Monitoring salivary concentrations of tedizolid and linezolid using rats

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Short title

Monitoring concentrations of tedizolid and linezolid in saliva

Abstract

Background and Objective

Therapeutic drug monitoring (TDM) is an effective tool for the management of patients who are administered linezolid. The use of saliva for TDM has potential advantages over the use of plasma; however, only a few reports have compared drug concentrations in the saliva and plasma. Moreover, there are no reports on the salivary concentration of tedizolid, an oxazolidinone antibiotic similar to linezolid. In the present study, the concentrations of tedizolid and linezolid in rat submandibular saliva were compared with those measured in the plasma.

Methods

Tedizolid (10 mg/kg, n=6) and linezolid (12 mg/kg, n=5) were administered *via* the rat tail vein. Submandibular saliva and plasma samples were collected for up to 8 h after the initiation of drug administration, and assayed for the concentrations of tedizolid and linezolid.

Results

A strong correlation was found between the saliva and plasma concentrations of tedizolid (r=0.964, $p<0.001$) and linezolid (r=0.936, $p<0.001$). The value of tedizolid maximum concentration of drug (C_{max}) was 0.99 ± 0.08 μg/mL in the saliva and 14.46 ± 1.71 μg/mL in the plasma. Meanwhile, the C_{max} of linezolid was 8.01 ± 1.42 μg/mL in the saliva and 13.00 ± 1.90 μg/mL in the plasma. According to these results, the saliva/plasma concentration ratios of tedizolid and linezolid in rats were 0.0513 ± 0.0080 and 0.6341 ±

0.0339, respectively.

Conclusions

Considering the correlation between saliva and plasma concentrations of tedizolid and linezolid, as well as, the characteristics of saliva, the results of this study suggest that saliva is a useful matrix for TDM.

Key points

Tedizolid and linezolid concentrations in the saliva and plasma were found to be strongly correlated.

Considering this correlation, as well as the characteristics of saliva, our results suggest that saliva is a useful matrix for therapeutic drug monitoring.

Monitoring these drugs using saliva contributes to the in-depth determination of their pharmacokinetics and will help reduce serious adverse effects that are associated with them.

1. Introduction

Oxazolidinones are synthetic antibiotics used for the treatment of infections caused by drug-resistant pathogens, especially methicillin-resistant *Staphylococcus aureus* [1]. Linezolid (Fig. 1) is a first-generation oxazolidinone drug, while tedizolid (Fig. 2) is a second-generation oxazolidinone. Infections involving either the bone or joint prostheses present a particularly difficult problem for patient management. A previous report showed that linezolid penetrates the bone and tissues surrounding the infected prosthetic joints. Therefore, it has been widely used to treat orthopedic infections [2]. There is a need to carefully monitor patients for severe linezolid toxicity. Thrombocytopenia is a major adverse event associated with linezolid therapy [3, 4]. Our previous study using a large Japanese electronic medical record database showed that the proportion of linezolid-induced thrombocytopenia (LIT) is approximately 45% of the patients administered linezolid [5]. The risk of thrombocytopenia with tedizolid has been reported to be less than that caused by linezolid; therefore, switching from linezolid to tedizolid is considered one of the effective means for patients with LIT [6, 7].

Several findings provide a strong rationale for the routine application of therapeutic drug monitoring (TDM) as a tool to predict and prevent serious adverse events in linezolid, such as LIT [8-10]. However, clear clinical guidelines for the TDM of linezolid are yet to be established. Additionally, TDM is routinely performed using plasma or serum samples, which is a burden on both patients and medical professionals. Tedizolid was approved by the U.S. Food and Drug Administration in 2014, less than 10 years ago [11];

thus, there is scarce information about the real-world use of tedizolid, particularly its pharmacokinetics. Plasma protein binding between tedizolid and linezolid is different, therefore the pharmacokinetics of these two drugs is considered to be different; Ong et al. showed that tedizolid protein binding was 97.2% in rats and 86.6% in humans [12]. Gentry-Nielsen et al. reported that linezolid protein binding was 26% in rats, which is similar to the results of other human studies [13]. Pharmacokinetic analysis also has many disadvantages, because multiple samples must be collected; yet, an understanding of pharmacokinetics is essential for the safe use of tedizolid.

Considering these circumstances, other matrices, such as dried blood spots and saliva, are likely to be attractive alternatives to solve these issues [14, 15]. Samples for dried blood spots testing were prepared by applying plasma to a cellulose substrate and drying it at room temperature. There is growing interest in dried blood spots sampling, because only a small volume of blood is required [14]. On the other hand, it is known that most compounds found in the plasma are also present in the saliva, especially linezolid. The U.S. Food and Drug Administration showed that the ratio of linezolid in the saliva, relative to that in the plasma was 1.0 to 1.2 [16]. Saliva collection is simple and noninvasive, and thus, allows for the collection of multiple samples, while avoiding the risks associated with drawing blood. Hara et al. measured the changes in linezolid concentrations in the saliva, at 3, 7, and 12 h after intake in healthy volunteers, and reported that saliva was useful for monitoring the trough concentration of linezolid [17]. A linezolid plasma trough concentration of >8 mg/L has been reported as a predictor of LIT [18]. If saliva could be collected

from patients at least at the trough concentration of linezolid, the drug concentration could be assessed, and the dosage could be reduced before the development of LIT.

In this study, we examined the penetration of tedizolid and linezolid into rat submandibular saliva, by measuring their concentrations in the saliva at each time-point and compared them to the concentrations in the plasma. We also evaluated the correlation between the plasma and saliva concentrations of tedizolid and linezolid. This is the first study to investigate tedizolid concentrations in the saliva.

2. Materials and methods

2.1. Chemicals and reagents

Linezolid and urethan were purchased from Tokyo Chemical Industry Co. Ltd. (Tokyo, Japan). Tedizolid for calibration curve was purchased from MedChem Express (New Jersey, USA). Tedizolid (SIVEXTRO®) infused to rats was obtained from MSD (Tokyo, Japan). Quinoxaline (internal standard [IS] for linezolid) was obtained from Sigma-Aldrich (Tokyo, Japan). 3-(α-acetonylbenzyl)-4-hydroxycoumarin sodium salt (IS for tedizolid), acetylcholine, acetonitrile, methanol, dimethyl sulfoxide, potassium dihydrogen phosphate, and potassium phosphate dibasic were purchased from FUJIFILM Wako Pure Chemical Corp. (Osaka, Japan). All reagents were of the highest grade available and were used without further purification.

