

# Sparfloxacin Distribution in Human Saliva

Mikaela Kolaci<sup>1\*</sup>, and Leonard Deda<sup>2</sup>

<sup>1</sup>National Agency of Medicines and Medical Devices, Tirana, Albania

<sup>2</sup>Department of Pharmacology, Faculty of Medicine, Tirana, Albania

\*Corresponding author: Mikaela Kolaci, National Agency of Medicines and Medical Devices, Tirana, Albania, Tel: 0695303079; E-mail: mikaela\_kolaci@yahoo.com

Received: 23 Nov, 2020 | Accepted: 21 Dec, 2020 | Published: 29 Dec, 2020

**Citation:** Kolaci M, Deda L (2020) Sparfloxacin Distribution in Human Saliva. J Drug Res Dev 6(2): dx.doi.org/10.16966/2470-1009.157

**Copyright:** © 2020 Kolaci M, et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

## Abstract

**Aim:** The aim of this study is to assess the penetration of sparfloxacin in mixed human saliva after a single oral dose of 400mg in Caucasian healthy subjects.

**Background:** Fluoroquinolones are a group of relatively new antibiotics with a broad and effective spectrum of antimicrobial activity. Fluoroquinolones have been reported to distribute well into saliva. Data on the distribution of sparfloxacin in human saliva are very scarce and limited to Japanese subjects.

**Method:** Six healthy volunteers participated in the study. Blood and saliva samples were taken prior to sparfloxacin administration and thereafter at 2,4,6,8,10,28,54 hours after dosing. The concentrations of sparfloxacin in plasma and saliva were determined by a validated HPLC method, for each biological matrix. The maximal concentration ( $C_{max}$ ) and time to reach  $C_{max}$  ( $T_{max}$ ) of sparfloxacin in plasma and saliva were determined by direct observation of the data. The AUC, for both plasma and saliva, were calculated using trapezoidal rule.

The mean penetration of the drug into saliva was calculated by the ratio  $AUC_{0-\infty} \text{ saliva} / AUC_{0-\infty} \text{ plasma}$  and also by the average of Saliva/Plasma ratio for each concentration during the elimination phase.

**Results:** The mean  $C_{max}$  of sparfloxacin in plasma was 1.98 $\mu\text{g/mL}$  with a mean  $T_{max}$  of 4.3 h after oral administration. Mean terminal elimination half-life ( $t_{1/2\beta}$ ) from plasma was 18.4 h (range 13.4-23.2 h). The  $AUC_{0-54}$  and  $AUC_{0-\infty}$  were 46.9 $\mu\text{g}\cdot\text{h/mL}$  and 53.6 $\mu\text{g}\cdot\text{h/mL}$ , respectively. Penetration of sparfloxacin in saliva was good and rapid. Two peak saliva concentrations were observed in 5 subjects, the first one appearing at 2 h after dosing, before the plasma  $C_{max}$  was reached. Post-absorption phase mean  $C_{max}$  in saliva was 1.8 $\mu\text{g/mL}$  with a  $T_{max}$  of 5.3 h after oral administration. Mean terminal elimination half-life ( $t_{1/2}$ ) from saliva was 15.8 h (range 13.9-18.2 h).

**Conclusions:** Following the administration of an oral dose of 400mg sparfloxacin in healthy Caucasian adults saliva concentrations were 62.8 to 71.3% of the corresponding plasma concentrations with an overall penetration of sparfloxacin into saliva of 68.4%.

**Keywords:** Sparfloxacin; Human saliva; Distribution; Pharmacokinetic parameters

## Introduction

Fluoroquinolones are a group of relatively new antibiotics with a broad and effective spectrum of antimicrobial activity against both gram-negative and gram-positive bacteria.

Sparfloxacin was approved for medical use in 1993. The main potential advantages of sparfloxacin over older fluoroquinolones are its improved activity against Gram-positive pathogens and its long half-life that allows once-daily dosing [1].

Sparfloxacin is readily absorbed and has oral bioavailability of 92% and half-life of 16-20 hours [2-4]. Peak serum concentrations are reached 3-5 hours following oral administration. Sparfloxacin binds weakly to plasma protein (37%), and exhibits excellent tissue

distribution and effective penetration into extracellular fluids. Concentrations of the drug in most tissues are similar to, or higher than, concomitant plasma concentrations [5]. Studies performed in animals and humans have demonstrated that fluoroquinolones, such as ciprofloxacin, norfloxacin, ofloxacin, pefloxacin and moxifloxacin distribute well into human saliva. Recently, a systematic review and a qualitative review of the literature on the pharmacokinetics of antibiotics in saliva have been published [6,7]. However, data on sparfloxacin distribution in human saliva are very limited.

