

Study on the efficacy of cefaclor for the treatment of asymptomatic bacteriuria and lower urinary tract infections in pregnant women with a history of hypersensitivity to penicillin

K. Stamatiou¹, A. Alevizos³, G. Petrakos², I. Lentzas³, M. Papathanasiou³,
A. Mariolis³, P. Panagopoulos², F. Sofras⁴

¹Department of Urology, Tzaneion General Hospital, Piraeus,

²Department of Obstetrics and Gynecology, Tzaneion General Hospital, Piraeus, ³Health Center of Vyronas, Athens

⁴Department of Urology, University of Crete, Herakleion (Greece)

Summary

Purpose: The purpose of this study was to compare the efficacy and safety profile of twice daily versus the conventional three daily intake of cefaclor administrated orally for five to seven days in the treatment of asymptomatic bacteriuria or acute cystitis in pregnant women with a history of hypersensitivity to penicillin. **Methods:** Between August 2003 and August 2004, 63 pregnant women with a positive urine culture and a history of suspicion of hypersensitivity to penicillin were randomly divided into two groups. The women in the first group received 500 mg of cefaclor while those in the second group received 750 mg of cefaclor for five to seven days. Laboratory and clinical results were assessed a week and a month after completion of the therapy. **Results:** Final therapy (bacteriologic eradication) succeeded in 93.7% (30/32) of the first group and in 90.3% (28/31) of the second group. **Conclusion:** Dosage of cefaclor at 750 mg is as effective as conventional cefaclor at 500 mg and better tolerated.

Key words: Uncomplicated urinary tract infection; Hypersensitivity to penicillin; Pregnancy.

Introduction

Lower urinary tract infections (LUTI) are a frequent implication of pregnancy and are present in between 2.5 to 9% of normal pregnancies. Their manifestation in healthy pregnant women with an anatomically normal genitourinary tract depends on the frequency of bacteriuria [1]. The last is one of the most frequent conditions in pregnancy and its impact accounts for 5-15% of pregnant women [2]. Bacteriuria in pregnancy is normally asymptomatic while LUTI are characterized by frequency, hesitancy and nocturia. Both bacteriuria and LUTI are considered important when more than 10⁵ colonies of bacteria are present in the urine culture and if left untreated they lead to pyelonephritis which is associated with poorer pregnancy outcomes [3-5]. The most common uropathogens isolated and identified from women with acute uncomplicated episodes of LUTI are members of the enterobacteria group, with 80% of community-acquired infections caused by *Escherichia coli* [6]. The second most common cause of LUTI is *Staphylococcus saprophyticus*, particularly in younger pregnant women. Other common uropathogens include enterococci and gram-negative bacteria as *Klebsiella* and *Proteus*. A definition of the optimal antimicrobial agent for the treatment of asymptomatic bacteriuria or uncomplicated UTI in pregnant women is controversial. Proper-

ties of an antibiotic that influence its suitability as a therapy for UTI include: its concentration in the urine (ability to achieve high and prolonged urinary concentrations to guarantee bactericidal activity), its concentration in vaginal secretions, its spectrum of activity against infecting organisms, its half life, its safety, and its cost. Important factors in the choice of empiric therapy of uncomplicated UTI in pregnant women to consider are: toxicity, clearance (pregnant women have increased GFR), special patterns of microbial resistance (dilatation and stasis) tolerability (several pregnant women present gastrointestinal dysfunction), and patient convenience (frequency of dosing). Although ampicillin is considered the first choice for short term therapy of urinary tract infections, history of hypersensitivity to penicillin constitutes a serial limitation to its use. The restrictions on use of TMP/SMX (because of the risk of teratogenesis if used during the first trimester while kernicterus of the neonate if used in the third semester) as well as the restrictions on use of ciprofloxacin (should be avoided because of their possible effects on fetal bone growth), tetracycline (because of risk of damage to the fetus liver) and/or the resistance in one of the aforementioned antimicrobial agents results in a shift towards empiric antimicrobial therapy based on cephalosporins. Although cephalosporins of first generation are not efficient in the treatment of UTI, cephalosporins of second and third generations as well as cefaclor have been considered an efficient second choice.

