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A pilot study of oral fleroxacin once daily compared with conventional therapy in patients with pyogenic liver abscess

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The object of this open-label, randomized, comparative study was to evaluate the efficacy and safety of fleroxacin versus conventional therapy (cefazolin plus gentamicin/cephalexin) in the treatment of patients with bacterial liver abscess. Thirty-one adult patients (26 men and 5 women) received fleroxacin 400 mg orally once daily for 3 weeks, and 30 adult patients (21 men and 9 women) received conventional therapy for 3 to 4 weeks. Patients was assessed on day 3 of treatment, thereafter every week during treatment, and at 7 to 14 days (compulsory follow-up) after treatment for assessment of bacteriologic, clinical, and safety parameters. A total of 20 patients in the fleroxacin group and 22 patients in the conventional therapy group were evaluated. *Klebsiella pneumoniae* was the predominant pathogen isolated in all evaluable cases. Bacteriologic cure was achieved in 14 (70%) of 20 patients on fleroxacin therapy compared with 18 (81.8%) of 22 patients on conventional therapy (p=0.48). Clinical cure was achieved in 12 (60%) and 18 (81.8%) patients, and improvement in 2 (10%) and 1 (4.5%) patients in the fleroxacin and conventional therapy group, respectively. Most of adverse effects were of mild intensity. Oral fleroxacin once-daily administration is an effective, alternative treatment of bacterial liver abscess.

Key word: Bacterial liver abscess, clinical trial, fleroxacin, *Klebsiella pneumoniae*

Fleroxacin (Ro 23-6240/AM 833) is a fluoroquinolone belonging to a novel chemical compound, which act by inhibition of an essential bacterial enzyme, the DNA gyrase [1]. Fleroxacin has an extremely broad antimicrobial spectrum [2], a long elimination half-life of 8 to 12 h with peak serum levels of 4.6 μ/mL following a single oral dose of 400 mg [3], and excellent penetration into biological fluids and tissues [4,5]. *In vitro* susceptibility tests showed that pathogens causing pyogenic liver abscess, such as *Klebsiella pneumoniae* and *Escherichia coli* are highly susceptible to fleroxacin [2,6,7]. However, no clinical data was available in the literature, especially in Taiwan, an endemic region of *K. pneumoniae* liver abscess [8-10]. The object of this study was to compare the efficacy and safety of fleroxacin with conventional therapy in the treatment of pyogenic liver abscess.

Materials and Methods

The enrollment criteria

This is a prospective, open-label, randomized, comparative study. Patients were of either sex and over 18 years of age. The diagnosis of pyogenic liver abscess was established if computed tomography (CT) revealed one or more filling defects, or a hepatic sonogram showed one or more echolucencies, combined with a positive bacterial culture from blood or purulent material obtained by CT-guided percutaneous aspiration of the liver. Exclusion criteria included pregnancy or nursing, allergy to quinolones, β-lactams, or aminoglycosides, severe renal impairment (creatinine clearance ≤30 mL/min), granulocytopenia (≤500/mm^3), and treatment with an effective antimicrobial agent within 48 h prior to entry into the study. Patients were excluded if the liver abscess was caused by anaerobes or nonbacterial (eg, *Entamoeba histolytica*), or if severe complications developed within 48 h after study-entry.

Dosage and regimen

At screening, patients were randomized to receive either fleroxacin 400 mg orally once-daily for 3 weeks, or conventional therapy with cefazolin 1 g intravenously every 8 h plus gentamicin 1 mg/kg every 8 h intravenous drip infusion for 2 weeks followed by cephalexin 1 g orally every 6 h for another 1 to 2 weeks. All enrolled cases were drained from pigtail catheter under CT-guide except in cases with draining failure because of immature abscess or abscess lesions too small to be drained. The investigators monitored the responses to

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therapy with daily visits for inpatients and clinical visits at least every week for outpatients during treatment.

Definitions

To assess the bacteriologic outcome of infection and superinfection, we defined cure as the eradication of all initially susceptible pathogens during the period of treatment, and failure as the persistence of one or more original pathogens during the period of treatment.

Clinical response was evaluated at 2 weeks after discontinuation of the study drug. Clinical cure was assumed if there was no evidence of infection, improvement if there was incomplete resolution of the infection clinically, and clinical failure if there was a lack of significant improvement or clinical response. Incidence of clinical adverse events was recorded to assess safety.