2.2. Animals

Twelve-week-old male Wistar rats (body weight: 340 ± 20 g) were obtained from CREA Japan Inc. (Tokyo, Japan) and housed in conventional conditions, in a temperature- and humidity-controlled room, with a 12 h–12 h light–dark cycle (light period: 08.00–20.00 h; temperature: 23 ± 2°C; relative humidity: 50 ± 10%). The rats had *ad libitum* access to food and water. The experimental protocols were reviewed and approved by the Hokkaido University Animal Care Committee, in accordance with the "Guide for the Care and Use of Laboratory Animals" (study protocol no. 21-0101). This study was conducted between May 2022 and January 2023.

2.3. Salivary secretion in the rat submandibular glands (SMGs)

The three major salivary glands are parotid, submandibular, and sublingual glands, all of which empty into the oral cavity through excretory ducts. SMGs produce most of the resting saliva [19]. To collect saliva from rat SMGs, a fine polyethylene tube (Intermedic PE-10; BD Diagnostic Systems, Sparks, MD, USA) was inserted intraorally into the orifice on one side of the SMG duct, according to Nezu et al. [20]. This process allowed us to obtain fresh saliva directly from the SMG ducts. During the experiment, the rats were placed on a heating pad and anesthetized with urethane, because anesthesia with other drugs was inadequate and burdened the rat's body. The standard dose range for intraperitoneal administration of urethane to rats is 1.0–1.5 g (kg, bodyweight); in our study 1.0 g (kg, bodyweight), 20% w/v solution in saline was used [21, 22]. At this concentration of urethane, anesthesia could be maintained for ≥10 h. Tracheas were

128 cannulated to maintain clear airways during the experiments. While collecting about 50 μL of saliva from
129 the SMGs for 5 min at each point, acetylcholine (12 mM, 260–320 nmol/min) was infused intravenous
130 through the femoral vein, using a programmable single syringe pump, to stimulate saliva secretion. Nezu
131 et al. reported that after acetylcholine (10–720 nmol/min) infusion through the rat femoral vein, the
132 salivary flow rate increased in a dose-dependent manner; however, the salivary flow rate in our rats
133 (male Wistar rat) was lower than that in their paper (male Wistar/ST rat) (data not shown). A possible
134 reason for this is that a different rat species was used. Therefore, in our study, acetylcholine was infused
135 at 260–320 nmol/min [20]. Infusion rates ranged from 2.0–2.3 mL/h. After collecting saliva for 5 min, the
136 infusion of acetylcholine was stopped until the next point.
137
138 **2.4. Blood and saliva sample collection**
139 Tedizolid (10 mg/kg, body weight; SIVEXTRO®, MSD, Tokyo, Japan) dissolved in saline was infused
140 intravenously through the rat tail vein, using a programmable single syringe pump. The infusion rates were
141 5.0 mL/h and infusion time was 1 h. Linezolid (12 mg/kg body weight) dissolved in saline was administered
142 in the same manner as tedizolid in rats. Blood and saliva samples were collected at 65, 90, 120, 180, 270,
143 360, 420, and 480 min after the start of the infusion. We collected 0.4 mL of blood samples from the jugular
144 vein into heparinized tubes. The samples were centrifuged at 750×*g*, 4°C, for 10 min and the supernatant
145 was used as a sample. Saliva samples were collected as previously described. Each saliva sample was

cumulative for 5 min, because the flow rate of saliva is much slower than that of blood. All samples that were not used immediately were stored at −20°C.

2.5. Calibration and sample preparation

2.5.1. Preparation of tedizolid samples

The stock solutions (each 0.25 mg/mL) of tedizolid used to make calibration standards were prepared by dissolving 5 mg of the compound in 20 mL dimethyl sulfoxide. Twenty microliters of the stock solution diluted with 50% methanol were added to 80 μL of drug-free rat plasma or saliva, to obtain final tedizolid concentrations of 0.05, 0.5, 2.0, 4.0, 8.0, 14.0, and 20.0 μg/mL for plasma and 0.025, 0.05, 0.5, 1.0, 2.0, and 3.0 μg/mL for saliva. Twenty-five microliters of 250 μg/mL IS [3-(α-acetonylbenzyl)-4-hydroxycoumarin sodium salt] was added to 100 μL of each tedizolid plasma sample. Three hundred microliters of acetonitrile were added to each sample and vortexed for 30 s, to deproteinize the plasma. Samples were left at normal temperature (15°C–25°C [23]) for 10 min and centrifuged for 15 min at 14,000×*g*, 4°C. The samples were then transferred to a high-performance liquid chromatography (HPLC) autosampler. Tedizolid samples were prepared as described in the above procedure, except that 25 μL of 250 μg/mL IS was added to 100 μL of each tedizolid plasma sample. For the saliva samples, saliva was used instead of plasma, and each volume was 0.4-times.

164 **2.5.2. Preparation of linezolid samples**

165 Calibration standards were made from stock solutions (each 0.25 mg/mL) of linezolid prepared by
166 dissolving 5 mg of the compound in 20 mL water. Ten microliters of these dilutions were added to 90 μL
167 of drug-free rat plasma or saliva, to obtain final linezolid concentrations of 0.5, 1.0, 5.0, 10.0, 20.0, and
168 30.0 μg/mL. Twenty-five microliters of 100 μg/mL IS (quinoxaline) was added to 100 μL of each linezolid
169 plasma sample. Two hundred-fifty microliters of acetonitrile were added to each sample and vortexed for
170 30 s, to deproteinize the plasma. Samples were left at normal temperature (15°C–25°C [23]) for 10 min.
171 After centrifugation at 14,000×*g*, 4°C for 15 min, the supernatant was collected and diluted two-fold with
172 water. The mixture was then transferred to a HPLC autosampler. Linezolid samples were prepared as
173 described in the above procedure, except that 25 μL of 100 μg/mL IS was added to 100 μL of each linezolid
174 plasma sample. For the saliva samples, saliva was used instead of plasma, and each volume was 0.4-times.

