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Randomised Double-Blind Study of Norfloxacin and Cefadroxil in the Treatment of Acute Pyelonephritis

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In a coordinated, double-blind multi-centre trial, adults with symptoms of acute pyelonephritis were randomly assigned to receive a two-week course of oral treatment with either 400 mg norfloxacin twice daily or 1 g cefadroxil twice daily. Of 197 patients enrolled in the study, 140 could be evaluated for drug efficacy and 193 for drug safety. Norfloxacin gave a significantly higher bacteriological cure rate than cefadroxil, both at 3 to 10 days (98 % versus 65 %; $p < 0.0001$; 95 % confidence interval (CI) for difference in proportions 21–46 %) and up to eight weeks (87 % versus 48 %; $p < 0.0001$; 95 % CI 25–54 %) after cessation of treatment. The differences between the two regimens were most pronounced in men and in patients with complicating factors such as diabetes mellitus and urinary tract abnormalities. The clinical response during treatment did not differ between the two groups, but symptomatic recurrences at follow-up were more common in the cefadroxil group (28 % versus 3 %; $p < 0.0001$; 95 % CI 14–36 %). Adverse events were more often reported by patients receiving cefadroxil (39 % versus 22 %; $p = 0.011$; 95 % CI 4–30 %) and consisted mainly of gastrointestinal disturbances and vulvo-vaginitis. In terms of bacteriological and clinical efficacy and safety, a two-week course of norfloxacin was superior to a two-week course of cefadroxil for oral treatment of community-acquired acute pyelonephritis.

The efficacy and safety of various antibiotic regimens for treatment of acute pyelonephritis have been infrequently studied in controlled clinical trials. Those studies published (1, 2, 3) have included insufficient numbers of patients to allow definite conclusions about the comparable therapeutic efficacy of the regimens studied.

Norfloxacin is a fluorinated quinolone derivative with excellent activity in vitro against potential uropathogens (4). In earlier comparative studies of lower urinary tract infections (UTI), norfloxacin was shown to be highly effective and well tolerated (5, 6). Cefadroxil belongs to the first generation of cephalosporins (7), drugs which are often used for treatment of both upper and lower UTI (8, 9, 10). This study was undertaken to compare the clinical and bacteriological efficacy and safety of norfloxacin versus cefadroxil in the treatment of adults with community-acquired acute pyelonephritis.

Materials and Methods

Study Design. This study was a coordinated, randomised, double-blind multi-centre trial which was conducted at six departments of infectious diseases in Sweden from March 1986 to July 1987. The study protocol was approved by the ethical review committees at the universities of Göteborg, Lund, Umeå and Uppsala. Informed consent to participate was obtained from all patients.

Patient Selection. Men and women 15 years of age or older with a presumptive diagnosis of acute pyelonephritis (flank pain and/or costo-vertebral angle tenderness and fever ≥ 38.0 °C or chills) and who were not considered to require parenteral antibiotic treatment were eligible for the study. Patients were excluded from enrollment for any of the following reasons: pregnancy; indwelling urinary catheters; known hypersensitivity to quinolones, cephalosporins or penicillin; impaired renal function (estimated creatinine

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clearance < 30 ml/min); known liver disease (serum levels of bilirubin, aminotransferases or alkaline phosphatase more than five times the upper normal levels); concomitant treatment with theophylline; antibiotic treatment within the previous seven days; or previous inclusion in the study.

Clinical Procedures. A detailed clinical history was obtained and physical examination performed upon admission to the study. The infection was classified as sporadic infection (less than two previous episodes of UTI during the last six months or less than three during the last 12 months) or as recurrent infection. The current episode was also classified as uncomplicated or complicated (known functional or structural abnormalities of the urinary tract, renal scarring, urolithiasis or diabetes mellitus). Patients were subjected to intravenous urography unless this had been performed during the preceding three years. Patient management was on an outpatient basis although two-thirds of the patients were initially hospitalised at the discretion of the clinican.

Using randomisation lists in blocks of four at each study centre, patients were assigned to receive a 14-day course of oral treatment with either 400 mg norfloxacin twice daily, or 1 g cefadroxil twice daily. Blinding was achieved with the double-dummy technique. Compliance was ascertained by inquiry and by counting the amount of unused trial drug at the first follow-up visit after treatment. To assess safety of the drugs, and clinical and bacteriological responses, patients were scheduled for three return visits after 3 to 5 days of treatment, and 3 to 7 days and 4 to 6 weeks after completion of treatment. The resolution of symptoms was evaluated at each visit. The body temperature was measured twice daily until normal (< 38.0 °C).

