

Original Article

# Pharmacokinetics and dosage regimen of roxithromycin in adult healthy female subjects

Hira Naeem <sup>a</sup>, Mudassar Ashraf <sup>b</sup>, Aisha Shehzad <sup>b,\*</sup>

<sup>a</sup> Institute of Pharmacy, Physiology and Pharmacology, University of Agriculture, Faisalabad, Pakistan

<sup>b</sup> Faculty of Pharmaceutical Sciences, Government College University, Faisalabad, Pakistan

\* Correspondence: aishashehzad333@gmail.com; Telephone: +923326486646



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## Abstract

Macrolides are a group of antibiotics produced by *Streptomyces* bacteria commonly used to treat bacterial infections, including gum infections, gingivitis, and stomach and intestinal ulcers. Roxithromycin is a macrolide antibiotic that effectively targets bacterial cells and inhibits their growth, promoting symptom relief and recovery. Despite this, there is limited research on roxithromycin pharmacokinetics and dosing regimens, particularly in healthy female volunteers from the local population. Thus, this study aimed to investigate roxithromycin's pharmacokinetic parameters and dose regimen in ten healthy female volunteers aged 18 to 30 years. Participants received an oral dose of 300 milligrams of roxithromycin, and blood samples were collected at various intervals for 48 hours. Pharmacokinetic parameters were assessed using two open compartmental models and high-performance liquid chromatography (HPLC). The results showed that the  $C_{max}$  of roxithromycin was  $10.13 \pm 0.43$   $\mu\text{g/mL}$ , attained at a time to reach  $t_{max}$  of  $2.42 \pm 0.34$  hours. Moreover, the drug exhibited a volume of distribution of  $1.38 \pm 0.55$  L/kg, an elimination half-life of  $34.95 \pm 22.51$  hours, and a total body clearance of  $0.04 \pm 0.01$  L/hr/kg. In accordance with these results, the calculated dosage regimen for 24-hour intervals was 975 milligrams as a priming dose and 372 milligrams as a maintenance dose. In conclusion, this study found that the elimination half-life ( $t_{1/2\beta}$ ) of roxithromycin was higher than literature values, leading to less clearance and ultimately increased  $C_{max}$ ,  $t_{max}$ , and area under the curve (AUC) values of the orally administered drug, indicating the need for dose adjustment in patients.

## Keywords

Macrolide, Pharmacokinetic Profile, High-performance liquid chromatography, Dose adjustment, Chromatography, Rulide®

## 1. Introduction

Studying a drug's pharmacokinetics and therapeutic schedule is crucial to determine its effectiveness and safety and to adjust the dosage for each patient. The pharmacokinetics of a drug depend on various factors, such as its administration site and concentration [1]. Moreover, factors such as age, sex, diet, other medications, liver and kidney function, ethnicity, and genetic differences can affect drug metabolism. In addition, differences based on gender can have a notable impact on the effectiveness of medications and their potential side effects. For instance, there may be differences in drug absorption between males and females due to variations in the gastrointestinal tract. Therefore, it is essential to consider these factors when prescribing a drug to a patient [2, 3, 4].

Environmental and topographical conditions in Asia differ from those in Europe, as do the population's genetic makeup and dietary habits [5, 6, 7, 8]. For example, antibiotic therapy is commonly used in European countries, but this may not be true in Asian

countries. These differences can affect how the body processes drugs, including the CYP enzyme system, which plays a role in drug metabolism and response [9, 10].

Macrolides are a type of antibiotic that treats bacterial infections. They are made from *Streptomyces* and have a lactone ring with sugar and other substances attached. Macrolides are easy to use because they are usually taken orally and have a long half-life of 10 – 14 hours [11]. Newer macrolides such as roxithromycin, azithromycin, and telithromycin are better than earlier macrolides because they work on more bacteria, are more comfortable for patients to take, penetrate tissues better and have fewer side effects [12]. Roxithromycin is one such macrolide that is more effective than other macrolides because it binds permanently to the bacterial 50S ribosomal subunit, thus stopping protein synthesis [13]. It treats ear, nose, throat, soft tissues, urinary tract infections, and atypical and community-acquired pneumonia [14]. Roxithromycin can also cure gum infections such as gingivitis and bacterial infections in the stomach and intestines [15].

