A comparison of pefloxacin/metronidazole and doxycycline/metronidazole in the treatment of laparoscopically confirmed acute pelvic inflammatory disease


"Department of Gynecology and Reproduction, Leiden University Medical Center, Leiden, The Netherlands, Department of Gynecology, Municipal Hospital 'Leyenburg', The Hague, The Netherlands "Department of Medical Microbiology, Leiden University Medical Center, Leiden, The Netherlands and "Department of Internal Medicine, University Hospital Nijmegen, Nijmegen, The Netherlands

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Summary

A double-blind, randomised study was conducted to compare the efficacy and safety of a combination of pefloxacin and metronidazole versus doxycycline and metronidazole in patients with pelvic inflammatory disease (PID). The clinical diagnosis had to be confirmed by laparoscopy before patients were included. Of the 74 patients who fulfilled the clinical criteria for PID, laparoscopy confirmed the diagnosis in only 40 patients (54%). The microorganism most frequently found as causative pathogen was *Chlamydia trachomatis*. Both treatment groups showed a good response to the study-medication. At discharge 9 patients in the pefloxacin group (45%) were cured and 10 patients (50%) had improved. In the doxycycline group 7 patients (35%) were cured and 10 patients (50%) had improved. Obviously pefloxacin/metronidazole and doxycycline/metronidazole are equally effective in the treatment of PID.

Pelvic inflammatory disease; Antibiotics; Laparoscopy

Introduction

Most patients with pelvic inflammatory disease (PID) are treated on an epidemiological basis. The major pathogens causing PID include *Chlamydia trachomatis*, *Neisseriae gonorrhoeae*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, anaerobes (*Peptococcus*, *Peptostreptococcus* and *Bacteroides*), aerobes (*Streptococcus*, *Haemophilus influenzae* and *Escherichia coli*) [1,2]. In the Netherlands, the recommended treatment regimen consists of doxycycline combined with metronidazole. The Centers for Disease Control recommend combined antimicrobial therapy for PID, including: (1) cefoxitin plus doxycycline or (2) clindamycin plus gentamicin [3].

Doxycycline is active against Gonococci, *Streptococci*, *C. trachomatis*, *Mycoplasma*, *Ureaplasma*, *H. influenzae*, *E. coli* as well as several anaerobes. However, doxycycline is not suitable for use as monotherapy because, of the anaerobes,
only the Bacteroides species are sensitive to doxycycline. As metronidazole is especially active against anaerobes, the combination of doxycycline and metronidazole is thought to cover all the possible etiologic agents involved in PID. The tetracycline-resistant gonococci, however, have proved to be an increasing problem in the management of PID [4].

One of the therapeutic goals in the management of PID is prevention of the late sequelae, such as chronic pelvic pain (18%) [13,14], recurrent PID (23%) [14], ectopic pregnancy (a seven- to tenfold risk increase) [14] and infertility. In a cohort study in Sweden Weström [13] noted a direct relationship between the number of episodes of infection the infertility rate, which ranged from 11% for a single episode to more than 50% in women with three or more episodes.

Pefloxacin is a new broad-spectrum antimicrobial agent that belongs to the fluoroquinolones. What is important as far as gynecological infections are concerned, pefloxacin is active against Gram-negative diplococci, C. trachomatis, Ureaplasma and M. hominis [5-8]. The favourable pharmacokinetic properties of pefloxacin consist of a long plasma elimination half-life (12 h), a low protein binding and a high tissue affinity, independent of the route of administration (intravenously or oral).

Because of the interesting microbiological and pharmacokinetic properties of the new quinolones such as pefloxacin, a double-blind clinical study was performed at the Departments of Gynecology of the Leiden University Medical Center and the municipal hospital 'Leyenburg' in The Hague. In this study we compared the efficacy and safety of a combination of doxycycline and metronidazole versus pefloxacin and metronidazole.

Laparoscopical studies have shown that the diagnosis of PID based on clinical criteria is often inaccurate [9-11], and that laparoscopy is a safe way to make an accurate diagnosis of PID and an excellent means to obtain representative cultures. It was for this reason that in this study the clinical diagnosis had to be confirmed by laparoscopy.

Patients and Methods

The design of this clinical trial was a double-blind randomized comparative study. Patients were randomised using a computer-generated table. The study was approved by the ethical committees of both hospitals.

