

# REVIEW: COMPERATIVE PHARMACOKINETIC STUDY OF AZITHROMYCIN AND ROXITHROMYICIN IN ALTERED GASTRIC MOTILITY ON WISTAR RATS

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**Abstract:** Pharmacokinetics of macrolides affect serum concentration of other drugs. Azithromycin and Roxithromycin are antimicrobial macrolides. Azithromycin is derived from erythromycin containing methyl substituted nitrogen in lactone ring whereas Roxithromycin is an ether oxime derivative of Erythromycin. These modifications in structure result in better gastrointestinal tolerability and tissue penetration of both these drugs. Azithromycin and Roxithromycin are acid stable therefore both exhibit better oral bioavailability and more favorable pharmacokinetic properties. Azithromycin and Roxithromycin have greater distribution in tissues, a longer elimination half-life and a lower incidence of adverse effects. These both drugs are used against gram negative bacteria and commonly used for respiratory tract infection .Azithromycin have clinical uses such as used in sexually transmitted diseases, upper and lower respiratory tract infections, skin and structure infections. Roxithromycin is used against the organisms such as Mycobacterium avium complex, Helicobacter pylori, Borrelia spp., Legionella, pneumophila. Clinically the Roxithromycin is used for Lower respiratory tract infections including pneumonia, atypical pneumonia, chronic obstructive lung disease and bronchitis. Upper respiratory tract infections including tonsillitis, pharyngitis, otitis media and sinusitis. Acute or chronic non - gonococcal urethritis, non - gonococcal sexually transmitted infections and cervicovaginitis. Skin and soft tissue infections including pyoderma, infective dermatitis and leg ulcers. Prophylaxis of meningococcal meningitis.

**Index Terms – Azithromycin, Roxithromycin, Pharmacokinetics. Serum pharmacokinetics**

## I. INTRODUCTION

Azithromycin [9-deoxy-9a-aza-9a-methyl-9a-homoerythromycin dehydrate, is an azalide, a subclass of macrolide antibiotics for oral administration Azithromycin belongs to a new class of antibiotics known as the azalides<sup>[1]</sup>. Azithromycin is white or almost white powder. It is practically insoluble in water, freely soluble in ethanol and in methylene chloride. Azithromycin is derived from erythromycin containing methyl substituted nitrogen in lactone ring, it has been stable to be more acid stable therefore it exhibit better oral bioavailability and more favorable pharmacokinetic properties. These modifications in structure result in better gastrointestinal tolerability and tissue penetration. Following oral administration, absorption of azithromycin is rapid. The absolute bioavailability of azithromycin capsules [no longer commercially available] is 38%. According to the manufacturer, the azithromycin 250 mg tablets are bioequivalent to the azithromycin 250 mg capsules in the fasted state. Azithromycin has a greater distribution in tissues, a longer elimination half-life, and a lower incidence of adverse effects. Peak plasma concentrations are achieved within 2 to 3 hours. Although somewhat structurally similar to the macrolides [e.g., erythromycin], azithromycin has superior activity against gram-negative organisms while retaining good activity against gram-positive microorganisms<sup>[2]</sup>. Azithromycin a new 15-member-ring macrolide, the first of a novel subclass referred to as the azalides, and shows significantly improved potency against gram-negative bacteria<sup>[3]</sup>. Azithromycin penetrates cells and accumulates intracellularly, which suggest that it would be useful in the treatment of infections caused by intracellular pathogens such as mycobacteria, chlamydia, and Legionella pneumophila. Azithromycin, a macrolide antibiotic structurally similar to erythromycin, exhibits a broad spectrum activity and is effective against gram-positive, gram-negative, and atypical bacteria<sup>[4]</sup>. It is an effective therapeutic agent for oral treatment of sexually transmitted diseases, upper and lower respiratory tract infections, and skin and structure infections. The incidence or severity of adverse effects is mainly because of high peak plasma concentrations of AZI that are seen within 2–3 hr after per oral administration.

Roxithromycin is a semi-synthetic macrolide antibiotic<sup>[5]</sup>. Roxithromycin is an ether oxime derivative of Erythromycin and acid stable macrolide antibacterial. Oxime derivatives are less prone to intramolecular cyclization, thus Roxithromycin is stable macrolide.