Statistical analysis

The efficacy was evaluated using Chi-square test. The bacteriologic finding and the homogeneity between the 2 treatments were also analyzed using Chi-square test or Student's *t* test. A p value less than 0.05 was considered significant.

Results

Demographics

A total of 61 patients were enrolled, of which 20 patients in the fleroxacin group and 22 in the conventional therapy group were evaluable. Eleven patients in the fleroxacin group and 8 in the conventional therapy group were excluded from the efficacy analysis for the following reasons: anaerobic liver abscess (6 cases), amebic liver abscess (2), culture negative (3), resistant bacteria (1), misdiagnosis (4), and severe complications within 48 h after study-entry–septic shock in 2 patients and liver abscess rupture in one. Demographic data including age, bodyweight, and underlying diseases was comparable between the 2 groups (Table 1). The median age was 61 and 67 years, median body weight 63 and 61 kg, in the fleroxacin group and conventional therapy group, respectively. Most patients had diabetes or impaired glucose intolerance, similar to previous reports [11].

Bacteriologic and clinical response

K. pneumoniae was the predominant pathogen isolated in all evaluable cases (Table 2). Superinfection occurred in 2 patients in the fleroxacin group and 5 in the conventional therapy group. Bacteriologic cures were seen in 14 (70%) of 20 fleroxacin patients with 6 failures, while 18 (81.1%) of 22 bacteriologic cures with 4 failures were seen in the conventional therapy group (Table 3). In the fleroxacin group, 12 (60%) patients achieved clinical cures, 2 had improvements, and 6 failures; and 18 (81.8%) patients in the conventional therapy group achieved clinical cures, one had improvement, and 3 failures (Table 3). Although the rate of bacteremia was significantly different

Table 1. Demographic data in patients with bacterial liver abscess

Variables	Fleroxacin n = 20	Cefazolin + Gentamicin n = 22	p
Sex			
Male	15	15	
Female	5	7	0.63[a]
Age (year)			
Median	61	67	
Mean	58.85	61.05	0.51[b]
Range	32-77	27-79	
Body weight (kg)			
Median	63	61	
Mean	61.68	62.43	0.61[b]
Range	46-77	37-96	
Underlying diseases			
Diabetes mellitus	16	15	
Impaired glucose tolerance	5	7	
Cholelithiasis	3	3	
Malignant neoplasm	2	1	
No underlying diseases	8	6	

[a]Chi-square test.
[b]Student's *t* test.

Table 2. Bacteriologic finding in patients with evaluable pyogenic liver abscess

	Fleroxacin n = 20	Cefazolin + Gentamicin n = 22	*p*
Polymicrobial	3	1	
Monomicrobial	17	21	0.33[a]
Bacteremia	4	12	0.02[b]
Microorganisms			
Klebsiella pneumoniae	15	19	
Escherichia coli	2	2	
Pseudomonas aeruginosa	1	0	
Serratia marcescens	1	0	
Proteus mirabilis	0	1	
Streptococcus milleri	1	0	
Group D non-*Enterococcus*	1	0	
Streptococcus constellatus	0	1	

[a]Fisher exact test.
[b]Chi-square test.

between the 2 groups (p=0.02, Table 2), it reflected only the open-label and randomized design in this study. In the fleroxacin group, one of 4 bacteremia cases was failure due to failure to pigtail catheter drainage (PCD); in contrast, 2 of 12 bacteremia cases in the conventional therapy group were clinical failures, one for suffocation and the other for treatment failure. However, bacteremia was not well related to rate of clinical failure in this clinical trial. Neither bacteriologic outcomes (p=0.48) nor clinical outcomes (p=0.29) were significantly different between the 2 groups. Two patients died in this trial, one due to superinfection in the fleroxacin group, the other for chocking in the conventional therapy group.

Safety evaluation and laboratory data

Clinical adverse events related to fleroxacin therapy included paresthesia in 2, skin rashes in one, dizziness in one, anemia in 3, eosinophilia in 3, and transient positive Coombs' test in 2 patients. Among these, only anemia was more frequent in the fleroxacin group than the conventional therapy group (9.6% vs 22.5%, Table 4). The majority of events were of mild intensity.

Discussion

In addition to *K. pneumoniae*, the predominating pathogen in this study, other pathogens including *E. coli*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Proteus mirabilis*, group D *Streptococcus* (non-*Enterococcus*), *Streptococcus milleri*, and *Streptococcus constellatus* were isolated from bacterial liver abscess (Table 2). More than 50% (31/61) of enrolled patients have a history of diabetes (Table 1). It is not surprising that in the past 20 years, *K. pneumoniae* liver abscess has become a common pyogenic liver abscess in Taiwan and up to 75% of patients with *K. pneumoniae* liver abscess were associated with diabetes [11].

