Roxithromycin and Erythromycin in Chlamydia-negative Non-gonococcal Urethritis

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The clinical efficacy and safety of roxithromycin 300 mg once a day was compared with that of erythromycin 500 mg twice a day in 87 men with chlamydia-negative non-gonococcal urethritis. In the roxithromycin group the clinical efficacy rate was 88% on day 8 and between 78% and 84% on day 21. In the erythromycin group the clinical efficacy rate was 98% on day 8 and 86% on day 21, a non-significant difference. Side effects were mainly gastrointestinal, occurring in about 15% of patients receiving each treatment.

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About half of all cases of non-gonococcal urethritis (NGU) are caused by *Chlamydia trachomatis* (1), whereas it has been difficult to isolate causative agents in the majority of chlamydia-negative NGU cases. *Ureaplasma urealyticum* (2), *Trichomonas vaginalis* (3), herpes simplex virus (3) and perhaps some anaerobic microorganisms (4) appear to account for some of the cases. The best treatment for chlamydia-positive (C+) and for chlamydia-negative (C−) NGU is tetracycline or erythromycin. Recently we found that roxythromycin, a new macrolide, was as efficacious as erythromycin for treating genito-urinary chlamydial infections in both men and women (5), and that it had the advantage that treatment is by a single daily dose.

In this study the efficacy and safety of roxithromycin 300 mg a day was compared with that of erythromycin 500 mg twice a day, both for 7 days, in patients with C− NGU.

MATERIAL AND METHODS

During a 4-month period, all men attending the outpatient venereal disease clinic of Copenhagen with symptoms and signs of urethritis (urethral discharge and dysuria) were asked to participate in the study if a methylene-blue-stained smear of urethral exudate contained more than five polymorphonuclear leucocytes per high-power microscope field (×1000) and no intracellular diplococci.

Patients who had received antibiotics within the last 3 days, patients in whom cultures for *Chlamydia trachomatis* (6) and/or *Neisseria gonorrhoeae* were found positive, patients with penile lesions of genital herpes simplex, patients with a history of hypersensitivity to macrolide antibiotics and patients with severely impaired hepatic or renal function were excluded.

The patients were randomly assigned to a double-blind, double-dummy trial, comparing roxithromycin 300 mg once a day with erythromycin ethylsuccinate 500 mg twice a day for 7 days.

The patients were asked to return for clinical assessments on day 8 and day 21 after the start of the treatment. Laboratory tests (haematology, liver and kidney function tests and urine analysis) were performed before entering the study and again at the first follow-up visit. Patients' complaints of urethral discharge and pain were registered before entering the study and again at both follow-up visits. Clinical efficacy was based on lack of symptoms and urethral discharge with leukocytes. If symptoms and signs of urethritis were still present on day 8, the patient was treated with tetracycline 500 mg twice a day for 7 days. Sexual partners of the patients were not treated epidemiologically. The results were compared statistically by the χ^2-test or Fisher's exact test.

RESULTS

Altogether 87 men with C− NGU were enrolled in the study. In the roxithromycin (R) group 43/45 men were evaluable on day 8 and 41/45 men on day 21 and in the erythromycin (E) group 40/42 men were evaluable on day 8 and 37/42 men on day 21. Those evaluable had taken the complete course of the drug, returned for the follow-up visits and had not been treated with any other medication that could confuse the results.

Of those excluded on day 8, one patient in each treatment group failed to attend any follow-up visit, one patient in group R did not complete the treatment, and one patient in group E stopped taking the medication due to side effects. Furthermore 2 patients in group R and 3 in group E did not attend the last follow-up visit.

Clinical efficacy

The clinical efficacy rate was 88% (38/43) in group R and 98% (39/40) in group E on day 8.

On day 21 the clinical efficacy rate ranged between 78% (32/41) and 84% (32/38) in group R,

depending upon inclusion or exclusion of the 3 persons who reported that the symptoms recurred after contact with their sexual partner. In group E there was a clinical efficacy rate of 86% (32/37) on day 21. None of the failures in group E had had any sexual contacts during the study period. The difference between the clinical cure rates was not significant ($p > 0.05$).

Side effects

The most common side effects were gastrointestinal complaints, including abdominal pain and nausea, which were recorded in 15% of the patients receiving roxithromycin and in 16% of those receiving erythromycin. Other minor side effects such as tiredness, headache and slight itching were registered equally often in 1–5% of the patients receiving either treatment regimen. One patient in group E discontinued the treatment due to gastrointestinal complaints. None of the other recorded side effects necessitated discontinuation of the treatment.

Laboratory tests

One patient who was treated with roxithromycin, and had normal results before treatment, showed an increased serumglutamyl-transferase (SGOT) value. The patient had no known history of liver disease, and the other liver function tests were normal. None of the other patients tested showed any signs of haematological, renal or hepatic toxicity during treatment.

DISCUSSION

Tetracycline and erythromycin are the preferred treatments for both chlamydia-positive and chlamydia-negative NGU. The fact that C− NGU responds to antibiotic treatments gives cause to believe that the complaint is provoked by one or more transmissible microorganisms.

Ureaplasma urealyticum may be the cause of a small but uncertain proportion of C− NGU (2, 3, 7). *Trichomonas vaginalis* and herpes simplex virus may account for a small percentage (3) and, as shown recently, *Bacteroides ureolyticus* and perhaps some other anaerobes may play a significant role in a small proportion of C− NGU cases (4). In the majority of C− NGU cases, however, causative microorganisms cannot be proved and the condition is defined on the basis of patients' complaints and the clinical findings of urethritis. It must be mentioned, however, that a number of the so-called C− NGU cases may still be caused by *Chlamydia trachomatis*, as not even the culture method can detect all chlamydial infections.

The clinical efficacy rate of tetracycline in patients with C− NGU is equal to (8) or somewhat lower (9) than that found in patients with C+ NGU. The efficacy rate of erythromycin has been less extensively studied in patients with C− NGU but in a few studies it was found as efficacious as tetracycline (10, 11).

In an open study (12), the new macrolide roxithromycin gave clinical cure rates of 90% when given to patients with C+ and C− NGU. Recently we showed that roxithromycin appears to be as safe and efficacious as erythromycin for treating chlamydial infections in both men and women (5).

In the present study roxithromycin 300 mg/day also seemed to be as safe and as efficacious as erythromycin 500 mg twice a day for treating men with C− NGU. The advantage of the less frequent administration of treatment for patient compliance has been pointed out in another study (13).

The side effects were mainly gastrointestinal and were recorded in about 15% of the patients, irrespective of the treatment, but not to a degree that caused discontinuation by any of the patients evaluable, except for one patient who was treated with erythromycin.

Cure rates in different studies of patients with both C+ and C− NGU are difficult to compare because of differences in duration of follow-up and whether or not sexual partners are treated epidemiologically. In this study the overall clinical efficacy rates was between 78% and 84% for roxithromycin, depending upon exclusion or inclusion of 3 men with a possible 'reinfection', and 86% for erythromycin, a non-significant difference. It is therefore concluded that roxithromycin seems to be a safe and effective alternative treatment for C− NGU and has the advantage of being administered as a single daily dose.

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