Clinical study

AZITHROMYCIN IN THE TREATMENT OF CHLAMYDIAL CERVICITIS AND URETHRITIS

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ABSTRACT

In a first step, the efficacy and safety of azithromycin as compared to doxycycline in the treatment of uncomplicated chlamydial cervicitis were assessed in a randomized, open clinical study. 32 female patients were enrolled in the study and treated either with a single oral dose of 1 g azithromycin or with a conventional course of doxycycline 100 mg b.i.d. for 7 days. In a second step, an open prospective evaluation was carried out comprising another 37 patients (25 males, 12 females) with chlamydial urethritis and/or cervicitis. The infection was verified by a non-radioactive RNA:DNA hybridization test and - in case of the comparative study groups - confirmed by positive culture. In a first follow up control all patients - except one treated with azithromycin - turned out to be clinically and microbiologically cured. The exceptional case rather seemed to be due to reinfection than to therapeutic failure. Both antibiotics were tolerated well; mild gastrointestinal side effects were reported in rare cases only. Our study confirms that in the treatment of uncomplicated chlamydial cervicitis and/or urethritis a single dose of 1 g azithromycin is as effective as doxycycline 100 mg b.i.d. for 7 days.

KEY WORDS

azithromycin, doxycycline, Chlamydia trachomatis, cervicitis, urethritis

INTRODUCTION

Conventional antibiotics used for treatment of infections with Chlamydia trachomatis (Ct) have to be administered in multiple doses for several days. Within such a course treatment failures due to minor compliance bear the risk of persisting infections. This could be avoided by use of a single-dose treatment.

Azithromycin is a new semi-synthetic azalide antibiotic with an antimicrobial spectrum similar to that of erythromycin. Additionally azithromycin has enhanced potency against gram-negative organism (14). Its bactericidal effect is based on the inhibition of polypeptide synthesis by binding to the 50S ribosomal subunit. Cross-resistancy of erythromycin-resistant gram-positive organisms is to be expected, for azithromycin appears to bind also to the erythromycin ribosomal binding site.

The activity of azithromycin against Ct is similar to that of erythromycin and doxycycline with regard to the values of minimal bactericidal concentration

(MBC) and minimal inhibition concentration (MIC). However, there exist pharmacokinetic differences between these drugs (5).

High concentrations of azithromycin have been observed in a wide range of tissues 24-96 hours after single oral administration. The substance preferentially accumulates in leukocytes, where concentrations even exceed serum values.

Elimination is slow due to a half-life period of approximately 70 hours (5,8). These pharmacological features provide the chance for a once-daily regimen or a single dose therapy.

The objective of our two-step evaluation was to evaluate the efficacy and safety of azithromycin in the treatment of uncomplicated chlamydial cervicitis and/or urethritis.

PATIENTS AND METHODS

A. Randomized, open comparative study

In the first step within an open, randomized study our objective was to compare the clinical efficacy and safety of a single oral dose of 1 g azithromycin vs. a conventional course of doxycycline 100 mg b.i.d. throughout seven days in the treatment of women with uncomplicated chlamydial cervicitis.

The study was approved by the institutional ethic committee.

36 female patients >18 years (mean 26.7 a) attending our STD department with clinical signs and symptoms of cervicitis and verified infection with Ct were attached to one of two comparative treatment groups. Group 1 received a conventional oral regimen of doxycycline 100 mg b.i.d. for 7 days; group 2 a 1 g single dose of azithromycin. Finally 16 patients in each group remained fully evaluable.

Clinical and microbiological efficacy were assessed at weekly follow-up visits within a month.

Symptoms related to the infection such as cervical discharge, dysurea, burning pain, bleeding, adnexal and cervical complaints were recorded, their severity rated on a 4 point scale.

Patients in both treatment groups showed comparable background data like age, number of sexual partners and means of contraception. Related to these female patients, 19 Ct infected male partners could be found and were treated by conventional therapy.

B. Open, prospective evaluation

Based on encouraging observations we consequently added an open prospective study. 37 patients > 18 a (25 males, 12 females; mean age 27.3 a) with different kinds of clinical indications were involved in this evaluation (Tab 2). Thereby a single dose of 1 g azithromycin was used as standard medication for verified uncomplicated chlamydial cervicitis and/or urethritis. Follow up controls were done 2 weeks after therapy.