Standardized treatment of pyogenic liver abscess included PCD and combination antimicrobial therapy (cefazolin + gentamicin) for 2 to 3 weeks, followed by

Table 3. Bacteriologic and clinical outcomes in patients with evaluable pyogenic liver abscess

Outcome	Fleroxacin n = 20 (%)	Cefazolin + Gentamicin n = 22 (%)	*p*
Bacteriologic			
Cure	14 (70.0)[a]	18 (81.1)[b]	
Failure	6 (30.3)	4 (18.1)	0.48[c]
Clinical			
Cure	12 (60.0)	18 (81.8)	
Improvement	2 (10.0)	1 (4.5)	
Failure	6 (30.0)	3 (13.6)	0.29[d]

[a]2 with superinfection: *Enterococcus* + *Xanthomonas hydrophilia* in 1 and *S. aureus* in 1.
[b]5 with superinfection: *Stenotrophomonas maltophilia* in 1, *Enterococcus* sp. in 1, *S. epidermidis* in 1, *S. epidermidis* + *S. capitis* in 1, *Pseudomonas aeruginosa* + *Candida albicans* in 1.
[c]Fisher exact test.
[d]Chi-square test.

Table 4. Adverse events in patients with enrolled pyogenic liver abscess

Adverse effect	Fleroxacin n = 31 (%)	Cefazolin + Gentamicin n = 30 (%)
Paresthesia	2 (6.4)	1 (3.2)
Skin rashes	1 (3.2)	1 (3.2)
Dizziness and tinnitus	1 (3.2)	0 (0.0)
Anemia	3 (9.6)	7 (22.5)
Eosinophilia	1 (3.2)	1 (3.2)
Transient positive Coombs' test	2 (6.4)	3 (9.6)

oral cephalosporin for an additional 1 to 2 months to prevent relapse [11]. This regimen was used as a comparison in this study, because it has been used clinically for pyogenic liver abscess for about 18 years in Taiwan [12]. Its antibacterial activity against pathogens causing pyogenic liver abscess was comparable to that of fleroxacin (data on file, Hoffmann-La Roche). Therefore, a clinical study comparing the 2 different regimens (fleroxacin vs cefazolin + gentamicin/cephalexin) seemed a rational approach.

In both groups, more than 70% of the causative pathogens were eradicated. One patient with *K. pneumoniae* infection in each group was bacteriologic failure associated with clinical improvement. This may be explained by the escape of pathogens from the bactericidal action of antibiotics within the abscess. Other causes of bacteriologic failure in the 2 groups were related to failure to perform PCD.

The rates of clinical cure in the both groups were not significantly different (60% vs 81.8% in the fleroxacin and conventional therapy group, respectively; p=0.29; Table 3). Six cases in the fleroxacin group and 3 cases in the conventional therapy group were clinical failures. The major cause of clinical failures was either failure to drain (2 in fleroxacin group) or inadequate drainage (2 in fleroxacin group, 1 in conventional therapy group). Pigtail catheter drainage is the treatment of first choice for pyogenic liver abscess, because it increases the rate of both bacteriologic cure and clinical success and decreases the mortality and morbidity [12]. Other causes of clinical failures were superinfection (1 in conventional therapy group) and death of suffocation (1 in conventional therapy group). Septic metastatic lesions of *K. pneumoniae*, which is a common complication of *K. penumoniae* liver abscess in Taiwan [9], did not occur in this study.

The proportion of patients with adverse effects was similar in the 2 groups except for anemia, which accounted for 3 (9.6%) and 7 (22.5%) cases in the fleroxacin treatment and the conventional treatment, respectively. Most events were not serious and were generally tolerated. The safety profile of fleroxacin was similar to that reported in the other studies [13,14].

The success rate for fleroxacin therapy (cure plus improvement, 70%) was comparable to that of conventional therapy (cure plus improvement, 85%) in the treatment of pyogenic liver abscess. In addition to its well absorption, long half-life (8-12 h), and the similar kinetics of the oral and intravenous preparations [15], monotherapy with oral fleroxacin once-daily administration in the treatment of pyogenic liver abscess is more convenient, economic, and selective (ie for renal function impairment patients) than conventional therapy. More cases pooled in the clinical evaluation of fleroxacin therapy for *K. pneumoniae* liver abscess is required to confirm this result.

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