175

176 **2.6. HPLC apparatus and conditions**

177 **2.6.1. HPLC fluorescence (FL) for tedizolid**

178 The HPLC system consisted of a prominent HPLC unit (L2000 series, Hitachi Ltd., Tokyo, Japan)
179 comprising a binary pump, a column oven, an autosampler, and an FL detector. Chromatographic separation
180 was carried out on TSKgel® ODS-80Ts, 150 mm×4.6 mm, 5 μm; protected by a guard column (TSKgel®
181 guardgel ODS100V 5 μm, 2 mm×1 cm, TOSOH Corp., Tokyo, Japan). The mobile phase was a mixed

182 solution [(0.1 M potassium phosphate buffer, pH 7.3:methanol=60:40):acetonitrile=90:10 (vol)]. Tedizolid
183 was measured in terms of FL intensity, with excitation and emission wavelengths for optimum detection
184 set to 300 and 340 nm, respectively. The temperatures of the column oven and autosampler were set to 40°C
185 and 4°C, respectively. The injection volume was 10 μL, while the flow rate was constant at 1.0 mL/min.
186 The present method using plasma or saliva showed good linearity for tedizolid (r^2>0.995). The results of
187 relative error (%) were ≤±15%, except for the lowest concentration (those of the lowest concentrations were
188 within 20%) every time. These tedizolid results indicated that the proposed method has good precision and
189 accuracy.
190
191 **2.6.2. HPLC ultraviolet (UV) for linezolid**
192 The HPLC system consisted of a prominent HPLC unit (L2000 series, Hitachi Ltd, Tokyo, Japan)
193 comprising a binary pump, a column oven, an autosampler, and a UV detector. The column was the same
194 as that used for the tedizolid measurement. The mobile phase was [50 mM potassium dihydrogen
195 phosphate:acetonitrile=83:17 (vol)]. Linezolid was measured in terms of the UV intensity, with the
196 wavelength for optimum detection set to 250 nm. The temperatures of the column oven and auto-sampler
197 were set to 50°C and 4°C, respectively. The injection volume was 40 μL, while the flow rate was constant
198 at 1.2 mL/min.
199 The present method using plasma or saliva showed good linearity for linezolid (r^2>0.995). The results of

relative error (%) were ≤±15%, except for the lowest concentration (those of the lowest concentrations were within 20%) every time. These results demonstrated that the proposed linezolid method has good precision and accuracy.

2.7. Pharmacokinetic analyses

The pharmacokinetic parameters of tedizolid and linezolid, including their maximum drug concentrations (C_{max}) and the area under the concentration-time curve (AUC) between 0 and 8 h were determined from plasma or saliva concentration–time profiles. The AUC was calculated using the trapezoidal rule.

2.8. Data and statistical analyses

The saliva/plasma concentration (S/P) ratio of each drug was calculated as the total concentration of the drug in the saliva/the total concentration in the plasma. The correlation analysis of saliva and plasma concentrations was performed using the Pearson correlation coefficients. All data are expressed as mean ± standard deviation (S.D.). Statistical analysis was conducted using ORIGIN2023 (LightStone). Statistical significance was set at $p<0.05$.

3. Results

3.1. Plasma and saliva concentrations of tedizolid in rats

We monitored the tedizolid concentration in the plasma and saliva, for up to 8 h after beginning of drug administration (Fig. 3). The value of tedizolid C_{max} was 14.46 ± 1.71 μg/mL in the plasma and 0.99 ± 0.08 μg/mL in the saliva. The AUC_{0-8} of tedizolid was 34.19 ± 4.10 h·μg/mL in the plasma and 1.74 ± 0.41 h·μg/mL in the saliva (Table 1). The S/P ratio of tedizolid was 0.0513 ± 0.0080 (from 0.0424 to 0.0683) (Table 2).

3.2. Plasma and saliva concentrations of linezolid in rats

We also investigated the plasma and saliva concentrations of linezolid, for up to 8 h after the start of the infusion (Fig. 4). The value of linezolid C_{max} was 13.00 ± 1.90 μg/mL in the plasma and 8.01 ± 1.42 μg/mL in the saliva. The AUC_{0-8} of linezolid was 38.95 ± 7.15 h·μg/mL in the plasma and 24.60 ± 5.37 h·μg/mL in the saliva (Table 3). The S/P ratio of linezolid was 0.6341 ± 0.0339 (from 0.5877 to 0.7093) (Table 4).

3.3. Correlation between the plasma and saliva concentrations of tedizolid and linezolid

The significance of correlation between the saliva and plasma concentrations, at each time-point, was tested using the Pearson correlation coefficients. The concentrations of tedizolid and linezolid in the saliva showed significantly correlated with that in the plasma ($r=0.964$, $p<0.001$ for tedizolid and $r=0.936$, $p<0.001$ for linezolid) (Figs. 5-6).

4. Discussion

Several drugs, including linezolid, have been investigated for drug monitoring in the saliva, and could be an alternative to traditional blood-based TDM reported in previous studies [24-26]. Kim et al. reported that the concentration of perampanel (an antiepileptic drug) in the saliva correlated with that in the plasma, and this correlation was not affected by cytochrome P450 (CYP) 3A4 inducers. They suggested the potential of saliva for perampanel TDM matrix. Perampanel is a drug with a high degree of protein binding (95%–96%), similar to that of tedizolid [27]. However, there are no reports revealing the tedizolid concentrations in the saliva. There are no detailed data on the salivary concentration profiles of tedizolid and linezolid. In the present study, we measured the plasma and saliva concentrations of tedizolid and linezolid, for up to 8 h after the beginning of administration, and found a strong correlation between the plasma and salivary concentrations of tedizolid and linezolid. In case of linezolid, our results were consistent with the findings of Bolhuis et al., and showed a significant correlation between linezolid in the plasma and that in the saliva, with r values of 0.95 (p<0.01) [28].