SRoxithromycin is chemically designated as [E]-erythromycin-9-o-[[2-methoxyethoxy]methyl]oxim<sup>[1]</sup> Roxithromycin is bacteriostatic at low concentrations and bactericidal at high concentrations<sup>[5]</sup> Roxithromycin is a semi-synthetic 14-membered-ring macrolide antibiotic in which the erythronolide A lactone ring has been altered to prevent inactivation in the gastric milieu. It exhibits excellent antimicrobial activities *in vivo* because of its outstanding stability in acidic conditions and superior pharmacokinetic properties. Roxithromycin is characterized by high concentrations in serum.

Mean peak concentrations in serum measured 7.90, 10.82, and 12.24 µg/ml after administration of 150, 300, and 450 mg, respectively. Preliminary information available on the pharmacokinetics of roxithromycin suggests that it is well absorbed and gives levels in serum; thus, it is possible that roxithromycin may be administered at lower doses. The cellular uptake of Roxithromycin is more. Roxithromycin is used for treatment of respiratory tract, urinary and soft tissue infections. A lot of reports clearly showed that roxithromycin [RXM], a macrolide antibiotic, strongly inhibits inflammatory cytokine production from T cells and macrophages *in vitro* and *in vivo*. The solubility of drug in water is less [0.0189 mg/lit] and therefore its oral bioavailability is only 50%. Roxithromycin is active against *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Branhamella catarrhalis*, *Mycoplasma pneumoniae*. The *in-vitro* activity of roxithromycin is well documented and similar to that of other macrolide antibiotics<sup>[6]</sup>. The Macrolides—azithromycin, roxithromycin do not have more adverse effects and seem to be effective *in vitro*; for this reason, they have emerged as a potential alternative therapy. Roxithromycin plasma samples were determined by HPLC-ED with mobile phase phosph. buff.—MeOH—ACN—iPrOH. Influence of a macrolide antibiotic, roxithromycin [RXM], on the production of pro-inflammatory cytokines, interleukin [IL]-1b and tumor necrosis factor [TNF]-α. Azithromycin and Roxithromycin have both anti-inflammatory and immune-modulatory properties and are thus beneficial to chronic pulmonary diseases such as diffuse pan-bronchiolitis, cystic fibrosis, asthma and bronchiectasis. Antibacterial activity of roxithromycin is reduced at pH values below 7.4. Some methods based on reversed phase HPLC have been developed for quantitative determination of Azithromycin and Roxithromycin. UV absorption, Fluorescence and Electrochemical detection methods have been used but these methods achieved only relatively high detection limits so they are not suitable to determine low level of Azithromycin and Roxithromycin in serum. Roxithromycin and Azithromycin may reach similar concentrations in human polymorphonuclear leucocytes when conditions mimic clinical administration of these drugs.

## II. HISTORICAL ASPECTS

Azithromycin is distinguished from other antibiotics by their unusual pharmacokinetics notably high and sustained tissue concentrations and long tissue half-life. Azithromycin penetrates intracellularly but serum level remains relatively low. Traditionally serum concentration in relation to minimum inhibitory concentration [MIC] has been predictor of antibiotic efficacy<sup>[7]</sup>. Azithromycin extensively penetrates cells, including tissue fibroblasts and it appears to be localized primarily in lysosomes. However, azithromycin has been shown to be effective in animal models as treatment of infections caused by both intracellular and extracellular organisms<sup>[8]</sup>. Azithromycin has shown potency up to 4 times higher than erythromycin against *Haemophilus influenzae* and *Neisseria gonorrhoeae* and is particularly effective against the intracellular microorganism *Chlamydia trachomatis*, the leading cause of infectious blindness<sup>[4]</sup>. Azithromycin [AZM] has demonstrated immune modulating activity and impairment of the formation of alginate biofilm from mucoid *P. aeruginosa*. Meta-analysis study was undertaken in order to measure the efficacy of azithromycin versus first line antibiotics [cephalosporins, quinolones and chloramphenicol] in the therapeutic management of typhoid fever. The *in-vitro* activity of roxithromycin is well documented and similar to that of other macrolide antibiotics. Roxithromycin is active against Gram-positive and Gram-negative cocci, Gram positive bacilli and some Gram-negative bacilli, but has no significant effect on the predominant faecal flora. It also displays good activity against atypical pathogens, such as *Mycobacterium avium* complex, *Helicobacter pylori* and *Borrelia* spp. It penetrates and accumulates within cells, such as macrophages and polymorphonuclear neutrophils [PMNs], where it is distributed between the cytosol and cellular granules<sup>[6]</sup>.

