Azithromycin in the Treatment of Chlamydial Cervicitis and Eradication of Ureaplasma Urealyticum in Female Lower Genital Tract

ANGKANA CHAROENWATANACHOKCHAI, M.D.*,
PATCHARA SIRIWONGRANGSUN, M.D.*,
NARUEMOL YENYASUN, R.N.*,
ANUPONG CHITWARAKORN, M.D., Dip. Ven.*,
WANIDA PARIYASAK, R.N.*,
SUCHITRA SUKWIT, M.Sc.**

Abstract

From May 1995 to May 1996, thirty-six females with chlamydial cervicitis were enrolled at Bangrak Hospital's Venereal Disease Clinic in an open study to assess the efficacy and safety of a single, 1-gram oral dose of azithromycin. Thirty-five had positive *C. trachomatis* and one had a positive Gen-probe test. Twenty-two returned for their first and second follow-ups and 18 came back for their final follow-up (visit 4). Eradication rate was 100 per cent on all visits. Fourteen patients were excluded from the final analysis- three had dropped out from the beginning, ten had sexual intercourse without a condom and one had a positive Gen-probe test but negative *C. trachomatis* culture. *U. urealyticum* was isolated from the vaginal wall of 15 of the 36 cases and eradication rate was 0 per cent at visit 2 and visit 4. In conclusion, this study shows that a single, 1-gram oral dose of azithromycin is an effective and well-tolerated alternative therapy for chlamydial cervicitis.

Chlamydia trachomatis and *Ureaplasma urealyticum* are the main demonstrable causes of non-gonococcal urethritis in men. *C. trachomatis* is known to be present in 30-50 per cent of the cases[1]. In women, where the majority of infections are asymptomatic, *C. trachomatis* infection can cause mucopurulent cervicitis, urethral syndrome, pelvic inflammatory disease (PID), ectopic pregnancy and infertility[2,3]. Infected pregnant women can transmit the infection to their infants, resulting in neonatal conjunctivitis and pneumonia[3]. Human and animal inoculation studies provide indisputable evidence of a causal role for *U. urealyticum* in nonchlamydial, nongonococcal urethritis[1,4]. *U. urealyticum* is probably commensal in female genital tracts. Only in a subpopulation of individuals infected in the lower genital tract do the organisms reach the upper tract and

* Venereal Disease Control Division, Department of Communicable Disease Control, Ministry of Public Health, Bangkok 10120,
** Armed Forces Research Institute of Medical Science, Bangkok 10400, Thailand.

only in some of these individuals does a disease ensue. This disease is chorioamnionitis. *U. urealyticum* is a significant cause of respiratory tract and central nervous system infections in premature infants[4].

Although present treatment regimens appear effective in most patients with chlamydial infections, the length of the recommended treatment (at least 7 days), the inconvenient multiple-dose therapy, and the drug's side-effects may cause the patient to stop therapy prematurely. Single-dose therapy with minimal or no side effects is expected to minimize these compliances and adverse drug problems. Index patients and their sexual partners could be easily treated, thereby eliminating disease recurrences resulting from non-compliance and reinfection[3,5,6].

Azithromycin is a novel acid-stable azalide antibiotic which rapidly enters tissues and cells and sustains high tissue levels. It is released slowly with a half-life of 68 hours. The minimum inhibitory concentration (MIC) for *C. trachomatis* ranges from 0.032 mg/l to 1.02 mg/l. For *U. urealyticum* the MIC_{90} ranges from 0.062 mg/l to 2 mg/l[7]. Recent clinical studies have reported that a single, 1-g oral dose of azithromycin is effective in the treatment of genital chlamydial infections [6,8-11]. and eradication of *U. urealyticum*[11]. This study was designed to further evaluate the efficacy and safety of a single, 1-g dose of orally administered azithromycin in the treatment of chlamydial cervicitis and eradication of *U. urealyticum* from female lower genital tracts.