Laboratory Procedures. Voided midstream urine samples for culture were obtained within 72 hours prior to treatment and at each follow-up visit. After collection, urine specimens were kept at 4 °C until examined. The urine was cultured semiquantitatively using the calibrated loop technique. Significant growth was defined as $\geq 10^5$ CFU/ml urine for gram-negative bacteria and $\geq 10^4$ CFU/ml for *Staphylococcus saprophyticus*. Urine samples containing more than two bacterial species were considered contaminated. Blood specimens for culture were obtained before treatment from most of the hospitalised patients.

After initial screening for sensitivity to trial drugs, isolated bacteria were kept in deep agar. All isolates were identified by standard methods. O and K serotyping of *Escherichia coli* strains was performed as previously described (11). Antimicrobial susceptibility testing was performed by the disc diffusion method (12), using discs containing norfloxacin (10 µg) or cefadroxil (30 µg) (AB Biodisk, Sweden). MICs were determined using an agar dilution technique (12). The breakpoints used for classification of strains in the sensitive, intermediate and resistant categories, respectively, were for norfloxacin 1 mg/l (zone diameter 21 mm) and 16 mg/l (10 mm), and for cefadroxil 4 mg/l (23 mm) and 16 mg/l (17 mm).

Assessment of Efficacy. To be included in the bacteriological analysis, patients must have met the inclusion criteria; have had significant bacteriuria with a pathogen in the sensitive or intermediate category for both trial drugs which was verified by culture no more than 72 hours before treatment started; have taken the trial drug for at least the first seven days; and have delivered at least one follow-up urine culture no earlier than three days post-treatment. Concomitant treatment with other antimicrobial drugs was not allowed. Patients who received the trial drug for less than seven days because of clinical failure were considered evaluable for efficacy.

The end-points for assessment of bacteriological efficacy were defined as cure (elimination of the infecting strain and no recurrence of bacteriuria during follow-up), relapse (post-treatment bacteriuria with the same organism as that originally isolated) or reinfection (post-treatment bacteriuria with an organism different from that originally isolated). In case of *Escherichia coli* infection, serotyping made it possible to differentiate between relapse and reinfection. Results are given as short-term efficacy (3 to 10 days post-treatment) and cumulative efficacy (3 to 56 days post-treatment).

Assessment of Safety. All patients who had received at least one dose of trial drug and for whom follow-up data were available, were included in safety assessments. Adverse experiences were reported spontaneously by the patient and were also recorded by asking the patient a non-leading question about unusual events during the treatment. Adverse events were classified as mild, moderate or severe.

Statistical Analysis. Assuming a short-term bacteriological cure rate of 70 % for both treatment regimens, a type I (α) error of 0.05, and a type II (β) error of 0.2, 170 evaluable patients were required to exclude that one of the two drugs was more than 20 %-units less effective than the other based on a two-tailed chi-square test (13). Assuming that an estimated 25 % of randomised patients would for various reasons be excluded from the efficacy analysis, it was planned to enroll a total of 220 patients in the study. Differences in proportions between groups were compared using a two-tailed chi-square test as well as two-sided 95 % confidence intervals (CI). Mantel-Haenszel tests were used to compare the cure rates adjusted for the centre. Possible differences in cure rates between centres were investigated using the Breslow-Day test for homogeneity of the odds ratios. All analyses were made before the randomisation code was broken.

Results

Study Population. A total of 197 patients were enrolled in the study. The number of patients enrolled at each centre varied between 12 and 60. Demographic data were similar for both treatment groups (Table 1). Of the 140 patients who could be evaluated for drug efficacy, 28 (20 %) were men. Fifty-seven (29 %) randomised patients were excluded from the efficacy analysis (Table 1), the main reason for exclusion being a negative pretreatment urine culture. In most of these cases the initial diagnosis of acute pyelonephritis turned out to be wrong, and treatment with the trial drug was therefore discontinued. Six patients had low-count bacteriuria (3×10^3–75×10^3 CFU/ml), thus not fulfilling the criteria for assessment of efficacy. However, four of these patients were cured (two received norfloxacin and two cefadroxil), one was infected with a strain resistant to cefadroxil, and one did not return for follow-up. Eleven patients who were seriously ill with vomiting and/or circulatory

Table 1: Characteristics of patients and reasons for exclusion from efficacy analysis.