There is limited literature on the pharmacokinetics and dose regimens of roxithromycin in the local population, and no studies have been conducted on female subjects. Therefore, this research aims to investigate roxithromycin's pharmacokinetics and dose regimen in healthy female study volunteers from the local population.

## 2. Methods

This analytical study was conducted with the aim of establishing the pharmacokinetic parameters of roxithromycin 300-milligram orally administered as a single dose. It was conducted in Faisalabad, Punjab Province, and was duly approved by the Research and Ethics Committee of the Institute of Pharmacy, Physiology and Pharmacology Department, University of Agriculture, Faisalabad, Pakistan (No. REC/IP/1638). The study recruited ten healthy female volunteers between the ages of 18 and 30 years who were physically normal, had no ongoing medical conditions, and had not taken any medications within seven days before the study. Before the start of the research, all volunteers provided written consent and received a clear explanation of the study's purpose, potential side effects, and sampling frequency. However, females who did not provide consent to participate were not included in the study.

### 2.1. Drug administration and collection of blood samples

The volunteers underwent an overnight fast to collect blood samples before receiving a single oral dose of 300 milligrams of roxithromycin (Rulide®, Sanofi-Aventis Private Limited, Karachi, Pakistan). Control blood samples were collected from each volunteer before drug administration. After a two-hour postmeal interval, the volunteers received roxithromycin. Blood samples were taken at 1, 2, 4, 6, 8, 10, 12, 24, and 48-hour intervals and contained in heparinized centrifuge plastic tubes. The pH of the blood samples was measured at 37°C using an electric pH meter (Beckman HS, Germany). The plasma was separated by centrifugation at 4000 rpm for 20 minutes and subsequently stored at -20°C for analysis [16].

### 2.2. Analytical methods

We determined the concentration of roxithromycin in the collected samples using high-performance liquid chromatography (HPLC). We utilized an array of equipment, including an analytical balance from (Sartorius, Germany), a centrifugation machine [MSE Micro Centaur, Sanyo, United Kingdom (UK)], a filtration assembly with a pore size of 0.45 µm, micropipettes ranging between 10 µL and 1000 µL from Oxford in the UK, a sonication apparatus from Oqawaseiki Co in Japan, a Sykam S1122 system controller unit

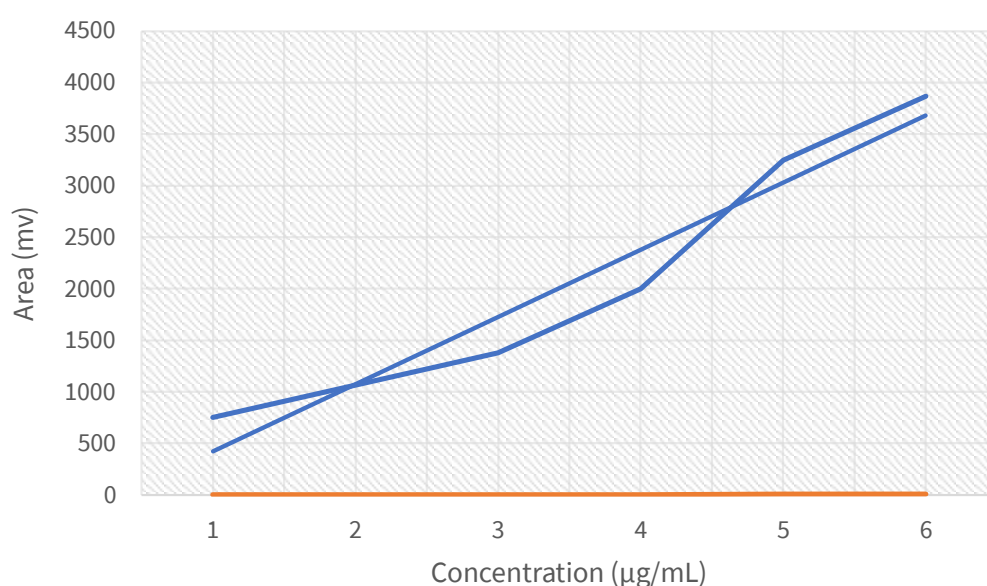
and liquid chromatographic pump, a Sykam S3210 UV visible detector, a Sykam S5111 valve bracket sample injector, and a C-18 thermohypersil column [17].