Patients and Methods

Pregnant women were eligible for enrollment if they were between the ages of 18 and 40 years old, had a primary diagnosis of acute uncomplicated UTI, and could be treated on an outpatient basis. Each patient had to have a positive culture in ordinary screening urinalysis or had to show more than two of the characteristic signs or symptoms suggestive of an acute uncomplicated UTI (dysuria, frequency, urgency, nocturia, suprapubic pain), with an onset of symptoms within 72 hours of enrollment. At enrollment, a clean-catch midstream urine specimen was obtained from each patient. A positive culture was defined as isolation of the uropathogen in quantities $> 10^5$ colony-forming units/ml of urine. The primary exclusion criteria were history of cefaclor hypersensitivity, history of cross hypersensitivity between penicillin and cephalosporin, and no previous use of cefaclor, suspicion of complicated UTI (e.g., presence of fever, flank pain, known urologic structural abnormality), symptoms of a UTI within the previous four weeks, > 3 previous UTIs within the past year, evidence of predisposing factors to UTI (e.g., calculi, stricture), use of another systemic antimicrobial agent within 48 hours before enrollment, ingestion of sucralfate or a cation-containing antacid < 6 hours before or < 2 hours after administration of study drug, and serum creatinine level > 3.0 mg/dl or creatinine clearance < 30 ml per min/1.73 m². Patients were assessed three times during the study: at the pretreatment visit, the test-of-cure visit (7 days after completion of therapy) and the late follow-up visit (30 days after completion of therapy). Antimicrobial effectiveness was assessed in terms of conventional clinical and laboratory determinations, including serial urine cultures from clean-catch midstream specimens. Bacteriologic response at the test-of-cure visit was the primary efficacy variable. Identification of causative organisms and susceptibility testing were performed in our hospital laboratory. Tolerability was monitored by information obtained by each patient, measurement of vital signs, urinalysis, and routine serum testing. Adverse events were classified according to their severity as mild, moderate, or severe. Adverse events were recorded through the test-of-cure visit, and serious adverse events were recorded through the late follow-up visit. Validation of drug efficiency has been supported on the basis of the following criteria: diagnosis of UTI confirmed by clinical signs and symptoms, positive culture from a pretreatment clean-catch mid-stream urine specimen for an infecting organism (with a count $> 10^5$ CFU/ml), study drug administered for a minimum of five and a maximum of seven days, and patients who received no other concomitant antimicrobial agent with activity against the causative organism. The bacteriologic response was assessed based on a comparison of the results of urine culture performed before treatment and at the test-of-cure and late follow-up visits. At the test-of-cure visit, bacteriologic outcomes were categorized as *eradication* ($< 10^4$ CFU/ml of original uropathogen), *persistence* ($> 10^4$ CFU/ml of original uropathogen), *superinfection* ($> 10^5$ CFU/ml of a uropathogen other than the original pathogen at any time during active therapy), *new infection* ($> 10^5$ CFU/ml of a uropathogen other than the original pathogen at any time after the end of active therapy), or *indeterminate* (not evaluable for any reason, such as no post-treatment culture). At the late follow-up visit, bacteriologic outcomes were categorized as *continued eradication* ($< 10^4$ CFU/ml of original uropathogen at the test-of-cure and late follow-up visits), *persistence* (as before), *superinfection* (as before), *recurrence* ($< 10^4$ CFU/ml of original organism at the test-of-cure visit, but $> 10^4$ CFU/ml of the same organism before or at the late follow-up visit), *new infection* (as before),

or *indeterminate* (as before). The clinical outcome was evaluated based on serial assessments of the effect of therapy on the signs and symptoms of UTI (dysuria, frequency, urgency, and suprapubic pain). At the test-of-cure visit, the clinical response was categorized as *cure* (disappearance of or improvement in signs and symptoms of the infection such that additional antimicrobial therapy was not required), *failure* (no apparent response to therapy, persistence of signs and symptoms of infection, reappearance of signs and symptoms at or before the test-of-cure visit, or use of additional antimicrobial therapy for the current infection), or *indeterminate* (could not be evaluated). At the late follow-up visit, the clinical response was classified as *continued cure* (continued absence of or improvement in all signs and symptoms of infection such that additional antimicrobial therapy was not needed), *failure* (patients with a response of *failure* at the test-of-cure visit carried forward), *relapse* (reappearance of signs and symptoms of original infection requiring antimicrobial therapy in a patient with a response of cure at the test-of-cure visit), or *indeterminate* (could not be evaluated). In addition to the assessment of the bacteriologic and clinical responses in all patients who were valid for efficacy analysis, an intent-to-treat analysis was conducted including all patients who received the study drug. Urine samples were obtained from a subset of patients from our institution for determination of cefaclor concentrations. Samples were collected at the end of the dosing interval. A 10-ml urine sample was collected and stored in a polypropylene vial at -20°C . The laboratory analyzed urine samples for cefaclor concentrations using a validated high-performance liquid chromatography assay. Parametric and non parametric analyses were used to determine the statistical significance of this study.

