Azithromycin in Non-Gonococcal Urethritis

ANGKANA CHAROENWATANACHOKCHAI, M.D.*,
THANIT PALANUVEJ, M.D.*,
MALAI KHUMHAENG, C.L.A.*,
ANUPONG CHITWARAKORN, M.D., Dip. Ven.*,
SOMSAK PAKDEEWONG, M.D., M.P.H.*,
MANU KREAURAT, C.L.A.**

Abstract

The efficacy and safety of a single 1 g oral dose of azithromycin was evaluated in 100 male patients with non-gonococcal urethritis (NGU). Enrolled were men with ≥ 5 polymorphonuclear leukocytes (PMNL) / high power field (HPF) (x 1000 magnification) in a Gram-stained smear of urethral discharge with or without symptoms and signs of NGU. Of the 66 evaluable patients, *Chlamydia trachomatis* was isolated from 18 cases (27.3%) and *Ureaplasma urealyticum* from 12 cases (18.2%). After treatment, signs and symptoms disappeared from 59 cases (89.4%). Forty-four cases (66.7%) showed reduced PMNL/HPF. *C. trachomatis* was eradicated in 18 cases (100%) and *U. urealyticum* in 12 cases (83.3%). One patient complained of mild dizziness, moderate nausea, and palpitations. Single 1 g oral dose of azithromycin appears to be effective and safe for treating chlamydial, non-chlamydial, and ureaplasmal NGU. In addition, its ease of use encourages patient compliance.

Non-gonococcal urethritis (NGU) is one of the most common sexually transmitted diseases (STD) among Thai men[1]. *Chlamydia trachomatis* is the cause of 30-50 per cent of the NGU cases, *Ureaplasma urealyticum* is the cause of 10-40 per cent of the NGU cases while 20-30 per cent of the cases having unidentified etiologies[2]. Diagnostic tests for *C. trachomatis* and *U. urealyticum* are expensive and technically demanding so they are not normally performed. Tetracycline and its derivatives have been the treatment of choice for many years. Although they are highly effective against *C. trachomatis*, they are only 70-80 per cent effective for NGU[3,4]. Its multiple dosing and long regimen are additional disadvantages[4]. Erythromycin is an alternative agent for pregnant and lactating patients as well as those who are allergic to tetracycline, although a 37 per cent failure rate has been recorded among these patient groups[5]. Erythromycin also produces more side

* 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.

effects[6]. Because of these problems, there is a strong need for a single-dose oral therapy which is safe, effective, and well-tolerated. Like erythromycin, azithromycin is a 15-member macrolide, an azalide antibiotic that, unlike erythromycin, contains a nitrogen atom in its lactone ring. Azithromycin also has a unique pharmacokinetic profile which is characterized by improved bioavailability, greater acid-stabilizing capacity, low serum concentration, sustained high tissue level, rapid and excellent tissue penetration and distribution, and a long half-life (68 hours after a single 500 mg oral dose). Azithromycin acts by binding to the 50s ribosomal component of the susceptible organism and thus interferes with its protein synthesis[7]. It is active against both *C. trachomatis* and *U. urealyticum*. The single-dose therapy with azithromycin has previously been reported to be effective in NGU[4,8,9]. The purpose of this study was to further evaluate the clinical and microbiological efficacy and safety of a single 1 g oral dose of azithromycin in the treatment of NGU and its minimal inhibitory concentration (MIC) for *C. trachomatis*.

