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2 **Single- and multiple-dose pharmacokinetics of oral clarithromycin**  
3 **in soft tissues determined by microdialysis**

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22 Running title: Microdialysis of clarithromycin in soft tissues

## 1 **Abstract**

2 The antimicrobial spectrum of clarithromycin renders this antibiotic a frequently used  
3 option in the treatment of skin and soft tissue infections. In most cases, these  
4 infections are caused by extracellularly proliferating microorganisms. Thus,  
5 clarithromycin concentrations achieved in the interstitial space are considered  
6 particularly important for clinical efficacy. In the present study, clarithromycin  
7 concentrations in plasma and interstitial space fluid of subcutaneous adipose tissue  
8 and skeletal muscle of six healthy male volunteers were assessed by means of the  
9 microdialysis technique after oral single-dose administration of 250 mg and multiple-  
10 doses of 500 mg of clarithromycin *bis in die* (b.i.d.). The ratio of the area under the  
11 concentration-*versus*-time curve of free clarithromycin from 0-24 hours calculated for  
12 a single dose of 250 mg ( $fAUC_{0-24}$ ) in interstitial space fluid to the  $fAUC_{0-24}$  in plasma  
13 was  $0.29 \pm 0.17$  and  $0.42 \pm 0.18$  for subcutis and skeletal muscle, respectively. For  
14 500 mg of clarithromycin at steady-state (3-5 days of twice daily intake) the  $fAUC_{0-24}$   
15 (b.i.d.) ratios at steady-state were  $0.39 \pm 0.04$  and  $0.41 \pm 0.19$  for subcutis and skeletal  
16 muscle, respectively. The half-life was around 2 hours after single dose, but  
17 increased to approximately 4 hours in plasma and tissues after repetitive  
18 clarithromycin administration. Based on subsequently performed pharmacokinetic-  
19 pharmacodynamic calculations, a dosing regimen of 500 mg b.i.d may be ineffective  
20 in the treatment of soft tissue infections caused by pathogens with an MIC higher  
21 than 0.125 mg/l.

## 1 INTRODUCTION

2

3 Clarithromycin, a 14-membered ring macrolide, is antimicrobially active  
4 against a broad range of gram-positive and certain gram-negative pathogens  
5 frequently isolated from soft tissue infections and bite wounds (12). Clarithromycin is  
6 considered as a therapeutic alternative in special cases with minor soft tissue  
7 infections and penicillin allergy or in non-tuberculous mycobacterial skin infections  
8 (20, 21). In literature, high tissue concentrations of the class of the macrolides are  
9 reported (11, 14, 22). Indeed, intracellular accumulation of macrolides has been  
10 demonstrated in isolated peripheral blood phagocytes, alveolar macrophages and  
11 tissue culture cells of human origin (10, 17). To date, *in vivo* tissue pharmacokinetics  
12 of clarithromycin are confined to concentrations derived from homogenized biopsies  
13 of the upper and lower respiratory tract and epithelial lining fluid collection obtained  
14 by bronchoalveolar lavage (11, 14, 22). The results from homogenized biopsies, as  
15 frequently used in previous studies, represent an average concentration of all tissue  
16 components extracted, including blood cells, intracellular fluid, interstitial fluid, and  
17 structural tissue components, and may therefore cause confusion with regard to the  
18 actual concentration of an antimicrobial agent in a defined compartment. These data,  
19 thus, provide only limited insight into the time course of concentration at the relevant  
20 site of most bacterial infections, namely the extracellular space fluid. Hence, we used  
21 the microdialysis technique, which is capable of the continuous assessment of  
22 unbound, i.e. microbiologically active concentrations of clarithromycin in the  
23 interstitial space fluid of soft tissues (16).

24 The knowledge about the concentration-*versus*-time profiles of free  
25 clarithromycin achieved in the interstitial space fluid of soft tissues can be considered  
26 as a prerequisite for dosage recommendations in the treatment of extracellularly

1 proliferating bacteria causing soft tissue infections. Hence, the aim of the present  
2 study was to determine free interstitial concentrations of clarithromycin in  
3 subcutaneous adipose tissue and skeletal muscle after oral single- and multiple-dose  
4 administration to healthy male volunteers.

