

Azithromycin levels in cervical mucus and plasma after a single 1.0g oral dose for chlamydial cervicitis

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Abstract

Objective—To determine the kinetics of azithromycin in cervical mucus and plasma.

Subjects and methods—Azithromycin concentrations were determined in plasma and mucus samples from 20 women with cervical chlamydial infection one, seven and fourteen days after a single oral 1.0 g dose.

Results—In mucus, all measurable azithromycin concentrations were above the minimal inhibitory concentration against *Chlamydia trachomatis* on day 7 as well as on day 14.

Conclusion—The high cervical mucus concentrations of azithromycin can explain the high clinical and microbiological efficacy.

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Keywords: Azithromycin; *Chlamydia trachomatis*; cervicitis

Introduction

Azithromycin is an acid-stable orally administered macrolide antimicrobial drug, structurally related to erythromycin with a similar spectrum of antimicrobial activity.^{1,2} Following oral administration, serum concentrations of azithromycin are lower than those of erythromycin, but this reflects the rapid movement of the drug from the circulation into intracellular compartments resulting in tissue concentrations exceeding those seen with erythromycin.³ Azithromycin is subsequently slowly released, reflecting its long terminal phase elimination half-life, relative to that of erythromycin. These factors allow for a single dose therapy, a regimen that in chlamydial urethritis/cervicitis has been found as effective as erythromycin and other commonly used drugs administered for seven days.⁴⁻⁸

The aim of this study was to determine the kinetics of a single oral 1.0 g dose of azithromycin in cervical mucus and plasma, and also to evaluate bacteriological efficacy and tolerance in women with chlamydial cervicitis.

Materials and methods

A total of 20 women were included. All had a culture proven cervical chlamydial infection within the last week before inclusion. The patients were recruited at the out-patient

venereal disease clinic of Copenhagen, after informed consent. The patients had not been treated with any antimicrobial agent within the preceding two weeks, had no known hypersensitivity to macrolides, or any known gastrointestinal, hepatic or renal disease.

A medical history including signs and symptoms of cervicitis, a cervical culture for *Chlamydia trachomatis*, cervical mucus, blood and urine samples together with standard laboratory tests were collected on day 0 before the oral intake of 1 g azithromycin in the clinic.

The patients were instructed to refrain from sexual intercourse until the end of the study, or, if not feasible, then to use a condom. The patients were asked to return for control visit on day 1, 7 and 14 where the medical history was updated, blood and cervical mucus were collected for determination of azithromycin concentration, cervical cultures for *Chlamydia trachomatis* (day 7 and 14) were performed, adverse events were recorded and blood for safety analysis was collected (day 7). Cervical samples were collected with cotton-tipped aluminium swabs.

Cervical mucus samples were collected by sucking the cervical canal with a syringe-tipped catheter. Mucus and plasma samples were stored in plain plastic tubes at -20° until analysed. Azithromycin concentrations were determined by a high performance liquid chromatographic procedure (Huntingdon Research Centre Ltd, UK).

Before the analysis of test samples, the analytical method was revalidated for plasma by the construction of a calibration line and by the analysis of spiked samples at three concentrations (low, medium and high) to establish intra (within)-batch accuracy. Owing to the nature of the samples of cervical mucus, it was not possible to construct calibration and quality control samples from that matrix. Calibrants were therefore prepared in dilute phosphate buffer (which was used to suspend the mucus samples prior to extraction) and the assay validated as for the plasma assay. The lower limit of quantification was set at $0.02 \mu\text{g/ml}$ for the plasma assay and $0.01 \mu\text{g/ml}$ for the cervical mucus assay, these being the lowest calibration datum point on the respective calibration lines. As the cervical mucus samples were too viscous or of insufficient volume to sample by volume, they were weighed and suspended in phosphate buffer before analysis. Azithromycin concentrations in mucus are therefore expressed as a weight basis as $\mu\text{g/g}$.

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Chlamydia trachomatis was identified by cell culture using cycloheximide treated McCoy cells.⁹ Inclusion bodies were detected by staining with a fluorescein labelled monoclonal antibody (SYVA, Culture Confirmation Test).

