Eur. J. Clin. Microbiol. Infect. Dis., October 1991, p. 807–812
0934-9723/91/10 0807-06 $ 3.00/0

The Pharmacokinetics of Azithromycin and Their Clinical Significance

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The usefulness of erythromycin is limited by its poor pharmacokinetic profile which is characterised by low blood levels and poor gastric acid stability. Erythromycin's short half-life means that a four-times daily dosage schedule is required for effective treatment. In comparison, the azalide structure of azithromycin confers a much improved pharmacokinetic profile. The bioavailability of azithromycin is approximately 37 % in humans (25 % for erythromycin). Serum concentrations decline in a polyphasic manner and the relatively short serum half-life (11–14 hours recorded 8–24 hours after last dose) is an indication of the initial rapid distribution of drug into the tissues. The low serum levels recorded 24 hours or more after the end of administration are thought to reflect the slow release of azithromycin from tissues. Tissue concentrations exceed serum concentrations by as much as 100-fold following a single 500 mg oral dose. Macrophages and polymorphonuclear leucocytes concentrate azithromycin at levels greater than those found in tissues themselves. During multiple dosing, tissue half-life increases with duration of administration and the tissue to serum ratio further increases. High concentrations of drug are found in tissues such as tonsil, lung, prostate, liver and lymph nodes with relatively low concentrations in fat and muscle. Significantly, the sustained high levels of drug in the tissues appears to correlate with good in vivo activity. Two 1.5 g regimens have been investigated in clinical trials: 500 mg on day 1, followed by 250 mg daily on days 2 to 5; or 500 mg daily for three days. These regimens are expected to maintain azithromycin levels in tissue sites of infection above the MIC for many clinically significant pathogens, and to continue to do so for several days after administration has ceased. In addition, single-dose (1 g) azithromycin has demonstrated excellent clinical efficacy in the therapy of chlamydial urethritis/cervicitis, the high and prolonged tissue levels of antibiotic enabling such a regimen to be effective.

Azithromycin is the prototype of a new class of antibiotics known as azalides. It differs structurally from the macrolide erythromycin by the insertion of a methyl-substituted nitrogen at position 9a in the lactone ring, creating a 15-membered structure. This modification leads to an extension of the broad spectrum of activity against gram-positive and gram-negative bacteria in comparison with macrolides (1). In particular, azithromycin demonstrates in vitro activity against *Haemophilus influenzae* as well as other commonly encountered respiratory pathogens (1–3).

Azalide antibiotics are distinguished from other antibiotics by their unusual pharmacokinetics – notably high and sustained tissue concentrations and a long tissue half-life. Azithromycin penetrates intracellularly but serum levels remain relatively low. Traditionally, serum concentration in relation to minimum inhibitory concentration (MIC) has been the predictor of antibiotic efficacy. The pharmacokinetics of azithromycin suggest that the tissue concentration to MIC ratio may be a better index for predicting its activity.

This paper reviews the pharmacokinetic profile of azithromycin and discusses it in the context of clinical practice.

Serum Pharmacokinetics

Table 1 provides a summary of the pharmacokinetics of azithromycin in serum.

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Table 1: Summary of the serum pharmacokinetics of azithromycin with different dosage regimens. (From reference 5.)

Pharmacokinetic parameter		Dosage regimen			
		500 mg single oral dose	500 mg single intravenous dose	500 mg every 12 h (day 1) 500 mg daily (days 2–6)	250 mg every 12 h (day 1) 250 mg daily (days 2–10)
C_{max} (mg/l)	first dose	0.4		0.41	0.2
	last dose			0.62	0.21
AUC_{0-12} (mg x h/l)	first dose			1.77	0.80
	last dose			3.18	1.22
AUC_{0-24} (mg x h/l)		2.36	6.48		
AUC_{0-48} (mg x h/l)		3.08	8.07		
AUC_{0-72} (mg x h/l)		3.39	9.08		
$t_{1/2}$ (8–24 h)			11–14 h		
$t_{1/2}$ (24–72 h)			35–40 h	48 h[b]	
Urinary excretion[a]		4.5 %	12.2 %		

[a] 72 h after administration
[b] After the last dose.

