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An Open Label Comparative Study of Azithromycin and Doxycycline in the Treatment of Non-Gonococcal Urethritis in Males and Chlamydia Trachomatis Cervicitis in Female Sex Workers in an STD Clinic in Singapore

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ABSTRACT

Aim of Study: The aim of this study was to compare the clinical and microbiological efficacy of a single 1 gram dose of azithromycin against 1 week of doxycycline at 100 mg twice a day in the treatment of: (1) uncomplicated non-gonococcal urethritis (NGU) in male patients, and (2) culture proven *Chlamydia trachomatis* cervicitis in female sex workers.

Method: The subjects were 53 male patients who attended the clinic and were diagnosed to have non gonococcal urethritis based on clinical symptoms and a urethral smear, and 63 female sex workers, who had both a positive enzyme immunoassay (EIA) test and *Chlamydia trachomatis* cultures. Follow-up visits were made at one and two weeks post-treatment to assess efficacy, subsequent relapse and presence of side effects. The male patients were also assessed at four weeks post treatment to determine default and reinfection rates.

Results: Both azithromycin (clinical cure rates 62.5% at one week, 86.4% at two weeks in male patients; 96.6% at two weeks in female sex workers) and doxycycline (clinical cure rates 65.4% at one week, 90.9% at two weeks in male patients; 100% at two weeks in female sex workers) were effective in treating non-gonococcal urethritis and chlamydial cervicitis. Both drugs were very effective in eradicating proven *Chlamydia trachomatis* infections, with success in 100% of cases of *Chlamydia trachomatis* NGU in males, and 96.6% and 100% cure rates, for azithromycin and doxycycline respectively, in female sex workers with cervicitis. There were no statistically significant differences between the two drugs in terms of clinical efficacy, influence on default rates or subsequent risk of reinfection.

Conclusions: We conclude that a single dose of azithromycin is as effective as a one week course of doxycycline in treating non-gonococcal urethritis in males and in the elimination of *Chlamydia trachomatis* in females with cervicitis, with the added advantage of a convenient single dose that can be supervised.

Keywords: *chlamydia trachomatis*, urethritis, cervicitis, antibiotic, compliance

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INTRODUCTION

Non-gonococcal urethritis (NGU) occurs worldwide and is the most common sexually transmitted disease (STD) seen in the Department of STD control (DSC) clinic in Singapore[1].

NGU is an infection of multiple aetiology. *Chlamydia trachomatis* is recognised as the major source of NGU in men, being detected in 30% to 50% of patients[2]. Infections caused by *Chlamydia trachomatis* are amongst the most common bacterial STDs in the world, causing substantial morbidity in young sexually-active people and is the most frequent identifiable single cause of pelvic inflammatory disease and infertility. In two previous local studies, the rate of isolation of *Chlamydia trachomatis* in cases of NGU in male patients ranged from 13.8%[3] to 30.2%[4].

The current treatment of choice for NGU and *Chlamydia trachomatis* cervicitis in our clinic is doxycycline, given for 7 days. Patient non-compliance is a problem, and this is particularly significant in patients and sex workers with asymptomatic infections.

Azithromycin is a new, long-acting azalide antibiotic which has been shown to be effective in the treatment of *Chlamydia trachomatis* infections[5,6]. Its single dose usage is advantageous, and arises from its interesting pharmacokinetic properties. In contrast to low serum levels, high and sustained concentrations are achieved in a variety of different tissues, including the urogenital tract[7,8]. The aim of this study was to compare its efficacy and side effects with doxycycline in treating NGU in males and culture proven *Chlamydia*

trachomatis infections in female sex workers, as well as to identify differences in follow-up rates and the risk of reinfection in male patients who were treated.

MATERIALS AND METHODS

Study population

The study was carried out at the DSC clinic in Singapore, in two parts: (1) male patients, aged 18 years or more, presenting with symptoms and signs of acute urethritis were examined, and recruited if they had NGU as defined by 5 or more white blood cells per high power field (WBC/hpf) in the microscopic examination of a Gram-stained urethral smear, and (2) female commercial sex workers on the Medical Surveillance Scheme were identified based on a positive *Chlamydia trachomatis* EIA screening test. Only female sex workers who had a positive endocervical swab for *Chlamydia trachomatis* culture were analysed.