Results

The intent-to-treat population consisted of 92 patients (46 cefaclor at 750 mg, 46 cefaclor at 500 mg), of whom only 63 could be evaluated for efficacy (32 cefaclor at 750 mg and 31 cefaclor at 500 mg). Of the 29 patients not valid for efficacy, nine were excluded because no causative organism was isolated in sufficient quantity, seven used concomitant antimicrobial agents before treatment and the remaining 13 patients were prematurely discontinued from the study or lost to follow-up. There were no statistically significant differences between the two treatment groups with respect to age (mean age, 32 years), health status, or presence of concomitant diseases. More than two thirds of patients reported no history of a UTI within the past year. The majority of patients reported having symptoms of the current UTI for two to three days. Overall, urinary frequency and nocturia were the most common symptoms, followed by urgency, dysuria, and suprapubic pain. Most patients reported that the intensity of their symptoms was mild to moderate. The most common pretherapy uropathogens were *E coli* (27 cefaclor - 750 mg, 29 cefaclor - 500 mg), *Enterococcus faecalis* (2 cefaclor - 750 mg, 1 cefaclor - 500 mg), *Klebsiella pneumoniae* (1 cefaclor - 750 mg), *Proteus mirabilis* (2 cefaclor and 1 cefaclor - 500 mg). Most of all pretherapy isolates were found to be susceptible to cefaclor (minimum inhibitory concentration [MIC] < 1 mg/l). One isolate of *E coli* from the cefaclor 750 mg group was resistant to cefaclor (MIC 16 mg/l). Bacterio-

logic eradication was achieved in 93,75% (30/32) of the cefaclor 750 mg group and 90.3% (28/31) of the cefaclor 500 mg group. It is noteworthy that at the initial visit the cefaclor 500 group had a slightly higher clinical success rate than the cefaclor 750 group which was not statistically significant. Most adverse events like abdominal pain, nausea, vomiting and, diarrhea (reported on day 5) were mild or moderate and were more evident in the second group. All these events resolved or improved. No serious adverse events were reported.

Discussion

Asymptomatic bacteriuria and acute cystitis in pregnant women are probably not dissimilar to the rate of uropathogens in non pregnant women of the same age [7] but even if uncomplicated and non progressive they are associated with poorer pregnancy prognosis. Thus there is no doubt that they need to be properly treated. Antimicrobial choices for such treatment in pregnant women with a history of hypersensitivity to penicillin are few (mostly second and third generation cephalosporines). Efficacy in terms of total eradication of bacteria is very high in both forms (500 and 750 mg). The only problem is that they need an interval of at least five days to act effectively. Since short courses of therapy (3 days) have been recommended (since the last decade) for acute episodes of uncomplicated UTI in both pregnant and non pregnant women it is possible that treatment with cefaclor could be insufficient if given for less than seven days. This finding is in accordance with some authors [8]. According to other authors the duration of treatment in pregnant women is controversial [9]. Although trials have failed to show any benefit of longer courses (4-7 days) of antibiotics, over short courses (1-3 days) the limitation of choices in pregnant women with a history of hypersensitivity to penicillin renders a longer, definitive therapy necessary. Several authors have recommended that antibiotics should be used for between four to seven days [10].

Conclusion

The results of this trial add to the evidence that cefaclor is a well-tolerated antimicrobial agent with a good safety profile. The efficacy and tolerability of 750 mg of cefaclor administered for seven days to pregnant women with a history of hypersensitivity to penicillin as treatment for acute uncomplicated asymptomatic bacteriuria and LUTI were comparable to those of conventional cefaclor (500 mg) administered for seven days. Furthermore the twice-daily formulation exhibited a safety profile similar to that of 500 mg of cefaclor.

References

- [1] Millar LK., Cox SM.: "Urinary tract infections complicating pregnancy". *Infect. Dis. Clin. North. Am.*, 1997, 11, 13.
- [2] Andrews W., Cox S., Gilstrap L.: "Urinary tract infections in pregnancy". *Int. Urogynecol. J.*, 1990, 1, 155.
- [3] Cattell R.: "Urinary tract infection: Definitions and classifications". In: Cattell R. (ed.). "Infections of the Kidney and Urinary Tract". London, Oxford University Press, 1996.
- [4] Little P.: "Prevention of pyelonephritis in pregnancy". *Lancet*, 1965, 1, 567.
- [5] Romero M., Oyarzun E., Mazor M.: "Meta analisis of the relationship between asymptomatic bacteriuria and preterm delivery/ low birth weight". *Obstet. Gynecol.*, 1989, 73, 576.
- [6] Kariowsky J.A., Jones M.E., Thornsberry C. *et al.*: "Prevalence of antimicrobial resistance among urinary tract pathogens isolated from female outpatients across the US in 1999". *Int. J. Antimicrob. Agents.*, 2001, 18, 121.
- [7] Meis P.J., Michielutte R., Peters T.J.: "Factors associated with preterm birth in Cardiff, Wales". *Am. J. Obstet. Gynecol.*, 1995, 173, 597.
- [8] Orenstein R., Wong E.: "Urinary tract infections in adults". *Am. Fam. Phys.*, 1999, 59, 1225.
- [9] Gupta K., Scholes D., Stamm W.E.: "Increasing prevalence of antimicrobial resistance among uropathogens causing acute uncomplicated cystitis in women". *JAMA*, 1999, 281, 736.
- [10] Patterson T., Andriole V.: "Detection significance and therapy of bacteriuria in pregnancy. Update in the managed health care era". *Infect. Dis. Clin. North Am.* 1997, 11, 593.

Address reprint requests:
P. PANAGOPOULOS, Ph.D.
69 Lasithiou Str.
16679 Glyfada (Greece)