Azithromycin is relatively stable at the low pH of the stomach. At pH 2, erythromycin decays by 10 % in 3.7 seconds while 10 % azithromycin decay is observed in 20 minutes (4). After a single oral 500 mg dose, the bioavailability of azithromycin is approximately 37 % (5).

Foulds et al. (5) carried out single-dose studies with 500 mg and found a C_{max} value of 0.4 mg/ml; $AUC_{(0-24)}$, $AUC_{(0-48)}$ and $AUC_{(0-72)}$ values recorded were 2.36, 3.08 and 3.39 mg x h/l, respectively (Table 1). The serum elimination follows a polyphasic pattern. The initial rapid decline in drug blood concentration implies a rapid redistribution into tissues, the second component representing further distribution and elimination. Apparent elimination into the urine within 72 hours of administration was 12.2 % after intravenous administration and 4.5 % after oral administration (5).

Foulds et al. (5) have also investigated the pharmacokinetics of multiple dose regimens (Table 1). Using a five day regimen (two doses of 500 mg on the first day, followed by 500 mg daily for four days), the $AUC_{(0-12)}$ increased from 1.77 to 3.18 mg x h/l and the C_{max} from 0.41 to 0.62 mg/l. With a separate regimen (two 250 mg doses on day 1, followed by 250 mg/day for nine days), mean values of the $AUC_{(0-12)}$ increased from 0.80 mg x h/l to 1.22 mg x h/l and the C_{max} remained similar (0.2 mg/l to 0.21 mg/l) after the last dose on day 10.

The apparent serum half-life of azithromycin recorded between 8 and 24 hours after a single dose, or following the last multiple dose, was 11 to 14 hours. Over the interval of 24 to 72 hours after a single dose of 500 mg, a half-life of between 35 and 40 hours was recorded. Following a schedule of 500 mg b.i.d. for five days, a half-life of 48 hours was recorded between 24 and 72 hours post-dose, and a half-life of 2.6 days was recorded between 1 and 6 days after the end of administration (5).

Protein binding is low, the percentage drug bound increasing with decreasing serum concentration: 50 % binding of azithromycin is observed at a serum concentration of 0.05 mg/l but binding is only 12 % at 0.5 mg/l (5).

Tissue Penetration of Azithromycin

The high affinity of azithromycin for tissues is thought to be due to the presence of two basic tertiary amine groups which give azithromycin amphiphilic properties (6). Behaving as a lysosomotropic agent, azithromycin may be concentrated in lysosomes of tissues and host defense cells (7).

The rapid uptake of azithromycin by tissues gives a tissue to serum concentration estimated to be between 10- and 100-fold (5). In comparison, the