MATERIAL AND METHOD

One hundred (100) men aged between 17 and 35 with NGU who were treated at Bangrak Hospital's Venereal Disease Clinic from May 1995 to May 1996 were enroled in this open, non-comparative study. The criteria for inclusion were:

1. A gram-stained smear of the urethral discharge showing ≥ 5 polymorphonuclear leukocytes (PMNL) / high power field (HPF)(x 1000 magnification)
2. A negative culture of urethral discharge for *N. gonorrhoeae*
3. No treatment with antibiotics (within two weeks) or investigational drugs (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 have given their informed consent

Efficacy Analysis

Clinical cure, microscopic cure, and microbiological cure are defined as the absence of presenting symptoms and signs, a reduction in urethral PMNL to <5 HPF at visit 2 (14 ± 2 days after initiation of azithromycin), and the eradication of *C. trachomatis* and/or *U. urealyticum* from the urethra at visit 2 respectively. Persistent urethritis is defined as the presence of ≥5 PMNL/HPF at visit 2. Patients who had <5 PMNL/HPF at visit 2 but ≥5 PMNL/HPF at visit 4 (28 ± 2 days after initiation of azithromycin), with or without symptoms, were categorized as having a relapse. Both persistent urethritis and relapse of NGU were treated with doxycycline (Vibramycin®) 100 mg orally twice daily for 7-14 days.

RESULTS

One hundred patients were recruited. Twenty-nine per cent had *C. trachomatis* and 18 per cent had *U. urealyticum* in the urethra. Thirty-four patients were excluded from the analysis: 22 did not come back for follow-ups, 8 had unprotected sex, and 4 changed antibiotics early in the treatment. The age range of the remaining 66 evaluable patients was 17-35 years with the mean age at 29.7 years. Forty-four were married, 12 single, and the remaining five either separated or divorced. Their weight ranged from 50-80 kg with the mean weight at 63.6 kg. Thirty-five patients did not come back for visit 4, leaving 31 evaluable patients.

Of the original 66 patients, *C. trachomatis* was isolated from 18 cases (27.3%), *U. urealyticum* from 12 cases (18.2%), and both organisms from four cases (6.5%). Efficacy analysis of NGU is shown in Table 1. The 66 patients were divided into four NGU groups - chlamydia/ureaplasma-positive, chlamydia-positive/ureaplasma-negative, chlamydia-negative/ureaplasma-positive, and chlamydia/ureaplasma-negative.

At visit 2, 18 patients in the chlamydia-positive group and 48 in the chlamydia-negative group were evaluated. Clinical cure was registered in 16 cases in the chlamydia-positive group (88.9%) and 34 cases in the chlamydia-negative group (70.8%). Microscopic cure in the chlamydia-positive group was 11 cases (61.1%) and 34 cases in the chlamydia-negative group (70.8%).

At visit 4, 10 patients in the chlamydia-positive group and 21 in the chlamydia-negative group were evaluated. Clinical cure was registered in 9 cases in the chlamydia-positive group (90%) and 17 cases in the chlamydia-negative group (81%). Microscopic cure in the chlamydia-positive group was 8 cases (80%) and 17 cases in the chlamydia-negative group (81%). Clinical cure and microscopic cure in all groups at visit 2 were assessed to be

Table 1. Efficacy analysis of NGU.

	No. of Cases				
	C. trachomatis+ n=18 (27.27%)		*C. trachomatis*- n=48 (72.72%)		Total n=66 (100%)
	U. urealyticum+ n=4 (22.22%)	*U. urealyticum*- n=14 (77.78%)	*U. urealyticum*+ n=8 (16.67%)	*U. urealyticum*- n=40 (83.33%)	
Visit 1					
Clinical cure	1	8	7	28	44 (66.67%
Microscopic cure	1	7	3	24	35 (53.03%)
Microbiological cure	4*/4**	14	6	0	
	C. trachomatis+ n=18 (27.27%)		*C. trachomatis*- n=48 (72.72%)		Total n=66 (100%)
	U. urealyticum+ n=4 (22.22%)	*U. urealyticum*- n=14 (77.78%)	*U. urealyticum*+ n=8 (16.67%)	*U. urealyticum*- n=40 (83.33%)	
Visit 2					
Clinical cure	4	12	6	28	50 (75.76%)
Microscopic cure	2	9	6	28	45 (68.18%)
Microbiological cure	4*/4**	14	6	0	
Persistent urethritis	2	5	2	12	21 (31.82%)
	C. trachomatis+ n=10 (32.26%)		*C. trachomatis*- n=21 (67.74%)		Total n=31 (100%)
	U. urealyticum+ n=1 (10%)	*U. urealyticum*- n=9 (90%)	*U. urealyticum*+ n=3 (14.29%)	*U. urealyticum*- n=18 (85.71%)	
Visit 4					
Clinical cure	1	8	3	14	26 (83.87%)
Microscopic cure	1	7	3	14	25 (80.65%)
Microbiological cure	1*/1**	9	2	0	
Relapse	0	2	0	4	6 (19.35%)