### 2.3. Chromatographic conditions

The concentration of roxithromycin in the collected samples was analyzed using a mobile phase consisting of a blend of methanol, acetonitrile, and deionized water with a ratio of 45:30:25, flowing at a rate of 0.5 mL/min. The UV-visible detector had a wavelength set at 300 nm and an injection volume of 20  $\mu$ L. For chromatographic separation, we employed a C-18 thermohypersil column with dimensions of 250  $\times$  4.6 nm and a particle size of 5  $\mu$ m. The system temperature was kept constant at 30°C for the duration of the analysis [18].

### 2.4. Preparation of standard solutions and standard curve

To create the standard stock solution of roxithromycin, 3.2 milligrams of the standard substance was dissolved in 1 milliliter of distilled water, resulting in a concentration of 3200 micrograms per milliliter ( $\mu$ g/mL). Afterward, the stock solution was diluted to the desired concentrations of 1, 1.5, 2, 3, 5, and 6  $\mu$ g/mL to prepare the working solutions. Finally, a calibration curve was constructed by plotting the corresponding concentrations against the peak area data, as shown in Figure 1. The calibration curve showed a linear relationship with an R-squared value of 0.9954 and the equation  $Y = 623.81x + 127.07$ .



**Figure 1.** Standard curve of roxithromycin.

### 2.5. Sample preparation

Plasma samples (250  $\mu$ L) were prepared for analysis by transferring them to 2 mL polyethylene vials with a blend of acetonitrile and acetic acid (1 mL). The aqueous layer was discarded after centrifugation at 4000 rpm for 1 minute, and the organic layer was collected and transferred to a 2 mL glass vial. The solvent was then evaporated at 40°C using nitrogen gas to obtain a dry residue. Afterward, the remaining material was reconstituted with 250  $\mu$ L of the mobile phase, and 20  $\mu$ L of the reconstituted solution was then injected into the chromatographic column for the analysis of roxithromycin [16].

## 2.6. Determination of roxithromycin

We employed a standard solution to compare the peak area of the drug and determine the concentration of roxithromycin in the plasma samples. The drug concentration was then calculated using the equation  $Y = a + bx$ , where  $Y$  is the peak area of the unknown sample,  $a$  is the intercept,  $b$  is the slope of the regression line, and  $x$  is the concentration of roxithromycin.

## 2.7. Calculations and statistical analysis

Plasma concentration vs. time data were analyzed using a two-compartment open model and plotted on a semilogarithmic graph. Pharmacokinetic calculations were performed with a computer program from the American Pharmacological Association. The mean  $\pm$  standard deviation was calculated for both the plasma drug concentrations and pharmacokinetic parameters. Using the pharmacokinetic parameters, Baggot's formula was used to determine the optimum roxithromycin dose regimens for adult females. The maintenance dose ( $D$ ) was calculated using the following formula, i.e.,  $D = C_{P(\min)} \times V_d (e^{\beta\tau} - 1)$ , where  $C_{P(\min)}$  is the minimum therapeutic plasma level,  $V_d$  is the volume of drug distribution,  $\beta$  is the overall elimination rate constant, and  $\tau$  is the dosage interval. "-1" was omitted from the equation to obtain the priming dose [19].