ACCEPTED

## 1 **MATERIALS AND METHODS**

2

3 The study took place at the Department of Clinical Pharmacology, Medical University  
4 of Vienna, Austria. The study protocol was approved by the local Ethics Committee  
5 and the study was performed in accordance with the Declaration of Helsinki 1964  
6 (including current revisions), the Austrian Drug Law, and the Good Clinical Practice  
7 Guidelines.

8

### 9 **Healthy volunteers**

10 Seven healthy male volunteers between the ages of 25 and 37 years were enrolled  
11 into the study. Written informed consent was obtained from each volunteer prior to  
12 any study related investigation or intervention. Each volunteer underwent a screening  
13 examination consisting of the following: medical history, physical examination, routine  
14 laboratory tests, heart rate, blood pressure and a 12-lead electrocardiography.  
15 These assessments were provided prior to inclusion and after completion of the  
16 study. All volunteers were initially drug free and received standardized meals on  
17 study days and were instructed to avoid caffeine and grapefruit juice during the entire  
18 study period.

19

### 20 **Study protocol**

21 *Study day 1 (250 mg clarithromycin single dose):*

22 The volunteers were admitted to the clinical research ward in the morning of study  
23 day 1. A plastic cannula was inserted into an antecubital vein to monitor blood  
24 concentrations of clarithromycin at defined time points. Concentrations in interstitial  
25 space fluid of skeletal muscle and subcutaneous adipose tissue were determined by  
26 microdialysis. The principle of microdialysis has been described previously in detail

1 (16). In brief, a microdialysis probe with molecular mass cut-off of 20000 (CMA12;  
2 CMA/Microdialysis AB, Solna, Sweden) was inserted into one thigh muscle and into  
3 the subcutaneous adipose tissue at the ventrolateral side of the thigh under aseptical  
4 conditions by use of a guidance cannula. The probe was constantly perfused with  
5 Ringer's solution at a flow rate of 1.5 µl/min by means of a precision pump (Precidor;  
6 Infors-AG, Basel, Switzerland). After a 60-min equilibration period, 250 mg of  
7 clarithromycin (Klacid™ 250 mg tablet, Abbott, Abbott Park, Illinois, US) was  
8 administered orally to the fasting volunteer. Sampling of microdialysates and venous  
9 blood was performed at 20-min intervals from 0 to 4 hours and at 30-min intervals  
10 from 4 to 8 hours. After completion of the 8 h sampling period, the individual recovery  
11 values of clarithromycin were determined by use of the "retrodialysis method" (4). For  
12 that reason, clarithromycin was added at a concentration of 5 mg/l to the perfusion  
13 fluid and its rate of disappearance through the microdialysis membrane was  
14 determined. The individual recovery was calculated by using the mean of two  
15 measurements by the equation:  $\text{Recovery (\%)} = 100 - (100 \times C_{\text{dialysate}} / C_{\text{perfusate}})$ .  
16 Blood was collected in tubes containing the lithium salt of heparin, kept on ice for a  
17 maximum of 30 minutes, and centrifuged at 1,600 x g for 5 minutes at 4°C. Plasma  
18 and microdialysates were stored at minus 80°C until analysis.

19 Twelve hours after the initial single dose of 250 mg, each volunteer continued oral  
20 intake of clarithromycin at a dosage of 500 mg b.i.d. for 3 to 5 days until the morning  
21 of study day 2.

22

23 *Study day 2 (steady-state of 500 mg clarithromycin b.i.d.):*

24 After clarithromycin intake over a period of 3-5 days b.i.d., the last dose of 500 mg of  
25 clarithromycin was administered in the morning of study day 2 under supervision of  
26 the study staff. Before the last dosage of clarithromycin was taken, a baseline blood

1 sample was drawn and a microdialysate for the determination of the through  
2 concentrations in tissue was collected over 2 hours. The setting of study day 2 was  
3 identical to study day 1.

