SYNOPSIS

Name of Sponsor/Company: Johnson & Johnson Pharmaceutical Research and Development, L.L.C.
Protocol ID: CR005488

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

PRINCIPAL INVESTIGATORS: 30 principal investigators; 1 investigator did not enroll

STUDY DATES: January 15, 1993 to January 18, 1995

OBJECTIVES:
The objective of this study was to compare the safety and efficacy of 250 mg of levofloxacin administered orally once daily for seven to 10 days with that of 400 mg of lomefloxacin administered orally once daily for 14 days in the treatment of complicated urinary tract infections (UTI) or acute pyelonephritis due to susceptible organisms in adults.

STUDY DESIGN:
This was a randomized, open-label, active-control, multicenter study. Subjects who met the entry criteria were assigned randomly to receive levofloxacin or lomefloxacin. Efficacy evaluations were based on the assessments of clinical signs and symptoms, overall clinical response (evaluated as cured, improved, failed, or unable to evaluate), microbiologic eradication of the suspected pathogen(s) isolated at admission (baseline), and microbiologic eradication of each subject's infection 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 variables were clinical response assessed by the resolution of signs and symptoms at posttherapy compared with those at the start of the study and microbiological response assessed by the eradication at posttherapy of infectious organism identified at the start of the study. 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 analyses based on subjects who were classified as microbiologically evaluable according to the protocol-specified evaluability criteria of this study and who had complicated UTI or acute pyelonephritis.

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 counted in their assigned treatment group regardless of any dosing or dispensing errors. An alternative approach — Modified Intent-to-Treat — takes into account the small number of drug dispensing errors that occurred by grouping subjects according to the drug actually received. These two approaches classify only three subjects differently; one was randomized to treatment with levofloxacin but received lomefloxacin, and two were randomized to treatment with lomefloxacin but received levofloxacin. The Modified Intent-to-Treat approach — grouping subjects by treatment received rather than by treatment assigned — should be more reflective of the relative efficacy of the comparative treatments and is therefore given greater attention than the Intent-to-Treat analysis. Consistent with this reasoning, the microbiologically evaluable group is also determined by treatment actually received rather than by treatment assigned. Supportive efficacy analyses also include an additional analysis group — Modified Intent-to-Treat Subjects with an Admission Pathogen — representing those subjects in the modified intent-to-treat group who had a pathogen isolated at admission.

NUMBER OF SUBJECTS (planned and analyzed):
Planned enrollment: 600 subjects for a minimum of 294 microbiologically and clinically evaluable subjects (147 per treatment group). Six hundred fifty subjects were enrolled in the study at 29 centers, including 326 subjects who received levofloxacin and 324 who received lomefloxacin (modified 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, 86.6% were cured and 6.7% improved at the posttherapy visit (five to nine days after completion of therapy), compared with 81.9% and 7.8% in the lomefloxacin treatment group. Fourteen (6.7%) subjects in the levofloxacin group and 21 (10.3%) subjects in the lomefloxacin group failed treatment.

When the clinical response categories "cured" and "improved" were combined into a single category of "Clinical Success," levofloxacin resulted in 93.3% clinical success and lomefloxacin resulted in 89.7% clinical success, with a 95% confidence interval of [-9.2, 2.0] for the difference (lomefloxacin 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 lomefloxacin groups were 94.9% and 92.3%, respectively, with a 95% confidence interval of [-7.5, 2.3] for the difference between treatments (lomefloxacin minus levofloxacin), assuming independence of multiple pathogens and multiple strains within a subject. The corresponding eradication rates by subject were 94.7% and 92.6%, respectively, with a 95% confidence interval of [-7.0, 2.8] for the difference (lomefloxacin minus levofloxacin) in eradication rates. Using a confidence interval upper bound of 10% for eradication rates greater than 90%, this interval supports 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 the levofloxacin and lomefloxacin treatment groups were gram-negative aerobes (91.2% and 91.3% of pathogens for the two treatment groups); the remaining pathogens were gram-positive aerobes (8.8% and 8.7% of pathogens in the two treatment groups). The microbiologic eradication rates for gram-negative and gram-positive aerobes were 96.5% and 78.9% in the levofloxacin group and 94.2% and 72.2% in the lomefloxacin group. There was 99.2% eradication of the most common pathogen (*Escherichia coli*) and 93.5% eradication of the second most common pathogen (*Klebsiella pneumoniae*) in the levofloxacin treatment group versus eradication rates of 98.3% and 92.0% in the lomefloxacin treatment group. There was 100% eradication of the third most common pathogen (*Proteus mirabilis*) in both groups.

