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In Adult Patients with Acute Pyelonephritis, is Levofloxacin a More Effective Treatment than Ciprofloxacin?

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Abstract

OBJECTIVE: The objective of this systematic review is to determine whether or not levofloxacin is a more effective treatment than ciprofloxacin in adult patients with Acute Pyelonephritis (AP).

STUDY DESIGN: Review of three English language primary double-blind randomized controlled trial studies comparing levofloxacin to ciprofloxacin for the treatment of AP in adults.

DATA SOURCES: Randomized controlled double-blind comparative trials were found using Cochrane, PubMed, and Science Direct databases.

OUTCOME MEASURED: All studies measured three outcomes: microbiologic eradication, clinical response, and safety and tolerability of the medication. Microbiologic eradication was measured by urine culture which demonstrated a reduction of pathogens to $<10^4$ CFU/mL. Clinical response was measured by: cured (complete resolution of signs and symptoms associated with active infection); improved (incomplete resolution of signs and symptoms but no additional antimicrobial therapy required); failed (no response to therapy); or unable to evaluate (patient did not return for follow-up evaluation). Safety and tolerability information was collected through post therapy follow up visits.

RESULTS: The dichotomous data systematically reviewed in all three RCTs determined that there is a minimal relative and absolute benefit increase in the use of levofloxacin over ciprofloxacin in the treatment of AP in adults. Confidence Intervals calculated in all studies prove that this data is statistically significant. Adverse events and/or serious adverse events were noted in all three trials with the use of both levofloxacin and ciprofloxacin, however, very few were considered to be treatment related.

CONCLUSIONS: The results of these three studies show that the use of levofloxacin for the treatment of AP in adult patients is as effective as ciprofloxacin in regard to microbiologic eradication, efficacy, and safety and tolerability.

KEY WORDS: Acute Pyelonephritis, Urinary Tract Infection, Ciprofloxacin, Levofloxacin

Introduction

Urinary tract infection (UTI) is a broad term encompassing any infection along the urinary tract or in urinary organs such as the kidney or bladder. Microorganisms detected in the urine at $>10^5$ colony forming units (CFU) per milliliter from a midstream clean catch urine specimen is a significant laboratory finding in the diagnosis of a UTI[1]. Additionally, more than 5 white blood cells per high power field[1], hematuria, and cloudy or malodorous urine may be present in the specimen.

Acute Pyelonephritis (AP) is classified as a UTI, specifically of the renal parenchyma. Patients may present with varying symptoms, however, urinary frequency, urgency, and dysuria, along with costovertebral angle (CVA) tenderness radiating to the groin are most commonly seen[2]. Systemic symptoms such as fever, tachycardia, nausea, vomiting, or diarrhea will also be present. AP is a treatable condition but can become very dangerous if not tended to quickly or properly. Infection can spread from the kidney to the peritoneum which can become life threatening[3]. This paper evaluates three double blind randomized controlled trials comparing levofloxacin use to ciprofloxacin use for the effectiveness in the treatment of AP in adults. Microbiologic eradication, clinical response, and safety and tolerability of the medications are assessed.

AP is most commonly seen in women and affects an estimated 250,000 Americans each year[1]. Results from a 1995-96 survey showed that there are about 4,922,000 visits for unspecified UTIs each year, and of the visits that prove to be AP, 10-30% require hospitalization[2]. Cost has proven to be incredibly high, not just in the treatment of AP, but also in work loss and non-medical expenses. A study conducted by Brown et al in 2005 demonstrates what has been spent annually: $351 million as a result of work loss due to death, $398 million as

a result of work loss due to disability, $92.5 million due to non-medical expenses, and $1.3 billion due to medical expenses. This adds up to $2.14 billion being spent annually for the treatment and associated issues caused by AP [2].

Gram negative bacteria, specifically *Escherichia coli*, are the most common causative agent of AP. *Proteus mirabilis, Klebsiella pneumoniae, and Enterobacter cloacae* are other common uropathogens[1]. Antimicrobial therapy, therefore, is aimed at targeting these gram negative bacteria. Fluorquinolone therapy for 7-14 days is currently the treatment of choice for AP[5]. Patients should be hospitalized and given intravenous fluoroquinolone therapy if they have severe infection or co-morbidities. Uncomplicated AP is treated with outpatient oral antibiotics such as 500 milligrams of Ciprofloxacin twice a day for 10 days or 250 milligrams of Levofloxacin once a day for 10 days. Both of these fluorquinolones are considered to be effective treatments for AP[3]. Levofloxacin, however, may provide a higher cure rate, quicker reduction in signs and symptoms, and less adverse drug reactions as compared to Ciprofloxacin in the treatment of AP in adult patients.

