Efficacy and Safety of Ofloxacin in the Treatment of Non-Gonococcal Sexually Transmitted Diseases

Ricardo M. Manalastas, M.D., Noel R. Juban, M.D., Noel L. Espallardo, M.D., Guadalupe Natividad-Villanueva, M.D., Arlene Icasiano, M.D., Patricia M. Kho, M.D., Martha Millar-Aquino, M.D, Mary Jane Bonoan, M.D. and Suzette H. Lazo, M.D.

ABSTRACT

Non-gonococcal infections of the genital tract are usually due to *Chlamydia trachomatis*. In females, this sexually transmitted pathogen can cause cervicitis and if inadequately treated, can lead to pelvic inflammatory disease, infertility and ectopic pregnancy.

The study aimed to determine the efficacy and safety of ofloxacin in the treatment of non-gonococcal STD (chlamydial infections) among Filipino female workers with high-risk behavior. It also aimed to determine the prevalence of chlamydial infection among this group .

An uncontrolled open clinical trial was used to determine the efficacy of ofloxacin. Females with high-risk behavior working in massage parlors in the three cities of Quezon, Makati, Pasay were screened for chlamydial infection using the chlamydia optical immunoassay (OIA). Subjects with positive results on the assay were recruited and were given a complete (7-day) course of ofloxacin at 200 mg BID. Repeat chlamydial OIA was done after completion of the antibiotic course. Primary outcome was the cure rate and was defined as the number of subjects with a negative OIA test post-treatment over the total number of treated subjects. Intention-to-treat and per-protocol analysis were used for cure rate and the 95 % Confidence Intervals were computed.

Eighty four out of the four hundred and eighty two (482) female workers with high-risk behavior screened tested positive to chlamydia infection giving a prevalence rate of 17.4% (95% CI:14.1% and 21.1%). Thirteen of the 84 were excluded due to pregnancy, mixed infections and refusal to participate in the study and the remaining 71 subjects were given the ofloxacin treatment. Sixty six (66) out of 71 returned for repeat OIA test and all were negative with a per-protocol cure rate of 100.0% (95% CI:94.6% and 100.0%) and an intention-to-treat cure rate of at 93.0% (95% CI: 84.3% and 97.7%). Mild adverse events noted were headache, dizziness, nausea, and vomiting in only 10 patients.

In this study, the prevalence of chlamydial infection was 16.8 % among Filipino female workers with high-risk behavior. Ofloxacin given at 200 mg BID for 7 days was efficacious for non-gonococcal (chlamydial) infection among this population with a cure rate of 93.0 %. Minimal adverse events were also noted with the use of ofloxacin. *[Phil J Microbiol Infect Dis 2003; 32(3):133-138]*

Key Words: Chlamydia trachomatis, ofloxacin, female high-risk behavior, sexually transmitted disease

INTRODUCTION

Chlamydial trachomatis may infect the cervix without any accompanying inflammation at all.[1] Cervical inflammation is surprisingly confusing to diagnose, it being clinically evident or apparent only on colposcopy or histological examination. It is variably associated with recovery of etiological agents.

According to Handsfield,[2] the prevalence rate of *Chlamydia trachomatis* infection among female workers with high-risk behavior is 15-20 %. STD clinics in the US have reported prevalence of 4.5- 32% among patients with mucopurulent cervicitis secondary to chlamydial infection.[1] A local study conducted among female sex workers in Cebu and Manila demonstrated a prevalence rate of 19.7%.[3]

Standard therapeutic regimen recommends drugs such as doxycycline and azithromycin for genital chlamydial infection. Though proven to be effective, these cause

frequent side effects and must be taken 2-4 times daily.[4] Therapeutic alternatives would be of benefit to patients exhibiting adverse reaction to standard treatment.

Previous studies have shown that ofloxacin is as effective as doxycycline in the treatment of non-gonococcal urethritis and cervical chlamydia infection.[5,6] However there is no local study on the efficacy of ofloxacin against chlamydia infection. It would be of interest to know if ofloxacin would be an effective alternative treatment regimen.

The objectives of the study are to determine the efficacy of ofloxacin in the eradication of genital *Chlamydia trachomatis* infections and to determine the prevalence rate of genital *Chlamydia trachomatis* infection among female workers with high-risk behavior.