	Norfloxacin group (n = 99)	Cefadroxil group (n = 98)
Patients valid for safety analysis	97	96
Patients valid for efficacy analysis	71	69
Mean age in years (range	49.5 (16–80)	49.6 (17–87)
Male/female	16/55	12/57
Type of infection (%)		
Sporadic	55 (77)	52 (75)
Recurrent	15 (21)	17 (25)
Unknown	1 (1)	0
Uncomplicated	52 (73)	53 (77)
Complicated	19 (27)	16 (23)
No. (%) with fever ≥ 39.0 °C	46 (65)	39 (57)
No. (%) with positive blood cultures	5/38 (13)	10/43 (23)
Reasons for non-evaluation		
Negative initial urine culture	13	9
No significant bacteriuria	3	3
Initial pathogen resistant to cefadroxil	4	6
Premature discontinuation of treatment[a]	6	7
Other reasons[b]	2	4

[a]Change to parenteral antibiotic therapy due to serious illness or vomiting (11), adverse drug reaction (1), or patient refusal to continue (1).
[b]No pyelonephritis (2), no follow-up visit (2), indwelling urinary catheter (2).

disturbances were withdrawn from the study after having taken only a few doses of the trial drug. They required intravenous administration of antibiotics and may thus be regarded as early treatment failures. Compliance was excellent. All but two evaluable patients, one in each group, completed the 14-day course of treatment.

An abnormal intravenous urogram was reported in 18 % of the 123 patients investigated. Of patients with complicated infections, 11 were diabetics and 24 had urinary tract abnormalities (renal scarring (7), renal calculi (7), hydronephrosis and/or ureter dilatation (5), duplication of the collecting system (4), renal cysts (3), bladder diverticulum (1), ureterocele (1) and residual urine (2)). Some patients had more than one abnormality.

Microbiological Findings. Escherichia coli was the predominant urinary pathogen, accounting for 89 % of the initial isolates (Table 2). Blood samples for culture were obtained from 81 (58 %) patients valid for efficacy analysis and yielded bacterial growth in 15 (19 %) cases. In these patients bacteria of the same species, and same serotype in the case of *Escherichia coli*, were recovered from concurrent blood and urine samples. Bacteremia was demonstrated in 23 % of the patients in the cefadroxil group and in 13 % of those treated with norfloxacin (Table 1).

Table 2: Bacteria isolated from pretreatment urine cultures.

Organism	Norfloxacin (n = 71)	Cefadroxil (n = 69)
Escherichia coli	64	62
Klebsiella spp.	4	2
Staphylococcus saprophyticus	2	5
Proteus vulgaris	1	0
Enterococcus faecalis	0	1[a]

[a]Mixed infection with *Klebsiella oxytoca*.

There was full agreement between the results of susceptibility testing with the disc diffusion method and the MICs. Of the urinary isolates from all randomised patients, none was resistant to norfloxacin while ten were resistant to cefadroxil. In the patients who could be evaluated for efficacy, the range of MICs for gram-negative bacteria was ≤ 0.03–1.0 mg/l and 8–16 mg/l for norfloxacin and cefadroxil, respectively. Ninety per cent of isolates had MICs of ≤ 0.06 and ≤ 16 mg/l, respectively. For the seven strains of *Staphylococcus saprophyticus* the MICs of norfloxacin ranged from 2 to 4 mg/l and those of cefadroxil from ≤ 2 to 4 mg/l. None of the strains causing recurrent infection developed resistance to any of the trial drugs.

Table 3: Bacteriological outcome according to sex and complicating factors.

	No. (%) of patients					
	Norfloxacin			Cefadroxil		
	Cure	Relapse	Reinfection	Cure	Relapse	Reinfection
Short-term efficacy[a]	64 (98)	0	1 (2)	41 (65)	21 (33)	1 (2)
Male	16 (100)	0	0	3 (27)	8 (73)	0
Female	48 (98)	0	1 (2)	40 (77)	11 (21)	1 (2)
Type of infection						
Uncomplicated	45 (98)	0	1 (2)	38 (78)	11 (22)	0
Complicated	19 (100)	0	0	5 (36)	8 (57)	1 (7)
Cumulative efficacy[b]	62 (87)	4 (6)	5 (7)	33 (48)	32 (46)	4 (6)
Male	14 (88)	1 (6)	1 (6)	3 (25)	9 (75)	0
Female	48 (87)	3 (6)	4 (7)	30 (53)	23 (40)	4 (7)
Type of infection						
Uncomplicated	46 (88)	3 (6)	3 (6)	29 (55)	21 (40)	3 (6)
Complicated	16 (84)	1 (5)	2 (11)	4 (25)	11 (69)	1 (6)

[a] 3 to 10 days post-treatment. Note that in some patients the first post-treatment follow-up was so late that these patients only appear in the cumulative results.
[b] 3 to 56 days post-treatment.