#### 5 **Chemical analysis:**

6 Clarithromycin concentrations in plasma and microdialysates were analyzed by use  
7 of a validated high-performance liquid chromatography method (24) applying  
8 moderate modifications. Pure clarithromycin was a gift from Abbott (Abbott  
9 Laboratories, Abbott Park, Illinois, US). Pure roxithromycin and all other chemicals  
10 were purchased from Sigma-Aldrich (Steinheim, Germany). In brief, 150  $\mu$ l plasma  
11 containing the internal standard roxithromycin (1 mg/l) and 10  $\mu$ l of 1 M sodium  
12 hydroxyd were extracted with 2 ml of *tert.*-butyl methyl ether. The organic layer was  
13 evaporated to dryness and the residue was dissolved with 50  $\mu$ l of the mobile phase.  
14 The mobile phase consisted of 0.05 M citrate buffer (pH 6.5) and acetonitrile (71:29,  
15 v/v). The flow rate was 0.450 ml/min. Separation was performed isocratically on a  
16 reverse-phase column Synergi max RP, 150 x 2 mm, particle size 4  $\mu$ m  
17 (Phenomenex, Torrance, California, USA) at ambient temperature. Microdialysates  
18 were spiked with the internal standard at a final concentration of 0.05 mg/l and  
19 analyzed without further preparation. Clarithromycin and roxithromycin in the eluent  
20 were detected with an amperometric detector (BAS, West Lafayette, Indiana, US) at  
21 +950 mV oxidation potential. The lower limit of quantification was 0.04 mg/l and  
22 0.012 mg/l in plasma and microdialysates, respectively. Intra-day and inter-day  
23 inaccuracy were < 9%. Intra-day and inter-day imprecision were < 12%.

24

## 1 **Protein binding studies**

2 Protein binding of clarithromycin was determined individually for each volunteer.  
3 Aliquots of 300 µl plasma from samples drawn at 80 and 180 min after administration  
4 of the drug (for both single dose and steady-state) were ultrafiltered by use of  
5 centrifugal filter units with a low-binding regenerated cellulose membrane (nominal  
6 relative molecular mass cut-off 5000; Ultrafree-MC, Millipore Corp., Bedford, Mass.,  
7 US) at 5,000 x g for 30 min at ambient temperature. Ultrafiltrates were analyzed as  
8 described above for plasma. For determination of the binding of clarithromycin to the  
9 ultrafiltration membrane during the filtration process, standards in Ringer's solution  
10 were ultrafiltered and analyzed in the same way. The ultrafiltrate concentrations  
11 were subsequently corrected by the mean membrane binding of 5% ( $C_{\text{ultrafiltrate corr}}$ ).  
12 The protein binding was calculated using the equation: Protein binding (%) = 100 –  
13  $(100 \times C_{\text{ultrafiltrate corr}} / C_{\text{plasma total}})$ .

## 15 **Pharmacokinetic calculations and statistical analysis:**

16 The individual protein binding values were used for the determination of free  
17 clarithromycin concentrations in plasma. The absolute interstitial concentrations were  
18 calculated by use of the formula: Interstitial concentration = 100 x ( $C_{\text{dialysate}} /$   
19 recovery).

20 Pharmacokinetic calculations were carried out by use of commercially available  
21 computer software (Kinetica, version 3.0; Innaphase, Philadelphia, US).  
22 Concentrations at 12 h and 24h were calculated by the equation:  $C = C_8 \times e^{-k_{el} \times t}$ ,  
23 where C is the concentration at 12 h or 24 h,  $C_8$  is the last concentration measured *in*  
24 *vivo* (at 8 h),  $k_{el}$  is the elimination rate constant, and t is the time difference between  
25  $C_8$  and C. The areas under the concentration-time curves from 0-8h ( $AUC_{0-8}$ ), 0-12h  
26 ( $AUC_{0-12}$ ) and 0-24h ( $AUC_{0-24}$ ) in plasma and interstitial fluid were calculated by use

1 of the linear trapezoidal rule. For calculation of the total drug clearance (CL) and the  
2 apparent volume of drug distribution during the terminal phase after single dose ( $V_z$ )  
3 and at steady-state ( $V_{ss}$ ) the oral dose of clarithromycin was corrected for  
4 bioavailability ( $F$ ) of 55% (7). CL,  $V_{ss}$  and  $V_z$  of clarithromycin were calculated for  
5 plasma as follows:  $CL = \text{dose} * (F) / AUC_{0-\infty}$ , where  $AUC_{0-\infty}$  represents the AUC  
6 from zero to infinity,  $V_{ss} = CL * MRT$  and  $V_z = D * (F) / (AUC_{0-\infty} * k_e)$ , respectively. The  
7  $AUC_{0-24}$  (b.i.d.) for 500 mg at steady-state was corrected for twice daily dosing by the  
8 equation  $AUC_{0-24} (500 \text{ mg b.i.d.}) = AUC_{0-12} * 2$ . Wilcoxon's paired test was used for  
9 comparison of AUCs in plasma and interstitial fluids within individuals. A two-sided  $P$   
10 value of  $< 0.05$  was considered significant.