Population

To be eligible for the study, patients had to meet the strict criteria for the clinical diagnosis PID [12], after having given informed consent. The diagnosis had to be confirmed by laparoscopy before the patients could enter the study. Minors under the age of 16, pregnant or lactating women, and patients with two different infections, as defined by two sites infected by two different pathogens, were excluded from the study.

Diagnosis

Laparoscopy was performed in all patients with the presumed diagnosis of PID. The criteria were: (A) hyperemia or edema of the tube; (B) exudate coming from the fimbrial end of the tube; (C) purulent exudate in the pelvis; and/or (D) pelvic abscess.

Microbiology

Specimens were taken from the cervix, from the suspected infected sites (by laparoscopy), from a pelvic abscess (by aspiration of the abscess), from the urine, and from the blood (in the case of temperatures ≥38.5°C). These samples were transported, stored and cultured according to routine procedures for aerobic and anaerobic bacteria. Standard laboratory techniques were used for isolation and identification of causative pathogens. Specific investigations for C. trachomatis and for N. gonorrhoeae were performed. C. trachomatis was identified by culture, antigen detection and serology. For transport and preservation of C. trachomatis we used a well tested transport-medium (phosphate buffered glycerol), a maximum transport time of 2 h, and, if necessary, storage at 4°C for at most 48 h. HELA 229 cells were used for culture. C. trachomatis was identified by antigen detection with monoclonal antibodies. The antibody titers were defined as suspicious for C. trachomatis for IgG titers ≥1:128, or a significant (> 4-fold) increase in antibody concentration. Antibiotic susceptibility testing was carried out by means of the standardized
disc diffusion test according to the guidelines of the W.R.G. (Werkgroep Richtlijnen Gevoeligheidsbepalingen, this is the Dutch study group which draws up guidelines for susceptibility tests). In the case of pefloxacin 10 µg discs were used. Strains were considered susceptible to pefloxacin if MIC was ≤ 1 µg/ml, intermediate if the MIC was 2–4 µg/ml and resistant if the MIC was ≥ 8 µg/ml. These values corresponded with breakpoints in the diffusion test of 20 mm and 14 mm, respectively.

Treatment
The study medication in one regimen consisted of pefloxacin 800 mg/day. In the other regimen doxycycline was administered in an initial dose of 200 mg, followed by 100 mg daily. In both regimens metronidazole was added, in the form of 500 mg every 8 h. The route of administration (i.v. or oral) depended on the condition of the patients, using the physical findings and the body temperature as parameters.

Treatment allocation was performed as soon as specimens were sampled and stored under suitable conditions. At the end of therapy or upon discharge sampling was repeated. Duration of treatment was at least 10 days, and maximal 14 days, unless the clinical response was considered insufficient after 5 days. The minimal duration of therapy to allow efficacy assessment was 5 days.

Evaluation
The clinical outcome was defined and rated as follows:

- **Cure**: durable apyrexia and resolution of all clinical symptoms.
- **Improvement**: amelioration of signs and symptoms without complete cure.
- **Failure**: lack of favorable clinical response or deterioration of clinical condition.
- **Relapse**: recurrence of clinical symptoms after cessation of therapy.

The clinical condition was evaluated daily. Clinical response was evaluated after 3 and 5 days of therapy, and at discharge or on cessation of treatment. A final clinical examination took place between day 7 and day 15 after drug discontinuation (earlier in case of early clinical relapse). Patients who had not undergone this post-treatment follow-up were not considered suitable for efficacy assessment.

If clinically indicated, patients were eligible for second-look laparoscopy after 3–6 months, to assess the late sequelae of the PID and the treatment. The findings were registered according to Siegler [14].

Safety
All patients who received at least one dose of the study medication were analysed for safety of therapy. Any clinical adverse reaction observed during the study period was reported, as well as the severity, the relationship to the study medication (in the investigators’ opinion) and the outcome.

Standard laboratory tests were performed before therapy initiation, after 5 days of therapy and at the end of therapy.

Statistics
The chi-square test was used to compare the efficacy and the safety of the two treatment regimens.

Results

**Patient characteristics**
Between August 1987 and December 1990, 74 patients fulfilled the clinical criteria for PID. However, laparoscopy confirmed the diagnosis in only 40 of those patients (54%) (Table I). Of the 40 patients with a laparoscopically diagnosed PID, 27 were diagnosed and treated at the University Hospital Leiden, 13 were diagnosed and treated at the municipal hospital ‘Leyenburg’ in The Hague. The study groups consisted of 40 patients, 20 of whom received pefloxacin and metronidazole, and 20 doxycycline and metronidazole. Both study groups were distributed equally over the two hospitals.