Among modified intent-to-treat subjects with an admission pathogen and a diagnosis of complicated UTI or acute pyelonephritis, the infection eradication rates after treatment with levofloxacin or lomefloxacin were 89.5% and 87.8%, respectively. The confidence interval for the difference between treatment groups in eradication rates [-7.7, 4.3] supports therapeutic equivalence of the two treatments. Microbiologic eradication rates were generally comparable for the individual diagnosis of UTI, and across analysis groups.

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 approximately 90% or greater for microbiologically evaluable subjects and >80% for modified intent-to-treat subjects with an admission pathogen. 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]		Lomefloxacin Clinical Success or Microbiologic Eradication Rates[a]		95% Confidence Interval[b]	
Clinical Response						
Microbiologically Evaluable						
Complicated UTI	159/171	(93.0)	146/165	(88.5)		
Acute Pyelonephritis	36/ 38	(94.7)	37/ 39	(94.9)		
Complicated UTI/Acute Pyelonephritis	195/209	(93.3)	183/204	(89.7)	(-9.2,	2.0)
Modified Intent-to-Treat						
Complicated UTI	216/232	(93.1)	193/230	(83.9)		
Acute Pyelonephritis	49/ 55	(89.1)	50/ 56	(89.3)		
Complicated UTI/Acute Pyelonephritis	265/287	(92.3)	243/286	(85.0)	(-12.7,	-2.0)
Microbiologic Response						
Microbiologically Evaluable						
Complicated UTI	163/171	(95.3)	152/165	(92.1)		
Acute Pyelonephritis	35/ 38	(92.1)	37/ 39	(94.9)		
Complicated UTI/Acute Pyelonephritis	198/209	(94.7)	189/204	(92.6)	(-7.0,	2.8)
Modified Intent-to-Treat With an Admission Pathogen						
Complicated UTI	170/187	(90.9)	162/183	(88.5)		
Acute Pyelonephritis	35/ 42	(83.3)	40/ 47	(85.1)		
Complicated UTI/Acute Pyelonephritis	205/229	(89.5)	202/230	(87.8)	(-7.7,	4.3)

[a] Denominator for clinical success rate = cured + improved + failed + unable to evaluate.
Denominator for microbiologic eradication = eradication + persistence + unknown.
[b] Two-sided 95% confidence interval around the difference (lomefloxacin minus levofloxacin) in clinical success or microbiologic eradication rates.
NOTE: Microbiologic eradication rates presented in this table are by subject, i.e., reflect eradication of all pathogens isolated for a 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					Lomefloxacin				
Microbiologic Response	N	Cured		Improved	Failed	N	Cured		Improved	Failed
Complicated UTI										
Eradicated	163	144	(88.3)	13 (8.0)	6 (3.7)	152	134	(88.2)	10 (6.6)	8 (5.3)
Persisted	8	1	(12.5)	1 (12.5)	6 (75.0)	13	2	(15.4)	0 (0.0)	11 (84.6)
Acute Pyelonephritis										
Eradicated	35	3	(100.0)	0 (0.0)	0 (0.0)	37	31	(83.8)	5 (13.5)	1 (2.7)
Persisted	3	1	(33.3)	0 (0.0)	2 (66.7)	2	0	(0.0)	1 (50.0)	1 (50.0)
Complicated UTI/Acute Pyelonephritis										
Eradicated	198	179	(90.4)	13 (6.6)	6 (3.0)	189	165	(87.3)	15 (7.9)	9 (4.8)
Persisted	11	2	(18.2)	1 (9.1)	8 (72.7)	15	2	(13.3)	1 (6.7)	12 (80.0)

NOTE: Microbiologic eradication rates presented in this table are by subject, i.e., reflect eradication of all pathogens isolated for a subject at admission.
UTI = urinary tract infection.

SAFETY RESULTS:

Summary of All Adverse Events

Six hundred forty-seven (99.5%) of 650 subjects enrolled were evaluated for safety. Of the 647 subjects, 325 received levofloxacin and 322 received lomefloxacin. Three subjects (one in the levofloxacin treatment group and two in the lomefloxacin treatment group) were lost to follow-up with no safety information available and were therefore excluded from the safety analysis.