Plasma contains unbound (free) and bound drugs, whereas saliva generally contains free drugs [29]. Measuring the concentrations of free drugs is valuable in pharmacokinetic studies, because only free drugs are pharmacologically active. This means that salivary concentrations of drugs may be more strongly associated with therapeutically active drug concentrations than plasma concentrations. Regarding the protein binding of plasma, we verified the protein binding of tedizolid and linezolid in rats using a

254 Centrifree® ultrafiltration device (Merck, Darmstadt, Germany), which indicated that tedizolid protein
255 binding was 98.38 ± 0.22% and linezolid protein binding was 27.32 ± 2.56% (Supplementary Table 1). The
256 C_{max} of tedizolid was 0.99 ± 0.08 μg/mL in the saliva and 14.46 ± 1.71 μg/mL in the plasma. Meanwhile,
257 that of linezolid was 8.01 ± 1.42 μg/mL in the saliva and 13.00 ± 1.90 μg/mL in the plasma. Based on these
258 results, it is thought that the significant difference in plasma protein binding between tedizolid and linezolid
259 affects drug passage into the saliva. According to previous reports [12,13] and our results which were
260 discussed earlier, especially those of tedizolid, rat plasma protein binding is different from that of human;
261 however, transfer to saliva is considered to be generally dependent on the percentage of free forms.
262 With regard to the saliva concentration of linezolid, the results obtained using rats were different from those
263 expected. In contrast to the S/P ratio of linezolid in healthy volunteers, which has been reported to be >1.0,
264 the S/P ratio of linezolid in rats was lower (approximately 0.63). Bolhuis et al. showed the C_{max} was 10.9
265 mg/L (from 6.8 to 11.5) in the plasma and 10.1 mg/L (from 8.2 to 10.7) in the saliva [28]. Except for protein
266 binding in plasma, the primary drug properties that play a key role in the passage of drugs into saliva are
267 salivary pH and the acid dissociation constant (pKa) of the drug. Linezolid is a weakly basic drug, with a
268 pKa of 1.8 [30]. One reason for the difference in salivary concentrations between rats and humans is the
269 difference in the salivary pH values between the two species. The normal human saliva is slightly acidic,
270 pH 6.0–7.0; contrary to this, the pH of rat saliva is significantly higher, pH 9.1 [31, 32]. Langman shared
271 certain similarities with our results, in that the S/P ratio increased as the pH of saliva decreased [33]. Only

272 the unionized forms can penetrate the saliva. After free drugs pass through the saliva, they may ionize and
273 become trapped in a more acidic fluid. The pH of human saliva is usually lower than that of human plasma,
274 and basic drugs, such as linezolid, are usually concentrated in the saliva. We believe that this could be the
275 reason for the higher S/P ratio of linezolid in humans than in rats. There are several differences between rat
276 and human saliva, including pH. Furthermore, salivary properties are known to change according to diet
277 [34,35]; in this study, rats consumed the same type of food, however, it is difficult to control a patient's diet.
278 It is possible that these differences may also affect salivary drug concentrations. A prospective study using
279 human participants is required to overcome species differences and differences in real-world clinical dietary
280 management; nevertheless, we have obtained fundamental information on the feasibility of saliva
281 monitoring in rats in this study. The present investigation using rats suggests that saliva could be an
282 alternative TDM tool. The ability to obtain detailed data on drug concentrations is valuable and allows us
283 to advance our research. We previously identified high-risk combinations for LIT. Risk factors for LIT, such
284 as longer linezolid therapy duration [36], renal dysfunction [37], and low body weight [38], have been
285 reported in several studies. Among them, linezolid therapy of ≥14 d and renal dysfunction have drawn
286 particular attention [5]. In contrast, a previous study reported a patient with a high plasma concentration of
287 linezolid and LIT was observed, regardless of renal function [39]; however, this study was limited by a
288 sample size of one case. This is not an obvious observation since linezolid is not routinely performed in
289 TDM; however, there is a high possibility that there are patients with similar situations. The use of saliva

instead of plasma for drug monitoring helps overcome certain limitations encountered in previous studies, because it enables easy collection of multiple samples using noninvasive procedures and details from patients who have actually used linezolid. In addition, saliva is considered to be a beneficial matrix for sample preparation. Saliva is much easier to use than plasma because it consists of 99.5% water, 0.3% protein, and 0.2% inorganic compounds, whereas plasma is composed of 90% water and 10% protein [40, 41]. We did not skip the process of deproteinization, to avoid the burden on devices such as columns. However, according to the components of saliva, saliva samples can be measured using HPLC, without deproteinization. Additionally, only a small volume of samples is required for measurement (40 μL for saliva *versus* 100 μL for plasma); thus, this method using saliva for TDM seems optimal to prevent distress and ensure the safety of patients.

In this study, we determined the concentration profiles of tedizolid and linezolid in the saliva. The therapeutic range for tedizolid and linezolid concentrations in the saliva is presently unknown; however, using saliva for monitoring these two drugs is considered helpful in determining their pharmacokinetics in detail and reducing serious adverse effects.

5. Conclusions

This is the first study to investigate the tedizolid concentration in saliva, which helped reveal a strong correlation between saliva and plasma concentrations of both tedizolid and linezolid. We also found that

the S/P ratios of tedizolid and linezolid in rats were 0.0513 ± 0.0080 and 0.6341 ± 0.0339, respectively. As with other drugs reported in previous studies, the tedizolid and linezolid concentrations in the saliva represented the free concentrations in the plasma, and thus, salivary concentrations may be considered more closely related to therapeutically active drug concentrations than plasma concentrations.

6. Statements and Declarations

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Conflict of interests: The authors declare no conflicts of interest.

Author Contributions: All authors contributed to the conception and design of the study. YI and YT performed material preparation, data collection, and analysis. The first draft of the manuscript was written by YI, and all authors commented on previous versions of the manuscript. All the authors have read and approved the final version of the manuscript.

Ethics Approval: The experimental protocols were reviewed and approved by the Hokkaido University Animal Care Committee, in accordance with the "Guide for the Care and Use of Laboratory Animals" (study protocol number 21-0101). This study protocol was approved on November 5th, 2021.

Consent to Participate: Not applicable

Consent for Publication: Not applicable

Code Availability: Not applicable

Data Availability Statement: The data supporting the findings of this study are available from the corresponding author upon reasonable request.

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Tables

Table 1 Plasma and saliva concentration profiles of tedizolid

parameter	plasma	saliva
C_{max} (μg/mL)	14.46 ± 1.71	0.99 ± 0.08
AUC_{0-8} (h·μg/mL)	34.19 ± 4.10	1.74 ± 0.41

Notes: Dose: 10 mg/kg, *n*=5-6, mean ± S.D.