## III. CHEMISTRY OF AZITHROMYCIN AND ROXITHROMYCIN

Azithromycin [9-deoxy-9a-aza-9a-methyl-9a-homoerythromycin] is derived structurally from erythromycin A by replacing the 9a carbonyl in the aglycone ring with a methyl-substituted nitrogen, as well as expansion of the ring to 15 members. This structural difference blocks the internal reaction to form the hemiketal, leaving acid hydrolysis of the ether bond to the neutral cladinose sugar as the main decomposition pathway.

In solution at 37°C and pH 2 with ionic strength  $\mu = 0.02$ , azithromycin is degraded with 10% decay in 20.1 min, whereas the equivalent value for erythromycin is only 3.7 sec. The activation energy for hydrolysis of the ether bond linking cladinose to azithromycin is 25.3 kcal/mol; in contrast, the internal dehydration reaction of erythromycin has an activation energy of 15.6 kcal/mol. In general, these results indicate a 300-fold increase in acid stability for azithromycin, compared with erythromycin over the gastric pH range<sup>[8]</sup>.

Azithromycin [9-deoxy-9a-aza-9a-methyl-9a-homoerythromycin] is formed by inserting a methyl-substituted nitrogen in place of the carbonyl group at the 9a position of the aglycone ring. The resulting dibasic 15-membered ring macrolide derivative is more appropriately referred to as an “azalide.” This structural change makes the compound more stable in acid, significantly increases the serum half-life and tissue penetration, and results in increased activity against gram-negative organisms and decreased activity against some gram-positive organisms when compared with erythromycin. Azithromycin is available as 250-, 500-, or 600-mg tablets; oral suspension [100–200 mg per 5 mL]; and intravenous preparation [lyophilized 500 mg per 10 mL vial]<sup>[14]</sup>.

Roxithromycin is chemically designated as [3R,4S,5S,6R,7R,9R,11S,12R,13S,14R]-6-[[2S,3R,4S,6R]-4-dimethylamino-3-hydroxy-6-methyloxan-2-yl]oxy-14-ethyl-7,12,13-trihydroxy-[[2R,4R,5S,6S]-5-hydroxy-4-methoxy-4,6-dimethyloxan-2-yl]oxy-10-[2methoxyethoxymethoxyimino]-3,5,7,9,11,13-hexamethyl-1oxacyclotetradecan-2-one<sup>[9,56,81]</sup> It is a semi-synthetic 14-membered ring macrolide antibiotic in which the erythronolide . A lactone ring has been modified to prevent inactivation by gastric acid.1 Roxithromycin differs from erythromycin by their placement of the 9-keto group by an etheroxime side chain<sup>[6]</sup>

Azithromycin had a long elimination half-life [t<sub>1/2</sub>] [median 20.32 h] and a large volume of distribution at steady state [median: 18.56 L/kg]<sup>[11]</sup> whereas pharmacokinetic profile of Roxithromycin is characterised by high plasma, tissue and body fluid concentration and long half-life permitting an extended dosage interval. After IG administration, the time to peak serum concentration [T<sub>max</sub>] ranged between 1.5 and 3 h, and bioavailability ranged between 31% and 86%.<sup>9</sup> Following oral administration, azithromycin is distributed extensively into both animal tissues. This prominent characteristic of the pharmacokinetics of azithromycin results in high tissue concentrations which are sustained long after serum concentrations have declined to very low levels.