* *C. trachomatis*

** *U. urealyticum*

higher than at visit 1 (7±2 days after initiation of azithromycin).

Microbiological eradication for *C. trachomatis* was 100 per cent at all visits (18 at visit 1 and 2 and 10 at visit 4) and 83.3 per cent (10 cases) for *U. urealyticum* at visit 2 with one (25%) recurrence but this case showed clinical and microscopic cure at visit 4.

The MIC of azithromycin for *C. trachomatis* ranged from 0.0156 mg/L to 0.0625 mg/L. *C. trachomatis* was re-isolated from three of the eight patients who had unprotected sex with un-

treated/new partners. One patient in the excluded group (intend-to-treat patients) complained of side effects (mild dizziness, moderate nausea, and palpitations) which disappeared spontaneously after three days. Two patients with persistent ureaplasmal infection had clinical and microscopic cure without further antibiotic treatment.

Of the seven (38.9%) patients in the chlamydia-positive group with persistent urethritis, one was symptomatic and two had their urethritis cured spontaneously by visit 4. Of the five who received doxycycline, three resolved at visit 3 (21±2 days after initiation of azithromycin). Of the 14 (29.2%) in the chlamydia-negative group with persistent urethritis, five were symptomatic. One did not receive further chemotherapy and the urethritis resolved spontaneously. Of the 13 who received doxycycline, four resolved at visit 3, two did not come back, and three never resolved from any other antibiotic treatment.

Of the two (20%) patients in the chlamydia-positive group with NGU relapse, one did not come back and the other did not resolve after receiving doxycycline. Of the four (19.1%) in the chlamydia-negative group with NGU relapse, two did not come back and the other resolved with doxycycline at visit 3.

DISCUSSION

These findings show that a single 1 g oral dose of azithromycin in the treatment of NGU produces satisfactory results (78.8% clinical cure, 68.2% microscopic cure, 100% eradication of *C. trachomatis*, and 83.3% eradication of *U. urealyticum*) without serious side effects. These results are similar to those reported in the Lister et al[4], Lauharanta et al[8], and Whatley[9] studies and compare favorably with two other studies in Thailand using standard seven-day doxycycline therapy and the same criteria and where the microscopic cure was 51.1 per cent[12] and 75.7 per cent[13] respectively.

The clinical and microscopic cure rates were higher at 14 days after treatment initiation than at 7 days. Handsfield et al[10] stated that clinical response in NGU was determined at 14-21 days after initiation or 10-14 days after completion of treatment. Lister et al[4] also noted that some patients with persistent urethritis seven days after initiation of therapy resolved spontaneously one week later without further chemotherapy, so they argued that reassessment should be delayed until two weeks after initiation of treatment. Nayagum et al[3] and Oriel et al[14] also evaluated cure rate for NGU two weeks after completion of treatment.