Gonorrhoea was excluded by the absence of intracellular Gram-negative *diplococci* and by negative culture on modified Thayer-Martin medium. Exclusion criteria included consumption of antibiotics in the previous 2 weeks, a known allergy to either drug, concurrent treatment with ergotamine or carbamazepine, and a history of chronic diarrhoeal disease which might interfere with absorption.

Procedure

Urethral smears were taken by means of cotton-tipped urethrogenital swabs inserted 3 cm into the urethra. For females, endocervical swabs were taken after wiping the cervix with a cotton swab. Specimens were taken for Gram-stained smears, gonococcal cultures and *Chlamydia* enzyme immunoassays (EIA) for detection of *Chlamydia trachomatis* antigen. In addition, for the female sex workers, specimens were sent for cultures.

Chlamydia trachomatis antigen was identified by EIA (Chlamydiazyme diagnostic kit, Abbott Laboratories, Abbott Park, Illinois). Specimens collected were analysed within 48 hours. One mL of specimen dilution buffer was added and vortexed for 3 cycles of 15 seconds each. Immediately after vortexing, 200 uL of the specimen was pipetted to each well with one bead added, and incubated at 37°C ± 2°C for 60 minutes. The liquid was aspirated and each bead washed 4 times with 4 – 6 mLs of deionised water for a total rinse volume of 11 – 17 mLs. Two hundred uL of anti-*Chlamydia trachomatis* and 200 uL of enzyme conjugate were pipetted sequentially into each well and incubated at 37°C for 60 minutes. Three hundred uL of OPD (o-phenylenediamine) substrate solution was added for colour development and incubated for 30 minutes at room temperature. The reaction was stopped by adding 1 N sulphuric acid and the absorbance read in a spectrophotometer.

Chlamydia trachomatis cultures were performed by inoculating specimens onto cycloheximide treated monolayers of McCoy cells on cover slips in glass vials. Culture is considered positive if the monolayers contain one or more chlamydial inclusions, identified by its typical crescent shape and intracytoplasmic location.

Consecutive patients were openly assigned to one of each treatment group on an alternating basis. Patients assigned azithromycin were given 1000 mg of the drug under supervision at the clinic, and those assigned to the doxycycline treatment arm were prescribed doxycycline 100 mg bid for 7 days. Male patients were told to return at weeks 1, 2 and 4 post treatment. Female sex workers were assessed at weeks 1 and 2 post-treatment. At each visit, a record of the patient's symptoms and signs and any side effects were recorded. A urethral or cervical smear was also done. *Chlamydia* EIA tests and cultures were done weekly at 0, 1 and 2 weeks in female patients and during the first visit and after 2 weeks in male patients. Male patients were dropped from the study if they did not return for the first two follow-up visits, while the last follow-up visit was used to assess their risk of reinfection and relapse following a clinical cure. No additional treatment was given until the assessment at week 2, where failure to achieve clinical cure was regarded as treatment failure.

Analyses

Clinical cure for male patients was defined as a normal urethral smear (< 5 WBC/hpf) with resolution of symptoms and signs of urethritis. Microbiological cure for males was defined as a negative EIA result if the initial one was positive, while for the females, microbiological cure was achieved if the repeat culture after treatment was negative for *Chlamydia trachomatis*. Reinfection was defined as a recurrence of signs and symptoms of urethritis after a cure was achieved, coupled with a history of re-exposure during the follow-up period. A relapse was defined as a recurrence of signs and symptoms of urethritis following achievement of cure without any re-exposure during the treatment and follow-up period. Only male patients were assessed for reinfection and relapse rates. Fisher's exact probability test was used for statistical analysis, and $p < 0.05$ was considered statistically significant.

RESULTS

A total of 160 patients were initially recruited, consisting of 60 male patients and 100 female patients. Of these, 116 patients could be evaluated: of the 53 male patients, 27 were in the azithromycin group (group A) and 26 patients were treated with doxycycline (group B); of the 63 female patients, 29 were in group A and 34 in group B. The mean age for male patients was 28.8 years (range, 21 – 46) in group A and 29.3 years (range, 18 – 50) in group B. The mean age for female sex workers in the azithromycin group was 24.9 years, and 27.7 years for the doxycycline group. Seven male patients were excluded initially because of protocol violation; by the end of the first week, only 50 male patients were evaluable, and by the end of the second week, 44 male patients

were evaluable. Of the 100 female subjects recruited into the study, 37 could not be evaluated for the following reasons: (i) 31 were excluded because the swab culture on the first visit did not grow *Chlamydia trachomatis* although EIA was positive; (ii) 4 female patients were lost to follow-up, and (iii) 2 violated the protocol.