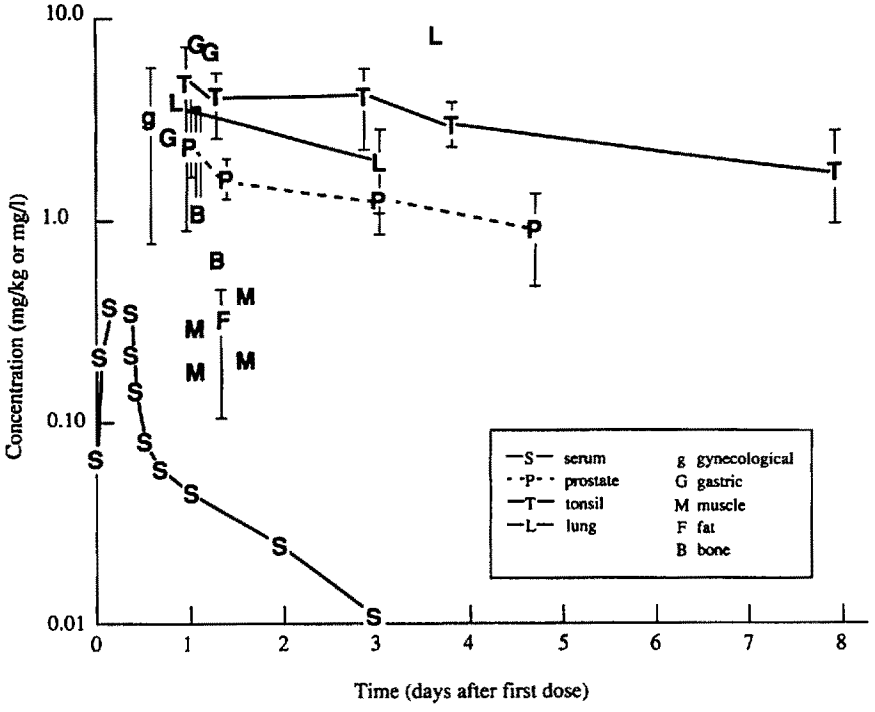

Figure 1: Tissue concentrations of azithromycin in man after administration of a single oral 500 mg dose (mean ± SD). (Adapted from reference 5.)

ratio of tissue to serum concentration for erythromycin is estimated to be between 0.5 and 5 in humans (8). In most tissues, at 12 hours post-dose the concentration of azithromycin is between 1 and 9 mg/kg following a single oral dose of 500 mg (Figure 1) (5). The high levels of azithromycin in the tissue are sustained and remain above 2.0 mg/kg at 12 and 24 hours post-dose in tonsil and prostate, for example. The average tissue half-life is estimated to be between 2 and 4 days. However, four days after a single oral dose of 500 mg, the concentration in the prostate is still between 0.8 mg/kg and 2.3 mg/kg, in pulmonary tissue 2.3–8.1 mg/kg, and in gynaecological tissues 0.27–1.48 mg/kg. Four-day tissue concentrations in the tonsils are 0.26–2.0 ml/kg and remain above detectable levels for over a week after dosing (9). These levels exceed the MIC90 for key target pathogens such as *Chlamydia trachomatis, Ureaplasma urealyticum, Neisseria gonorrhoeae* and *Haemophilus ducreyi.* Much lower concentrations (0.2–1.0 mg/kg) are found in samples of fat, muscle and bone but all tissue levels are higher than those of concurrently obtained serum samples (5).

Azithromycin concentrations in the eye and brain exceed serum concentrations by a factor of 20 and 1.2, respectively (5). For most antibiotics penetration into these tissues is very low and this unusual feature of azithromycin suggests that it has some potential for the treatment of organ-specific infections.

Recent UK data from patients undergoing elective fibreoptic bronchoscopy have shown concentrations in bronchial mucosa greater than 3 mg/kg, which last for five days after a single 500 mg oral dose (10). Serum concentrations over the same period were less than 0.1 mg/l. Azithromycin was also found at high levels in epithelial lining fluid and in sputum, these findings together suggesting that azithromycin will be useful in the treatment of infective exacerbations of chronic bronchitis and pneumonia.

Cooper et al. (11) have also demonstrated rapid penetration of the agent into tissue and inflammatory fluid of male volunteers. The mean peak concentration in inflammatory fluid of chemically induced blisters was 0.13 mg/l, achieved at a mean time of 3.25 hours after a single 500 mg oral dose. The authors commented that such penetration by antibiotics could lead to better in vivo results than would be expected from comparing serum concentrations with MICs.

Important to the understanding of the clinical activity of this agent are findings from in vivo and in vitro studies which show that azithromycin is rapidly and highly concentrated in human phago-

cytic cells. In vitro, the concentrations of azithromycin achieved in peritoneal macrophages is up to 26-fold greater than that of erythromycin (6). The penetration of azithromycin into phagocytes has been attributed to its lysosomotropic behaviour. It has also been suggested that phagocytes may transport and target the drug to areas of inflammation and infection (6). In mice, caseinate-induced polymorphonuclear leucocyte (PMNL) infiltration of the peritoneal cavity increases the overall azithromycin levels in the peritoneal cavity sixfold. The increase was coincident with the increase in cell numbers and was predominantly cell-associated (PMNLs contained 79 mg/l of azithromycin) (6). It is assumed that this targeting of drug to the site of inflammation is a result of uptake and transport of azithromycin by phagocytes, although further studies in humans are required.