MATERIAL AND METHOD

Patient population and study design

Thirty-six women aged between 18 and 45 with positive *C. trachomatis* cervicitis treated at Bangrak Hospital's Venereal Disease Clinic from May 1995 to May 1996 were enrolled in an open, non-comparative study. The criteria for inclusion in the study were :

1. Negative culture for *N. gonorrheoa* from cervical discharge
2. No evidence of pregnancy or lactation
3. No treatment with antibiotics (within two weeks) or investigational drug (within one month) prior to the visit
4. No clinical evidence of terminal illness, hepatic or renal disease, or history of allergy to macrolides
5. Patients had given their informed consent

All patients were given a single, 1-g oral dose of azithromycin at the clinic in the form of four 250-mg capsules on an empty stomach.

Efficacy analysis

Clinical investigations including culturable samples for *C. trachomatis* (Cyclohexamide-treated McCoy cell), *U. urealyticum* (U9B plate A7) and *N. gonorrhoea* (modified Thayer Martin media), were performed on day 0 (visit 0), 7 ± 2 (Visit 1), 14 ± 2 (visit 2) and 28 ± 2 (visit 4).

At each visit the patients were asked about the frequency of intercourse, number of partners and condom usage. The patients at risk of acquiring a new infection were excluded from the analysis. The microbiological efficacy was assessed as follows : eradication, relapse and persistence. At each visit the drug's possible side-effects were recorded.

RESULTS

Of the 36 women with chlamydial cervicitis enrolled in this study, 14 were excluded from the analysis -three did not come back for follow-ups, ten had sexual intercourse without a condom, and one tested positive for Gen-probe (DNA hybridization) but was not cultured. Of the 22 evaluable patients, their age ranged from 18-45 years (mean age 26.64 years). Their weight ranged from 42-75 kilograms (kg). All but one (divorced) were married. Their signs and symptoms at each visit are shown in Table 1. *C. trachomatis* was not recovered from the cervix of any of these patients at visit 1 and visit 2. Eighteen patients were evaluable at visit 4 and *C. trachomatis* was not isolated from any of them. *U. urealyticum* was isolated from the vaginal wall of 15 of the 22 evaluable patients, *U. urealyticum* was still isolated from all of these patients at visit 2 and from all 12 patients who returned for visit 4 (Table 2).

Of the ten patients who had sexual intercourse without a condom, nine returned for visit 2 and eight returned for visit 4. Only one case yielded a positive chlamydial culture at visit 4. This patient said that her husband had been treated but this is questionable. *U. urealyticum* was eradicated in one case at visit 2 and four cases at visit 4. There was a superinfection of *U. urealyticum* in one case at visit 1 and 2.

No side-effect was reported by all 22 patients who were evaluable and by the ten patients who were excluded because of sexual intercourse without a condom. We lost complete contact with the other three patients.

The MIC of azithromycin for *C. trachomatis* in our study ranged from 0.012 mg/l to 0.25 mg/l.

Table 1. Clinical characteristic for each follow-up visit.

	Visit 1	Visit 2	Visit 3	Visit 4
None	4	12	15	10
Discharge				
(Character of discharge)				
Clear	3	1	1	1
White	4	2	1	3
Purulent	8	4		
Dysuria	2			
Abdominal pain	5	2	2	
Itching	2		1	1
Hematuria			1	

DISCUSSION

As shown in this study, a single, 1-g oral dose of azithromycin is highly effective in the treatment of chlamydial cervicitis. Bacteriological eradication was 100 per cent. The drug was well tolerated. There was only 1 intend-to-treat case having mild nausea. These findings are in line with those reported in the controlled multicenter study by Martin DH et al[8]. In our study the cumulative eradication rate after four weeks (100%) was slightly higher than in the larger (185 evaluable patients) multicenter study in which the eradication rate was 97 per cent for azithromycin and 98 per cent for doxycycline. The side-effect in the Martin DH et al[8] was 17 per cent for azithromycin and 20 per cent for doxycycline while our study reported none. Our study's cumulative eradication rate after two weeks (100%) was comparable to that reported by two smaller studies (15 and 9 evaluable chlamydial cervicitis patients) done by Bush MR et al[9] and Lassus A[10]. None of the patients in the three studies showed any side effects. In our study, the MIC of azithromycin for *C. trachomatis* was also similar to those previously reported[7].