Although *C. trachomatis* was totally eradicated from all 18 chlamydia-positive patients, 7 still had persistent urethritis compared with 14 in the chlamydia-negative group. These same results were also observed by Nayagum et al[3], Lister et al[4], and Oriel et al[5] in their studies with ofloxacin, azithromycin *vs* doxycycline, and tetracycline respectively. The urethritis in such cases might be caused by other pathogens or it might be non-infectious in origin. Another explanation might be the ≥5 PMNL/HPF of urethral smear being too sensitive for diagnosing microscopic urethritis. Arya et al[15] proposed that ≥4 PMNL/HPF in a urethral smear should be used as an indicator of significant urethritis while Nayagum[3] and Oriel[14] used ≥10 PMNL/HPF.

The microbiological eradication for *U. urealyticum* in this study (83.33%) was similar to the studies by Steingrimsson et al[11] (78.5%). At visit 2, two patients had persistent *U. urealyticum* without NGU signs and symptoms and with reduced (≤5) PMNL/HPF in urethral smear. In both cases, the NGU probably came from other etiologies or the *U. urealyticum* did not cause any inflammation. A longer follow-up period might have revealed the true cause.

In conclusion, single 1 g oral dose of azithromycin appears to be a safe, effective, and well-tolerated therapy for NGU. The results were comparable to those obtained with current standard therapies. The convenient single-dose therapy is expected to provide significant benefits through total compliance by patients and their partners. Studies involving a much larger number of patients will be needed not only to determine the efficacy of azithromycin in the treatment of NGU but also to evaluate the response of NGU to current standard therapies in Thailand.

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การใช้ยาอซิโธรมัยซิน ในการรักษาโรคหนองในเทียมในผู้ป่วยชาย

อังคณา เจริญวัฒนาโชคชัย, พ.บ., อนุพงศ์ ชิตวรากร, พ.บ.*, ฐานิศ พลานุเวช, พ.บ.*, สมศักดิ์ ภักดีวงศ์, พ.บ.*, มาลัย คำแหง, ป.วพ.**, พันตรีมนู เครือรัตน์, ป.วพ.***

ได้ศึกษาประสิทธิผลและความปลอดภัยของยาอซิโธรมัยซิน ขนาด 1 กรัม รับประทานครั้งเดียวในการรักษาโรคหนองในเทียมในผู้ป่วยชาย 100 คน โดยคัดเลือกผู้ป่วยที่ตรวจพบเซลล์เม็ดเลือดขาวจากท่อปัสสาวะ ≥ 5 เซลล์ต่อหนึ่งสนามกำลังขยาย 1000 เท่า ซึ่งมีหรือไม่มีอาการและอาการแสดงของโรคหนองในเทียม จากผู้ป่วยซึ่งสามารถวิเคราะห์ผลได้ 66 ราย ตรวจพบเชื้อ *C. trchomatis* 18 ราย (ร้อยละ 27) และ *U. urealyticum* 12 ราย (ร้อยละ 18.2) ผลการรักษาพบว่าผู้ป่วย 59 ราย (ร้อยละ 89.4) มีอาการและอาการแสดงหายไป ผู้ป่วย 44 ราย (ร้อยละ 66.7) ตรวจพบเม็ดเลือดขาวในท่อปัสสาวะ < 5 เซลล์ ต่อหนึ่งสนามกำลังขยาย 1000 เท่า ผลการเพาะเชื้อในผู้ป่วยที่พบเชื้อ *C. trachomatis* พบว่าเชื้อหายไปทั้ง 18 ราย (ร้อยละ 100) และผู้ป่วยที่พบเชื้อ *U. urealyticum* พบว่าเชื้อหายไป 10 ราย (ร้อยละ 83.3) มีผู้ป่วย 1 ราย มีอาการใจสั่น, คลื่นไส้ และมึนงง หลังรับประทานยา 2-3 ชั่วโมงเป็นเวลา 3 วันซึ่งอาการหายไปได้เอง

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* กองกามโรค, กรมควบคุมโรคติดต่อ, กระทรวงสาธารณสุข, กรุงเทพ ฯ 10120

** สถาบันวิจัยวิทยาศาสตร์การแพทย์ทหาร, กรุงเทพ ฯ 10400