Correlation between Extravascular Concentrations and Efficacy

The significance of the extravascular concentrations of azithromycin on efficacy have been demonstrated in a number of in vivo models of infection (12–14).

The importance of improved intracellular concentration becomes particularly apparent when comparing the in vitro and in vivo activity of antibiotics against tissue associated infection caused by organisms such as *Salmonella enteritidis* (12, 13). Despite an in vitro potency of ciprofloxacin 100 times that of azithromycin, in vivo studies in mice have demonstrated that a dose of 5 mg/kg azithromycin was superior to 100 mg/kg ciprofloxacin in reducing the colony forming units count at the primary site of infection – the liver. Significantly, the efficacy of azithromycin in this model correlated directly with levels of drug in the liver, but not with levels in the blood which were well below the MIC value.

As a consequence of sustained high tissue levels, the activity of azithromycin observed in localized infections is frequently bactericidal. In a *Streptococcus pneumoniae* mouse lung infection model, Retsema et al. (14) demonstrated azithromycin's superior bactericidal activity compared with erythromycin and roxithromycin. In vitro killing kinetics revealed that both azithromycin and erythromycin were bacteriostatic for the first eight hours of incubation but were bactericidal (greater than 99.9 % kill) at 24 hours. By contrast, in vivo studies clearly demonstrate that only azithromycin (25 mg/kg) had bactericidal activity with greater than 99.9 % cell kill. Erythromycin (100 mg/kg) did not have any bactericidal activity, and roxithromycin reduced the colony count by more than 96 % only at a dose of 50 mg/kg. These observations are consistent with the findings which show that high levels of azithromycin remain detectable in lung tissue beyond 90 hours, even at doses as low as 10 mg/kg.

Recently, azithromycin (200 mg/day for 10 days) has also been shown to be active against a lethal inoculum of *Toxoplasma gondii* given intracerebrally on day 35. These findings are significant because they illustrate that azithromycin attains active concentrations in the inflamed central nervous system (15).

Metabolism and Excretion

Demethylation is the primary route of metabolism and the metabolites are not thought to have any significant antimicrobial activity (16). Urinary excretion of the unchanged drug in humans appears to be a minor elimination route, amounting usually to less than 6 % within one week after an oral dose. About 20 % of the drug that reaches the systemic circulation is excreted unchanged in the urine. Renal clearance is generally in the range of 100–189 ml/min. The faeces are an important route of elimination. Biliary concentrations of azithromycin are much greater than the serum levels, suggesting biliary concentration (16). Over half the drug-related material in the bile is unchanged.

Drug Interactions

Azithromycin, like erythromycin, interacts with the cytochrome P-450 system of hepatocyte smooth endoplasmic reticulum and causes significant elevation of azithromycin and erythromycin N-demethylase activity in rat studies. However, no clinically significant drug interaction has been observed with either warfarin or theophylline, although the routine monitoring of prothrombin and theophylline plasma concentrations is prudent.

Some macrolides are reported to precipitate er-

Table 2: MIC90 values of azithromycin for four common respiratory pathogens.

Organism	MIC90 range (mg/l)	Reference
Haemophilus influenzae	0.06–1.0	17
Staphylococcus aureus (erythromycin susceptible)	0.25–1.0	18
Staphylococcus aureus (erythromycin resistant)	32 – > 64	18
Moraxella catarrhalis	≤ 0.015	19

gotism and therefore co-administration of azithromycin with ergotamine derivatives should be avoided. Similarly, some macrolides have been reported to impair the metabolism of digoxin and there is the possibility that such a reaction may occur with azalides also. Erythromycin has been shown to prevent the intestinal breakdown of digoxin, thereby increasing plasma levels.

Foulds et al. (6th International Congress for Infectious Diseases, Montreal, 1990, Abstract 159), have demonstrated recently that there is no statistically significant effect on the pharmacokinetics of either azithromycin or cimetidine following co-administration. However, co-administration of azithromycin with the antacid, Maalox, resulted in a decrease (up to 25 %) in the peak plasma levels of azithromycin, although the extent of absorption (AUC) was not reduced. C_{max} values do not have a critical effect on azithromycin's efficacy, but it is probably prudent to avoid simultaneous administration with antacids.