The aim of this study was to assess the penetration of sparfloxacin in mixed human saliva after a single oral dose of 400mg in healthy Caucasian subjects.

## Materials and Methods

### Ethics

The study protocol was reviewed and approved by the National Ethics Committee. The study was conducted in accordance with the requirements of the GCP and the principles of the Helsinki Declaration. Informed written consent was obtained from all subjects.

### Study design

This was a prospective, open-label, paired-sample controls study. A single dose of sparfloracin 400mg (SPARFLO 200mg tablets, Dr. Reddy's) was administered orally with 200ml of water to each overnight fasted subject. There was no restriction on fluid intake. Food was allowed 4 hours after the administration.

### Volunteers

Six healthy volunteers participated in the study. Physical examination, electrocardiograms, and laboratory screening (hematological and biochemical parameters) were all normal before and after the study. Exclusion criteria were acute or chronic diseases, blood donation 8 weeks prior to study, known or suspected hypersensitivity to the quinolones, alcohol consumption, pregnancy, or intention to become pregnant. The use of any additional medication 2 weeks prior to or during the study period was not allowed.

### Sample collection and processing

Blood samples (5mL) were taken from a peripheral vein, through an indwelling catheter, prior to sparfloracin administration and then at 2,4,6,8,10,28,54 hours after dosing. Blood specimens were collected in heparinized tubes and were subsequently centrifuged at 3500 rpm for 10 minutes. A 100µL of perchloric acid 12% was added to a 100µL aliquot of plasma to precipitate the proteins. The mixture was vortexed for 30 sec. and centrifuged for 5 min at 5000 rpm. The supernatant was injected manually.

Whole mixed saliva was collected at the same intervals, after previous rinse of the oral cavity with 50mL of water, which was discharged. Saliva production was stimulated by chewing of a parafilm and collected (2ml) by spitting into a tube, which was centrifuged at 9000 rpm for 10 minutes to remove mucus or particulate matter. Saliva was filtered and injected without further preparation.

Plasma, saliva and standard solutions were stored at -4°C until analysis.

### Drug analysis

The concentrations of sparfloracin in plasma and saliva were determined by HPLC, using a validated method for each biological matrix. A reversed-phase LiChrospher RP18, 5µm column (250mm × 3mm i.d: Hewlett Packard), a binary pump (Hewlett Packard 1100) and a manual injector (Rheodyne), 20µL loop, were used. UV detection was made at 300nm, for both plasma and saliva, using a UV-VIS detector (Hewlett Packard 1100) was pumped isocratically.

The lower limit of quantification for plasma and saliva were 0.125µg/mL and 0.05µg/mL, respectively. The intra-run and between-run coefficients of variation were less than 12.6% for plasma and less than 8.7% for saliva.

Mobile phase, a mixture of acetonitrile 25% and 0.05M KH<sub>2</sub>PO<sub>4</sub>, to which 5% dimethylformamide was added.

### Pharmacokinetic analysis

The maximum concentration (C<sub>max</sub>) of sparfloracin in plasma

or saliva and time to reach C<sub>max</sub> (T<sub>max</sub>) were determined by direct observation of the data. AUC<sub>0-54</sub> for both plasma and saliva, were calculated using trapezoidal rule. AUC<sub>54-∞</sub> was calculated by the ratio of last measured concentration and the terminal elimination rate constant (K<sub>el</sub>). K<sub>el</sub> was estimated by linear regression of the linear portion of the log transformed concentration versus time. The terminal elimination half-life (t<sub>1/2</sub>) was calculated by the formula: t<sub>1/2</sub>=ln(2)/K<sub>el</sub>.

The mean penetration of the drug into saliva was calculated by the ratio AUC<sub>0-∞</sub> saliva / AUC<sub>0-∞</sub> plasma and also by the average of Saliva/Plasma ratio for each concentration during the elimination phase.

### Statistical analysis

Results are shown as arithmetic means ± SE. In case of comparisons the appropriate parametric or nonparametric test was chosen after testing the respective data for normal distribution. Statistical significance was defined as a P value of <0.05.