Objective

The objective of this systematic review is to determine whether or not levofloxacin is a more effective treatment than ciprofloxacin in adult patients with AP.

Methods

Three randomized controlled trials (RTCs) were selected through a detailed search of articles via the Cochrane, PubMed, and Science Direct databases. Key words searched included “acute pyelonepthritis”, “urinary tract infection”, “levofloxacin”, and “ciprofloxacin”. These words in combination provided three double-blind RCTs comparing levofloxacin to ciprofloxacin in the

Table 1: Demographics of included studies

Study	Type	# pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Intervention
Richard[1], 1998	Double blind, RCT	186	18-91	Male or female ≥18 with > 5 WBC per high power field (hpf) or > 20 WBC per low power field and > 10^5 CFU/ mL in urine; two of the following: flank pain or CVA tenderness, fever, peripheral WBC count >15,000/ mm^3, WBC casts in urine	Treated with antibiotic in the past 24 hrs; requiring IV antibiotics; history of allergic reaction to quinolone; obstruction, prostatitis, resistant pathogen pregnancy, seizure d/o; renal clearance < 50 ml /min; weight < 40 kg	0	Levofloxacin 250 mg QD for 10 days
Klausner[3], 2007	Double blind, RCT	311	≥18	Male or female ≥18; + dipstick for leukocytes; ≥ 5 WBC per hpf in urine; 2 of the following: fever, flank pain or CVA tenderness, peripheral WBC > 12,500/mm3 or ≥ 10% bands, WBC casts in the urine; 1 of the following: nausea, vomit, dysuria, urgency, frequency	Cystitis, chronic pyelonephritis, obstruction, prostatitis, PKD, renal transplant, HIV, pregnancy; received > 1 dose antibiotic for presenting UTI w/i 5 days of study entry; resistant pathogen Renal clearance < 50 ml/min	8	Levofloxacin 750 mg QD for 5 days
Peterson[4], 2008	Double blind, RCT	506	≥18	Male or female ≥18; > 10^5 CFU in urine; 2 of the following: fever; flank pain or CVA tenderness; peripheral WBC > 12,500/mm^5 or 10% bands; WBC casts in the urine	Obstruction, need for lithotripsy, additional antimicrobial therapy; resistant pathogen; renal abscess; prostatitis; epididymitis	0	Levofloxacin 750 mg QD for 5 days

treatment of adults with AP and addressed patient-oriented evidence that matters (POEMs). Studies were excluded if subjects were suffering from unspecified urinary tract infections or if subjects were under the age of 18. Outcomes measured were microbiologic eradication, clinical response, and safety and tolerability of the medication.

Variation between studies was minimal. In both the Klausner 2007 study and the Peterson 2008 study, 750 mg of levofloxacin once daily for 5 days was compared to the control group of 500 mg of ciprofloxacin twice daily for 10 days. In the Richard, 1998 study, 250 mg of levofloxacin once daily for 10 days was compared to the control group of ciprofloxacin 500 mg twice daily for 10 days. Lastly, the Peteron 2008 study includes treatment of complicated urinary tract infections in addition to AP.

All articles were published in English in peer reviewed journals from 1998-2007. Statistics used in the studies included RBI, ABI, NNT, NNH, and CI. Table 1 provides demographic information of all articles included.

Outcomes Measured

Outcomes of all three studies were measured by microbiologic eradication, clinical response, and safety and tolerability of the medication. Microbiologic eradication was defined as a urine culture demonstrating an absence or reduction of uropathogens to $<10^4$ CFU/mL[1,4,5].

Clinical response was measured by signs and symptoms experienced by the subject. "Clinically cured" was defined as the complete absence of signs and symptoms associated with active infection including flank pain, fever, and painful urination. "Clinically improved" was incomplete resolution of signs and symptoms, however, subjects would not require further antimicrobial therapy. "Clinically failed" was defined as no response to the antimicrobial

therapy. Lastly, “unable to evaluate” was assigned to subjects who did not return for follow-up evaluation[1,4,5].

Safety and tolerability information was collected through post therapy follow up visits. Information on adverse events was collected throughout the study up to 30 days after the last dose of medication was administered. Serious adverse events were reported by subjects or witnessed in the laboratory.