Comments

The serum kinetics of azithromycin are consistent with its good oral absorption, rapid tissue distribution and slow release back into the blood. Tissue concentrations are much greater than those in the serum and persist for days rather than hours. In a number of animal models of infection, azithromycin has proved effective when serum levels are below the MIC but tissue concentrations are at or above the MIC. Facultative intracellular organisms such as *Legionella, Listeria* and *Chlamydia* species may also be subject to azithromycin's cellular penetration and concentration.

Azithromycin's unusual pharmacokinetic profile would appear to offer clinical benefits, particularly in the treatment of respiratory infections and tissue-associated or localised infections. The once-daily regimens developed (1.5 g total dose given over three or five days) are expected to produce levels above 2 mg/kg in a wide variety of tissues during and for several days after administration. These short, simplified dosage regimens have proved successful in clinical trials in respiratory tract infections, and skin and soft tissue infections, and azithromycin should therefore be particularly acceptable to patients through its ease of administration.

In respiratory tract infections, the predicted tissue concentrations can be compared with the MIC values for key target organisms (Table 2). Pharmacokinetic studies in humans indicate that the concentrations of azithromycin in the respiratory tract are above 3 mg/kg during the proposed regimens (5). Therefore, it can be predicted that once-daily dosage regimens of azithromycin will be effective in the treatment of many upper and lower respiratory tract infections.

Concentrations of azithromycin in the prostate and tonsils are considered representative of the concentrations observed in many soft tissues. From Figure 1, it can be seen that the projected levels of drug in the tonsils and prostate remain above 6 mg/kg and 3 mg/kg, respectively.

Following a 1 g oral dose of azithromycin, gynaecological tissue levels are above the MIC90 for key target organisms *(Chlamydia trachomatis, Ureaplasma urealyticum, Neisseria gonorrhoeae, Haemophilus ducreyi)* (5). Results from clinical trials to date demonstrate the potential of such a regimen (20, C. van den Bosch, 6th International Congress for Infectious Diseases, Montreal, 1990, Abstract 163). Steingrimsson et al. (20) found that a 1 g single dose was as effective as a three-day regimen (500 mg on day 1 and 250 mg q.i.d on days

2 to 3) in patients with *Chlamydia trachomatis, Neisseria gonorrhoeae* and *Ureaplasma urealyticum.* Moreover, the single dose regimen was comparable with a seven-day regimen of doxycycline. This finding has important implications for the treatment of chlamydial infections for which there are currently no single dose treatments available.

In summary, consideration of the tissue concentrations and tissue half-lives of azithromycin provides a pharmacokinetic rationale for using a once-daily regimen of 500 mg for common infections of the respiratory tract, skin and soft tissues and some sexually transmitted diseases. Such a regimen given over three or five days appears to produce drug concentrations greater than 2 mg/kg in many tissues for several days after administration has ceased. Thus, azithromycin shows promise as an antibiotic with novel pharmacokinetics that call into question the use of serum concentrations alone to predict efficacy. The ability of an antibiotic to penetrate tissues where the infection is based must now be considered a critical element in understanding antibiotic activity.