Azithromycin is delivered to sites of infection by two mechanisms—direct uptake by tissues, at least in part by fibroblasts, and uptake by phagocytic cells from the blood or interstitial fluid and/or directly from fibroblasts. In the second mechanism, phagocytes then deliver the drug to sites of infection [as part of the body's normal response to infection] where the drug is released in response to phagocytosis to deliver effective, locally high concentrations of drug by a targeted delivery mechanism .pharmacokinetics of azithromycin results in high tissue concentrations which are sustained long after serum concentrations have declined to very low levels<sup>[8]</sup>

Azithromycin had good oral bioavailability in rats and dogs [46% and 97%, respectively]<sup>[12]</sup> .Azithromycin is relatively stable at the low pH of the stomach<sup>[7]</sup> When a drug's half-life is constant; each of kinetic parameters will change with the dose magnitude and the frequency of drug administration. For a given total daily dose of drug the 24-hour AUC will be relatively constant regardless of the dosing regimen

#### IV. PHARMACOKINETICS

##### a) Absorption

The bioavailability of Z<sub>max</sub> relative to azithromycin immediate release [IR] [powder for oral suspension] was 83% with compare to this, Roxithromycin is absorbed after oral administration with an absolute bioavailability of approximately 50%<sup>[5]</sup>.

**Effect of food on absorption:** A high-fat meal increased the rate and extent of absorption of a 2 g dose of Z<sub>max</sub> [115% increase in C<sub>max</sub>, and 23% increases in AUC<sub>0-72</sub>] compared to the fasted state. A standard meal also increased the rate of absorption [119% increase in C<sub>max</sub>]<sup>[13]</sup> where as food intake delays absorption, roxithromycin should be administered atleast 15 minutes before food or, alternatively, on an empty stomach [i.e. more than three hours after a meal]<sup>[5]</sup> .

**Effect of antacids:** Following the administration of Z<sub>max</sub> with an aluminum and magnesium hydroxide antacid, the rate and extent of azithromycin absorption were not altered<sup>[13]</sup>

##### b) Distribution

The serum protein binding of azithromycin is concentration dependent, decreasing from 51% at 0.02µg/mL to 7% at 2µg/mL. Roxithromycin is 92 to 96% bound to plasma proteins [principally alpha-1-acid glycoprotein, but also albumin] at concentrations less than 4.2 mg/L. The binding is saturable. Following oral administration, azithromycin is widely distributed throughout the body with an apparent steady-state volume of distribution of 31.1 L/kg<sup>[13]</sup> . Roxithromycin is highly concentrated in polymorphonuclear leucocytes and macrophages, where levels 30 times those in serum have been reported<sup>[5]</sup> .

##### c) Excretion

Biliary excretion of azithromycin, predominantly as unchanged drug, is a major route of elimination. Over the course of a week, approximately 6% of the administered dose appears as unchanged drug in urine<sup>[13]</sup>. Approximately 7% of a dose of roxithromycin is excreted in the urine and 13% is eliminated via the lungs<sup>[5]</sup> .

#### V. SERUM PHARMACOKINETICS

**Table 1** provides a summary of the pharmacokinetics of azithromycin in serum<sup>7</sup>

Pharmacokinetic parameter	Dosage regimen			
	500 mg single oral dose	500 mg singal intravenous dose	500 mg every 12 h [day 1]	250 mg every 12 h [day1]
			500mg daily [days 2-6]	250 mg daily [days 2-10]
C <sub>max</sub> [mg/l]	0,4		0.41	0.2
			0.62	0.21
AUC <sub>0-12</sub> [mgx h/l]			1.77	0.80
			3.18	1.22
AUC <sub>0-24</sub> [mg x h/l]	2.36	6.48		



t <sub>1/2</sub> [8-24 h]		11-14 h	
Urinary excretion	4.5 %	12.2 %	

**Table 2** provide summary of pharmacokinetics of Azithromycin and Roxithromycin<sup>21S</sup>

Macrolides	Dose[mg]	Time to peak[h]	Peak conc.[mg/l]	AUC[mg.h/l]
Azithromycin	500	2-3	0.4	6.7
Roxithromycin	150	1-3	5.4-7.9	53.0-81.0
Roxithromycin	300	1.6	10.8	81