Abbreviations: C_{max}, maximum drug concentration; AUC_{0-8}, area under the concentration-time curve between 0 and 8 h

Table 2 S/P ratios of tedizolid, *n*=5-6

Time (min)	S/P, mean
65	0.0683
90	0.0584
120	0.0528
180	0.0465
270	0.0424
360	0.0473
420	0.0445
480	0.0503
mean ± S.D.	0.0513 ± 0.0080

Notes: Abbreviations: S/P, saliva/plasma concentration ratio

Table 3 Plasma and saliva concentration profiles of linezolid

parameter	plasma	saliva
C_{max} (μg/mL)	13.00 ± 1.90	8.01 ± 1.42
AUC_{0-8} (h·μg/mL)	38.95 ± 7.15	24.60 ± 5.37

Notes: Dose: 12 mg/kg, *n*=4-5, mean ± S.D.

Abbreviations: C_{max}, maximum drug concentration; AUC_{0-8}, area under the concentration-time curve between 0 and 8 h

Table 4 S/P ratios of linezolid, *n*=4-5

Time (min)	S/P, mean
65	0.6164
90	0.6340
120	0.6334
180	0.5877
270	0.6571
360	0.6687
420	0.6418
480	0.7093
mean ± S.D.	0.6341 ± 0.0339

Notes: abbreviations: S/P, saliva/plasma concentration ratio

Figure legends

Fig. 1 Chemical structure of tedizolid

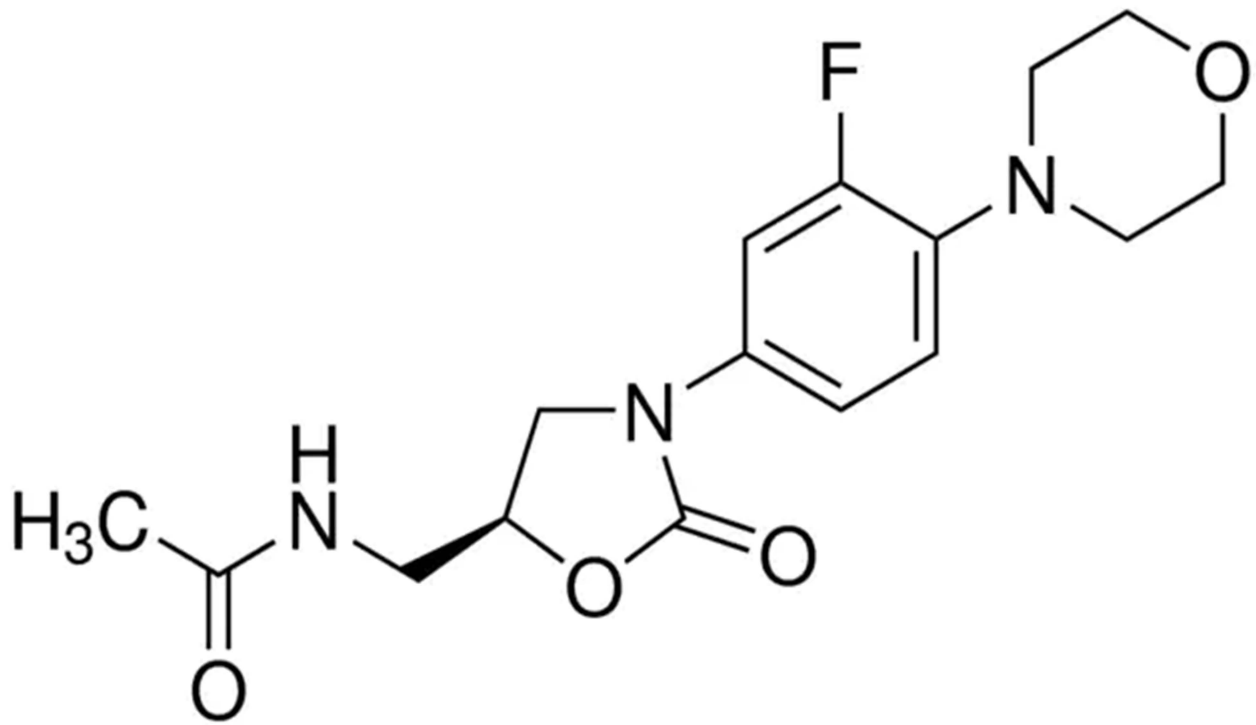
Fig. 2 Chemical structure of linezolid

Fig. 3 Plasma and saliva concentration profiles of tedizolid after administration of tedizolid (10 mg/kg, body weight) to rats; samples were collected at 65, 90, 120, 180, 270, 360, 420, and 480 min after the beginning of administration. Each point represents the mean ± S.D. of 5-6 measurements.

Fig. 4 Plasma and saliva concentration profiles of linezolid after administration of linezolid (12 mg/kg, body weight) to rats; samples were collected at 65, 90, 120, 180, 270, 360, 420, and 480 min after the beginning of administration. Each point represents the mean ± S.D. of 4-5 measurements.

Fig. 5 Correlation between tedizolid concentrations in rat plasma and saliva, *n*=5 for each sample; total number of samples=40); The correlation analysis of saliva and plasma concentrations was performed using the Pearson correlation coefficients (r=0.964, $p<0.001$).

Fig. 6 Correlation between linezolid concentrations in rat plasma and saliva, *n*=4 for each sample; total number of samples=32); The correlation analysis of saliva and plasma concentrations was performed using the Pearson correlation coefficients (r=0.936, $p<0.001$).


