For Single Dosing, Levofloxacin Is Superior to Ciprofloxacin When Combined With an Aminoglycoside in Preventing Severe Infections After Prostate Biopsy

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OBJECTIVE To investigate whether there is benefit with a longer acting oral fluoroquinolone, we compared the rate of infection after transrectal ultrasound-guided prostate biopsy between 2 prophylactic antibiotic regimens: ciprofloxacin vs levofloxacin, each combined with an aminoglycoside (AG).

METHODS A retrospective review was performed of all transrectal ultrasound-guided prostate biopsies from September 2011 to January 2013. Initially our regimen entailed 1 dose of 500-mg ciprofloxacin and an AG. In June 2012, we switched to 1 dose of 750-mg levofloxacin and an AG. Infections were categorized as severe if requiring hospital admission, overnight observation, or emergency room treatment for fever or chills. Those treated as an outpatient were defined as mild.

RESULTS Of 1189 total biopsies, the total infection rate was 3.18% (17 of 535) in the ciprofloxacin group and 2.14% (14 of 654) in the levofloxacin group ($P = .26$). The rate of mild infection was 0.75% (4 of 535) in the ciprofloxacin group and 1.22% (8 of 654) in the levofloxacin group ($P = .56$). The rate of severe infection was significantly higher in the ciprofloxacin group at 2.43% (13 of 535) compared with that of 0.92% (6 of 654) in the levofloxacin group ($P = .04$). On multivariate analysis, use of ciprofloxacin rather than levofloxacin was associated with an increased risk of severe infection (odds ratio, 4.59; $P = .04$).

CONCLUSION Empiric prophylaxis for prostate biopsies with a single-dose fluoroquinolone augmented with an AG is optimal to reduce infectious complications. We found 750-mg levofloxacin resulted in significantly fewer severe infections compared with 500-mg ciprofloxacin potentially because of its longer half-life. UROLOGY 85: 1241–1246, 2015. © 2015 Elsevier Inc.

Transrectal ultrasound-guided prostate biopsy (TRUSBx) is the primary method used for diagnosing prostate cancer. Although minor complications after biopsy such as hematospermia and hematuria are common, infectious complications such as fever, urinary tract infection, and hospitalization historically have been uncommon.[1] Postbiopsy infections have been further reduced with the use of periprocedural antibiotic prophylaxis, although a standard regimen does not exist.

Traditionally, the fluoroquinolone (FQ) ciprofloxacin has been used owing to its broad coverage of both gram-positive and gram-negative bacteria and high tissue penetration of the prostate. In a randomized, double-blinded, multicenter trial, a single dose of 500-mg oral ciprofloxacin compared with placebo reduced the incidence of postbiopsy bacteriuria.[2] Further studies revealed that there was no difference in infectious complications between single-dose FQ compared with a 3-day course.[3-6] Because of this evidence, the American Urological Association Best Practice Policy Statement on Urologic Surgery Antimicrobial Prophylaxis recommends use of a single dose or <24 hours of therapy with an oral FQ at the time of biopsy.[7] However, infectious complications have been increasing dramatically over recent years based on the emergence of bacterial resistance to FQs.[8,9] To combat this, the addition of an intramuscular (IM) aminoglycoside (AG) at the time of biopsy has proven effective.[10-12]

A similar increase in TRUSBx infections was noted at our institution. Despite the use of both 500 mg of oral

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ciprofloxacin and an IM AG, our infection rates remained elevated compared with historical experience. It was hypothesized that an oral FQ with a longer half-life may provide better protection. The serum half-life of 750-mg oral levofloxacin is over twice that of 500-mg oral ciprofloxacin (7.7 vs 3.7 hours), and its oral bioavailability is nearly 100% compared with that of 55% for ciprofloxacin. Its bactericidal activity is concentration dependent making it ideal for high-dose therapy (750 mg) and once-daily dosing.[13] Use of levofloxacin as prophylaxis vs ciprofloxacin ensured 24 hours of antibiotic coverage with a single dose at the time of biopsy. Therefore, in June 2012, in an attempt to further reduce our rates of infection, we changed our prophylaxis regimen to a single 750-mg dose of oral levofloxacin plus a single dose of an IM AG.

The purpose of this study was to compare the rates of TRUSBx infection between the 2 FQ regimens: 500 mg of ciprofloxacin vs 750 mg of levofloxacin, both used in combination with an IM AG.