## 3. Results

### 3.1. Plasma concentrations of the drug

Table 1 presents the pharmacokinetic parameters of roxithromycin in 10 healthy adult females, indicating that the maximum plasma concentration ( $C_{\max}$ ) of roxithromycin occurred at 1 hour with a value of  $7.69 \pm 0.71$   $\mu\text{g/mL}$ , peaked at 4 hours ( $9.34 \pm 0.59$   $\mu\text{g/mL}$ ), and gradually decreased to  $2.30 \pm 0.35$   $\mu\text{g/mL}$  at 48 hours. We utilized MW-PHARM APO version 3.02 pharmacokinetic software to evaluate the pharmacokinetic parameters by analyzing the plasma concentration-time data.

**Table 1.** Roxithromycin levels in plasma ( $\mu\text{g/mL}$ ) at different time points.

Time (hours)	Plasma Concentration ( $\mu\text{g/mL}$ )
	Mean $\pm$ SD
1	$5.69 \pm 0.51$
2	$8.14 \pm 0.71$
4	$9.34 \pm 0.59$
6	$7.22 \pm 0.54$
8	$6.16 \pm 0.55$
10	$5.31 \pm 0.53$
12	$4.43 \pm 0.41$
24	$3.25 \pm 0.36$
48	$2.30 \pm 0.35$

### 3.2. Pharmacokinetic parameters

Table 2 presents the pharmacokinetic parameters of roxithromycin in 10 healthy adult females, along with their mean  $\pm$  standard deviation values. The trapezoidal method was employed to calculate the area under the plasma concentration-time curve, which was found to be  $3.93 \pm 3.80$   $\mu\text{g}\cdot\text{hr/mL}$ . After oral administration, the maximum plasma concentration ( $C_{\max}$ ) of roxithromycin was attained at  $2.42 \pm 0.34$  hours with a value of  $10.13 \pm 0.43$   $\mu\text{g/mL}$ . The absorption half-life and elimination half-life were determined to be  $3.04 \pm 1.26$  hours and  $34.95 \pm 22.51$  hours, respectively. The pharmacokinetic

parameters of roxithromycin were estimated, including the absorption rate constant, elimination rate constant, volume of distribution ( $V_d$ ), total body clearance ( $Cl_B$ ), and mean residence time (MRT). Additionally, the first-order rate constants for the movement of roxithromycin between the central and peripheral compartments ( $K_{12}$  and  $K_{21}$ ) were determined. These parameters are presented in Table 2, along with their mean  $\pm$  standard deviation values.

**Table 2.** Roxithromycin pharmacokinetic parameters.

Pharmacokinetic Parameters	Units	Mean $\pm$ SD
$C_{max}$	$\mu\text{g/mL}$	$10.13 \pm 0.43$
$t_{max}$	hr.	$2.42 \pm 0.34$
$K_{abs}$	$\text{hr}^{-1}$	$0.42 \pm 0.13$
$t_{1/2 \text{ abs}}$	hr.	$3.04 \pm 1.26$
B	$\mu\text{g/mL}$	$3.96 \pm 2.04$
B	$\text{hr}^{-1}$	$0.02 \pm 0.01$
$t_{1/2\beta}$	hr.	$34.95 \pm 22.51$
$V_d$	L/kg	$1.38 \pm 0.55$
$Cl_B$	L/hr/kg	$0.04 \pm 0.01$
AUC	$\mu\text{g.hr/mL}$	$155.59 \pm 11.79$
MRT	hr.	$39.40 \pm 25.98$
$K_{12}$	$\text{hr}^{-1}$	$0.12 \pm 0.07$
$K_{21}$	$\text{hr}^{-1}$	$0.07 \pm 0.06$

### 3.3. Dosage regimen

To optimize the therapeutic effectiveness of roxithromycin for healthy female individuals, we used pharmacokinetic parameters to determine appropriate dosage regimens. The minimum inhibitory concentration (MIC) of the drug in blood was calculated at intervals of 8, 12, and 24 hours using MIC values of 0.05, 0.25, 0.5, 1, 8, and 16  $\mu\text{g/mL}$ . We calculated priming doses, which are higher initial doses used to achieve therapeutic levels quickly, for roxithromycin in healthy female individuals with an MIC of 8  $\mu\text{g/mL}$ . The priming doses for dosing intervals of 8, 12, and 24 hours were 12.20, 13.20, and 16.81 mg/kg, respectively. The corresponding maintenance doses, which are lower doses used to maintain therapeutic levels, were 1.81, 2.72, and 6.41 mg/kg, as summarized in Table 3. These dosages were based on the pharmacokinetic parameters of roxithromycin and the MIC of the drug in the blood, enabling us to optimize its therapeutic effectiveness for healthy female individuals.