Bacteriological Outcome. No patient had significant bacteriuria at the visit 3 to 5 days after start of treatment. The short-term cure rate was 98 % and 65 % in the norfloxacin and cefadroxil groups, respectively ($p < 0.0001$; 95 % CI for difference in proportions 21–46 %; Table 3), while the cumulative cure rate up to 56 days after cessation of treatment was 87 % and 48 %, respectively ($p < 0.0001$; 95 % CI 25–54 %). The differences remained when patients were stratified according to important prognostic factors (Table 3). Comparable results were obtained at all participating centres.

Among patients who received norfloxacin, there were no differences in bacteriological cure rates with respect to gender or the occurrence of complicating factors. In the cefadroxil group, however, the cure rate was low in males and in patients with complicated infections, both with regard to short-term efficacy (27 % and 36 %) and cumulative efficacy (25 % each). Of the patients with positive blood cultures, five (100 %) in the norfloxacin group and six (60 %) in the cefadroxil group were seen to be cured at short-term follow-up. The difference in bacteriological outcome between the two regimens was attributed to a high frequency of relapses in the cefadroxil group, most of which occurred within ten days of cessation of treatment. In contrast, no patient who received norfloxacin experienced early bacteriological relapse. Regardless of the treatment given, all patients with pyelonephritis caused by *Staphylococcus saprophyticus* were cured.

Clinical Outcome. The clinical response after 3 to 5 days' treatment was the same in both groups (38 % of the patients were clinically cured, 59 % were improved and 3 % had persisting symptoms). The median time for resolution of fever (< 38.0 °C) was three days. Symptomatic recurrences were, however, more common in the cefadroxil group (28 % versus 3 %; $p < 0.0001$; 95 % CI 14–36 %; Table 4). Thirteen of 19 symptomatic recurrences occurred within ten days after treatment, in three cases manifesting as relapsing acute pyelonephritis.

Safety Assessments. Only four of 197 randomised patients could not be assessed for safety. Adverse events were reported by 22 % of the patients in the norfloxacin group and by 39 % of those in the cefadroxil group ($p = 0.011$; 95 % CI 4–30 %; Table 5). The difference was mainly due to a high frequency of gastro-

Table 4: Clinical recurrence pattern during follow-up. Each patient with a recurrence is represented only once.

Type of recurrence	No. (%) of patients	
	Norfloxacin (n = 71)	Cefadroxil (n = 69)
Asymptomatic bacteriuria	7 (10)	17 (25)
Acute cystitis	1 (1)	15 (22)
Acute pyelonephritis	1 (1)	4 (6)

Table 5: Adverse reactions. Some patients reported more than one adverse event.

	Norfloxacin (n = 97)	Cefadroxil (n = 96)
No. reporting adverse events	21	37
No. discontinuing treatment[a]	3	1
Type of adverse events		
Gastrointestinal disorders	13	30
Vulvo-vaginitis	0	8
Exanthema	2	1
Central nervous system disorders	6	2
Others	5	7

[a]Reactions reported spontaneously.

intestinal disturbances (nausea, loose stools and diarrhoea) and vulvo-vaginitis among patients in the cefadroxil group. The symptoms were described as mild in 63 % and 69 % of cases in the norfloxacin and cefadroxil groups, respectively. Three norfloxacin-treated patients discontinued treatment because of urticaria (1), double-vision and headache (1), and exanthema with nausea (1), and one in the cefadroxil group because of stomatitis and vulvo-vaginitis.

