Norflaxacin versus Thiamphenicol for Treatment of Uncomplicated Gonorrhea in Rwanda

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Received 22 July 1986/Accepted 15 December 1986

In an open prospective study, single oral doses of norfloxacin (800 mg) and thiamphenicol (2.5 g) were used to treat, respectively, 122 and 46 consecutive patients with uncomplicated gonorrhea. Neisseria gonorrhoeae was eradicated from 119 (97.5%) patients treated with norfloxacin and from 35 (76.0%) patients treated with thiamphenicol. Norfloxacin treatment failure was not related to drug resistance or to insufficient absorption of the drug. Thiamphenicol failure correlated with low in vitro susceptibility of the infecting strain. In a single oral dose of 800 mg, norfloxacin appeared to be an excellent alternative treatment regimen for uncomplicated gonorrhea in an area with a high prevalence of penicillin-resistant gonococci.

Uncomplicated gonorrhea is extremely frequent in Rwanda. The official notifications, varying between 6,000 and 15,000 cases yearly for a population of about 5 million people (5), largely underestimate the reality. Penicillinase-producing Neisseria gonorrhoeae emerged late in 1982 and reached 40% of all isolates during 1984. High-level resistance to penicillin in non-penicillinase producing N. gonorrhoeae is also common (J. Bogaerts, J. Vandepitte, E. Van Dijck, R. Van Hoof, and P. Piot, Gentourin. Med., in press).

Therefore, alternative and, if possible, low-cost treatment regimens are needed that will be effective against such isolates and that can be administered as a single-dose therapy. Thiamphenicol is inexpensive and can be given as a single oral dose. Much research has been done on its toxicity and efficacy in the treatment of uncomplicated gonorrhea (11), with failures being correlated with MICs of $\geq$1 $\mu$g/ml (4, 6, 8, 12).

Norfloxacin, a new orally administered quinolone, seems to be a very promising agent in the treatment of gonorrhea. It shows very high in vitro activity against N. gonorrhoeae (3, 9) and has been used with success in uncomplicated gonorrhea (1), like other newer quinolones (2, 6, 7, 10). In vitro resistance to this group of antibiotics has not been reported until now.

The aim of this study was to compare two single-dose regimens for the treatment of uncomplicated gonorrhea: norfloxacin (800 mg) and thiamphenicol (2.5 g).

MATERIALS AND METHODS

Patient selection and study design. This study was done at the Centre Hospitalier de Kigali and at the Centre Médico-Social de Nyamirambo, a health care center, situated 3 km from the former. Between January and June 1985, 146 men and 37 women (ages, $\geq$16 years), who reported urethral or endocervical discharge and who had not taken antibiotics within the preceding 72 h were treated with norfloxacin or thiamphenicol. Pregnant women were excluded from the study. The treatment regimen was assigned on an alternating basis according to the week of the study. A total of 75 patients (67 male, 8 female) were treated with thiamphenicol, and 108 (79 male, 29 female) were treated with norfloxacin. Only patients from whom N. gonorrhoeae was isolated during the first visit and who returned for the control culture 2 to 5 days after treatment were considered as evaluable. All patients except one were Rwandese, and both treatment groups were similar with respect to age, body weight, and duration of symptoms.

The thiamphenicol treatment regimen was stopped when it became clear that the failure rate was unacceptably high. Another group of patients (78 males, 2 females), who were selected based on the same selection criteria described above, were treated with norfloxacin alone during December 1985.

Treatment regimens and evaluation. All patients were treated with single oral doses of 800 mg of norfloxacin or 2.5 g of thiamphenicol, which were administered by one of the investigators. Patients were instructed to abstain from sexual contact before the control culture. Classification of cure or failure was based on the result of the culture for N. gonorrhoeae at the follow-up visit. The chi-square test with the Yates correction and the Fisher exact test were used for statistical analyses. Tolerance and acceptability of the drug regimens was evaluated by interrogating patients specifically about nausea, vomiting, and headaches during the day of treatment, because there were no spontaneous complaints.