In this study, a single, 1-g oral dose of azithromycin failed to eradicate *U. urealyticum* from the lower genital tract. There are three possible causes for this failure:

1). *U. urealyticum* is commensal in the female lower genital tract[4] so it is resistant to most antibiotics;

2). quantitative culture method is preferred for *U. urealyticum* to the ordinary culture method used in this study[12];

Table 2. Bacteriological effect of a single 1-gram dose of azithromycin in female urethritis caused by *C. trachomatis* or *U. urealyticum*

	Total	Eradication	Persistence	Eradication with recurrence	Superinfection
Visit 1					
C. trachomatis	22				
U. urealyticum	15				
Visit 2					
C. trachomatis	22	22 (100%)	0	0	0
U. urealyticum	15				1
Visit 3					
C. trachomatis	22	22 (100%)	0	0	0
U. urealyticum	15	0	15 (100%)	0	0
Visit 4					
C. trachomatis	18	18 (100%)	0	0	0
U. urealyticum	12	0	12 (100%)	0	0

3). culturable specimens for *U. urealyticum* from the vaginal wall are more likely to contain mycoplasma than those obtained from the endocervical canal, posterior fornix and periurethral area[13]. We do not know whether the results would have been different if we had collected the specimens from the endocervix. Hence, we sent culturable specimens from both the vaginal wall and the endocervix in six cases and we found that out of six positive *U. urealyticum* cases from the endocervical specimen, only one was eradicated at visit 2 and 4 (data is not presented).

In conclusion, a single, 1-g oral dose of azithromycin is effective and safe for the treatment of chlamydial cervicitis. It would be particularly useful in patients who suffer from gastrointestinal side effects or do not strictly follow the current standard regimen. Because of its convenient, well-tolerated, and efficacious single-dose therapy, azithromycin is expected to provide significant benefits in epidemiologic treatments and should be offered to those patients within the chain of infections who are reluctant or unable to come for chlamydial infection tests.

ACKNOWLEDGEMENT

The authors wish to thank Pfizer International Corporation for supplying azithromycin and other support, and the staff of room no. 8, female clinic, Bangrak Hospital, for their assistance.

(Received for publication on November 20, 1996)

REFERENCES

1. Bowie WR. Urethritis in males. In: Homes KK, March PA, Sparling PF, Wiesner PJ. Sexually Transmitted Diseases, 2th ed. Newyork : McGraw-Hill Company, 1990: 627-39.
2. Cates W Jr, Wasserheit JN. Genital chlamydial infections : Epidermiology and reproductive sequelae. American Journal of Obstetrics and Gynecology 1991; 164: 1771-81.
3. Stamm WE. Azithromycin in the treatment of uncomplicated genital chlamydial infections. American Journal of Medicine 1991 ; 91 (Suppl 3A) : 19s-22s.
4. Lassell GH, Waites KB, Taylor-Robinson D. Genital mycoplasmas. In : Morse SA, Moreland AA, Thompson SE. Sexually Transmitted Diseases-Atlases. Singapore : Imago Productions (FE) PTE, Ltd, 1990; 7.2-7.15.
5. Faro S. Chlamydia trachomatis : Female pelvic infection, American Journal of Obstetrics and Gynecology 1991; 164: 1767-70.
6. Johnson RB. The role of azalide antibiotics in the treatment of chlamydia. American Journal of Obstetrics and Gynecology 1991; 164 : 1794-6.
7. Peters DH, Friedel HA, McTavish D. Azithromycin a review of its antimicrobial activity, pharmacokinetic properties and clinical efficacy. Drugs 1992 ; 44: 750-99.
8. Martin DH, Mroczkowski TF, Dalu ZA, et al. A controlled trial of a single dose of azithromycin for the treatment of chlamydial urethritis and cervicitis. New England Journal of Medicine 1992: 327; 921-5.
9. Bush MR, Rosa C. Azithromycin and erythromycin in the treatment of cervical chlamydial infection during pregnancy. Journal of Obstetric and Gynecology 1994; 84: 61-3.
10. Lassus A. Comparative studies of azithromycin in skin and soft-tissue infections and sexually transmitted infections by Neisseria and Chlamydia species. Journal of Antimicrobial Chemotherapy 1990; 25 (Suppl A): 115-21.
11. Steingrimsson O, Olafsson JH, Thorarinsson H, Ryan RW, Johnson RB, Tilton RC. Azithromycin in the treatment of sexually transmitted disease. Journal of Antimicrobial Chemotherapy 1990; 25 Suppl A; 109-14.
12. Handsfield HH, Ronald AR, Corey L, McCurchan JA. Evaluation of new antiinfective drugs for the treatment of sexually transmitted chlamydial infections and related clinical syndromes, Clinical Infectious Diseases 1992; (Suppl 1): s131-9.
13. Glatt AE, McCormack WM, Taylor Robinson D. Genital mycoplasmas. In : Homes KK, Mardh PA, Sparling PF, Wiesner PJ. Sexually Transmitted Diseases, 2th ed. Newyork : McGraw-Hill Company, 1990: 279-94.