## VI. EXPERIMENTAL PHARMACOLOGY

Comparative anti-inflammatory effects of roxithromycin, azithromycin were evaluated by The rat carrageenin paw oedema model<sup>[16]</sup> An open, multicentre study was undertaken in order to evaluate the efficacies and safety profiles of azithromycin and roxithromycin in treatment of acute respiratory tract infection<sup>[17]</sup>The in vitro activities of the macrolide antibiotics clarithromycin, 14-hydroxy-clarithromycin, azithromycin, and erythromycin against 19 isolates of *Borrelia burgdorferi* were investigated<sup>[18]</sup>Azithromycin pharmacokinetics in *Legionella pneumophila*-infected and uninfected guinea pigs were assessed by measuring the drug concentration in whole lungs or the drug content in bronchoalveolar lavage [BAL] fluid in separate experiments. Activity of azithromycin or erythromycin in combination with antimalarial drugs against multidrug-resistant *Plasmodium falciparum* in vitro was performed Azithromycin concentrations were measured by using a bioassay<sup>[19]</sup>. The aim of this study the in vitro efficacy of azithromycin and roxithromycin against *Toxoplasma gondii* were evaluated using acridine orange in the fluorescence microscopic assay<sup>[20]</sup>The effect of amikacin and two new macrolides [roxithromycin and azithromycin] used either alone or in combination with recombinant tumor necrosis factor [TNF] to inhibit or kill *Mycobacterium avium* complex in human macrophages sduodenum was studied<sup>[24]</sup>. In Vitro Effects of Four Macrolides [Roxithromycin, Spiramycin, Azithromycin [CP-62,993], and A-56268] on *Toxoplasma gondii* was studied<sup>[25]</sup> Comparison of the Effects of the New Azalide Antibiotic, Azithromycin, and Erythromycin Estolate on Rat Liver Cytochrome P-450<sup>[26]</sup> Trial of Roxithromycin activity in Asthma and serological evidence of infection with *Chlamydia pneumoniae* has been evaluated Therapeutic possibilities of long term Roxithromycin treatment for chronic diffuse sclerosing osteomyelitis of mandible has been evaluated Inhibitory action of a macrolide antibiotic, roxithromycin, on co-stimulatory molecule expressions in vitro and in vivo were evaluated Determination of roxithromycin in human plasma by HPLC with fluorescence and UV absorbance detection: Application to a pharmacokinetic study<sup>[27]</sup>. Efficacy of roxithromycin in preventing irreversible inflammatory damage leading to tubal infertility by using Mouse model of acute chlamydial salpingitis was evaluated<sup>[28]</sup>

## VII. Spectrum of activity

Azithromycin is more active against gram negative bacteria and less active against gram positive bacteria<sup>[33]</sup> with compare this Roxithromycin is active against gram negative and gram positive bacteria<sup>[6]</sup>

Azithromycin is active against following organism	Roxithromycin is active against following organism
<i>H.influenzae</i> , <sup>[38]</sup> <i>M.pneumoniae</i> , <sup>[33]</sup> <i>M.catarrhalis</i> , <sup>[35]</sup> <i>Legionella</i> <sup>[34]</sup> <i>Borrelia spp</i> <sup>[22]</sup> <i>Toxoplasma</i> <sup>[22]</sup>	<i>Mycobacterium avium complex</i> <sup>[6]</sup> <i>Helicobacter pylori</i> <sup>[6]</sup> <i>Borrelia spp.</i> <sup>[36]</sup> <i>Legionella pneumophila</i> <sup>[36]</sup> <i>Chlamydia</i> <sup>[37]</sup>

## VIII. Drug Interactions

Azithromycin interacts with the cytochrome P-450 system of hepatocyte smooth endoplasmic reticulum and causes significant elevation of azithromycin <sup>[6]</sup>. It having interaction with Theophylline, Carbamazepine, Warfarin, Terfenadine and

Cisapride<sup>[36]</sup> Whereas Roxithromycin have interaction with Theophylline. Ergotamine Disopyramide Astemizole, Cisapride, Pimozide Warfarin. Digoxin Midazolam Terfenadine<sup>[5]</sup>

## IX. Frequency of drugs

Azithromycin: This drug is available as 250mg, 500mg, 600mg once a day before meal

Roxithromycin: This drug is available as 150mg and 300mg twice a day before meal

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