## 1 RESULTS

2

3 The present study set out to test the ability of clarithromycin to penetrate the  
4 interstitial space fluid of subcutaneous adipose tissue and skeletal muscle in healthy  
5 volunteers. The results of one volunteer had to be excluded because plasma  
6 concentrations were almost zero indicating non-compliance of the subject to the  
7 study protocol. Thus, results of six volunteers were eligible for pharmacokinetic  
8 analysis.

9 The mean plasma protein binding of clarithromycin was  $71.3 \pm 7.4\%$  for 250  
10 mg single-dose and  $76.9 \pm 8.1\%$  for 500 mg b.i.d. at steady-state (drug intake of 3-5  
11 days). The mean individual *in-vivo* recoveries of clarithromycin in microdialysis were  
12  $57.7 \pm 7.2\%$  and  $54.3 \pm 9.0\%$  for adipose and muscle tissue, respectively. In separate  
13 *in vitro* experiments (data not shown), we demonstrated that recovery is not  
14 dependent on concentration and time. Variability between probes was minimal.

15

### 16 Pharmacokinetic data of a single dose of 250 mg clarithromycin

17 Main pharmacokinetic data are summarized in Table 1.

18 The concentration-*versus*-time profiles of free clarithromycin in the interstitial  
19 space fluid of adipose tissue resembled closely the concentration-*versus*-time  
20 profiles of skeletal muscle. Detectable interstitial concentrations were observed about  
21 one hour after drug administration (Fig. 1). The ratios of the  $fAUC_{0-24}$  in tissues to  
22 the  $fAUC_{0-24}$  in plasma were  $0.29 \pm 0.17$  (range 0.14 – 0.61) and  $0.42 \pm 0.18$  (range  
23 0.17 – 0.60) for subcutaneous adipose and skeletal muscle tissue after intake of a  
24 single oral dose of 250 mg clarithromycin, respectively. The differences between  
25  $fAUC_{0-24}$  of plasma and tissues were significant ( $P < 0.03$ ).

1

**2 Pharmacokinetic data of 500 mg clarithromycin at steady-state:**

3 Main pharmacokinetic data are summarized in Table 2.

4 Interstitial space fluid concentrations of free clarithromycin in subcutaneous adipose  
5 tissue and skeletal muscle were descriptively identical (Fig. 2). The ratios of the  
6  $fAUCs_{0-24 (b.i.d.)}$  in tissues to the  $fAUCs_{0-24 (b.i.d.)}$  in plasma were  $0.39 \pm 0.04$  (range  
7  $0.32 - 0.44$ ) and  $0.41 \pm 0.19$  (range  $0.19 - 0.75$ ) for subcutaneous adipose tissue  
8 and skeletal muscle, respectively. The differences between  $fAUCs_{0-24 (b.i.d.)}$ s of  
9 plasma and tissues were significant ( $P < 0.03$ ).

10 The clearance values at steady state differed from the single dose data because  
11 dose and  $AUC_{0-\infty}$  did not increase proportionally (non-linear pharmacokinetics).

12

**13 Safety and tolerability**

14 The study drug was well tolerated by all subjects. Metal-like taste sensation and mild  
15 gastrointestinal disturbance were observed in one volunteer. Both adverse events  
16 subsided within the study period without therapeutic measures. No adverse events  
17 related to the microdialysis procedure were observed.

## 1 DISCUSSION

2

3 Excellent tissue penetration characteristics are a commonly ascribed attribute to the  
4 entire class of the macrolides (1) and clarithromycin is considered as a very typical  
5 representative of this class. In its label information, one can read that clarithromycin  
6 distributes readily into body tissues and tissue concentrations are higher than serum  
7 concentrations (2). These statements are based on high concentrations of  
8 clarithromycin measured in biopsy homogenates and isolated tissue culture cells (11,  
9 14,17). We set out and measured its concentrations in the interstitium of soft tissues,  
10 the site of infection.