Results

This systematic review includes three double-blind, randomized controlled trials, all of which were comparative ten day trials. The control group in all three studies was ciprofloxacin 500 mg taken twice a day for ten days, while the experimental group was levofloxacin 750 mg once daily for five days in two of the studies (Klausner 2007 and Peterson 2008), and levofloxacin 250 mg once daily for ten days in the third study (Richard 1998). The Klausner 2007 and Peterson 2008 studies performed blinded therapy for ten days with both drugs so as not to alter any results. Patients being treated with levofloxacin were given a placebo in the evening days one through five and a placebo twice daily days six through ten. Each study was performed in adult patients microbiologically and clinically diagnosed with AP. Patients were excluded if they had taken any antimicrobial therapy for their current condition. Treatment prior to administration of trial therapy would skew the results because patients would already be on the way to being cured. In all three studies, *Escherichia coli* were found to be the most commonly isolated uropathogen.

All three studies presented with “dichotomous” data, so no data had to be converted. The Relative Benefit Increase (RBI), Absolute Benefit Increase (ABI), and Numbers Needed to Treat (NNT) were calculated using efficacy rates for both the levofloxacin and ciprofloxacin treated

patients. These values were calculated using clinical success rates with levofloxacin as the Experimental Event Rate (EER) and clinical success rates with ciprofloxacin as the Controlled Event Rate (CER). A summary of these analyses along with the Confidence Interval (CI) from each study can be found in Table 2. The CI determines whether the data is valid by showing how precise the estimate of the cliabnical success rates (treatment effect) is. A CI that contains the relative risk of 1.00 proves that there is no significant difference between treatment effects.

Table 2: Analysis of Levofloxacin versus Ciprofloxacin on clinical success at post-therapy visit

	Levofloxacin EER (%)	Ciprofloxacin CER (%)	CI (%)	RBI	ABI	NNT
Klausner 2007	86.2	80.6	-15.1 to 6.1	6.9	5.6	18
Peterson 2008	79.8	77.5	-9.6 to 1.2	2.9	2.3	44
Richard 1998	92	88	-16.4 to 4.0	4.5	4	25

The Klausner 2007 study evaluated 80 levofloxacin-treated patients and 76 ciprofloxacin-treated patients. Results showed an 86.2% success rate with levofloxacin as compared to an 80.6% success rate with ciprofloxacin. The RBI and ABI are not high percentages but do show some benefit to using levofloxacin. Additionally, the NNT shows that for every 18 patients treated with levofloxacin, one more will have microbiologic eradication versus ciprofloxacin. A CI of -15.1 to 6.1, however, shows no statistical difference between clinical success rates of levofloxacin to ciprofloxacin.

265 participants were treated with levofloxacin while 241 participants were treated with ciprofloxacin in the Peterson 2008 study. Success rates for the experimental group were calculated to be 79.8% with the control group close behind at 77.5%. This study also shows a small RBI and ABI; however, they still indicate benefit to using levofloxacin. The NNT was higher compared to other studies, but showed that for every 44 participants treated with

levofloxacin, 1 more will have microbiologic eradication than with ciprofloxacin. The CI calculated for this study includes a relative risk of 1.00, meaning there is no statistical difference between the treatment effect of levofloxacin as compared to ciprofloxacin.

Lastly, the Richard 1998 trial showed similar results when compared to both other studies. The trial assessed 89 levofloxacin-treated patients and 58 ciprofloxacin-treated patients. An RBI of 4.5% and ABI of 4% show there is minimal benefit to the use of ciprofloxacin, and the NNT shows that for every 25 participants treated with levofloxacin, 1 more will have microbiologic eradication than with ciprofloxacin. Again, data recovered from this study does not prove a significant difference between treatment effect as shown by the calculated CI.

As previously discussed, safety and tolerability of both levofloxacin and ciprofloxacin were evaluated in all three studies. The analysis of outcomes and Numbers Needed to Harm (NNH) for each trial is provided in Table 3. A patient who experienced any adverse event or side effect thought to be related to treatment was included. The NNH was calculated by dividing 1 over the Absoulte Risk Increase (ARI), the value of which was rounded to a whole number.