Discussion

In this controlled, randomised multi-centre trial, a two-week course of norfloxacin proved superior to a two-week course of cefadroxil for oral treatment of community-acquired acute pyelonephritis, both in terms of clinical and bacteriological outcome and tolerance. There was no obvious selection bias accounting for these differences. Owing to the large number of patients enrolled in the study, the two treatment groups were well matched for underlying factors that might have adversely influenced the therapeutic response. Among study patients in whom blood cultures were performed, bacteremia was more often demonstrated in those treated with cefadroxil. Bacteremia is, however, a common finding in acute uncomplicated pyelonephritis which does not seem to affect the outcome of treatment (14). Norfloxacin was highly effective, regardless of the presence of complicating factors such as male gender, diabetes mellitus or urinary tract abnormalities. Indeed, at short-term follow-up all patients who received norfloxacin were cured of their renal infection, and only one woman experienced bacteriologically proven reinfection (acute cystitis due to *Staphylococcus saprophyticus*). Up to 56 days after completion of treatment, 87 % of the patients were still demonstrated bacteriologically to be cured.

The cure rate with norfloxacin is similar to that obtained after two weeks' treatment with trimethoprim-sulphamethoxazole (2). Although based on small numbers of patients, previous studies of treatment of acute pyelonephritis with β-lactam antibiotics such as ampicillin (2), pivampicillin (1) and the combination pivampicillin/pivmecillinam (1, 3) yielded cure rates varying from 52 % to 69 %, which agrees with the results achieved with cefadroxil in the present study.

There are several possible explanations for the high relapse rate found in patients treated with cefadroxil. Firstly, the slow bactericidal activity of oral cephalosporins (7) may possibly enhance bacterial survival and persistence at the site of infection. Maximum rates of bacterial killing occur at concentrations about four times the MIC (7). Therefore, average peak serum levels of 33 mg/l after oral administration of 1 g of cefadroxil (15) in conjunction with MICs of 8–16 mg/l for gram-negative strains isolated suggests that renal tissue concentrations might have been inadequate for efficient clearance of the infection. In addition, high urine concentrations of an antibiotic do not necessarily reflect concomitant drug levels in the renal parenchyma, as shown for ampicillin and cephalothin in experimental acute pyelonephritis (16). Secondly, although not proven, relapse after treatment with β-lactam antibiotics may be due to survival of spheroplasts of the original strain in the hypertonic environment of the renal medulla (17). Thirdly, after successful eradication from the urinary tract, the originally infecting strain may have remained in the faecal and/or periurethral flora (18, 19), allowing rapid recurrence when no more active drug was present in the urine.

In contrast to β-lactams (9), fluorinated quinolones such as norfloxacin rapidly eliminate *Enterobacteriaceae* from the faecal reservoir as well as from the periurethral area during therapy (20, 21). Re-establishment of the normal faecal flora occurs about two weeks after discontinuation of treatment with norfloxacin (21). Accordingly, in the short term, norfloxacin may have an advantage over cefadroxil in reducing both relapses and reinfections. Furthermore, norfloxacin is rapidly bactericidal at concentrations close to the MIC (22) and has a maximum killing effect at 1.5 mg/l (22), a concentration which is readily attainable in kidney tissue following oral doses of 400 mg of norfloxacin (23, 24).

Recurrences in men are usually relapses (25) which in the absence of urinary tract abnormalities are frequently associated with a

persisting bacterial focus in the prostate gland (25). In contrast to oral β-lactams, the fluorinated quinolones penetrate well into the prostate and achieve high tissue levels (23). This may possibly explain the marked differences in the long-term cure rate between men treated with norfloxacin (88 %) and cefadroxil (25 %).

Although three patients discontinued treatment due to adverse reactions, norfloxacin was well tolerated. The spectrum of adverse experiences was comparable with that observed in earlier clinical trials in patients with UTI (5, 6). The high frequency of gastrointestinal intolerance and vulvo-vaginitis reported by patients receiving cefadroxil may in part be attributed to unfavourable effects on the indigenous bacterial flora.

In view of its broad antimicrobial spectrum of activity, extremely low MICs for common uropathogens, favourable ecological properties and safety profile, norfloxacin seems to offer advantages in the therapy of both complicated and uncomplicated acute pyelonephritis. Even in patients with documented bacteremia, norfloxacin appears to provide a safe and effective means of therapy and should be considered as a convenient alternative to parenteral agents. The results of this and previous studies (1, 2, 3) strongly argue against the use of β-lactams as drugs of first choice for oral treatment of renal infections. This study also confirms that periods of treatment of more than two weeks are unnecessary for most patients with community-acquired acute pyelonephritis, provided norfloxacin or trimethoprim-sulphamethoxazole (2) is prescribed. Whether shorter courses are as effective should be ascertained in controlled, comparative trials including sufficiently large numbers of patients to ensure adequate statistical analysis.

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