Assays for norfloxacin in serum. Concentrations of norfloxacin in serum were determined by an agar well method in antibiotic medium no. 2 (Oxoid Ltd., London, England) adjusted to pH 7.8 with 1 N NaOH. Enterobacter cloacae ATCC 23355 was used as the test organism. The reliable lower limit of detection was 0.5 $\mu$g/ml, and the coefficient of variation was 5.6%. Blood samples were taken 1 h after administration of 800 mg of norfloxacin in 35 patients and 90 min after administration in 38 other patients.

Bacterial strains and susceptibility tests. Urethral and cervical specimens were immediately inoculated onto Thayer-Martin medium and incubated in a candle jar at 37°C for 3 days. Isolates were identified as N. gonorrhoeae by standard techniques and were tested for $\beta$-lactamase by the chromogenic cephalosporin (Nitrocefin; Oxoid Ltd.) technique. All isolates were kept in glycerol at $-20^\circ$C and sent to Belgium for confirmation and susceptibility tests.
MICs were determined on the surviving strains by an agar dilution method on diagnostic sensitivity test agar (Oxoid) supplemented with 1% IsoVitalex (BBL Microbiology Systems, Cockeysville, Md.) and 2% hemoglobin. The inoculum, corresponding to 10⁵ CFU per spot, was delivered with a multipoint inoculator. Cultures were incubated for 24 h at 37°C in a 5% CO₂ atmosphere. The MIC was read as the lowest concentration of the antimicrobial agent that allowed no visible growth.

RESULTS

Because the second group of patients treated with norfloxacin was selected on the same criteria as in the comparative study, the results were pooled. A total of 263 patients were enrolled in the study: 188 (37 women, 151 men) received norfloxacin and 75 (8 women, 67 men) received thiamphenicol. Evaluable data were obtained from 122 patients (18 women, 104 men) in the norfloxacin group and 46 (2 women, 44 men) in the thiamphenicol group. In the norfloxacin group, 119 (97.5%) patients were cured as opposed to only 35 (76.0%) cures in the thiamphenicol group. Treatment failures were treated and cured subsequently with 2 g of spectinomycin administered intramuscularly. With both regimens all women were cured. In Table 1 background data and the results of the study are summarized.

Clinical symptoms of urethritis persisted in the 11 men in whom thiamphenicol treatment failed. Surprisingly, in the three patients showing a positive control culture (with scanty growth) after norfloxacin treatment, no secretions nor clinical signs of urethritis nor subjective complaints were observed. None of the test-of-cure cultures in these three patients were probably not due to reinfection because they reported for a control culture on the second day after the drug was administered; however, reinfection cannot be ruled out with certainty.

The correlation between clinical outcome and in vitro susceptibility to thiamphenicol was assessed. The MICs of thiamphenicol for pretreatment isolates were determined in these patients. In 7 of the 10 treatment failures the MIC of thiamphenicol for the posttreatment isolates was also determined. Pretreatment isolates from patients in whom thiamphenicol treatment failure were not significantly less susceptible (MIC, 1 μg/ml) than the isolates from the patients that were successfully treated (Fisher exact test, P = 0.228), but the seven posttreatment isolates uniformly showed a MIC of 1 μg of thiamphenicol per ml. One patient in the failure group had a penicillinase-producing N. gonorrhoeae isolate in the first culture and a penicillinase-negative, high-level resistant strain (MIC for penicillin, 2 μg/ml) in the control culture. To control absorption a single blood sample was taken after administration of 800 mg of norfloxacin in one set of patients after 60 min and in another set of patients after 90 min. Measurable levels in serum ranging from 0.5 to 2.6 mg/liter (mean, 1.57 mg/liter) were present in 22 of 35 patients after 60 min, and levels in serum from 0.5 to 3.8 mg/liter (mean, 1.74 mg/liter) were observed in 32 of 38 patients with samples taken 90 min after administration. All patients with levels in serum below 0.5 mg/liter (limit of reliability) were nevertheless cured. The three patients that did not respond to norfloxacin treatment showed levels in serum after 90 min of 1.9, 2.0, and 2.6 μg/ml. Of these three patients only one pretreatment isolate (MIC, 0.06 μg/ml) and no posttreatment isolates were available for susceptibility testing. Penicillinase-producing N. gonorrhoeae isolates were common in both the norfloxacin (41.8%) and the thiamphenicol (32.6%) treatment regimens. No differences existed between patients of both treatment regimens with regard to body weight (Table 1). The rates of postgonococcal urethritis in men, as defined by the presence of a serous, culture-negative urethral discharge after treatment, were 24.8% (25 of 101) in the norfloxacin group and 15.2% (5 of 33) in the thiamphenicol group (x² = 0.97; P > 0.05). This difference was not statistically significant.