11

12 We interestingly found that the *fAUCs* of clarithromycin in the interstitial space fluid of  
13 soft tissues did not confirm the hypothesis of a significant accumulation of  
14 clarithromycin in the interstitial space at doses of up to 500 mg administered twice  
15 daily (Table 1 and 2). These findings can be explained by a) incomplete penetration  
16 of the drug from the central compartment into the interstitial space fluid, or b) forced  
17 intracellular uptake of clarithromycin or c) spontaneous degradation of clarithromycin  
18 in tissues. Spontaneous degradation and impaired transport of clarithromycin across  
19 the capillary barrier is unlikely to account for the above observation because a)  
20 clarithromycin is highly stable and b) the high density of negative charges in the  
21 basement membrane of the capillary endothelium should facilitate the diffusion of  
22 lipophilic basic drugs to the extracellular space fluid (13). Probably, a fast and high  
23 intracellular uptake of clarithromycin into lysosomes, likely assisted by a  
24 phenomenon called “ion-trapping”, is an explanation for the unexpectedly low  
25 concentrations of clarithromycin in the interstitium (6,10).

26

1 The elimination half-life of clarithromycin in tissues and plasma was about 2 hours in  
2 our study collective after a single dose of 250 mg. As observed previously in other  
3 studies (8,23), a non-linear plasma and tissue pharmacokinetic profile of  
4 clarithromycin was detected following administration of the higher dose of 500 mg  
5 twice a day in a twelve hours interval (Table 2). The non-linear increase in AUCs and  
6 prolongation of half-life is most likely attributed to the inhibition of the activity of  
7 cytochrom P<sub>450</sub> 3A4 caused by clarithromycin itself after repetitive dosing (26).

8  
9 For the class of macrolides, the ratio of  $AUC_{0-24 \text{ plasma}}$  to minimal inhibitory  
10 concentration (MIC) has been shown to be the most predictive PK-PD index for  
11 survival of animals (3,25). In literature, there is circumstantial evidence that optimal  
12 bacterial eradication of *S. pneumoniae* and survival of animals can be expected  
13 when the  $fAUC_{0-24 \text{ plasma}}/MIC$  ratio of macrolides is not lower than around 35 (3,25).  
14 PK-PD breakpoints for other bacteria than *S. pneumoniae* are currently almost  
15 completely lacking or show conflicting results. Another source of confusion to this  
16 point is that some authors reported on ratios of total AUC to MIC and did not correct  
17 for plasma protein binding (25). However, provided that a  $fAUC_{0-24 \text{ plasma}}/MIC$  target of  
18 at least 35 is also valid in humans for pathogens other than *S. pneumoniae* and  
19 taking a calculated  $AUC_{\text{tissue}}$  to  $AUC_{\text{plasma}}$  ratio of 0.40 for tissues into account, then  
20 the corresponding ratio  $fAUC_{0-24 \text{ tissue}}/MIC$  should be around 14. Thus, 6 out of 6  
21 volunteers would have a high probability of cure with 500 mg of clarithromycin b.i.d.  
22 in case of soft tissue infection caused by pathogens with MICs of less than 0.125  
23 mg/l. However, if the pathogen's MIC is  $\geq 0.25$  mg/l (12), it is tempting to conclude  
24 that the 500 mg b.i.d. regimen would not work sufficiently in any of the subjects in  
25 subcutaneous adipose tissue and would be active only in 3 out of 6 subjects in  
26 skeletal muscle.

1  
2 In general, one may argue that clarithromycin undergoes extensive hepatic  
3 metabolism and is converted to 14-(R)-OH-clarithromycin, which is a major active  
4 metabolite exerting an *in-vitro* activity similar to that of the parent compound (15,18).  
5 Data of four previous publications about the plasma concentrations of the 14-hydroxy  
6 metabolite in humans are in well agreement with an overall ratio of the  $AUC_{\text{metabolite}}$  to  
7 the  $AUC_{\text{parent compound}}$  of  $34.9 \pm 2.1\%$  (5,8,9,19). Interstitial concentrations of the  
8 hydrophilic 14-hydroxy metabolite are unknown at present. However, based on  
9 previous investigations as well as on the chemical and physical properties of the  
10 metabolite, it may be concluded that the ratio of the  $AUC_{\text{metabolite}}$  to the  $AUC_{\text{parent}}$   
11  $\text{compound}$  in the interstitium may be similar to plasma (14,22). Since it is unlikely that  
12 interstitial concentrations of 14-(R)-OH-clarithromycin of one third of the  
13 concentration of the parent compound would significantly affect antimicrobial action  
14 at the target site we did not include an estimation of concentrations of the active  
15 metabolite in the present PK-PD calculations. Thus, the concentrations of 14-hydroxy  
16 clarithromycin were not measured in the present study.