The two study groups did not differ significantly with regard to demographic data, gynecological history, contraceptive use or sexual activity. Nor were there any significant differences between both groups in presenting symptoms and laparoscopic findings. Table I shows the laparoscopic findings, Table II the clinical findings and laboratory results.
TABLE I

Laparoscopic findings in 74 patients with the presumed diagnosis PID

<table>
<thead>
<tr>
<th></th>
<th>n = 74</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PID</strong></td>
<td></td>
</tr>
<tr>
<td>Hyperemia or edema of the tube</td>
<td>40 (54%)</td>
</tr>
<tr>
<td>Exudate coming from the fimbrial end of the tube</td>
<td>39 (98%)</td>
</tr>
<tr>
<td>Purulent exudate in the pelvis</td>
<td>20 (50%)</td>
</tr>
<tr>
<td>Pelvic abscess</td>
<td>16 (40%)</td>
</tr>
<tr>
<td>No pathology</td>
<td>4 (10%)</td>
</tr>
<tr>
<td>Other pathology</td>
<td>22 (30%)</td>
</tr>
<tr>
<td>Appendicitis</td>
<td>12 (16%)</td>
</tr>
<tr>
<td>Ovarian cyst (Bleeding: 1) (Rupture: 2)</td>
<td>6 (50%)</td>
</tr>
<tr>
<td>Subserous myoma (torsion)</td>
<td>3 (25%)</td>
</tr>
<tr>
<td>Ectopic pregnancy</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td>Diverticulitis</td>
<td>1 (8.3%)</td>
</tr>
<tr>
<td><strong>Microbiological features</strong></td>
<td></td>
</tr>
<tr>
<td>The microorganism most frequently found as causative pathogen was <em>C. trachomatis</em> (see Table IV for causative pathogens).</td>
<td></td>
</tr>
<tr>
<td>The susceptibility data showed that the <em>E. coli</em> isolated had a better susceptibility in vitro for pefloxacin than for doxycycline. In one patient the <em>E. coli</em> was resistant to doxycycline, the antibiotic regimen this patient was treated with.</td>
<td></td>
</tr>
<tr>
<td>At discharge no microorganisms were cultured on the examination sites.</td>
<td></td>
</tr>
</tbody>
</table>

**Clinical response**

Both groups showed a good response to the study medication (Table III). In the cases where treatment failed, surgical intervention was necessary. The differences in treatment results were not significant.

The body temperature in both groups dropped to levels of 37.0°C or lower. The ESR decreased to 14 (median) in the pefloxacin group and to 20 (median) in the doxycycline group.

The physical findings in both groups improved after treatment. The differences between the two treatment groups were not significant. This also applied to the subjective pain score: in the pefloxacin group 11 patients had no pain and 9 patients had minimal pelvic pain after treatment. In the doxycycline group there were 16 patients without pain and 4 patients with minimal pain after treatment.

TABLE II

Clinical findings and laboratory results in 40 laparoscopically confirmed PID patients

<table>
<thead>
<tr>
<th></th>
<th>Pefloxacin/ metronidazole</th>
<th>Doxycycline/ metronidazole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Body temperature ≥ 38°C</strong></td>
<td>n = 20</td>
<td>n = 20</td>
</tr>
<tr>
<td>Presence of an inflammatory mass noted on pelvic examination or sonography</td>
<td>11 (55%)</td>
<td>8 (40%)</td>
</tr>
<tr>
<td>Leucocytosis &gt; 10 000 WBC/mm³</td>
<td>4 (20%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>ESR ≥ 25 mm</td>
<td>12 (60%)</td>
<td>15 (75%)</td>
</tr>
<tr>
<td>Gramstain suggesting <em>N. gonorrhoeae</em></td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Pelvic tenderness</td>
<td>20 (100%)</td>
<td>20 (100%)</td>
</tr>
<tr>
<td>Pelvic induration</td>
<td>9 (45%)</td>
<td>7 (35%)</td>
</tr>
</tbody>
</table>