Table I shows the demographic data of the groups. There were no significant differences between the two treatment groups in terms of racial composition, average age or age range.

Table II shows the results of treatment in male patients at weeks 1, 2 and 4 of follow up. Clinical cure rate at week 1 was recorded in 15/24 (62.5%) azithromycin-treated and in 17/26 (65.4%) doxycycline-treated subjects. The corresponding figures at week 2 were 19/22 (86.4%) and 20/22 (90.9%) respectively. These differences were not statistically significant. The rate of isolation of *Chlamydia trachomatis* at week 0 was also similar for both groups – 13/27 (48.1%) for group A and 12/26 (46.2%) for group B. Microbiological eradication rates at week 2 of follow-up was 100% for both groups (13/13 group A, 12/12 group B). The overall rate of isolation of *Chlamydia trachomatis* infections using EIA was 47.2% (25/53). Default rates were different between the two groups for the first week of follow up; 3/27 (11.1%) patients from group A defaulted after the initial visit while none defaulted from group B. This difference was not statistically significant. By the second week of follow-up, the default rates were fairly similar: 5/27 (18.5%) from group A and 4/26 (15.4%) from group B. This difference was not statistically significant. The overall default rate for attendance at week 2 of follow-up was 9/53 (17%). At week 4, only 32 of the original 53 (60.4%) entrants returned for the last follow-up visit (15 from group A, 17 from group B). There were 2 cases of reinfection in the azithromycin treated group and 3 in the doxycycline group. There was one case of relapsed NGU in both groups, giving a relapse rate of 6.7% for group A and 5.9% for group B. None of these cases were EIA positive initially.

Table III shows the symptomatic response of both groups in each treatment arm. There was statistically significant improvement in symptoms over the follow up period in both treatment arms, for both the male and female patients (azithromycin $p = 0.015$, doxycycline $p = 0.02$). There was no statistically significant difference between azithromycin and doxycycline. The majority of women with *Chlamydia trachomatis* cervicitis (54/63, 85.7%) tended to be aymptomatic.

Table IV shows the frequency of side effects recorded at the end of the first week of treatment. One hundred and thirteen patients were evaluated for side effects. Overall, adverse side effects were reported in low frequencies (15.1% in azithromycin, 16.7% in doxycycline). The most common side effect to both antibiotics was nausea. Other side effects were: epigastric pain and diarrhoea (with azithromycin), and vomiting, giddiness, fever, headache and drowsiness (with doxycycline). None of these side effects was serious enough to cause cessation of therapy.

Table I – Demographic data of patients in both treatment groups

	Azithromycin (Group A)	Doxycycline (Group B)
MALE (n = 53)		
Number	27	26
Age range (years)	20 – 46	18 – 50
Average age (years)	28.8	29.3
Chinese	18	19
Malay	4	3
Indian	2	3
Others	3	1
FEMALE (n = 63)		
Number	29	34
Age range (years)	18 – 35	19 – 38
Average age (years)	24.9	27.7
Chinese	8	15
Malay	4	5
Thai	17	14

p value comparing demographic data in group A to group B is not significant between the 2 treatment groups

Table II – Comparison of clinical efficacy and default rates in male patients

	Azithromycin (Group A) (n = 27)	Doxycycline (Group B) (n = 26)
Clinical cure		
Week 1	15/24 (62.5%)	17/26 (65.4%)
Week 2	19/22 (86.4%)	20/22 (90.9%)
Week 4	12/15 (80%) – 2 reinfections (13.3%) – 1 relapsed (6.7%)	13/17 (76.5%) – 3 reinfections (17.6%) – 1 relapsed (5.9%)
Default rate		
Week 1	3/27 (11.1%)	0/26 (0%)
Week 2	5/27 (18.5%)	4/26 (15.4%)
Week 4	12/27 (44.4%)	9/26 (46.2%)
EIA positive		
Week 0	13/27 (48.1%)	12/26 (46.2%)
Week 2	0/13 (0%)	0/12 (0%)

EIA = enzyme immunoassay
p value comparing group A to group B is not significant between the 2 treatment groups

DISCUSSION

Azithromycin is a novel azalide antibiotic with a spectrum of activity broadly similar to that of erythromycin[7]. A high concentration of the drug has been recorded in human macrophages, fibroblasts and leucocytes after oral administration[7,8]. The ability of the antibiotic to penetrate phagocytes explains its clinical efficacy in eradicating localised intracellular bacterial infections, such as those caused by *Chlamydia trachomatis*. It is also effective in treating some of the other causes of NGU, for example *Ureaplasma urealyticum*[9].

