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ORIGINAL RESEARCH

Population Pharmacokinetics of Tiapride in Children and Adolescents with Tic Disorders: Leveraging Plasma and Saliva Concentration to Guide Individualized Dosing

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Introduction: This study aimed to develop population pharmacokinetic (PopPK) models of tiapride based on plasma and saliva concentration in pediatric patients with tic disorders (TD) and evaluate the feasibility of non-invasive therapeutic drug monitoring (TDM) for precision dosing.

Methods: A prospective study was conducted in 38 TD patients aged 5–15 years. PopPK models of tiapride were sequentially developed using nonlinear mixed-effects modeling. Monte Carlo simulation was employed to optimize dosing regimens, and Bayesian maximum a posteriori (MAP) was applied to facilitate model-informed precision dosing (MIPD). The predictive performance of the established model was internally evaluated using saliva concentration.

Results: The PopPK model of tiapride using plasma concentration was best described by a one-compartment structure model. The typical estimates of the absorption rate constant (Ka), plasma clearance (CL/F), and volume of distribution (V/F) were 0.219 h^{-1}, 15.3 L/h, and 5.77 L, respectively. A plasma–saliva joint model was subsequently established, incorporating Michaelis-Menten nonlinear transport kinetics to characterize the drug distribution from plasma to saliva, with an estimated Michaelis-Menten constant (KM) of 762 ng/mL and a maximum transport rate (Vmax) of 34.7 mg/h. Saliva elimination was modeled as a first-order process. Fat-free mass (FFM) was identified as a significant covariate on both CL/F and saliva clearance (K30), scaled by power exponents of 0.553 and 0.38, respectively, relative to a reference FFM of 30.62 kg. Simulations based on the final model suggested that a dosing regimen of 75 mg administered three times daily (tid) is optimal for achieving target therapeutic concentration. MAP estimation confirmed that saliva concentration can reliably predict the systemic exposure of tiapride.

Conclusion: The PopPK models of tiapride enable MIPD in children and adolescents with TD and support saliva as a non-invasive matrix for TDM. Further prospective validation in independent pediatric cohorts is warranted before routine clinical implementation.

Keywords: tic disorders, tiapride, population pharmacokinetics, non-invasive sampling, therapeutic drug monitoring, model-informed precision dosing

Introduction

Tic disorders (TD) are common neuropsychiatric conditions in children and adolescents, characterized by recurrent, rapid, non-rhythmic motor and/or vocal tics. Severe cases may persist into adulthood, significantly impacting physical, psychological, and social functioning of suffering patients.[1,2] The reported prevalence of tics in children varies considerably, with a male-to-female ratio of 3–4:1.[3,4] An observational study showed that 22% of preschool children,

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7.8% of primary school children, and 3.4% of adolescents had experienced tics.[5] For patients with moderate-to-severe TD, behavioral interventions alone are often insufficient, and pharmacotherapy becomes necessary.[6] Tiapride is widely used as a first-line treatment for pediatric TD,[7–10] especially in Europe and Asia, with recommended doses typically ranging from 2–10 mg/kg/day (approximately 100–600 mg/day) administered in divided doses.[7,8]

Dysregulated dopaminergic activity in the central nervous system is closely associated with the pathogenesis of TD, and tiapride mitigates tic expression by modulating dopamine neurotransmission.[11] Orally administered tiapride is rapidly absorbed,[12] but exhibits considerable inter-individual variability (IIV) in plasma concentration, with dose explaining only approximately 57% of the variability.[13] Additionally, tiapride is mainly renal cleared, and variability in renal function may drive interindividual differences in individual systemic exposure.[14] A pharmacokinetic study in children and adolescents with TD preliminarily proposed a therapeutic reference range of 560–2000 ng/mL for tiapride. Given the substantial inter-individual pharmacokinetic variability, therapeutic drug monitoring (TDM) may provide a useful tool to assist dose titration and optimize the balance between efficacy and safety.[13]

Conventional TDM relies on plasma sampling, which may pose challenges in vulnerable populations, such as children and the elderly.[15] Saliva-based TDM offers advantages including improved patient compliance, reduced infection risk, minimal discomfort, and lower technical expertise.[16] Indeed, saliva-based TDM has been successfully applied to a variety of drugs[17–22] and represents a convenient, non-invasive alternative for concentration monitoring in clinical practice. In addition, its feasibility for population pharmacokinetic (PopPK) modeling and model-informed precision dosing (MIPD) has been demonstrated.[23–25] However, evidence regarding saliva-based monitoring of tiapride remains limited. To our knowledge, no previous studies have systematically investigated the relationship between plasma and saliva concentration of tiapride, highlighting the need for further investigation. Furthermore, no PopPK model of tiapride in adolescents with TD, either based on plasma alone or integrating plasma and saliva concentration, has been reported, despite its widespread clinical use.

This study aimed to develop PopPK models of tiapride in pediatric patients with TD, including a conventional plasma-based model and an integrated plasma–saliva model, to evaluate the feasibility of saliva-based TDM as a non-invasive alternative for supporting precision dosing strategies.