TABLE III

Found pathogens in 40 laparoscopically confirmed PID patients

<table>
<thead>
<tr>
<th></th>
<th>Pefloxacin/ metronidazole</th>
<th>Doxycycline/ metronidazole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>C. trachomatis</strong></td>
<td>n = 20</td>
<td>n = 20</td>
</tr>
<tr>
<td>— <em>C. trachomatis</em> alone</td>
<td>11</td>
<td>10</td>
</tr>
<tr>
<td>— <em>C. trachomatis</em> combined with:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ <em>G. vaginalis</em></td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>+ Anaerobes</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td>+ <em>E. coli</em></td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>+ Streptococcus</td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>+ Mixed flora</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>+ <em>S. aureus</em></td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td>+ <em>N. gonorrhoea</em></td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td><strong>N. gonorrhoea</strong></td>
<td>1</td>
<td>—</td>
</tr>
<tr>
<td>Anaerobes</td>
<td>—</td>
<td>1</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td><em>G. vaginalis</em></td>
<td>—</td>
<td>3</td>
</tr>
<tr>
<td>Mixed flora</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>No microorganisms isolated</td>
<td>7</td>
<td>2</td>
</tr>
</tbody>
</table>
TABLE IV

Results of treatment

<table>
<thead>
<tr>
<th></th>
<th>Pefloxacin/metronidazole</th>
<th>Doxycycline/metronidazole</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 20</td>
<td>n = 20</td>
</tr>
<tr>
<td>Day 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— Cured</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>— Improved</td>
<td>18 (90%)</td>
<td>17 (85%)</td>
</tr>
<tr>
<td>— No change</td>
<td>2 (10%)</td>
<td>3 (15%)</td>
</tr>
<tr>
<td>Day 5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— Cured</td>
<td>1 (5%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>— Improved</td>
<td>17 (85%)</td>
<td>19 (95%)</td>
</tr>
<tr>
<td>— No change</td>
<td>2 (10%)</td>
<td>1 (5%)</td>
</tr>
<tr>
<td>At discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>— Cured</td>
<td>9 (45%)</td>
<td>7 (35%)</td>
</tr>
<tr>
<td>— Improved</td>
<td>10 (50%)</td>
<td>10 (50%)</td>
</tr>
<tr>
<td>— No change</td>
<td>1 (5%)</td>
<td>3 (15%)</td>
</tr>
</tbody>
</table>

No significant differences (chi-square test).

In 10 patients of the pefloxacin group and in 11 patients of the doxycycline group a second-look laparoscopy was carried out. The indication for these second-look laparoscopies was (future) child wish. In the pefloxacin group no abnormalities were found in 7 patients, adnexal adhesions in 2 patients and tubal occlusion in 1 patient. In the doxicycline group no abnormalities were found in 7 patients, adnexal adhesions in 3 patients and tubal occlusion in 1 patient. In neither group was any case of persistent inflammation found.

Side-effects

In the pefloxacin group 1 patient had a side-effect (nausea) without any consequences for the projected therapy. In the doxicycline group 2 patients had side-effects requiring discontinuation of the study medication. These two side effects consisted of vomiting and a pruritic rash.

Comment

The classical combination of clinical symptoms and signs for PID was confirmed by laparoscopy in only 54% of the cases. This finding confirms the assumption that the clinical pattern of PID is uncharacteristic, and similar to that of other pathology. The use of laparoscopy for the diagnosis PID is, therefore, of great importance [15].

To preserve fertility and to prevent the sequelae of PID, treatment regimens should be instituted that are based on a knowledge of the microorganisms involved in PID. The initial step is to obtain specimens for microbiologic evaluation directly from the source of infection — the fallopian tubes — by means of laparoscopy.

To identify a C. trachomatis infection, the culture is still the most reliable technique. However, the isolation rates may be falsely low because C. trachomatis is an obligate intracellular pathogen that may not survive long in the exudate. Therefore, in this study we used culture, antigen detection and serology to determine a C. trachomatis infection.

In many western societies, the most common cause of sexually transmitted diseases is no longer N. gonorrhoeae but C. trachomatis [16], which was also the case in our study. The prevalence of N. gonorrhoeae and C. trachomatis infections seems to vary greatly, depending on the population studied. The literature [17,18] shows a higher prevalence of N. gonorrhoeae than we found in our study.

The two antibiotic regimens both demonstrated good efficacy in the therapy of patients with laparoscopically proven PID. However, our study showed that in vitro the susceptibility of E. coli was better for pefloxacin than for doxycycline. Although our study did not show a significant advantage in favour of pefloxacin, the E. coli susceptibility for doxycycline in combination with the increasing problem of tetracycline-resistant gonococci in the management of PID, supports the use of pefloxacin with metronidazole as an appropriate therapy for PID.

References