MATERIALS AND METHODS

Study design

The study was an uncontrolled open clinical trial. Female workers who were at high-risk of developing non-gonococcal sexually transmitted disease were recruited for the study. Onsite screening using the rapid monoclonal antibody test for chlamydia was done. Those with positive result who met other inclusion/exclusion criteria were given ofloxacin for seven days. A repeat monoclonal antibody was done after seven days. The change in clinical symptoms and results of the monoclonal antibody testing was considered as the primary outcome.

Setting

The study was done in 16 registered massage prior establishment in the cities Quezon, Pasay, and Makati in Metro Manila. Negotiations between the study investigators and the massage parlor establishments were made. It was agreed upon that during their regular scheduled check-up at the Social Hygiene Clinic or in their respective establishments, each attendant would also undergo chlamydial screening.

Procedures

The screening team was composed of Obstetric and Gynecologic fellows-in training and a medical technologist from the Philippine General Hospital, and 2 research assistants. Upon arrival at the screening areas previously mentioned, the attendants were informed of the screening procedures and were interviewed. Complete history taking and general physical examination were done.

The external genitalia were inspected for presence of abnormal lesions, discharge, or masses. A speculum was inserted into the vaginal canal to clearly visualize the vagina and cervix and to describe the color and character of the discharge, if present. Then specimens were taken from the endocervical canal. The 1st was used for chlamydial optical immunoassay test (OIA). The 2nd swab was utilized for gram staining to detect the presence of *Neisseria gonorrhea* and other organisms (e.g., clue/yeast cells). Finally, an internal exam was done to evaluate the pelvic organs for tenderness or masses. After the treatment intervention, during the follow-up visit, the following were assessed: drug

compliance, adverse reaction, intercurrent illness, and concomitant therapy. The same procedures for obtaining an endocervical specimen on the 1st day were done with specific attention for the signs relative initial visit. A bacteriological assessment of response was done based on test results: OIA negative (cure) and OIA positive (failure). Adverse events that occurred during the course of therapy were recorded.

Selection of Subjects

The subjects in this study were regular workers of sauna and massage parlors within Metro Manila. They were chosen because they are high risk of contacting non-gonococcal urethritis. The subjects were screened using a rapid monoclonal antibody test. An informed consent was obtained prior to screening and clinical interview.

Inclusion Criteria

Female workers 18 to 45 years old who are at the high risk of developing non-gonococcal sexually transmitted disease who were positive for monoclonal antibody testing for chlamydia were included in the study

Exclusion Criteria

Female workers who had clinical findings compatible with gonococcal urethritis, workers who have high probability of being lost to follow-up (temporary workers), no informed consent, pregnancy, lactation and other conditions that is a contraindication to use of ofloxacin were excluded from the study.

Treatment Intervention

Upon screening all workers were given educational advice composed of didactic lectures with the aid of simple educational materials that will promote the use of safe sex (condom use). Those who were found positive for the rapid monoclonal antibody test were given ofloxacin 200 mg twice daily for 7 days. An informed consent for clinical trial was obtained prior to administration of the drug.

Outcomes

Symptoms compatible with non-gonococcal urethritis were monitored before and after the treatment. These symptoms (urinary frequency, urgency, pain, urethral tenderness and discharge) were included in a standardized data collection from that was appropriately filled up by the investigators. The physician and the patient evaluated global response to the treatment after 7 days.

The primary outcome measure was a negative OIA test result indicative of cure after 1 week of complete treatment. Cure rate was defined as the proportion of subjects with negative OIA test results treatment over the total number of subjects positive for chlamydia.

An adverse event was defined as the presence of any of the following: any undesirable experience including intercurrent events (or disease), drug reactions (e.g. GIT or CNS manifestations), or significant laboratory test abnormalities.

Sample Size and Statistics

A total 482 female sauna and massage parlor attendants were screened. This was computed to get a 95% CI that the true value of ofloxacin efficacy is between 90-100%, the sample size computed 73 plus 20% allowance for drop-out gave a total of 87%. Since the estimated prevalence of *Chlamydia trachomatis* infection in the high-risk group was 20% a sample size of at least 450 for screening was computed to recruit 90 patients for the clinical trial.

Data was presented as mean (standard deviation) and proportion (percentage) and analyzed using descriptive statistics.