17  
18 Another potential limitation of the present study is that steady-state conditions may  
19 not be reached in all volunteers, even though subjects were asked to take the study  
20 drug twice daily over a period of at least 3 days. From a pharmacokinetic point of  
21 view, steady-state concentrations should be reached within this period, provided that  
22 study drug was taken as foreseen in the protocol and that the elimination half-life  
23 does not increase with further duration of dosing. An advanced increase of half-life of  
24 clarithromycin in tissues and plasma could theoretically lead to higher concentrations  
25 of clarithromycin and its active metabolite in the interstitium.

1 However, intake of study drug was monitored by pill count, and thus inadequate  
2 compliance of subjects would have required more sophisticated and tricky methods.  
3 Nevertheless, in one subject the plasma concentrations of clarithromycin were below  
4 the limit of quantification as mentioned in the methods. Thus, compliance was most  
5 probably not optimal in some volunteers.

6  
7 In summary, our results are indicative that plasma pharmacokinetics of clarithromycin  
8 may lead to overestimation of its interstitial concentrations in unaffected soft tissues.  
9 PK-PD calculations support the idea that even a dose of 500 mg b.i.d. may be  
10 ineffective in the therapy of skin infections caused by extracellular pathogens with  
11 MICs higher than 0.125 mg/l. However, subsequent studies looking at the interstitial  
12 concentrations of clarithromycin and its active metabolite after one week therapy are  
13 necessary to confirm these data.

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15  
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**Table 1**Main pharmacokinetic indices of clarithromycin following administration of a single oral dose of 250 mg (n=6) <sup>a</sup>

Compartment	AUC <sub>0-8</sub> (mg.h/liter)	AUC <sub>0-24</sub> <sup>b</sup> (mg.h/liter)	AUC <sub>0-24</sub> tissue/ fAUC <sub>0-24</sub> plasma	C <sub>max</sub> (mg/liter)	T <sub>max</sub> (h)	T <sub>1/2β</sub> (h)	V <sub>z</sub> (liters)	CL (liters/h)
Plasma (total)	3.63±1.32	4.45±1.94	—	1.09±0.35	2.6±0.5	1.9±0.6	94.0±25.0	37.2±14.9
Plasma (free)	0.99±0.28	1.21±0.35	—	0.31±0.14	2.6±0.5	1.9±0.6	—	—
Subcutis	0.24±0.16 <sup>c</sup>	0.35±0.25 <sup>c</sup>	0.29±0.17	0.07±0.03	3.0±0.5	2.4±1.2	—	—
Muscle	0.29±0.14 <sup>c</sup>	0.48±0.23 <sup>c</sup>	0.42±0.18	0.08±0.03	3.0±0.3	3.1±0.9	—	—

<sup>a</sup> Values represent mean ± SDs. <sup>b</sup> Calculated for single dose of 250 mg. Abbreviations: C<sub>max</sub>, maximum concentration of drug; T<sub>max</sub>, time to maximum concentration; t<sub>1/2β</sub> half-life at β phase; AUC, area under the concentration-*versus*-time curve; fAUC, AUC of free drug; V<sub>z</sub>, volume of drug distribution at the terminal phase after single dose; CL, total clearance.

<sup>c</sup> P < 0.03 compared to free plasma

**Table 2**Main pharmacokinetic indices of clarithromycin at steady-state after administration of 500 mg b.i.d. (n=6) <sup>a</sup>