Results

Plasma concentrations

On study day 1, 24 hours after the intake of 1 g azithromycin the plasma concentrations of azithromycin were above the limit of quantification in all samples with a median value of 0.071 µg/ml (range 0.024–0.126 µg/ml). On study day 7 and 14 concentrations of azithromycin were below limit of quantification in all plasma samples (table).

Mucus concentrations

On study day 1 the cervical mucus concentrations of azithromycin were above the limit of quantification in 19 samples with a median value of 2.67 µg/g (range 0.57–9.51 µg/g). Owing to interference from co-eluting endogenous material quantification of azithromycin was impossible in one sample on day 1. On study day 7 and 14 azithromycin concentrations were below the limit of quantification in two out of 18 and in seven out of 20 samples. On day 7 one sample was missing and one sample could not be quantified owing to interference. The median values on day 7 and 14 were 1.26 µg/g (range 0.39–5.65 µg/g) and 0.15 µg/g (range 0.07–1.06 µg/g), respectively (table).

Correlation

There was a linear correlation between plasma and mucus concentrations on day 1 ($r = 0.86$) (fig).

Efficacy

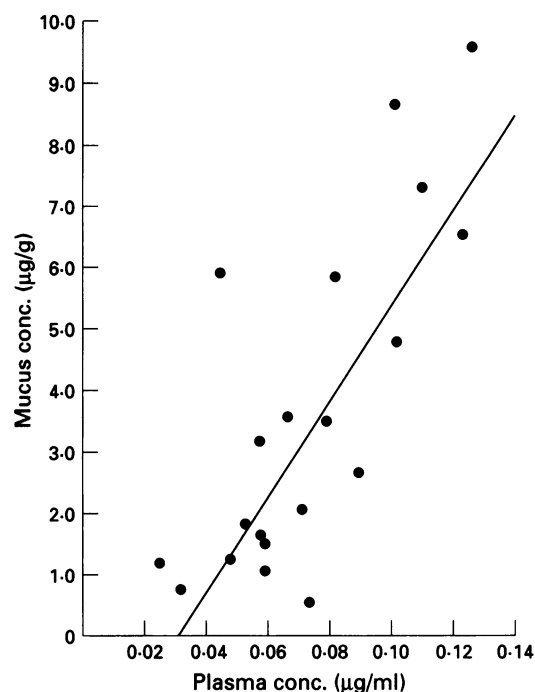
At the day of treatment (day zero) cervical chlamydial infection was only detectable in 16 out of the 20 treated women who had had a culture proven cervical chlamydial infection within the last week of enrolment. At day 7, 15 women were reexamined, 14 of whom were chlamydia culture negative giving a cure rate of 93%. At day 14, the patient declining at day 7, was examined together with the 14 patients found chlamydia negative, on day 7. One woman was chlamydia positive on day 14, most likely due to reinfection, giving a cure rate of either 93% or 100%.

Azithromycin concentrations in plasma and cervical mucus of 20 women with chlamydia cervicitis examined day 1, 7 and 14 after a single oral dose of azithromycin. (Median and range)

	Day 1	Day 7	Day 14
Mucus µg/g*	2.67 (0.57–9.51)	1.26 (0.39–5.56)	0.15 (0.07–1.06)
Plasma µg/ml	0.071 (0.024–0.126)	BLQ	BLQ

BLQ = Below limit of quantification.

*19 samples evaluable on day 1, 18 samples evaluable on day 7 with 2 BLQ, 20 samples evaluable on day 14 with 7 BLQ.



Azithromycin concentrations in plasma and cervical mucus from 20 women one day after a single oral dose of 1 g azithromycin ($r = 0.86$).

Adverse effects were limited to mild gastrointestinal discomfort in three out of all 20 women. There were no major abnormal biochemical changes.