Exclusion criteria

We excluded patients younger than 18 a, pregnant and lactating women; patients who had received any other antibiotic therapy within a two week period; patients with serious renal, cardiac or hepatal diseases as well as those with known hypersensitivity to macrolides or tetracyclines. All women had to use contraceptive measures.

Laboratory tests

Ct were detected from cervical and urethral swabs by use of a non-radioactive RNA:DNA hybridization test (Gene Probe™). Additionally in the comparative study a culture on McCoy cells was done. Routine laboratory screening tests covered blood counts; renal, hepatal and other parameters.

RESULTS

A. Randomized, open comparative study

In the azithromycin group all follow-up Ct control tests were negative. Within the observation period the cumulative group score of clinical symptoms faded from 3.7 to zero by visit #3 (Tab. 1).

Table 1: Azithromycin vs. doxycycline: Comparative study A., microbiological and clinical findings at primary status and three follow-up visits

		Group 1: Azithromycin	Group 2: Doxycycline
Ct positive culture / hybridization			
Visit #1:	day 1	16	16
Visit #2:	8-10	0	0
Visit #3:	14-16	0	1
Visit #4:	21-28	0	1
Clinical signs and symptoms: Sum of score			
Visit #1:	day 1	3.7±2.2	2.7±1.6
Visit #2:	8-10	0.1±0.2	0.2±0.5
Visit #3:	14-16	0	0.4±1.7
Visit #4:	21-28	0	0.4±1.0

All patients treated with doxycycline turned out to be Ct negative by visit #2. Due to suspected re-infections, one patient became positive again at visit #3; another one by visit #4. The clinical score declined from 2.7 to 0.4 (Tab. 1).

Both antibiotic regimens were well tolerated. Mild and transient gastrointestinal discomfort, such as nausea and loose stools were reported by two patients in the azithromycin group (12.5%) and by one patient in the doxycycline group (6.25%). No relevant shift in chemical laboratory data was observed.

B. Open, prospective evaluation

All 37 patients were Ct-positive as proved by hybridization tests at the beginning of the trial. At regular follow up controls two weeks after azithromycin all patients except one female revealed a negative Ct finding (cure rate 36/37 = 97.3%). In this particular case the patient admitted to have had unprotected sexual intercourse with a partner, who turned out to be Ct positive.

Although a reinfection rather than a therapeutic failure could be assumed, for the second treatment doxycycline was given. A further Ct control test was negative then.

No severe adverse effects were reported.

DISCUSSION

Azithromycin given in a single oral dose of 1 g proved to be highly effective in the treatment of uncomplicated chlamydial cervicitis and urethritis.

In our comparative study the cure rate as assessed by a first follow up visit was 100% and thereby equal to a conventional regimen of doxycycline 100 mg b.i.d., given throughout 7 days. The rate and severity of adverse effects was similar among azithromycin and doxycycline. These results are in accordance with those of other studies (1,10,13, 16,17,19).

The efficacy of azithromycin subsequently was confirmed in a prospective evaluation. Among 37 males and females with verified chlamydial cervicitis and/or urethritis there was only one case of positive control test. Since this case presumably was due to reinfection, among the remaining 36 patients again the cure rate was 100%.

Even if taking into account one case of therapeutic failure, the overall cure rate for azithromycin in both studies (52 of 53 patients) would be 98.1% and thereby highly successful (Tab. 3).

Due to its specific pharmacologic features, azithromycin concentrations in tissues and cells markedly exceed the serum levels, thus providing increased drug activity at the relevant site of infection (18). This is supported by leukocytes which take up the drug and migrate to the inflammatory site as kind of natural delivery system. Thus targeting the effect to the site where it is required, at the same time only minor systemic adverse effects are to be expected and observed.