METHODS

Starting in 2010, the standard TRUSBx prophylaxis regimen at our institution was 500 mg of oral ciprofloxacin and IM gentamicin. Tobramycin was substituted for gentamicin during a brief period of gentamicin shortage. In September 2011, as part of a quality improvement measure to evaluate our institution's rate of TRUSBx complications, patients who underwent the procedure completed a phone questionnaire within 1-2 weeks of their biopsy. Because of a relatively high rate of infectious complications, in June 2012, our protocol for antibiotic prophylaxis was changed to 1 dose of 750-mg oral levofloxacin in addition to a single dose of IM AG. Weight-based guidelines were recommended for AG dosing: 80 mg for <70 kg, 100 mg for 70-90 kg, and 120 mg for >90 kg. However, ultimately, the AG dosage was left to the discretion of the physician. Biopsy template used and number of cores taken varied between attending physicians.

After institutional review board approval, we examined our medical records of all consecutive TRUSBxs performed at our institution from September 2011 to January 2013. Two biopsy groups were compared. The first group included all biopsies whose prophylaxis consisted of a single 500-mg dose of oral ciprofloxacin and 1 IM dose of an AG. These were primarily performed between September 2011 and June 2012. The second regimen consisted of a single 750-mg dose of oral levofloxacin and 1 dose of an IM AG; these were mainly performed between June 2012 and January 2013. All patients received both the oral FQ and IM AG within 1 hour of prostate biopsy. Any patients on antibiotics at the time of biopsy were excluded. Any patients who received variants of this regimen were excluded. Patients did not receive an enema or a rectal swab with Betadine (Povidone-iodine 10% solution; Purdue Pharma, Yonkers, NY) before biopsy. Patient characteristics such as age, race, diabetes, body mass index, prostate-specific antigen, number of cores, prostate volume, and a history of biopsy were compiled. All patients were called 1-2 weeks after biopsy by a registered nurse to evaluate for infectious complications as part of an ongoing quality control initiative. Those reached were asked about symptoms of infection (dysuria, fever, chills, and frequency or urgency), as well as unplanned trips to the emergency department. The electronic medical records of all patients, including those not contacted by phone, were reviewed for documentation of infection after prostate biopsy. Infections were categorized as severe if requiring either hospital admission, overnight stay within an observation unit, or emergency room evaluation and treatment for fevers or chills. Infections treated as an outpatient were defined as mild. Urine and blood cultures and sensitivities were obtained if available for patients who were treated for severe infection. Positive culture results were defined as $>10^4$ CFU/mL of a specific organism growing in blood or in clean catch or catheterized urine.

Comparisons between the 2 antibiotic groups were performed using the Wilcoxon rank sum test for continuous variables and the chi-square test (or the Fisher exact test if event numbers were ≤ 5) for categorical variables. Multivariate logistic regression was used to evaluate factors associated with severe infection. The statistical software JMP 11 (SAS Institute Inc, Cary, NC) was used. Results were considered significant at the level of $\alpha = 0.05$.

RESULT

A total of 1189 biopsies were included in the study, with 535 in the ciprofloxacin group and 654 in the levofloxacin group. Patient characteristics for each group of biopsies were compared (Table 1). A total of 79.6% of patients were contacted by phone in the ciprofloxacin group and 78.6% in the levofloxacin group (n = 0.66). The ciprofloxacin group contained significantly more biopsies from patients with diabetes, specifically non−insulin dependent ($P = .04$), patients with an abnormal digital rectal examination (DRE) result ($P = .04$), and patients with inflammation evident on pathology ($P = .0001$). In addition, more patients received tobramycin rather than gentamicin in the ciprofloxacin group (17.4% vs 0.5%; $P < .0001$), and a mean lower dose/weight of AG was administered in the ciprofloxacin group (0.93 vs 1.14 mg/kg; $P < .0001$).

Of the 1189 biopsies performed, there were 31 infections: 14 in the levofloxacin group and 17 in the ciprofloxacin group. As shown in Figure 1, the total infection rate was lower in the levofloxacin group at 2.14% (14 of 654) vs 3.18% (17 of 535); however, this was not a statistically significant difference ($P = .26$). There was no difference in the rate of mild infections between the 2 groups, with 8 of 654 biopsies in the levofloxacin group and 5 of 535 biopsies in the ciprofloxacin group (1.22% vs 0.75%; $P = .56$). However, for severe infections, there was a significantly lower rate in the levofloxacin group, with 6 of 654 vs 13 of 535 biopsies in the ciprofloxacin group (0.92% vs 2.43%; $P = .04$).

Multivariate analysis was performed (Table 2) to evaluate whether more severe infections occurred in the ciprofloxacin group vs the levofloxacin group when controlling for the heterogeneity between the 2 FQ groups and other clinical factors. AG dose/weight, type of AG (gentamicin vs tobramycin), abnormal DRE result, diabetes, the presence of inflammation on biopsy, number of cores, age, prostate-specific antigen, body mass index, and a