Discussion

Azithromycin is an azalide antimicrobial agent. It is active in vitro against a wide spectrum of bacteria.¹⁰ The minimal inhibitory concentration (MIC) for azithromycin against *Chlamydia trachomatis* is in the range of 0.063–0.25 µg/ml with MIC₉₀ values around 0.12 µg/ml.^{1,2,10}

Animal model data indicate that azithromycin concentrations are increased at sites of localised infection, correlating with the presence of inflammation. The ability of phagocytes to take up the drug may be an important mechanism for its delivery to infected sites and for sustaining high levels at these sites.¹¹ The observation¹² that azithromycin concentrations in inflammatory fluid are dependent on total dose, rather than dosing interval, has resulted in rational dosage regimens of azithromycin based on pharmacokinetic modelling.¹³

The goal in selection of dosage regimens is to maintain therapeutic concentrations of azithromycin in relevant sites and tissues for a minimal of 5–10 days, following initiation of therapy. The in vitro activity of azithromycin against *Chlamydia trachomatis* suggests that a single 1 g dose should be sufficient as it leads to estimated tissue concentrations above the MIC for *Chlamydia trachomatis* for up to 10 days.¹³ During recent years several studies

have actually shown that this regimen is highly effective and well tolerated in both male and female genitourinary chlamydial infections,⁴⁻⁸ as shown in this study.

A recent study, on the pharmacokinetics of azithromycin, in healthy male volunteers¹⁴ showed that azithromycin was concentrated approximately two-fold higher in cantharidin induced inflammatory blister fluid compared with non-inflammatory suction blister fluid.

The penetration of azithromycin to tissues in the genital tract has been demonstrated in prostatic and seminal fluid in healthy volunteers.¹⁵ In that study azithromycin concentrations examined 24 hours after a single oral dose of 1 g azithromycin were much higher in prostatic fluid (mean 3.02 µg/ml) and in seminal fluid (2.39 µg/ml) than in plasma (0.07 µg/ml) with sustained concentrations after 48 hours. These data were taken as support for the efficacy of a single 1.0 g dose for chlamydial urethritis. The peripheral mucus and plasma concentrations after 24 hours in our study are very similar to the fluid and plasma concentrations in the latter study.¹⁵

In order to further substantiate the theoretical evidence for a sustained tissue concentration at the site of infection, azithromycin concentrations were measured in cervical mucus as late as seven and 14 days after a single oral 1 g azithromycin dose in our study in women with chlamydial cervicitis.

Technically it is difficult to suck cervical mucus if cervical secretion is minimal, which was the case in some women already the day after treatment and in almost all the women at day 7 and 14. The sucking procedure caused some bleeding in several cases, but owing to the much lower plasma concentrations already seen on day 1 it can be concluded that blood contamination did not contribute to the high mucus concentrations.

Women with the most prominent cervical discharge at the day of inclusion tended to have the highest mucus concentrations of azithromycin, a fact that is in line with a specific uptake of azithromycin by polymorphonuclear leucocytes at sites of inflammation.

The two women with concentrations below the level of quantification at day 7, had measurable levels at day 14. This discrepancy may be explained by the limited amount of samples, that also made it impossible to repeat these assays. All measurable concentrations as well on day 7 as on day 14 were higher than MIC₉₀ values for *Chlamydia trachomatis*. Of the 20 women culture positive one week before inclusion, repeat culture at the day of treatment was negative in four women, a degree of reproducibility lower than expected. Azithromycin concentrations in the mucus samples for these women did not differ from the overall measurements.

It can be concluded that the data from this study strongly support the clinical results from previous studies,⁴⁻⁸ that a single oral dose of azithromycin is sufficient for the treatment of uncomplicated chlamydial cervicitis, as the measured mucus concentrations exceeded MIC₉₀ values for at least seven days. This conclusion is, however, based on the assumption that mucus concentrations equate intracellular concentrations, this site being most relevant when treating an intracellular organism. It is well known that short-course therapy improves patient compliance and thus the therapeutic outcome with a faster resolution of infection and a lower incidence of recurrence.¹⁶ It seems therefore documented in clinical as well as in pharmacokinetic studies that a single 1.0 g dose of azithromycin is effective and safe in genitourinary chlamydial infections in both men and women.

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