SYNOPSIS

Name of Sponsor/Company: Johnson & Johnson Pharmaceutical Research and Development, L.L.C.
Protocol ID: CR005482

Title of Study: A Multicenter, Double-Blind, Randomized Study To Compare The Safety And Efficacy Of Oral Levofloxacin With That Of Ciprofloxacin HCl In The Treatment Of Complicated Urinary Tract Infections In Adults

PRINCIPAL INVESTIGATORS: 36 principal investigators; 3 investigators did not enroll subjects.

STUDY DATES: June 24, 1993 to January 23, 1995

OBJECTIVES:
The objective of this study was to compare the safety and efficacy of 250 mg of levofloxacin administered orally once daily for 10 days with that of 500 mg of ciprofloxacin administered orally twice daily for 10 days in the treatment of complicated urinary tract infections or acute pyelonephritis due to susceptible organisms in adults.

STUDY DESIGN:
This was a randomized, double-blind, active-control, multicenter study. Subjects who met the entry criteria were assigned randomly to receive levofloxacin or ciprofloxacin for 10 days. Efficacy evaluations were based on the assessments of clinical signs and symptoms, and overall clinical response (evaluated as cured, improved, failure, or unable to evaluate) and on microbiologic eradication of the suspected pathogen(s) isolated at admission (baseline) and of the subject's infections considering all pathogens isolated. Clinical signs and symptoms were assessed at admission and five to nine days after the end of therapy (posttherapy), with an overall clinical response rating at the posttherapy visit. Additionally, subjects who were clinically cured or improved were scheduled to return for evaluation of clinical signs and symptoms four to six weeks after the end of therapy (long-term follow-up). Urine cultures, and susceptibility testing were performed at admission, three to five days after the start of therapy (on-therapy visit), at the posttherapy visit, and at the long-term follow-up. The primary efficacy parameters were clinical response assessed as the resolution of signs and symptoms at posttherapy compared with those at study start and microbiologic response based on eradication at posttherapy of infectious organisms identified at study start. Safety evaluations consisted of treatment-emergent adverse events reported during the study period (through the posttherapy visit) and of clinical laboratory tests (hematology, blood chemistry, and urinalysis), vital signs, and pertinent physical examinations performed at baseline and posttherapy.

ANALYSIS GROUPS:
Treatment comparisons are based on several analysis groups to assess relative efficacy and consistency across different, standard approaches. The discussion and displays in this synopsis focus mainly on the efficacy analysis based on subjects classified as microbiologically evaluable according to the protocol-specified evaluability criteria. Supportive efficacy analyses include two types of analyses based on all subjects enrolled, i.e., randomized to a treatment group. One approach — Intent-to-Treat — adheres strictly to randomization; thus subjects are included in the analysis regardless of whether or not an admission pathogen was isolated. Supportive efficacy analyses also include an additional analysis group — Modified Intent-to-Treat with an Admission Pathogen — which represents those subjects in the intent-to-treat group who had a pathogen isolated at admission.

NUMBER OF SUBJECTS (planned and analyzed):
Planned enrollment: 500 subjects for a minimum of 294 clinically and microbiologically evaluable subjects (147 per treatment group). Five hundred sixty-seven subjects were enrolled in this study at 31 centers, including 285 subjects in the levofloxacin treatment group and 282 subjects in the ciprofloxacin treatment group (intent-to-treat group).

EFFICACY RESULTS:

Clinical Response

Among microbiologically evaluable subjects in the levofloxacin treatment group with a diagnosis of complicated UTI or acute pyelonephritis, 84.7% were cured and 7.3% were improved at the posttherapy visit (five to nine days after completion of therapy), compared with 81.9% and 8.8% in the ciprofloxacin treatment group. Fourteen (7.9%) levofloxacin-treated subjects and 16 (9.4%) ciprofloxacin-treated subjects failed treatment.