**Table 3.** Roxithromycin dosage (mg/kg) over time.

	Dosing Interval (hours)																	
	8						12						24					
MIC	0.05	0.25	0.50	1.00	8.00	16.00	0.05	0.25	0.50	1.00	8.00	16.00	0.05	0.25	0.50	1.00	8.00	16.00
P *	0.08	0.38	0.76	1.52	12.20	24.40	0.08	0.41	0.82	1.65	13.20	24.44	0.10	0.52	1.05	2.00	16.81	33.60
M **	0.01	0.05	0.11	0.22	1.81	3.60	0.02	0.08	0.17	0.35	2.80	5.64	0.04	0.22	0.41	0.81	6.41	12.81

\* P = priming dose. \* M = maintenance dose.

## 4. Discussion

When using antibiotics to treat infections, it is important to maintain a certain level of the drug in the bloodstream, known as the minimum inhibitory concentration (MIC), for it to be effective against pathogenic bacteria. The recommended MIC of the drug roxithromycin is reported to be 0.05-8  $\mu\text{g/mL}$ , which is typically sufficient. In this study,

roxithromycin plasma concentration was measured at various times after administration, and the drug was found to reach its highest level ( $9.34 \pm 0.59 \mu\text{g/mL}$ ) by 4 hours before declining gradually near  $2.30 \pm 0.35 \mu\text{g/mL}$  by 48 hours. Throughout the observation period, the MIC lower limit was achieved soon after drug administration and was maintained, while the MIC upper limit was reached and sustained. In the study, healthy female volunteers were given 300 milligrams of roxithromycin orally. The maximum concentration of drug in their plasma was  $10.13 \pm 0.14 \mu\text{g/mL}$ . This is higher than the  $C_{\text{max}}$  values reported in adult volunteers and elderly individuals,  $9.7 \mu\text{g/mL}$  and  $10.8 \mu\text{g/mL}$ , respectively [20]. Furthermore, the  $C_{\text{max}}$  of roxithromycin in healthy males, after oral administration of 150 milligrams, was reported to be  $6.7 \pm 2.6 \mu\text{g/mL}$ , which was lower than the  $C_{\text{max}}$  found in this study [21]. In patients with renal insufficiency, alcoholic cirrhosis, and elderly patients,  $C_{\text{max}}$  values of  $10.5\text{--}14.6 \mu\text{g/mL}$  were reported after single or multiple oral administrations of roxithromycin 150 milligrams [22]. The time taken for the drug to reach its maximum concentration ( $t_{\text{max}}$ ) after oral administration in this study was  $2.42 \pm 0.34$  hours, consistent with previously reported values in healthy volunteers [14, 21]. However, the  $t_{\text{max}}$  value in this study was longer than that reported in adult volunteers, which was  $1.5 \pm 0.34$  hours [20].

The present study calculated the mean area under the curve (AUC) using the trapezoidal method and reported it to be  $155.59 \pm 11.79 \mu\text{g}\cdot\text{hr/mL}$ . The value obtained in this study for the mean AUC of roxithromycin 300 milligrams administered orally to healthy female subjects was found to be higher than the literature values reported for adults. These values were  $132 \pm 17 \mu\text{g}\cdot\text{hr/mL}$  [20],  $116.9 \pm 32.7 \mu\text{g}\cdot\text{hr/mL}$  [23],  $98.6$  and  $69.4 \mu\text{g}\cdot\text{hr/mL}$  for 300 and 150 milligrams of roxithromycin, respectively, in healthy female study volunteers [22], and  $72.6 \mu\text{g}\cdot\text{hr/mL}$  for roxithromycin 150 milligrams in healthy female study participants [14]. A previous study conducted by Nilsen et al. (1992) reported AUC values of  $107.3 \pm 52.9$  and  $214.7 \pm 82.5 \mu\text{g}\cdot\text{hr/mL}$  in healthy males after oral administration of 150 and 300 milligrams of the drug, respectively [21]. There may be several factors that could contribute to the observed differences in  $C_{\text{max}}$ ,  $t_{\text{max}}$ , and AUC values between the current and previous studies, such as sex, genetic variations, metabolic differences, geographical locations, and environmental factors.