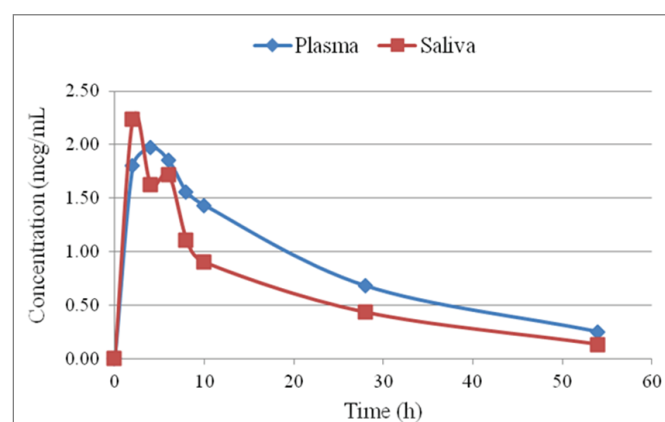
## Results

All six volunteers (three males and three females), mean age 34 ± 3.2 years, completed the study. Sparfloracin was well tolerated. No physical, biochemical or hematological abnormalities related to the administration of sparfloracin were observed.

The mean concentration-time curves for plasma and saliva, after the administration of a single oral dose of sparfloracin 400mg, are shown in the figure 1. Pharmacokinetic parameters are summarized in the table 1.

The mean C<sub>max</sub> in plasma was 1.98µg/mL with a T<sub>max</sub> of 4.3 h after oral administration. AUC<sub>0-54</sub> and AUC<sub>0-∞</sub> were 46.9µg\*h/mL and 53.6µg\*h/mL, respectively. The mean value of terminal elimination half-life (t<sub>1/2β</sub>) from plasma was 18.4 h (range 13.4-23.2 h).

Penetration of sparfloracin in saliva was good and rapid. Two peak concentrations of sparfloracin in saliva were observed in 5 subjects, the first one appearing at 2 h after dosing and before the maximal plasma concentrations were reached. Post-absorption phase mean C<sub>max</sub> in saliva was 1.8µg/ml with mean T<sub>max</sub> attained 5.3 h after oral administration. AUC<sub>0-54</sub> and AUC<sub>0-∞</sub> were 33.6µg\*h/ml and 36.7µg\*h/ml, respectively. The mean value of terminal elimination half-life (t<sub>1/2β</sub>) from saliva was 15.8 h (range 13.9-18.2 h).



**Figure 1:** Sparfloracin mean concentration in plasma over 54 h. The mean penetration percentage into saliva, calculated as AUC<sub>0-∞</sub>(S)/AUC<sub>0-∞</sub>(P) and AUC<sub>0-54</sub>(S)/AUC<sub>0-54</sub>(P) were 68.4% and 71.6%, respectively. The ratios of saliva/plasma concentrations at 8, 10 and 28 hours post dose were 71.3%, 62.8% and 63.6%, respectively.

**Table 1:** Sparfloxacin plasma and saliva pharmacokinetic parameters.

	Plasma		Saliva	
	Mean $\pm$ SE	CV	Mean $\pm$ SE	CV
$C_{max}$ (mcg/mL)	2.07 $\pm$ 0.31	36.4%	2.3 $\pm$ 0.52	54.8
			1.8 $\pm$ 0.31*	43.3
$T_{max}$ (h)	4.33 $\pm$ 0.33	18.8	3.33 $\pm$ 0.84	62
			5.33 $\pm$ 0.67*	30.6
$t_{1/2B}$ (h)	18.4 $\pm$ 1.34	17.9	15.8 $\pm$ 0.63	9.8
$AUC_{0-54}$ ( $\mu$ g*h/mL)	46.9 $\pm$ 6.85	35.7	33.6 $\pm$ 3.61	26.3
$AUC_{0-\infty}$ ( $\mu$ g*h/mL)	53.6 $\pm$ 6.99	31.9	36.7 $\pm$ 4.08	27.2

\*post-absorption phase

CV coefficient of variation

## Discussion

Sparfloxacin pharmacokinetics, as well as its tissue and body fluids penetration have been reported in several studies. In Caucasian volunteers and patients plasma sparfloxacin concentrations reached a peak of 1.2-1.5mg/L between 3 and 6 h after a single 400mg dose;  $t_{1/2}$  ranged from 16 to 22 h [3]. Zhanel GG, et al. [8] for an oral dose of 40mg has reported a  $C_{max}$  value of 1.30mcg/ml and a  $T_{max}$  of 4.5 hours. In an open, randomized, triple crossover study, the effects of cisapride and sucralfate on the pharmacokinetics of sparfloxacin were assessed. Fifteen healthy volunteers received 400mg of sparfloxacin as a single oral dose. Pharmacokinetic parameters for sparfloxacin alone were as follows (mean  $\pm$  standard deviation): maximum concentration of drug in serum ( $C_{max}$ ), 1.27  $\pm$  0.39mcg/ml; time to  $C_{max}$  ( $T_{max}$ ), 4.1  $\pm$  1.9 h; area under the concentration-time curve (AUC), 35.0  $\pm$  9.7 $\mu$ g\*h/ml [9]. In another study, a single 400mg oral dose of sparfloxacin was given to each of six healthy male volunteers, and the concentrations of the drug were measured in plasma. The mean peak concentration in plasma of 1.6micrograms/ml was attained at a mean time of 2.7 h post dose. The mean elimination half-life in plasma was 17.6 h [10]. In our study  $C_{max}$  and  $AUC_{0-\infty}$  were found to be slightly higher, while  $T_{max}$  was similar with the results of other studies. Was also higher than those of other studies.