F
O
N
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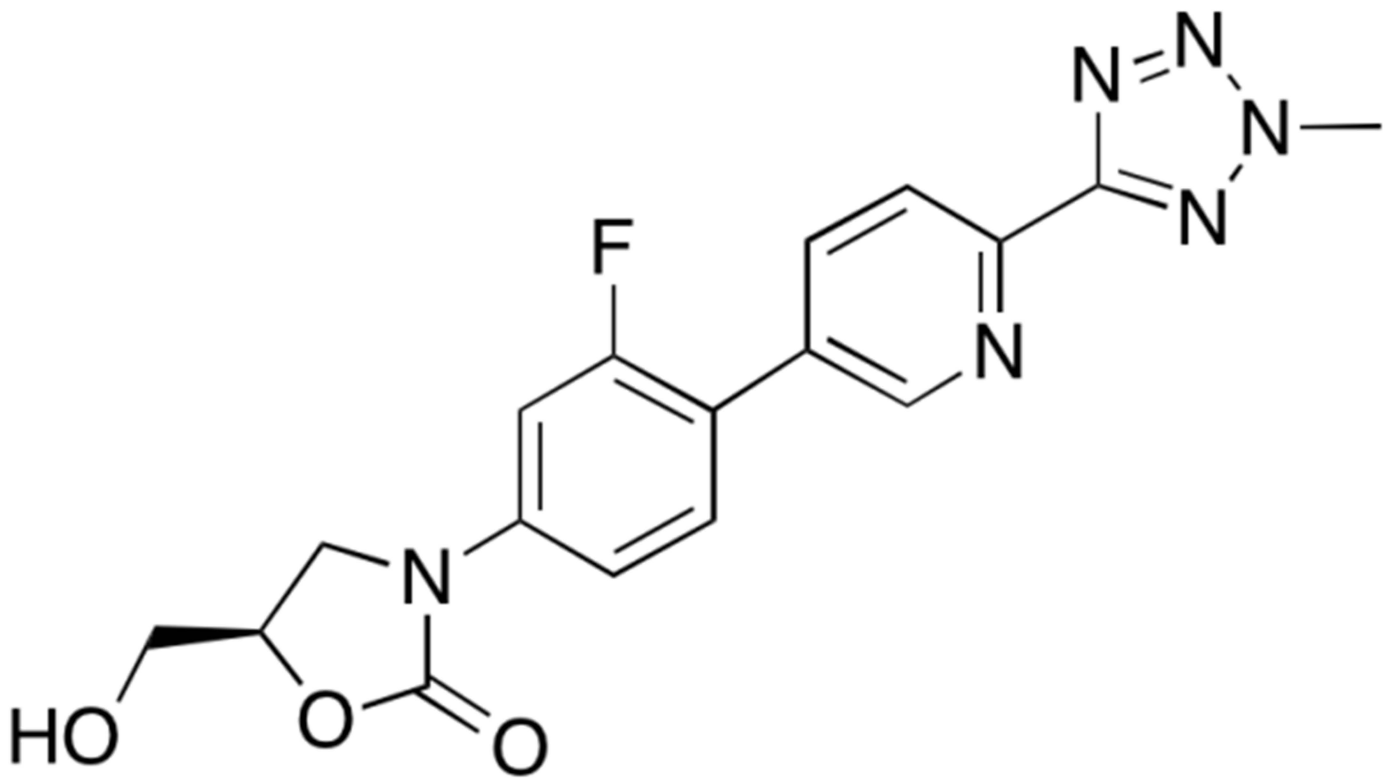
H3C
O
O
O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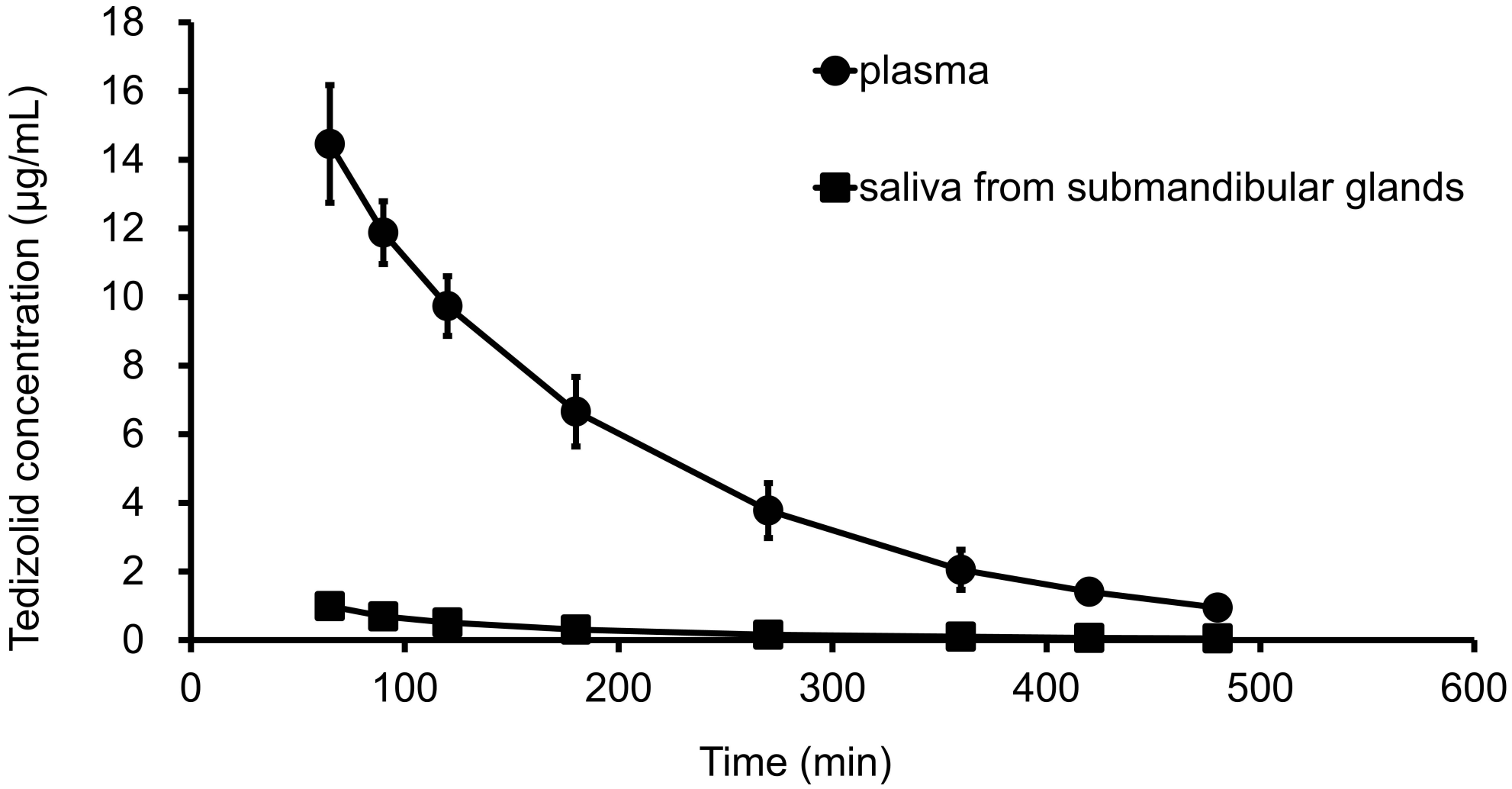
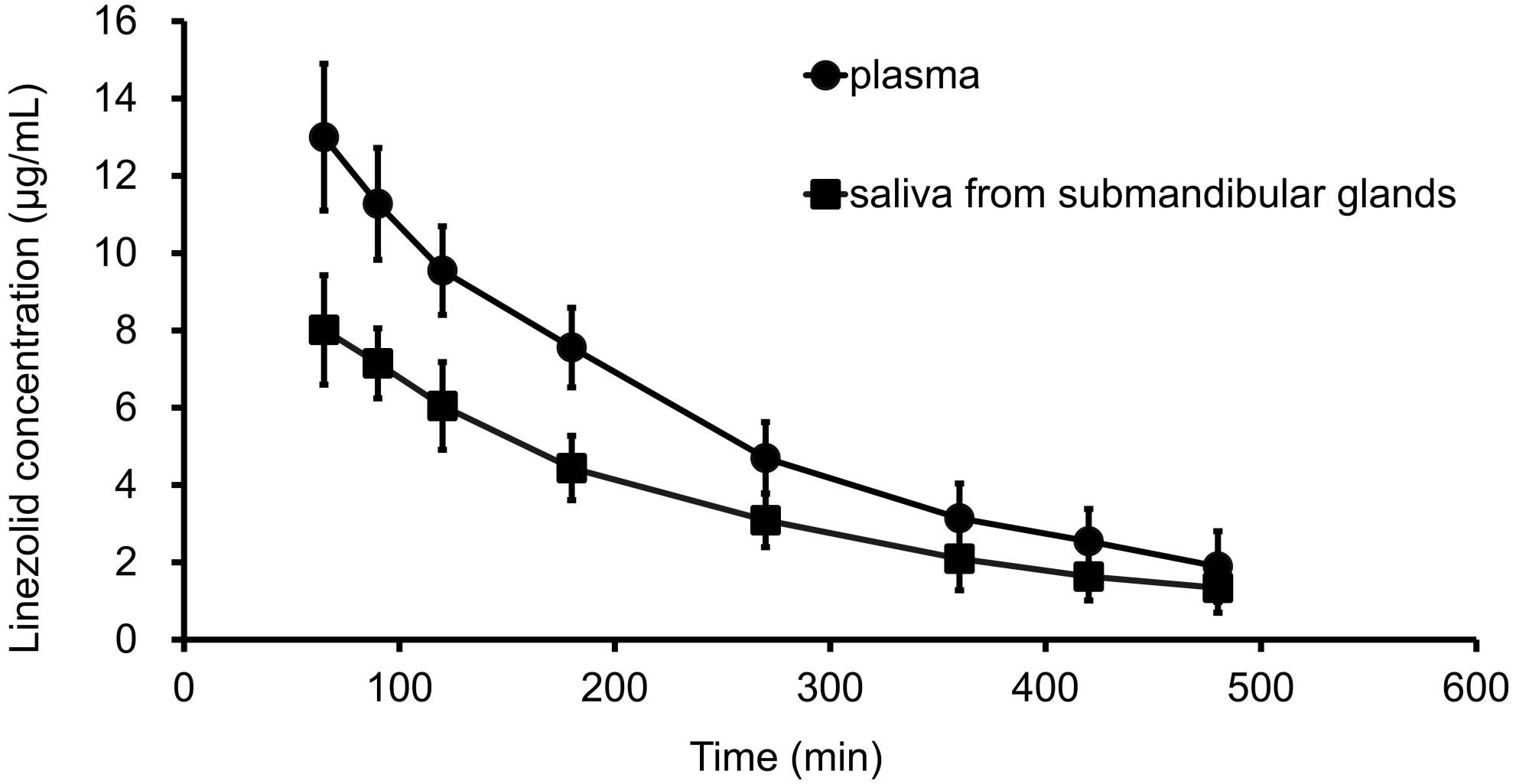
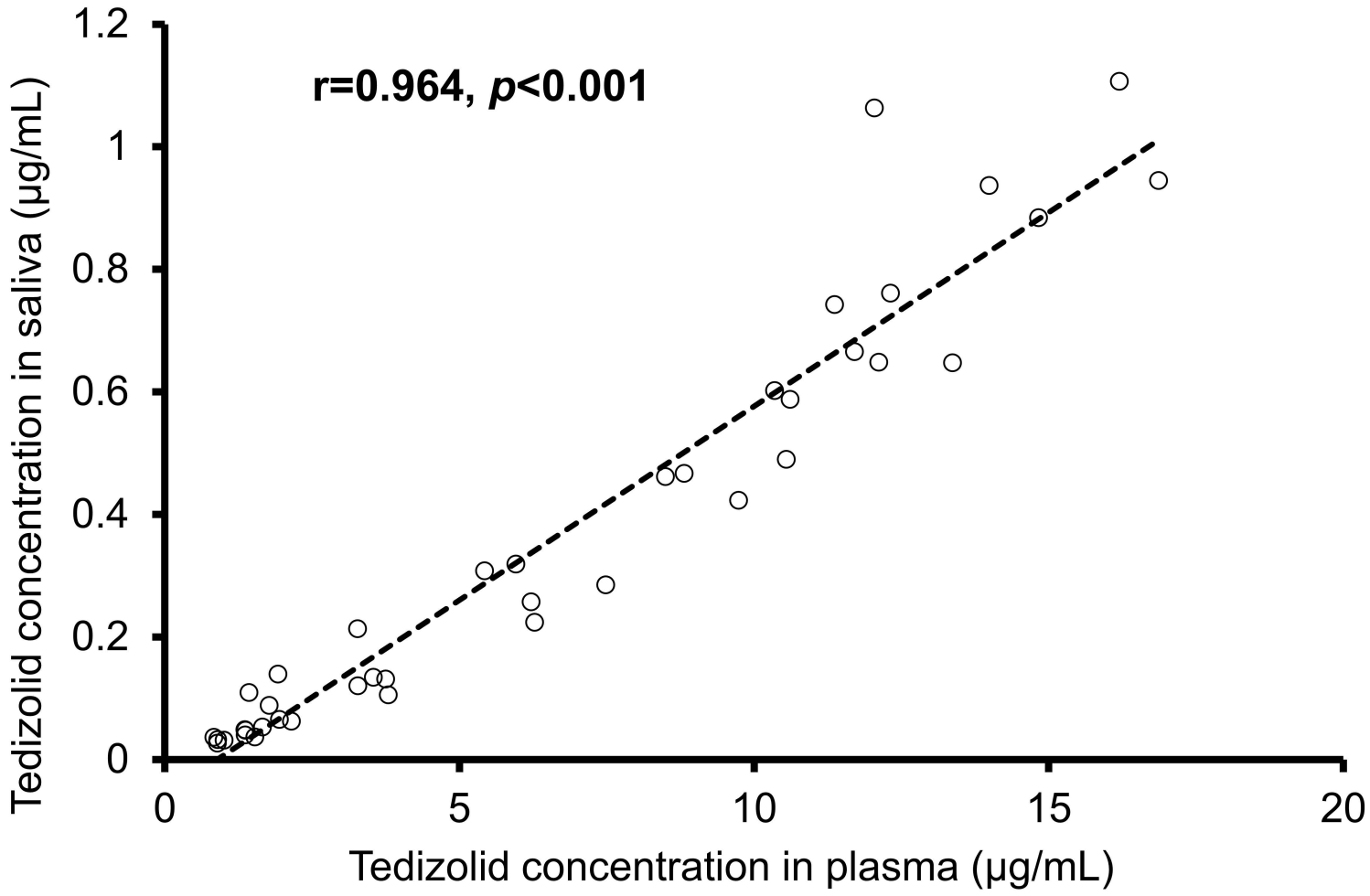