The apparent volume of distribution is a constant that links the drug plasma concentration to the amount present in the body once drug distribution equilibrium is achieved [6, 9]. When drugs have a higher volume of distribution, they are extensively metabolized by the liver. Such drugs must be closely monitored or discontinued to prevent drug interactions in patients [24]. The mean apparent volume of distribution of roxithromycin was calculated in this study. Healthy female subjects were administered a single oral dose of 300 milligrams, resulting in a  $V_d$  value of  $1.38 \pm 0.55 \text{ L/kg}$ . This value is higher compared to previous literature, which reported  $V_d$  values of  $0.87 \text{ L/kg}$  in male volunteers [25] and  $0.44 \pm 0.1 \text{ L/kg}$  in healthy volunteers [21]. A value of  $V_d$  higher than unity suggests that the drug rapidly distributes or penetrates the tissues [7, 5]. Therefore, differences in the values of the  $V_d$  (volume of distribution) of the drug in this study compared to preceding studies may be due to differences in the body mass index of the individuals included in the studies. The amount of albumin in the body can differ between individuals, leading to changes in the protein binding of roxithromycin and potentially influencing the volume of distribution values [26, 27]. Moreover, differences in body weight between men and women can cause variations in the distribution of drugs, affecting parameters such as volume of distribution, protein binding, and blood flow in organs [2, 9].

Total body clearance refers to the combined processes responsible for removing drugs from the body [2, 9]. In the present study, the total body clearance of orally administered 300 milligrams of roxithromycin was found to be  $0.04 \pm 0.01 \text{ L/h/kg}$ . This value



was significantly lower than the  $Cl_B$  values reported in the literature, which ranged from 0.34 L/h to  $10.7 \pm 1.18$  L/h, depending on the study population [25, 28, 29, 30, 31]. Therefore, substantial differences in the total body clearance values might arise when calculated in different populations and because of environmental and species variations [5, 6]. The current study's findings on the varying total body clearance of roxithromycin compared to previous studies can be attributed to several factors, including blood flow to organs, unbound drug fractions in plasma, and the organ's maximum capacity to eliminate the drug or drug extraction ratio [9, 32].

The present study revealed that the mean  $\pm$  standard deviation in half-life of the drug among healthy female volunteers of study after single 300 milligrams of orally administered dose was  $34.95 \pm 22.51$  hours; is much higher than the values reported by other studies: 20.6, 15.5, 11.9, 11.8, 10.9, 8.4, and 7.2 hours [14, 20, 22, 23, 24, 33, 34], and it could be due to lower rates of glomerular filtration in the local population because of the hot temperature in Pakistan's climate, leading to decreased drug elimination. Additionally, the extensive binding of roxithromycin to plasma proteins and its penetration in deep, less perfused tissues may contribute to its longer half-life in plasma [4, 27].

Inadequate tissue concentration is the most common cause of antibiotic treatment ineffectiveness. Microbes' susceptibility to roxithromycin varies among species and strains within the same species of microbe, which results in a wide range of MICs against susceptible microbes [2, 20]. Roxithromycin, a semisynthetic macrolide antibiotic, exhibits effectiveness against a range of pathogens, including *Chlamydia trachomatis* (MIC = 0.06 mg/L), *Legionella pneumophila*, *Chlamydophila pneumoniae*, *Mycobacterium avium* complex (MIC = roxithromycin 4 to 32 mg/L), *Mycobacterium leprae*, and *Rickettsia* species (MIC = 1 to 2 mg/L) [35, 36]. Roxithromycin also showed efficacy against *S. pyogenes* and *S. pneumoniae* with an MIC of 0.13 mg/L and against *H. influenzae* with an MIC of 8.0 mg/L [37]. Pankuch et al. (1998) reported that the roxithromycin MIC against *Catarrhalis* spp. was between 0.25-4.0; for *influenzae* spp., it was 8-32 [38].

