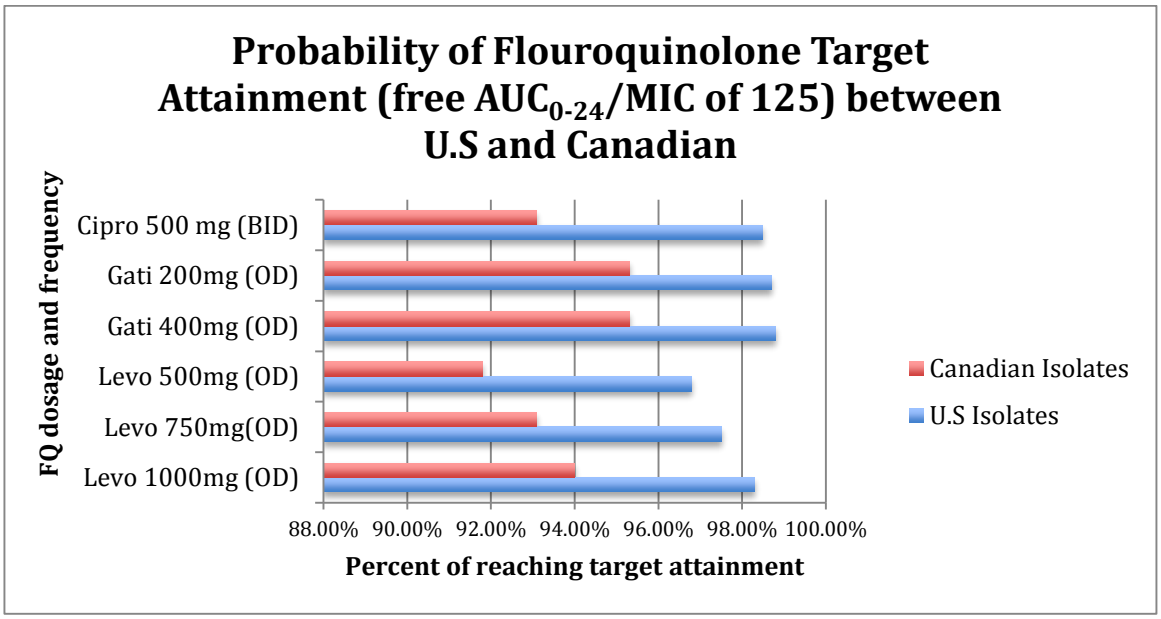

Figure 1. Difference in target attainment probability between Canadian and U.S isolates

The probability of attaining target attainment against *E.coli* for Cipro 500mg BID, Gati 200 and 400mg, and Levo 500, 750, and 1000mg between U.S and Canadian isolates are summarized in Table 1.

For Cipro 500mg BID the probability of reaching target potential 125 in Canadian isolates is 98.5%, and 93.1% for U.S isolates respectively. In Gati 200 and 400mg OD the probability of target attainment potential is 98.7% and 98.8% for Canadian isolates, and 95.3% for both in U.S isolates. Levo 500mg 750mg, and 1000mg show target attainment potential probabilities of 96.8%, 97.5% and 98.3% for Canadian isolates respectively, and 91.8%, 93.1%, and 94% probability against U.S isolates.

4. Conclusion

In hospitalized patients, Cipro 500mg BID, Gati 400mg OD and Levo 1000mg OD showed the highest probability for target attainment of free AUC_{0-24}/MIC of 125 or 250 against *E.coli*. There was little disparity in the dosage difference between Gati 200mg/400mg compared to the evident difference displayed between Levo dosage 500mg and Levo 1000mg. This information is relevant in reducing the costs for fluoroquinolones; by avoiding a high dosage if not necessary, and also reducing the resistance the bacteria can develop for a specific fluoroquinolone.

Compared to Canada, U.S isolates show a lower probability of achieving favorable outcome. These reduced probabilities are in agreement with the previously collected data showing that U.S isolates are more resistant to fluoroquinolones [10] The results were able to determine which FQ, and dosage should be used for treating patients. It also showed that there is a higher rate of drug resistance in the U.S compared to bacterial resistance in Canada. This is illustrated by the lower percentage of target attainment potential in U.S isolates with the same drug and dosage compared to the Canadian isolates. These factors are not conclusive, but could have been caused by weather and culture disparities, leading to the bacterial mutations increasing the bacteria's effectiveness and resistance to antibiotics. The gram-negative bacteria *E.coli* has developed higher levels of FQ resistance in the U.S then Canada due to the overuse of said drug in U.S patients. Easy access, and over prescription of antibiotics in the U.S may have caused this strain of bacteria to develop resistance compared to tight antibiotic regulations in Canada [15].

Future works with this topic includes: comparing target attainment for gram-positive bacteria, or testing out different FQs with varying dosages. Finally, a second part to this research could include an investigation as to why the levels of target attainment in the U.S were lower compared to Canada.

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