Ethical Consideration

All patients were asked to sign a written informed consent upon enrollment in the study. They were informed likewise of some symptoms that may be experienced during intake of the drug, and instructed to report those effects to the investigators.

RESULTS

Four hundred eighty two (482) female workers with high-risk behavior from the three cities of metro Manila, namely Quezon, Makati and Pasay were screened for inclusion in the study. Their ages ranged from 17 to 63 years with a mean of 28.2 years (SD 7.3 years). Most of these women were separated (45%) and had finished high school (59.3%). Of these women, eighty-four (84) or 17.4 % (95% CI: 14.1% -21.1%). Their age ranged from 19 to 44 years with a mean of 25.7 (SD 5.1). Most of them were single (66.7) had finished high school (73.8%) as shown in table 1.

Table 1. Demographic Profile of Patients Who Were Screened and Turned Positive to Chlamydia OIA Test, Metro Manila 1999

Screened Profile	Frequency/Mean	Positive %/SD	Frequency/Mean	%/SD
Age in Years	28.2	7.3	25.7	5.1
Status				
Single	216	45.0	56	66.7
Married	79	16.4	16	19.1
Separated/Widowed	146	30.4	12	14.2
Education				
None	4	0.8	5	4.8
Elementary	70	14.6	7	8.3
High School	285	59.3	62	73.8
College	112	23.3	10	11.9
TOTAL	482		84	

Total and Percent may not tally because of missing data in some variables. Prevalence of chlamydia infection is 17.4% (95% CI 14.1 and 21.1)

Out of eighty four who were tested positive by OIA, thirteen were excluded due to the following reasons: pregnancy in two (2%), mixed infections necessitating use of

other antibiotics not included in the protocol in four (4%) and seven (8%) refused to give consent for inclusion. The remaining seventy one (84%) participants were given the treatment drug. Among these, five (7%) were lost to follow-up and sixty-six (93%) were available for evaluation after 7 days of treatment. Results of chlamydial OIA on these sixty-six participants were all negative giving a per-protocol cure rate of 100.0% and an intention-to-treat cure rate of 93.0 %.

General genital symptoms at baseline and after seven days are presented in Table 2A. Seven (7) participants admitted having vaginal discharge while three (3) to experiencing urinary frequency at baseline. After treatment, only one participants claimed presence of vaginal discharge. There was there was therefore a marked decrease in reported genital symptoms after treatment from ten (10) to only one (1).

Available data on pertinent physical examination findings in the genital tract at baseline after 7 days treatment are presented in Table 2B. Discharge, erythema, and friability of the external genitalia, vagina and cervix generally decreased after 7 days of treatment. The decrease was more noticeable in the amount of vagina and cervical discharge.

Table 2A . Monitoring of reported Genital Symptoms at Baseline and After 7 days, Metro Manila 1999

	Baseline		After 7 days	
	N	%	N	%
Urinary frequency	3	4.2%	0	0
Urinary pain	0	0	0	0
Vaginal discharge	7	9.9%	1	1.5%

Table 2B. Monitoring of Genital Examination at Baseline and after 7 days, Metro Manila 1999

	Baseline		After 7 days	
External genitalia	N	%	N	%
Discharge	3	4.2	2	3.0
Erythema	2	2.8	1	1.5
Vagina				
Discharge	20	28.2	12	18.2
Erythema	0	0	1	1.5
Cervix				
Discharge	31	43.7	19	28.8
Erythema	3	4.2	2	3.0
Friability	3	4.2	2	3.0

Table 3 presents available data on evaluation of treatment. Among fifty-five (55) participants, forty-nine or 89% rated the study drug as excellent in terms of acceptability, (meaning absent of discomfort such as bad taste, large dose, pain on intake) while five (5) or 9 % rated it is good (mild discomfort). In terms of treatment response, twenty eight (28) or 48.3% were evaluated as clinical cure (disappearance of all signs and symptoms) six (6) or 10.3 % as clinical improvement and twenty four or 41.4 % as no change.

Table 4 shows the tabulations of the adverse reactions after seven (7) days of drug intake. Ten (10) participants reported the following: nausea (4), dizziness (3), vomiting (2) and epigastric pain (1). Most of these (9/10) were considered possibly related to the trial drug but all were apparently mild and self-limited thus did not require drug treatment or discontinuation of therapy.