Compartment	AUC <sub>0-8</sub> (mg.h/liter)	AUC <sub>0-24</sub> <sup>b</sup> (mg.h/liter)	AUC <sub>0-24</sub> tissue/ fAUC <sub>0-24</sub> plasma	C <sub>max</sub> (mg/liter)	T <sub>max</sub> (h)	T <sub>1/2β</sub> (h)	V <sub>ss</sub> (liters)	CL (liters/h)
Plasma (total)	10.59±1.78	26.81±5.49	—	2.21±0.33	3.2±0.3	3.7±0.6	126.5±17.4	18.7±5.2
Plasma (free)	2.26±0.71	5.85±1.79	—	0.58±0.19	3.2±0.3	3.7±0.6	—	—
Subcutis	0.84±0.19 <sup>c</sup>	2.22±0.59 <sup>c</sup>	0.39±0.04	0.23±0.10	4.0±0.9	3.4±1.2	—	—
Muscle	0.92±0.43 <sup>c</sup>	2.42±1.23 <sup>c</sup>	0.41±0.19	0.23±0.09	3.8±0.9	3.8±1.1	—	—

<sup>a</sup> Values represent mean ± SDs. <sup>b</sup> calculated for twice daily dosing. Abbreviations: C<sub>max</sub>, maximum concentration of drug ; T<sub>max</sub>, time to maximum concentration; t<sub>1/2β</sub> half-life at β phase; AUC, area under the concentration-*versus*-time curve; fAUC, AUC of free drug; V<sub>ss</sub>, volume of distribution at steady-state; CL, total clearance.

<sup>c</sup> *P* < 0.03 compared to free plasma.

Figure 1.

**Clarithromycin concentrations in plasma and interstitial space fluid of soft tissues after a single dose of 250 mg in six male healthy volunteers (mean + SD)**

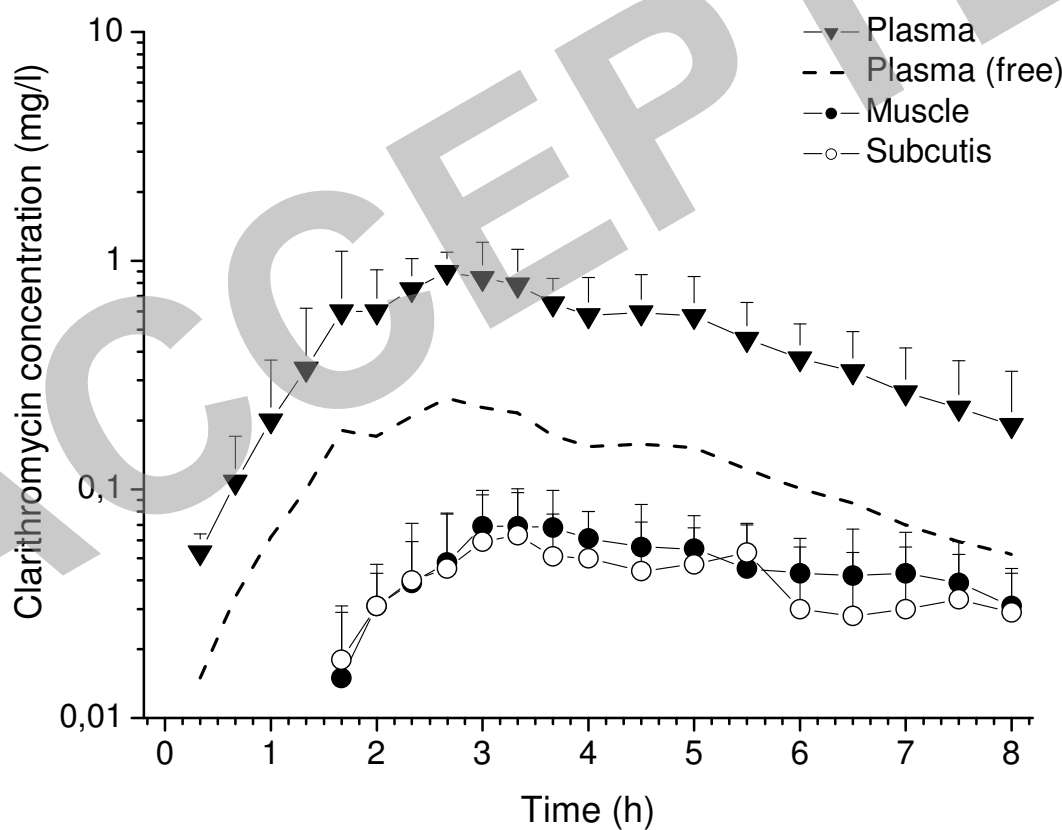


Figure 2.

**Clarithromycin concentrations in plasma and interstitial space fluid of soft tissues after multiple doses of 500 mg b.i.d. in six male healthy volunteers (mean + SD)**