When the clinical response categories "cured" and "improved" were combined into a single category of "clinical success", the clinical success rate was 92.1% for levofloxacin-treated subjects and 90.6% for ciprofloxacin-treated subjects, with a 95% confidence interval of [-7.6, 4.7] for the difference (ciprofloxacin minus levofloxacin) in success rates. The upper limit of this confidence interval lies below the upper bound of 10%, thereby providing additional support to the claim of therapeutic equivalence of the two treatments. Clinical response rates were generally comparable for the individual diagnoses of UTI (complicated UTI, acute pyelonephritis, and uncomplicated UTI), and across analysis groups and study centers.

Microbiologic Response

The overall microbiologic eradication rates by pathogen in the levofloxacin and ciprofloxacin treatment groups were 93.4% and 92.4%, respectively, with a 95% confidence interval of [-6.5, 4.4] for the difference between treatments (ciprofloxacin minus levofloxacin), assuming independence of multiple pathogens and multiple strains within a subject. The corresponding eradication rates by subject were 92.7% and 93.0%, respectively, with a confidence interval of [-5.4, 6.0] for the difference between treatments in eradication rates. Using a confidence interval upper bound of 10% for eradication rates greater than 90%, this interval establishes therapeutic equivalence between the two treatments. Confidence intervals computed for each study center with 10 or more microbiologically evaluable subjects in each treatment group and for all other centers pooled demonstrate the comparability in efficacy across centers.

The most prevalent pathogens for both levofloxacin and ciprofloxacin treatment groups were gram-negative aerobes (89.9% and 88.0% of pathogens in the two treatment groups); the remaining pathogens were gram-positive aerobes (10.1% and 12.0% of pathogens in the two treatment groups). The microbiologic eradication rates for gram-negative aerobes were comparable for the levofloxacin and ciprofloxacin treatment groups (93.8% and 95.7%, respectively). In contrast, for the relatively small group of gram-positive aerobes (primarily *S. faecalis*), levofloxacin treatment resulted in a somewhat higher eradication rate than ciprofloxacin (90.0% vs. 68.2%). The most common pathogen, *E. coli*, was eradicated by levofloxacin in 95.7% of cases, compared with a 97.0% eradication rate with ciprofloxacin treatment. The second most prevalent pathogen, *K. pneumoniae*, had an eradication rate of 96.9% with levofloxacin treatment, compared with 95.7% with ciprofloxacin.

Among modified intent-to-treat subjects with an admission pathogen and a diagnosis of complicated UTI or acute pyelonephritis, the microbiologic eradication rates by subject for treatment with levofloxacin and ciprofloxacin were 83.3% and 84.0%, respectively. The confidence interval for the difference between treatment groups in eradication rates [-6.5, 8.0] supports therapeutic equivalence of the two treatments. Microbiologic eradication rates were generally comparable for the individual diagnoses of UTI.

Summary

A summary of key efficacy results is presented in Tables Ia and Ib. Comparable results were seen across analysis groups for both clinical and microbiologic endpoints; clinical and microbiologic response rates were generally ≥90% for microbiologically evaluable subjects and >80% for the intent-to-treat subjects. In addition, there was concordance between the clinical and microbiologic responses based on a cross-tabulation of clinical response versus microbiologic response, further confirming the consistency of these response measures.

Table Ia: Summary of Key Efficacy Results: Clinical and Microbiologic Response Rates at Posttherapy for Subjects With Complicated UTI or Acute Pyelonephritis

Response/Group	Levofloxacin Clinical Success or Microbiologic Eradication Rates[a]		Ciprofloxacin Clinical Success or Microbiologic Eradication Rates[a]		95% Confidence Interval[b]
Clinical Response					
Microbiologically Evaluable					
Complicated UTI	116/126	(92.1)	100/113	(88.5)	
Acute Pyelonephritis	47/ 51	(92.2)	55/ 58	(94.8)	
Complicated UTI/Acute Pyelonephritis	163/177	(92.1)	155/171	(90.6)	(-7.6, 4.7)
Intent-to-Treat					
Complicated UTI	171/197	(86.8)	164/188	(87.2)	
Acute Pyelonephritis	62/ 69	(89.9)	74/ 80	(92.5)	
Complicated UTI/Acute Pyelonephritis	233/266	(87.6)	238/268	(88.8)	(-4.4, 6.9)
Microbiologic Response					
Microbiologically Evaluable					
Complicated UTI	115/126	(91.3)	105/113	(92.9)	
Acute Pyelonephritis	49/ 51	(96.1)	54/ 58	(93.1)	
Complicated UTI/Acute Pyelonephritis	164/177	(92.7)	159/171	(93.0)	(-5.4, 6.0)
Modified Intent-to-Treat With an Admission Pathogen					
Complicated UTI	124/152	(81.6)	123/149	(82.6)	
Acute Pyelonephritis	50/ 57	(87.7)	61/ 70	(87.1)	
Complicated UTI/Acute Pyelonephritis	174/209	(83.3)	184/219	(84.0)	(-6.5, 8.0)