Table 3: Analysis of Levofloxacin versus Ciprofloxacin on safety and tolerability at post-therapy visit

	Levofloxacin EER (%)	Ciprofloxacin CER (%)	RRI	ARI	NNH
Klausner 2007	43.8	39.2	11.7	4.6	22
Peterson 2008	35.5	33.1	7.2	2.4	42
Richard 1998	2	8	-75	-6	17

There were many adverse effects (AE) of reported throughout all three studies which comprises the safety and tolerability of both antimicrobial treatments. In the Klausner 2007 study, the most common side effects recorded were headache and nausea. 2.7% of levofloxacin-treated patients and 1.2% ciprofloxacin-treated patients experienced either one or both of these

symptoms. Serious adverse effects (SAEs) were seen in 5 of 146 patients treated with levofloxacin and 6 of 166 patients treated with ciprofloxacin, however, these SAEs were determined to be "unrelated to study medication"[4].

The Peterson 2008 trial most commonly reported nausea, headache, and diarrhea as adverse events, however, saw no noteworthy difference in the number of patients complaining of these symptoms between the two treatments. An allergic reaction to levofloxacin seen in one patient was the only AE determined to be related to treatment. Two deaths occurred in this study, however, neither was considered to be related to treatment.

A larger number of patients were considered evaluable for safety than were considered evaluable for microbiologic eradication in the Richard 1998 study. 3 of 124 levofloxacin-treated patients and 6 of 80 ciprofloxacin-treated patients experienced an AE, all of which are "gastrointestinal" in nature such as diarrhea, nausea, and flatulence. Vaginitis was also reported, however, there were no SAEs noted in this trial.

Discussion

Levofloxacin was approved by the FDA in 1996 for AP. Additionally, it was approved for chronic bronchitis, pneumonia, chronic bacterial prostatitis, sinusitis, skin infections, and inhalational anthrax[2]. There are, however, contraindications to the use of levofloxacin in the treatment of any of these conditions. For example, people with myasthenia gravis may experience exacerbations of muscle weakness so levofloxacin should not be prescribed for these patients. Hypokalemia and a prolonged QT interval are other noted contraindications. Lastly, a black box warning for all fluoroquinolones states there is an increased risk of tendon rupture with their use[2]. There are a number of non life-threatening AEs caused by levofloxacin, some of which were experienced by patients in the RCT's utilized for this systematic review. The

Klausner 2007 study showed five prominent AEs including “unintended pregnancy, urinary calculus, non-cardiac chest pain, pelvic inflammatory disease, and urinary retention”. Flatulence, vaginitis, and diarrhea were the most common AEs in the Richard 1998 study. Lastly, the Peterson 2008 study noted that headache, nausea, and diarrhea were the most frequent AEs.

There were limitations to each article. Both the Peterson 2008 and the Klausner 2007 articles analyzed results from larger trials which included patients with chronic UTIs in addition to AP. Additionally, they both compared a trial of Levofloxacin for 5 days to Ciprofloxacin for 10 days. The shortened duration of Levofloxacin therapy may skew end of therapy and post therapy values in favor of Ciprofloxacin, the antimicrobial agent which was used for a longer period of time. The Richard 1998 study specified that patients were required to have 10^5 CFU/mL of a uropathogen for inclusion, which they deemed may be too high of a threshold for treatment. However, all studies required a 10^5 CFU/mL threshold for inclusion so this is not a limitation in regard to this systematic review.

Conclusion

All three studies systematically reviewed concluded that levofloxacin is as effective as ciprofloxacin in treating adult patients with AP; however, it was not proven to be a more effective treatment in terms of microbiologic eradication, clinical success, and safety and tolerability.

Future studies should address the effectiveness of levofloxacin as compared to ciprofloxacin as far as compliance. Because levofloxacin is only taken once a day for five days, it is much more likely that patients comply with the prescribed treatment. Comparatively speaking, ciprofloxacin must be taken twice a day for ten days, making it less likely for patients to remember to take the medication or to finish the full length of treatment.

Further research can also be performed in determining uropathogen susceptibility differences between levofloxacin and ciprofloxacin. Resistance is a major issue being faced by all parts of the world, and extra research in this area would be helpful in determining how well levofloxacin and ciprofloxacin function in eradication of resistant pathogens. The studies systematically reviewed here touched upon these differences, however, did not go into any length or detail in showing whether one fluoroquinolone was superior to the other in these terms.

In conclusion, this systematic review proves that when compared with ciprofloxacin, levofloxacin is also a safe and effective empiric antimicrobial choice for therapy in the treatment of AP in adult patients. However, further studies showing resistance patterns and patient compliance could show that levofloxacin is the better choice.

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