According to Borsum, azithromycin at minimal inhibitory concentration (MIC) against Ct in vitro revealed only a bacteriostatic activity, while the bactericidal minimal lethal concentration (MLC) was 2-4 times higher (2). However, due to the specific distribution of azithromycin this is not relevant and does not impair the pharmacologic effect; which additionally is sustained by a long half-life (8). This allows a single-dose regimen in case of uncomplicated Ct infections, which easily can be controlled by the physician and naturally meets more compliance than

Table 2: Prospective study B, background data: Clinical indications, Ct positive sites

Clinical indications	*males*	*females*	*all*
Gonorrhoea	6	2	8
Non-gonococcal urethritis	10	0	10
Partner Ct positive	9	3	12
Genital warts	/	1	1
Cervical/vaginaldischarge	/	5	5
Chronic colpitis	/	1	1
Total	25	12	37
Ct positive	*males*	*females*	
Urethra	25	2	
Cervix	/	3	
Urethra + Cervix	/	7	
Total	25	12	

Table 3. Efficacy of azithromycin 1 g single dose in the treatment of chlamydial cervicitis and/or urethritis

	Azithromycin		Doxycycline	
	n	%	n	%
A. Randomized study	16/16	100,0	16/16	100,0
B. Prospective evaluation	36/37	97,3 *		
* 1 case of reinfection:	36/36	100,0	1/1	
A + B: All patients	52/52	100,0	17/17	100,0

courses throughout several days. Inconsequent application of multiple-day regimens potentially bear the risk of therapeutic failures and further spreading of the infectious disease.

A further advantage possibly rises from the long lasting drug activity. There are hopes that a single dose of azithromycin would provide some protection against reinfections with Ct for a limited time. This may explain, why in the comparative study we observed two cases of Ct reinfections only in the doxycycline group by follow-up visits #3 and #4, respectively (day 14-28). Presuming a protective period restricted to several days and certainly shorter than two weeks, the observation of another single case of suspected reinfection in our subsequent evaluation study would not contradict this conception: The positive follow-up examination was done by day 14. - A period of lasting protection could be used for tests and treatment of infected sexual partners, before they could be sources of reinfections. Further epidemiological data are required to verify the value of this hypothesis.

In the meantime more reports were published on the efficacy of azithromycin against a broad spectrum of infectious agents.

Lauharanta isolated Ct in 53% of patients revealing signs and symptoms of non-gonococcal urethritis (NGU). Using either azithromycin in a 1 g single dose or doxycycline 100 mg b.i.d. for 7 days, the author found identical cure rates in the Ct positive subset. Consequently azithromycin has been approved for the treatment of non-gonococcal urethritis and cervicitis due to Ct (3). Cure rates among Ct-negative patients were 79% (azithromycin) and 50% (doxycycline), respectively, which points to the need of complementary antibiotic treatment depending on the microbiological spectrum (11). In our prospective evaluation study NGU represented a major subset among males (10/25 = 40%, Tab. 2).

As for infections with N. gonorrhoeae, Handsfield by application of azithromycin reported disappointing cure rates not exceeding 85-90% (7).

This must be regarded as insufficient for clinical use. Although azithromycin in case of mixed gonococcal and chlamydial infections including pelvic inflammatory disease (PID) plays an important role (4,10), it is necessary to anticipate the potential effect of disguising a concomitant gonorrhoic infection. We suggest an initial clinical and microbiological examination. Verified infections with N. gonorrhoeae should be treated by ceftriaxone, according to WHO recommendations. In a second step azithromycin should be given against Ct. Since both substances are administered as single doses, the patients compliance would not be impaired by a long-lasting therapeutic course.

Besides that there were published encouraging reports concerning the in vitro or in vivo activity of azithromycin against Ureaplasma urealyticum and Mycoplasma hominis (15,17), Haemophilus ducrey, Gardnerella vaginalis, Bacteroides spp. and Mobiluncus spp. (9).

CONCLUSION

In the course of a comparative study azithromycin given in a 1 g single oral dose proved to be as highly effective against uncomplicated genital Ct infections as doxycycline 100 mg b.i.d. orally throughout seven days. Both substances were tolerated well. These results were confirmed by a subsequent prospective evaluation. Since an oral single-dose regimen increases the patients compliance, azithromycin will contribute to the reduction of infectious propagation and serious sequelae caused by Ct in the general population. A protective effect against reinfection for a limited time is to be discussed and should be subject to further evaluations. Mixed chlamydial and gonococcal infections require a two step therapy consisting of ceftriaxone and azithromycin.

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