References

1. **Retsema J, Girard A, Schelkly W, Manousos M, Anderson M, Bright G, Borovoy R, Brennan L, Mason R:** Spectrum and mode of action of azithromycin (CP-62,993), a new 15-membered-ring macrolide with improved potency against gram-negative organisms. Antimicrobial Agents and Chemotherapy 1987, 31: 1939–1947.
2. **Bright GM, Nagel AA, Bordner J, Desai KA, Dibrino JN, Nowakowska J, Vincent L, Watrous RM, Sciavolino FC:** Synthesis, in-vitro and in-vivo activity of novel 9-deoxo-9a-aza-9a homoerythromycin A derivative; a new class of macrolide antibiotics, the azalides. Journal of Antibiotics 1988, 41: 1029–1047.
3. **Fitzgeorge RB, Featherstone ASR, Baskerville A:** Efficacy of azithromycin in the treatment of guinea pigs infected with *Legionella pneumophila* by aerosol. Journal of Antimicrobial Chemotherapy 1990, 25, Supplement A: 101–108.
4. **Fiese EF, Steffen SH:** Comparison of the acid stability of azithromycin and erythromycin. Journal of Antimicrobial Chemotherapy 1990, 25, Supplement A: 39–47.
5. **Foulds G, Shepard RM, Johnson RB:** The pharmacokinetics of azithromycin in human serum and tissues. Journal of Antimicrobial Chemotherapy 1990, 25, Supplement A: 73–82.
6. **Gladue RP, Bright GM, Isaacson RE, Newborg MF:** In vitro and in vivo uptake of azithromycin (CP-62,993) by phagocytic cells: possible mechanism of delivery and release at sites of infection. Antimicrobial Agents and Chemotherapy 1989, 33: 277–282.
7. **de Duve C, de Barsy T, Poole B, Trouet A, Tulkens P, van Hoof F:** Lysosomotropic agents. Biochemical Pharmacology 1974, 23: 2494–2531.
8. **Dette GA:** Vergleich der Gewebegängigkeit von Erythromycin (tissue penetration of erythromycin). Infection 1979, 7: 129–145.
9. **Foulds G, Chan KH, Johnson JT, Shepard RM, Johnson RB:** Concentrations of azithromycin in human tonsillar tissue. European Journal of Clinical Microbiology and Infectious Diseases 1991, 10: 853–856.
10. **Baldwin DR, Wise R, Andrews JM, Ashby JP, Honeybourne D:** Azithromycin concentrations at the sites of pulmonary infection. European Respiratory Journal 1990, 3: 886–890.
11. **Cooper MA, Nye K, Andrews JM, Wise R:** The pharmacokinetics and inflammatory fluid penetration of orally administered azithromycin. Journal of Antimicrobial Chemotherapy 1990, 26: 533–538.
12. **Girard AE, Girard D, English AR, Gootz TD, Cimochowski CR, Faiella JA, Haskell SL, Retsema JA:** Pharmacokinetic and in-vivo studies with azithromycin (CP-62,993), a new macrolide with an extended half-life and excellent tissue distribution. Antimicrobial Agents and Chemotherapy 1987, 31: 1948–1954.
13. **Girard AE, Girard D, Retsema JA:** Correlation of the extravascular pharmacokinetics of azithromycin with in-vivo efficacy in models of localized infection. Journal of Antimicrobial Chemotherapy 1990, 25, Supplement A: 61–71.
14. **Retsema JA, Girard AE, Girard D, Milisen WB:** Relationship of high tissue concentrations of azithromycin to bactericidal activity and efficacy in-vivo. Journal of Antimicrobial Chemotherapy 1990, 25, Supplement A: 83–89.
15. **Araujo FR, Guptill DR, Remington JS:** Azithromycin, a macrolide antibiotic with potent activity against *Toxoplasma gondii.* Antimicrobial Agents and Chemotherapy 1988, 32: 755–757.
16. **Shepard RM, Falkner FC:** Pharmacokinetics of azithromycin in rats and dogs. Journal of Antimicrobial Chemotherapy 1990, 25, Supplement A: 49–60.
17. **Goldstein FW, Emiram MF, Coutrot A, Acar JF:** Bacteriostatic and bactericidal activity of azithromycin against *Haemophilus influenzae.* Journal of Antimicrobial Chemotherapy 1990, 25, Supplement A: 25–28.
18. **Maskell JP, Sefton AM, Williams JD:** Comparative in-vitro activity of azithromycin against gram-positive cocci, *Haemophilus influenzae* and anaerobes. Journal of Antimicrobial Chemotherapy 1990, 25, Supplement A: 19–24.
19. **Dunkin KT, Jones S, Howard AJ:** The in-vitro activity of CP-62,993 against *Haemophilus influenzae, Branhamella catarrhalis,* staphylococci and streptococci. Journal of Antimicrobial Chemotherapy 1988, 21: 405–411.
20. **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, Supplement A: 109–114.