This study has identified *Chlamydia trachomatis*, as detected by EIA methods, as accounting for close to half (47.2%) of all cases of NGU seen in male patients attending our centre. Two previous local studies which yielded rates of 13.8%[3] and 30.2%[4] were based on culture results, and the use of enzyme

Table III – Symptom resolution in patients in both treatment groups

	Symptomatic	Asymptomatic	Total
Azithromycin (group A)			
MALE			
Week 0	27/27	0/27	27
Week 1	3/24	21/24	24
Week 2	0/22	22/22	22
FEMALE			
Week 0	4/29	25/29	29
Week 1	0/29	29/29	29
Week 2	0/29	29/29	29
Doxycycline (Group B)			
MALE			
Week 0	26/26	0/26	26
Week 1	4/26	18/26	26
Week 2	1/22	21/22	22
FEMALE			
Week 0	5/34	29/34	34
Week 1	1/34	33/34	34
Week 2	0/34	34/34	34

azithromycin group: p = 0.015 comparing symptom resolution before and after treatment
doxycycline group: p = 0.02 comparing symptom resolution before and after treatment

p value comparing symptom resolution between A to group B is not significant between the 2 treatment groups

Table IV – Side effects of the medications

	Azithromycin (Group A) (n = 53)	Doxycycline (Group B) (n = 60)
Cases	8 (15.1%)	10 (16.7%)
Nausea	3 (5.7%)	4 (6.7%)
Vomiting	0 (0%)	2 (3.3%)
Epigastric pain	3 (5.7%)	0 (0%)
Diarrhoea	4 (7.5%)	0 (0%)
Giddiness	0 (0%)	3 (5.0%)
Fever	0 (0%)	1 (1.7%)
Headache	0 (0%)	1 (1.7%)
Drowsiness	0 (0%)	1 (1.7%)

p value comparing group A to group B is not significant between the 2 treatment groups

immunoassays has increased the detection of *Chlamydia trachomatis*. The use of antigen detection methods such as EIA has been shown in various studies to have a specificity of 95% or greater, with a sensitivity that exceeds 90% and reaches 100% in screening high-risk patients[10]. The sensitivity of *Chlamydia* antigen assays appear directly related to the number of *Chlamydia* in the specimens. It is most advantageous when used in symptomatic or high-risk, high-prevalence asymptomatic female subjects and in symptomatic male subjects[10]. At the DSC, this is used as a test of cure in the monitoring of female sex workers. In appropriate populations, the use of EIA offers advantages over culture methods as it is technically simpler, less expensive than culture methods for material and labour, less subjective than other antigen detection methods such as direct immunoflourescence (DFA), and allows numerous specimens to be processed per day[11].

Chlamydia trachomatis is a common infection amongst female sex workers. The study also highlights the fact that NGU is a disease that predominantly affects the younger age group, as 90.6% (48/53) of affected men were less than 40-years-old, and that the problem of compliance to follow-up visits certainly exists. By the end of the second week of the study, close to one in five male patients failed to return for follow-up despite calls from the nursing staff at the clinic to do so. There was however no significant differences in the default rate, whether a single dose regimen was chosen or the normal 7-day course of antibiotics prescribed. This contrasts with a recent study in the United Kingdom which showed that men in the azithromycin treated group were not only more likely to return for review, but that there was also a significant increase in the attendance of their traceable sexual contacts, compared to a group of men treated with oxytetracycline for a week[12].

The study also suggests that the ideal period to follow-up patients after an initial diagnosis of NGU should be in the second week, as clinical cures continued to improve in both groups compared to a review after one week. Culture results for *Chlamydia trachomatis* cervicitis were uniformly negative for all female sex workers (except for one case of treatment failure with azithromycin) by two weeks after treatment was initiated. A one week review might result in overtreatment of male patients if the urethral smear still shows evidence of residual inflammation. Patients must, however, be counselled that they are to avoid unprotected sexual activity during this period.