[a] Denominator for clinical success rate = cured + improved + failed + unable to evaluate. Denominator for microbiologic eradication rate = eradication + persistence + unknown.

[b] Two-sided 95% confidence interval around the difference (ciprofloxacin minus levofloxacin) in clinical success or microbiologic eradication rates.

NOTE: All microbiologic eradication rates presented in this table are by subject, i.e., reflect eradication of all pathogens isolated for a given subject at admission.

UTI = urinary tract infection.

Table Ib: Summary of Key Efficacy Results: Cross Tabulation of Microbiologic Response Versus Clinical Response at Posttherapy for Microbiologically Evaluable Subjects With Complicated UTI or Acute Pyelonephritis

	Clinical Response							
	Levofloxacin				Ciprofloxacin			
Microbiologic Response	N	Cured	Improved	Failed	N	Cured	Improved	Failed
Complicated UTI								
Eradicated	115	101 (87.8)	11 (9.6)	3 (2.6)	105	89 (84.8)	10 (9.5)	6 (5.7)
Persisted	11	3 (27.3)	1 (9.1)	7 (63.6)	8	0 (0.0)	1 (12.5)	7 (87.5)
Acute Pyelonephritis								
Eradicated	49	46 (93.9)	0 (0.0)	3 (6.1)	54	51 (94.4)	3 (5.6)	0 (0.0)
Persisted	2	0 (0.0)	1 (50.0)	1 (50.0)	4	0 (0.0)	1 (25.0)	3 (75.0)
Complicated UTI/ Acute Pyelonephritis								
Eradicated	164	147 (89.6)	11 (6.7)	6 (3.7)	159	140 (88.1)	13 (8.2)	6 (3.8)
Persisted	13	3 (23.1)	2 (15.4)	8 (61.5)	12	0 (0.0)	2 (16.7)	10 (83.3)

NOTE: All microbiologic eradication rates presented in this table are by subject, i.e., reflect eradication of all pathogens isolated for a given subject at admission.

UTI = urinary tract infection.

SAFETY RESULTS:

Summary of All Adverse Events

All but six of the 567 subjects enrolled were evaluable for safety. Of these 561 subjects, 282 received levofloxacin and 279 received ciprofloxacin. Six subjects (three in each treatment group) were lost to follow-up with no safety information and were therefore excluded from the safety analysis.

Ninety-four (33.3%) of the 282 subjects evaluable for safety in the levofloxacin treatment group and 105 (37.6%) of the 279 subjects evaluable for safety in the ciprofloxacin treatment group reported at least one treatment-emergent adverse event during the study, including events considered by the investigator as related or unrelated to study drug. The body system with the highest reported incidence of adverse events for both treatment groups was the gastrointestinal system. The incidence of GI system adverse events was statistically significantly higher in the ciprofloxacin-treated group (19.4%) than in the levofloxacin-treated group (12.4%) with a 95% confidence interval around the difference (ciprofloxacin minus levofloxacin) of [0.7, 13.1]. Although not statistically significant, the incidence of adverse events in the female reproductive and skin and appendages body systems was also greater in ciprofloxacin-treated subjects (9.5% and 5.0%, respectively) than in levofloxacin-treated subjects (4.8% and 2.5%, respectively). In addition, vision disorders occurred infrequently, but were reported by a statistically significantly higher (95% confidence interval of [-3.5, -0.1]) proportion of levofloxacin-treated subjects (1.8% vs. 0.0%). For all other body systems, the two treatment groups were generally comparable with regard to the type and incidence of adverse events.