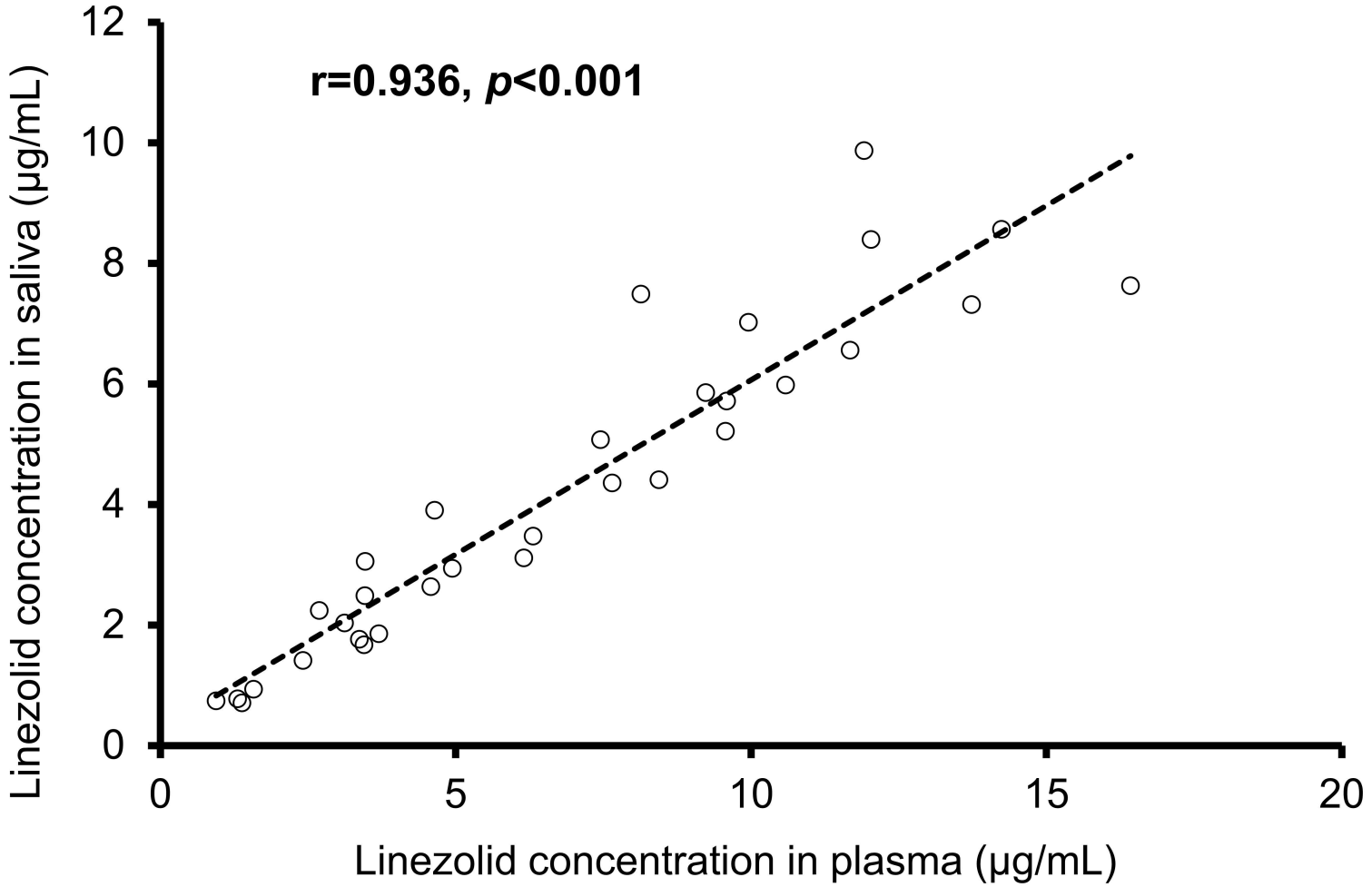

Tedizolid concentration (µg/mL)
18
16
14
12
10
8
6
4
2
0
0
100
200
300
400
500
600
Time (min)
plasma
saliva from submandibular glands


Linezolid concentration (µg/mL)
16
14
12
10
8
6
4
2
0
0
100
200
300
400
500
600
Time (min)
plasma
saliva from submandibular glands


r=0.964, p<0.001
Tedizolid concentration in saliva (µg/mL)
Tedizolid concentration in plasma (µg/mL)
0
0.2
0.4
0.6
0.8
1
1.2
0
5
10
15
20


r=0.936, p<0.001
Linezolid concentration in saliva (μg/mL)
Linezolid concentration in plasma (μg/mL)
0
2
4
6
8
10
12
0
5
10
15
20