In terms of clinical efficacy, azithromycin is as effective as doxycycline in treating NGU and in the eradication of *Chlamydia trachomatis*. It has a low rate of side effects. The low rate of side effects of both drugs in this study contrasts with a study done in Norway, where up to 30% of patients experienced some form of side effect from either doxycycline or azithromycin[13]; however, despite the higher incidence of side effects in that study, none of the side effects resulted in withdrawal of treatment in either group.

The obvious advantage of azithromycin is its single dose, which can be supervised at the clinic. This will prove particularly useful as a first-line treatment for patients and sex workers who are assessed to be at high risk for defaulting follow-up visits, and may also prove useful in the epidemiologic treatment of sexual contacts of patients with NGU and *Chlamydia* cervicitis. Many of these contacts may be asymptomatic, and may not be receptive to the idea of consuming a week of antibiotics.

The main disadvantage of azithromycin is its cost. As this present study shows no significant advantages of azithromycin compared to doxycycline given for a week in terms of clinical efficacy, follow-up rates or subsequent relapses in males, it would be difficult to justify its routine use in terms of drug expenditure. However, the

identification of certain groups who may benefit from this single dose treatment will enable us to save on potential additional clinic attendances in patients who regularly default. This would translate to cost savings in terms of repeat medications, clinic attendances and treatment costs for subsequent sexual transmission to partners.

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REFERENCES

1. Department of STD Control Singapore. Annual Report 1996.
2. Bowie WR. Urethritis in males. In: Holmes KK, Mardh PA, Sparling PF, Wiesner PJ, editors. Sexually Transmitted Diseases. 2nd ed. New York: McGraw Hill, 1990:627-39.
3. Tay YK, Goh CL, Chan RKW, Ling AE. Dual therapy with doxycycline and ketoprofen compared to doxycycline in the treatment of uncomplicated non-gonococcal urethritis. Ann Acad Med Singapore 1995; 24:519-22.
4. Lim KB, Lee CT, Thirumoorthy T, Arora PN, Tan T, Sng EH. The microbiology of non-gonococcal urethritis (NGU) in Singapore. Ann Acad Med Singapore 1985; 14:686-8.
5. Whatley JD, Thin RNT, Mumtaz G, Ridgway GL. Azithromycin vs doxycycline in the treatment of non-gonococcal urethritis. Int J STD and AIDS 1991; 2:248-51.
6. Martin DH, Mroczkowski TF, Dalu ZA. A controlled trial of a single dose of azithromycin for the treatment of chlamydia urethritis and cervicitis. New Engl J Med 1992; 327:921-5.
7. Peter DH, Friedel HA, McTavish D. Azithromycin: a review of its antimicrobial activity, pharmacokinetic properties and clinical efficacy. Drugs 1992; 44:750-99.
8. Foulds G, Madsen P, Cox C, Shepard R, Johnson R. Concentration of azithromycin in human prostatic tissue. Eur J Clin Microbiol Infect Dis 1991b; 10:868-71.
9. Steingrimson O, Olafsson HJ, Thorarinsson H, Ryan RW, Johnson RB, Tilton RC. Azithromycin in the treatment of sexually transmitted disease. J Antimicrob Chemother 1990; 25(Suppl A):109-14.
10. Kellogg JA. Clinical and laboratory considerations of culture vs antigen assays for detection of Chlamydia trachomatis from genital specimens. Arch Pathol Lab Med 1989; 113:453-60.
11. Chernesky MA, Mahony JB, Castriciano S. Detection of Chlamydia trachomatis antigens by enzyme immunoassay and immunoflourescence in genital specimens from symptomatic and asymptomatic men and women. J Infect Dis 1986; 154:141-8.
12. Carlin EM, Barton SE. Azithromycin as the first-line treatment of non-gonococcal urethritis (NGU): a study of follow-up rates, contact attendance and patient's treatment preference. Int J STD and AIDS 1996; 7:185-9.
13. Nilsen A, Halsos A, Johansen A, Hansen E, Torud E, Moseng D, et al. A double blind study of single dose azithromycin and doxycycline in the treatment of chlamydial urethritis in males. Genitourinary Med 1992; 68:325-7.