Consistent with the higher percentage of gastrointestinal adverse events reported by ciprofloxacin-treated subjects as compared with levofloxacin-treated subjects, several specific gastrointestinal complaints were more common in the ciprofloxacin group (e.g., nausea, diarrhea, and abdominal pain) than in the levofloxacin group. In the other body systems, vaginitis, headache and dizziness were the most common adverse events with ciprofloxacin-treated subjects showing a higher incidence of vaginitis (7.1%) compared with levofloxacin-treated subjects (4.8%) and a comparable number of subjects in each treatment group reporting headache and dizziness.

The majority of adverse events were assessed as mild or moderate in severity. Ten subjects in each treatment group reported one or more adverse events of marked severity, including pain in three levofloxacin-treated subjects and headache in two ciprofloxacin-treated subjects. No other adverse events of marked severity occurred in more than one subject within a given treatment group, and most were considered by the investigator as unrelated or remotely related to the study drug. Both subjects with marked drug-related (probably or definitely related to study therapy) adverse events were in the ciprofloxacin treatment group (diarrhea and vaginitis in one subject and abdominal pain and nausea in one subject).

Discontinuations Due to Adverse Events

Twenty-six (4.6%) of the 561 subjects evaluable for safety discontinued the study drug due to adverse events, including 10 (3.5%) of the 282 subjects evaluable for safety in the levofloxacin treatment group and 16 (5.7%) of the 279 subjects evaluable for safety in the ciprofloxacin treatment group. All but one of the adverse events leading to discontinuation in the levofloxacin-treated group, and all but five in the ciprofloxacin-treated group, emerged within the first four days of therapy. Treatment-limiting adverse events in both treatment groups included primarily gastrointestinal complaints or central and peripheral nervous system-related symptoms (e.g., diarrhea, nausea, abdominal pain, and dizziness).

Serious or Potentially Serious Adverse Events, Including Deaths

Fifteen (5.3%) subjects in the levofloxacin treatment group and eight (2.9%) subjects in the ciprofloxacin treatment group reported a serious or potentially serious adverse event during therapy or up to approximately one month after the end of study drug administration, including three levofloxacin-treated subjects who died after completing study therapy due to progression of their serious adverse event. The three serious adverse events that resulted in death were metastatic adenocarcinoma of the pancreas with an onset 14 days posttreatment, renal carcinoma with an onset 13 days posttreatment, and pulmonary carcinoma with an onset 11 days posttreatment. Each of the serious adverse events that resulted in death was considered unrelated or remotely related to the study medication. The serious or potentially serious adverse events reported mainly included GI system events and neoplasms. Of the 23 subjects with serious or potentially serious adverse events, five subjects withdrew from the study because of the adverse event. In all but two cases (cerebrovascular disorder possibly related to levofloxacin and granulocytopenia possibly related to ciprofloxacin), the serious or potentially serious adverse event was considered by the investigator to be unrelated or remotely related to the study drug, and in most cases was attributed to the subject's underlying condition.

Clinical Laboratory Tests

There were no significant treatment-emergent mean changes from admission to posttherapy for laboratory tests in either treatment group, with comparable results in both groups

Physical Examinations and Vital Signs

There were no clinically significant changes in vital signs from admission to posttherapy in the levofloxacin-treated or ciprofloxacin-treated subjects, with comparable results in the two groups. Similarly, there were no clinically significant treatment-emergent physical examination abnormalities.

CONCLUSIONS:

Levofloxacin was safe, well-tolerated and effective in the treatment of subjects with complicated urinary tract infections or acute pyelonephritis. The microbiologic eradication rates in the levofloxacin treatment group were therapeutically equivalent to those observed in the ciprofloxacin group. Moreover, the clinical response rates were therapeutically equivalent to those of ciprofloxacin. These data support the efficacy of levofloxacin for complicated urinary tract infections and acute pyelonephritis due to *E. coli*, *K. pneumoniae*, *P. mirabilis*, *E. cloacae*, *S. saprophyticus*, and *S. (Enterococcus) faecalis*.

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