Norfloxacin and thiamphenicol were well tolerated, and no side effects were noted in these patients. The MICs for 63 pretreatment strains isolated in this study are shown in Table 3. The high percentage of strains with decreased susceptibility (MIC, 0.06 to 0.25 μg/ml) or resistance to penicillin G in the non-penicillinase-producing N. gonorrhoeae strains, the excellent activity of norfloxacin, and the large number of strains that were only inhibited by 1 μg of thiamphenicol per ml are shown. A total of 70% of the penicillinase-producing N. gonorrhoeae strains and 80% of the non-penicillinase-producing N. gonorrhoeae strains that were resistant were only borderline susceptible to tetracycline (MIC, ≥2 μg/ml). All strains were susceptible to kanamycin and spectinomycin.

DISCUSSION

The high failure rate in the treatment of gonococcal urethritis with thiamphenicol was disappointing. The low
suspceptibility of our isolates was probably the cause of this phenomenon; the majority of the strains were only borderline susceptible (MIC, 1 μg/ml). It should be stressed that thiamphenicol has not been used for the treatment of gonorrhea or other infectious diseases in Rwanda at least for the past 5 years (unpublished data from major drug importers). Chloramphenicol is used on a large scale, however, in the treatment of typhoid fever. This may account for the decreased susceptibility of gonococci to thiamphenicol. In fact, our clinical results were predictable because a previous survey (Bogaerts et al., in press) showed that 26.0% of all isolates had a MIC for thiamphenicol of ≥1 μg/ml. As shown by the results of our susceptibility tests and by the previous survey, gonococcal strains from Rwanda are highly resistant to penicillin and tetracyclines and show a reduced susceptibility for thiamphenicol. The alternative regimes, as proposed by an expert group of the World Health Organization (13), for areas with a high prevalence of penicillinase-producing N. gonorrhoeae or a high prevalence of chromosomally resistant strains are too expensive for the first-line treatment of uncomplicated gonorrhoea in a developing country. Furthermore, broad-spectrum cephalosporins, although very efficient, should not be used in areas with high levels of sexual promiscuity, irrespective of the cost of treatment. Their use should be restricted to the treatment of serious infections with multiresistant gram-negative microorganisms which are highly endemic in the tropics. Multiple-dose regimens should also be avoided. The risk that the drug will be put aside for later use or sold to other patients is very high. The high prevalence of human immunodeficiency virus-associated infections in Central Africa, especially in patients with sexually transmitted diseases, makes oral administration of drugs preferable over parenteral administration. Indeed, sterile disposable materials are often not available and are a supplementary factor of cost.

Results of this study have demonstrated that a single oral dose of 800 mg of norfloxacin is effective in the treatment of uncomplicated genital gonorrhea due to strains of N. gonorrhoeae that are either resistant or susceptible to penicillin. It seems to be a suitable alternative for spectinomycin, provided that cost is lower and that resistance develops slowly toward this new antibiotic. Continuous monitoring of microbial susceptibility of N. gonorrhoeae is indispensable for selecting optimal therapeutic regimens.

ACKNOWLEDGMENTS

We are grateful to Merck Sharp & Dohme, Belgium, and to Zambon, Belgium, for providing the norfloxacin and the thiamphenicol used in this study.

This study was supported in part by a grant from Merck Sharp & Dohme, Belgium.

LITERATURE CITED


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**TABLE 3. Susceptibility of penicillinase-producing N. gonorrhoeae and non-penicillinase-producing N. gonorrhoeae pretreatment isolates**

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* MIC of penicillin G, ≥16 μg/ml.

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