To our knowledge, this is the first study which evaluates saliva penetration of sparfloxacin 400mg, given orally, in healthy Caucasian adults. We were unable to identify any data on salivary distribution of sparfloxacin in humans, apart those reported by Shimada J, et al [5]. In their work they make reference to a study of Naitoh done in 10 Japanese males, with a single oral dose of 200mg sparfloxacin, where they found saliva and plasma  $C_{max}$  to be respectively 0.97mcg/ml and 1.38mcg/ml, with a ratio of 70%, and to a study of Nakashima done in 6 Japanese males, also with a single oral dose of 200mg sparfloxacin, where saliva and plasma  $C_{max}$  respectively 0.43mcg/mL and 0.65mcg/ml, with a ratio of 66%, were found.

In our study, higher saliva concentrations than respective plasma concentrations was observed during the absorption phase. In general,

saliva concentration of fluoroquinolones during absorption phase are lower than corresponding plasma concentrations, but this may not be true for moxifloxacin. Stass H, et al. [11] reported moxifloxacin salivary concentrations to be higher than respective plasma concentrations during the absorption phase.

## Conclusions

In conclusion, following the administration of an oral dose of 400mg sparfloxacin in healthy Caucasian adults saliva concentrations were 62.8 to 71.3% of the corresponding plasma concentrations with an overall penetration of sparfloxacin into saliva of 68.4%.

## References

- Richard P, Gutmann L (1992) Sparfloxacin and other new fluoroquinolones. *J Antimicrob Chemother* 30: 739-744.
- Montay G, Bruno R, Vergniol JC, Ebmeier M, Le Roux Y, et al. (1994) Pharmacokinetics of sparfloxacin in humans after single oral administration at doses of 200,400,600 and 800mg. *J Clin Pharmacol* 34: 1071-1076.
- Montay G (1996) Pharmacokinetics of sparfloxacin in healthy volunteers and patients: a review. *J Antimicrob Chemother* 37: 27-39.
- Schentag JJ (2000) Sparfloxacin: a review. *Clin Ther* 22: 372-387.
- Shimada J, Nogita T, Ishibashi Y (1993) Clinical Pharmacokinetics of Sparfloxacin. *Clin Pharmacokinet* 25: 358-369.
- Troeltzsch M, Pache C, Probst FA, Troeltzsch M, Ehrenfeld M, et al. (2014) Antibiotic concentrations in saliva: a systematic review of the literature, with clinical implications for the treatment of sialadenitis. *J Oral Maxillofac Surg* 72: 67-75.
- Kiang TK, Ensom MH (2016) A Qualitative Review on the Pharmacokinetics of Antibiotics in Saliva: Implications on Clinical Pharmacokinetic Monitoring in Humans. *Clin Pharmacokinet* 55: 313-358.
- Zhanel GG, Walkty A, Vercaigne L, Karlowsky JA, Embil J, et al. (1999) The new fluoroquinolones: A critical review. *Can J Infect Dis* 10: 207-238.
- Zix JA, Geerdes-Fenge HF, Rau M, Vöckler J, Borner K, et al. (1997) Pharmacokinetics of sparfloxacin and interaction with cisapride and sucralfate. *Antimicrob Agents Chemother* 41:1668-1672.
- Johnson JH, Cooper MA, Andrews JM, Wise R (1992) Pharmacokinetics and inflammatory fluid penetration of sparfloxacin. *Antimicrob Agents Chemother* 36: 2444-2446.
- Stass H, Dalhoff A, Kubitzka D, Schühly U (1998) Pharmacokinetics, safety, and tolerability of ascending single doses of moxifloxacin, a new 8-methoxy quinolone, administered to healthy subjects. *Antimicrob Agents Chemother* 42: 2060-2065.