Table 3 Acceptability and treatment Response after 7 Days of Treatment, Metro Manila 1999

	After 7 days	
Acceptability	N	%
Excellent	49	89.1
Good	5	9.1
Fair	1	1.8
Treatment Response		
Cure	28	48.3
Improvement	6	10.3
No Change	24	41.4

Table 4. Adverse Reactions After 7 Days of Treatment, Metro Manila 1999

	After 7 days	
ADR	N	%
Nausea	4	4.9
Dizziness	3	3.7
Vomiting	2	2.5
Epigastric pain	1	1.2
TOTAL	10	12.3

Table 5 shows the overall results of the study. The prevalence rate of chlamydia infection among female workers with high-risk behavior was 17.4 % (95% CI; 14.1% and 21.1%). Among those with chlamydia infection the per-protocol cure rate was 100.0% (95% CI; 94.6% and 100.0%) and the intention-to-treat cure rate was 93.0% (95% CI; 84.3% and 97.7%).

Table 5. Overall Outcome After 7 Days of treatment, Metro Manila 1999

	After 7 days	
Prevalence Study	Frequency /Rate	95% CI
Patient Screened	482	
Positive Chlamydia OIA	84	
Prevalence Rate	17.4%	14.1 and 21.1
Clinical Trial		
Patients included in drug trial	71	
Negative Chlamydia OIA	66	
Lost to Follow-up	5	
Cure Rate (per-protocol)	100.0%	94.6 and 100.0
Cure Rate (Intention-to-treat)	93.0%	84.3 and 97.7

DISCUSSION

The results of this study show a *Chlamydia trachomatis* infection prevalence rate of 17.4 % among four hundred eighty two (482) female workers with high risk behavior in Metro Manila. This rate is comparable to prevalence studies previously done here and in other country.[3]

The main basis for the diagnosis of chlamydia cervicitis in this study is the chlamydia optical immunoassay (Chlamydia OIA). Non-culture (DFA, ETA, NA amplification) tests to diagnose chlamydial infections have been utilized but tissue culture remains to be the gold standard for diagnosis of *Chlamydia trachomatis* and the method of choice for detection of infections at uncommon sites.[7] Although most studies regard the newer amplification techniques for better diagnosis of chlamydial infections,

the test used in this study as regards performance shows a sensitivity of 83.8 % and a specificity of 100 %. Furthermore, the test was used in a high-risk population, which presumably has a high prevalence rate, thus increasing the test predictive value.

The incidence of asymptomatic chlamydial infection is high. This is especially true among high-risk individuals attending a social hygiene clinic for routine screening. This makes clinical signs and symptoms a relatively poor basis for diagnosis and treatment.

Outcome measures.

In this study, only ten participants reported symptoms attributed to chlamydial cervicitis. Even the physical examination findings are varied and non-specific. They do not seem to correlate with the result of chlamydial OIA. Although less frequently seen, signs of discharge, erythema and friability persist even when chlamydial OIA is already negative. Hence, it appears more appropriate that the primary treatment outcome measure is the result of the OIA test.

In comparing chlamydial OIA results with the McCoy culture isolation technique for *Chlamydia trachomatis*, overall sensitivity and specificity of the former were 83.6% and 100% respectively considering that the true positive include all culture positive on DFA confirmed chlamydia OIA samples.[8]

Previous studies on the use of standard regimen for chlamydial infections assessed bacteriologic response to treatment using a variety of rapid detection tests that were less costly than culture, and were acceptable for the diagnosis of chlamydia. This indicates that when isolation of *C. trachomatis* is not available, non-culture antigen detection method appears to be adequate.[2] Tests of cure, when performed are ideally done 3 or more weeks after treatment. The rationale for this is to eliminate the false-negative results in the face of a persistent infection suggestive of failed treatment. However, in a randomized controlled trial done in 7 public health clinics in the US, using single dose versus multidose regimens, recurrence of chlamydial infection at 1 month post treatment had behavioral risk factors as contributors of reinfection,[9] and not treatment failure.