Seventy-four (22.8%) of the 325 subjects evaluable for safety in the levofloxacin treatment group and 100 (31.1%) of the 322 subjects evaluable for safety in the lomefloxacin 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 proportion of subjects experiencing adverse events was statistically significantly lower in the levofloxacin group than the lomefloxacin group (95% confidence interval around the difference of [1.3, 15.2]). Body systems with the highest reported incidence of adverse events were the gastrointestinal system (approximately 11% in both treatment groups) and the central and peripheral nervous system (approximately 7% in both treatment groups). In addition, skin and appendages disorders such as pruritus and photosensitivity reaction were reported by a statistically significantly higher proportion of lomefloxacin-treated subjects (7.5%) than levofloxacin-treated subjects (1.8%; 95% confidence interval of [2.2, 9.0]). The most frequently reported adverse events were nausea (4.3% incidence rate for levofloxacin-treated subjects and 4.7% incidence rate for lomefloxacin-treated subjects), headache (4.6% versus 2.8%), and dizziness (0.9% versus 4.3%).

Eight (2.5%) subjects in the levofloxacin treatment group and 16 (5.0%) subjects in the lomefloxacin treatment group had adverse events considered by the investigator to be drug-related, i.e., probably or definitely related to study drug. The only drug-related adverse events reported by ≥1.0% of the subjects were vaginitis (1.0%) in the levofloxacin group and photosensitivity reaction (1.2%) in the lomefloxacin group.

The majority of adverse events were assessed as mild or moderate in severity. Ten subjects in the levofloxacin treatment group reported one or more adverse events of marked severity; with the exception of two reports of diarrhea in one levofloxacin-treated subject, no single event was reported more than once. Eleven subjects in the lomefloxacin treatment group reported one or more marked adverse events, including photosensitivity reaction in three subjects and gastrointestinal hemorrhage in two subjects. Most of the marked adverse events were considered by the investigator as unrelated or remotely related to the study drug. Of the two subjects with marked drug-related adverse events, one was in the levofloxacin treatment group (rash) and one was in the lomefloxacin treatment group (herpes simplex and photosensitivity reaction).

Discontinuations Due to Adverse Events

Twenty-seven (4.2%) of the 647 subjects evaluable for safety discontinued the study drug due to adverse events, including nine (2.8%) of the 325 subjects evaluable for safety in the levofloxacin treatment group and 18 (5.6%) of the 322 subjects evaluable for safety in the lomefloxacin treatment group. These adverse events included primarily gastrointestinal complaints or skin disorders in the levofloxacin group (e.g., nausea and pruritus) and gastrointestinal complaints, skin disorders, psychiatric disorders, or central and peripheral nervous system-related symptoms in the lomefloxacin group (mainly nausea, dizziness, insomnia, and pruritus). The treatment-limiting adverse event was considered serious or potentially serious in one subject in each group.

Serious or Potentially Serious Adverse Events, Including Deaths

Four (1.2%) subjects in the levofloxacin treatment group and seven (2.2%) subjects in the lomefloxacin treatment group reported a serious or potentially serious adverse event during or up to approximately one month after completing the study therapy. Of the 11 subjects with serious or potentially serious adverse events, two subjects withdrew from the study because of the adverse event (dyspnea in a levofloxacin-treated subject and ketosis in a lomefloxacin-treated subject). In all but one case, the serious or potentially serious adverse events were considered by the investigator to be unrelated or remotely related to the study drug (or of unknown relation). In most cases, they were attributed to the subjects' underlying conditions. One subject in each treatment group with serious adverse events died within approximately one month of completing the study; these deaths were considered unrelated to study drug.

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 Examination and Vital Signs

There were no clinically significant changes in vital signs from admission to posttherapy in the levofloxacin-treated or lomefloxacin-treated subjects, with comparable results in the two groups. Similarly, there were no clinically significant treatment-emergent pertinent 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 lomefloxacin group. Moreover, the clinical response rates were therapeutically equivalent to those of lomefloxacin. These data support the efficacy of levofloxacin for the treatment of complicated urinary tract infections or acute pyelonephritis due to *E. coli*, *K. pneumoniae*, *P. mirabilis*, *E. cloacae*, *S. (Enterococcus) faecalis*, and *P. aeruginosa*.

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