The minimum inhibitory concentration (MIC) should be equal to or less than 1 mg/L to determine whether bacteria are susceptible to roxithromycin. The bacteria were considered resistant if the MIC was greater than 8 mg/L. For *Haemophilus influenzae*, an MIC value of 8 mg/L or less is considered susceptible [39, 40]. Resistance prevalence may vary by geographical location, and knowing local resistance rates is important, especially when treating severe infections. To ensure effective treatment, the antibiotic plasma level should not fall lower than the MIC at the end of certain dosing intervals during chemotherapy [2]. Therefore, the manufacturer recommends a once-daily oral dose of 300 milligrams of roxithromycin.

Based on available scientific literature, optimal priming and maintenance doses of roxithromycin among healthy female volunteers, considering MIC at the end of 12, 24, and 48-hour intervals. These studies reveal that to achieve therapeutic plasma concentrations, the optimum dosage regimens and dosing intervals for females with an average weight of 58 kg should be a priming dose of 975 milligrams followed by a maintenance dose of 372 milligrams at 24-hour intervals to cover a broad spectrum of bacteria.

A comparison between the roxithromycin recommended dose and the investigated dose regimen in healthy females showed similar maintenance doses. However, the initial dose needed to be tripled to achieve maximum therapeutic effects. Therefore, it is important to define dosage regimens under local conditions to account for the specificity of drug pharmacokinetics. The present study found a higher  $t_{1/2\beta}$  value of roxithromycin, which led to less body clearance and more  $C_{max}$ ,  $t_{max}$ , and AUC values compared to values in the scientific literature. As a result, altering the dose may be necessary for patients.

Limited studies have highlighted the pharmacokinetic profile of macrolides in the local population; therefore, this study has added value to the available literature by determining the pharmacokinetics as well as dosage regimen among local females, which is a potential strength of the study. However, the study included a limited number of participants, which remains a weakness of the study.

## 5. Conclusions

Our study of local female participants observed higher values for certain roxithromycin pharmacokinetic parameters, such as  $\beta$  and  $t_{1/2\beta}$ , resulting in lower drug clearance from the body ( $Cl_B$ ). In addition, an observed deviation was found in  $t_{1/2\text{ abs}}$  when compared to previously reported values; however, the remaining pharmacokinetic parameters, such as  $C_{\text{max}}$ ,  $t_{\text{max}}$ , AUC, and MRT, were consistent with prior studies. Therefore, we conclude that there are differences in the pharmacokinetic parameters of roxithromycin, which may be due to environmental and genetic factors. To maintain an effective plasma concentration of roxithromycin, we suggest priming dose of 483 milligrams, followed by a maintenance dose of 338 milligrams for adult females.

**Author contributions:** Conceptualization, HN, MA, and AS; methodology, HN, MA, and AS; software, MA, and AS; validation, HN, and AS; formal analysis, MA, and AS; investigation, HN, MA, and AS; resources, HN; data curation, MA, and AS; writing—original draft preparation, MA, and AS; writing—review and editing, HN; visualization, MA, and AS; supervision, HN; project administration, HN. All authors have read and agreed to the published version of the manuscript.

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**Ethics statement:** The present study underwent a thorough review and received official approval from the Research and Ethics Committee of the Institute of Pharmacy, Department of Physiology and Pharmacology, University of Agriculture, Faisalabad, Pakistan (Approval No. REC/IP/1638).

**Consent to participate:** All participants provided written consent before the commencement of the study.

**Data availability:** The data supporting this study's findings are available from the corresponding author, Aisha, upon reasonable request.

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**Conflicts of interest:** The authors declare no conflicts of interest.

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