Single dose quinolones are ineffective for genital chlamydial infections, but a 7 days course; treatment with ofloxacin was comparable to doxycycline for the treatment of chlamydial cervicitis[4,10,11] as was demonstrated in this study. Thorpe et al[12] compared the effects of a single dose therapy with azithromycin and 7-day doxycycline for the treatment of uncomplicated chlamydial lower genital tract infections in a high prevalence group with an equally high cure rate. Cure rates were found to be 97% and 99%, respectively. Moreover, it is interesting to note that isolates causing asymptomatic infections, as what our subjects had, were found to be more susceptible to doxycycline and azithromycin to which ofloxacin is comparable in efficacy,[13,14] than isolates causing mucopurulent cervicitis or PID. As shown in the results, adverse drug reactions are few, of minor nature and severity and self limited.

Recent reports have highlighted the emergence of fluoroquinolone resistant *Neisseria gonorrhea* infections in some areas. This study seeks to determine if infections with *Chlamydia trachomatis* remain treatable with this class of drugs, in particular ofloxacin. Our results indicate that ofloxacin given at 200 mg orally twice a day for 7 days remains effective in the treatment of chlamydial cervicitis.

There may be some concern over the false-negative tests of cure, but these cases that tested negative after treatment with ofloxacin clearly represent apparent eradication of the organisms. Although further researches are needed, this study suggest that given a cure rate of 93% at a multiple dose regimen, ofloxacin is efficacious and safe for the treatment of non-gonococcal (chlamydial) cervicitis among high risk female workers.

REFERENCES

1. Stamm WE. Chlamydia trachomatis infections: progress and problems. J Infect Dis 1999;179(Suppl 2):S380-S383.
2. Handsfield H, Jasman L, Roberts P, Hanson V, Kothenbeutal R, Stamm W. Criteria for selective screening for Chlamydia trachomatis infection in women attending family planning clinics. JAMA 1986; 255(13):1730-1734.
3. Wi T, Mesola V, Manalastas R, et al. Syndromic approach to detection of gonococcal and chlamydial infections among female sex workers in two Philippine cities. Sex Transm Infect 1998; 74(Suppl 1):S118-S122.
4. Hooton TM, Batteiger BE, Judson FN, Spruance SL, Stamm WE.. Ofloxacin versus doxycycline for treatment of cervical infection with Chlamydial trachomatis. Antimicrob Agents Chemother 1992; 36(5):1144-1146.
5. Hartinger A, Korting HC, Neubert U, Blaufuss H. [In vitro effectiveness of ofloxacin and ciprofloxacin in genital Chlamydia Trachomatis isolates measured by minimal inhibitory concentration and minimal bactericidal concentration]. Z Haut Kr 1988; 63(1), 29-32.
6. Majeroni BA. Chlamydial cervicitis: complications and new treatment options. Am Fam Physician 1994; 49(8):1825-1829.
7. Ngan CC. Update on techniques in the diagnosis of Chlamydia trachomatis infections. Ann Acad Medicin e Singapore 1997; 26(6):801-807.
8. Jones MF, Smith TF, Houglum AJ, Herrman JE. Detection of Chlamydia trachomatis in genital specimens by the Chlamydiazyme test. J Clin Microbiol 1984; 20(3):465-467.
9. Hillis SD, Coles FB, Litchfiels B, et al. Doxycycline and azithromycin for prevention of chlamydial persistence or recurrence over one month after treatment in women. A use- effectiveness study in public health settings. Sex Transm Dis 1998; 25(1):5-11.
10. Boslego JW, Hicks CB, Greenup R, et al. A prospective randomized trial of ofloxacin vs. doxycycline in the treatment of uncomplicated male urethritis. Sex Transm Dis 1988; 15:186-191.
11. Kitchen VS, Donegan C, Ward H, Thomas B, Harris JR, Taylor-Robinson D. Ofloxacin vs. doxycycline in the treatment of non-gonococcal urethritis and cervical chlamydial infection. J Antimicrob Chemother. 1990; 26(Suppl D): 99-105.
12. Thorpe EM, Stamm WE, Hook EW 3rd, et al. Chlamydial cervicitis and urethritis: single dose treatment compared with doxycycline for 7 days in community-based practice. Genitourin Med 1996; 72(2):93-97.
13. Mortality and Morbidity Weekly Report. Guidelines on the treatment of sexually transmitted diseases. 1998; 47 (RR-1):56.
14. Mandell GL, Douglas RG, Bennett JE (eds): Principles and Practice of Infectious Diseases Fourth Edition. New York: Churchill-Livingstone, 1995. 364.