การใช้ยา Azithromycin ในการรักษาโรคติดเชื้อคลามัยเดียที่คอมดลูกและการกำจัดเชื้อ *Ureaplasma urealyticum* ในระบบสืบพันธุ์สตรี

อังคณา เจริญวัฒนาโชคชัย, พ.บ., อนุพงศ์ ชิตวรากร, พ.บ.*, พัชรา ศิริวงศ์รังสรรค์, พ.บ.*, วนิดา ปริยาศักดิ์, พย.บ.*, นฤมล เย็นยาชัน, พย.บ*, พันตรีหญิง สุจิตรา สุขวิทย์, วท.บ.***

ระหว่างเดือนพฤษภาคม พ.ศ. 2538 ถึง พฤษภาคม พ.ศ. 2539 สถานกามโรค โรงพยาบาลบางรัก ได้ทำการศึกษาผู้ป่วยหญิงที่ติดเชื้อ *Chlamydia trachomatis* ที่ปากมดลูก 36 ราย โดยใช้ยา Azithromycin 1 กรัมรับประทานครั้งเดียว มีผู้ป่วยที่สามารถนำมาวิเคราะห์ผลการรักษารวมทั้งสิ้น 22 ราย โดยสาเหตุที่ตัดผู้ป่วยออกจากการวิเคราะห์ผลเนื่องจาก 3 รายไม่มาติดตามผลการรักษา 10 รายมีเพศสัมพันธุ์โดยไม่ใช้ถุงยางอนามัย และ 1 รายเมื่อเริ่มทำการศึกษาให้ผลบวกต่อ Genprobe แต่ผลเพาะเชื้อไม่พบ *C. trachomatis* พบว่าผู้ป่วยที่นำมาวิเคราะห์ทั้ง 22 รายไม่พบเชื้อ *C. trachomatis* เมื่อติดตามผลการรักษาสัปดาห์ที่ 1 และ 2 สำหรับผู้ป่วยที่มาติดตามผลการรักษาในสัปดาห์ที่ 4 ทั้ง 18 รายนั้นไม่พบเชื้อเช่นกัน ผู้ป่วยที่มีผลการเพาะเชื้อพบ *Ureaplasma urealyticum* ทั้ง 15 รายในการติดตามผลในสัปดาห์ที่ 2 และ 4 ทุกรายยังคงพบเชื้อ *U. urealyticum* ใน lower genital tract โดยผู้ป่วยทั้ง 22 รายไม่พบฤทธิ์ข้างเคียงใดๆจากการรับประทานยา

โดยสรุป การรับประทานยา Azithromycin ขนาด 1 กรัมครั้งเดียวสามารถรักษาโรคติดเชื้อ *C. trachomatis* ที่ปากมดลูกได้ดีโดยสามารถกำจัดเชื้อ (eradicate) *C. trachomatis* ได้ 100% และไม่พบฤทธิ์ข้างเคียงใดๆ ดังนั้นยา Azithromycin ในขนาดดังกล่าวจึงเป็นอีกทางเลือกหนึ่งในการรักษาหญิงที่มีการติดเชื้อ *C. trachomatis* ที่ปากมดลูก

* กองกามโรค, กรมควบคุมโรคติดต่อ, กระทรวงสาธารณสุข, กรุงเทพ ฯ 10120

** สถาบันวิจัยวิทยาศาสตร์การแพทย์ทหาร, กรุงเทพ ฯ 10400