Method

Study Population

This single-center, prospective, observational study was conducted at the pediatric outpatient clinic of Fujian Medical University Union Hospital between April 2024 and October 2025. A total of 38 patients were recruited between April 2024 and April 2025, and each patient was followed up for 6 months. The inclusion criteria were: (1) diagnosis of TD according to the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5)[26] and ongoing treatment with tiapride; (2) age under 18 years; and (3) no known organic diseases. Exclusion criteria were: (1) incomplete medication records; (2) poor adherence or loss to follow-up; (3) concomitant use of drugs likely to significantly affect tiapride pharmacokinetics; and (4) presence of severe comorbidities or other neuropsychiatric disorders. This study was conducted in accordance with the principles of the Declaration of Helsinki and was approved by the Ethics Committee of Fujian Medical University Union Hospital (approval number: 2024KJCX026). Written informed consent was obtained from the guardians of all participants, and written assent was obtained from minor participants.

Study Design and Sample Collection

Patients received oral tiapride at a weight-based dose of 2–10 mg/kg/day,[7] administered 2–3 times daily. Tiapride is available as 100 mg tablets that can be divided into halves, thirds, or quarters, so clinicians round weight-based doses to convenient amounts (eg, 50 mg, 66.6 mg, or 75 mg per administration). Paired plasma (2 mL) and saliva samples were collected before and after the final dose following at least 7 days of continuous treatment, with dosing and sampling times precisely recorded. Venous blood was collected with EDTA anticoagulant tubes. Saliva samples were obtained using Salivette devices (SARSTEDT, Numbrecht, Germany). Participants were instructed to chew the cotton swab for approximately 60 seconds before returning it to the collection tube, which was subsequently centrifuged at 3000 rpm for 10 minutes. Extracted plasma and saliva samples were stored at –80 °C for up to 3 months prior to analysis.

Laboratory parameters (including alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], γ-glutamyl transferase [GGT], total bilirubin [TBIL], direct bilirubin [DBIL], indirect bilirubin [IBIL], albumin [ALB], and creatinine), demographic characteristics (sex, age, height, weight), tiapride dosing and frequency, and concomitant medications were obtained from electronic medical records.

Bioanalytical Assay and Correlation Analysis

Plasma and saliva concentration of tiapride were quantified using a LC-MS/MS method, with rac-sulpiride as the internal standard.[27] Samples were prepared by protein precipitation with methanol and separated on an Agilent Eclipse Plus C18 column. The mobile phase consisted of acetonitrile and 10 mM ammonium acetate containing 0.1% formic acid, applied in a gradient elution. Mass spectrometric detection was performed using positive electrospray ionization (ESI+) and multiple reaction monitoring (MRM) modes. The linear ranges of tiapride in plasma and saliva detection were 2–1000 ng/mL and 4–2000 ng/mL, respectively. The intra- and inter-batch precisions and bias for tiapride in both matrices were within 10%, lower limit of quantification (LLOQ) bias was −5.7% (plasma) and 5.4% (saliva) with CVs 5.5% and 5.8%, respectively. Extraction recovery ranged from 95.5% to 114.9% (CV < 15%), and selectivity and stability under storage and processing conditions were acceptable.

Paired plasma and saliva concentration were fitted using linear regression, and Pearson correlation analysis was conducted to evaluate their association with SPSS Statistics version 30.0 (IBM Corp). A p-value < 0.05 was considered statistically significant.

Population Pharmacokinetic Analysis

Patient dosing information, concentration data, and covariates were organized into CSV files compatible with NONMEM version 7.6.0 (ICON Development Solutions) for PopPK analysis. Model computation and validation were performed using PsN version 5.6.0 (Uppsala Pharmacometrics Group, GitHub), with Pirana version 3.0 (Certara) serving as the modeling interface. Data processing and visualization were conducted in R version 4.4.3 (R Foundation for Statistical Computing).

The plasma–saliva PopPK model of tiapride was developed using a sequential modeling approach. In the initial model-building phase, one- and two-compartment structural models with first-order absorption kinetics were evaluated to characterize the plasma concentration-time profile. IIV was estimated using an exponential model, and additive, proportional, and combined error models were evaluated to account for residual variability:

$$P_i = \theta \times exp(\eta_i) \tag{1}$$

$$Y = IPRED \times \left(1 + \varepsilon_p\right) + \varepsilon_a \tag{2}$$

Where P_i represents the individual pharmacokinetic parameter, θ represents the typical population value and η_i represents inter-individual variability which follows a normal distribution with a mean of 0 and a variance of ω^2. Y represents the observed drug concentration, IPRED represents the individual predicted value, ε_p represents the proportional error, ε_a represents the additive error, with ε following a normal distribution with a mean of 0 and a variance of σ^2.

After establishing the plasma base model, candidate covariates were incorporated using a stepwise approach and evaluated for statistical significance and clinical relevance. Only covariates available in more than 95% of patients were considered. During forward inclusion, covariates were added if the objective function value (OFV) decreased by > 3.84 (χ^2, df = 1, $p < 0.05$). During backward elimination, covariates were removed if OFV increased by < 6.63 (χ^2, df = 1, $p < 0.01$),[28–31] with clinical relevance also taken into account. Continuous covariates (eg, age, height, weight, liver and renal function indices) were incorporated using a power function, while categorical covariates (eg, sex, concomitant medications) were incorporated using a proportional function:

$$P_i = \theta \times \left(\frac{\mathrm{COV}}{\mathrm{COV}_{\mathrm{median}}}\right)^{\theta_{cov}} \tag{3}$$

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$$P_i = \theta + COV * \theta_{cov} \quad (4)$$

Where P_i represents the population-predicted pharmacokinetic parameter, θ represents the typical population value, COV represents the covariate value, COV_{median} represents the median value of the continuous covariate, and θ_{cov} represents the fixed effect of the covariate on the parameter.

Model evaluation included goodness-of-fit (GOF) plots, η- and ε-shrinkage, and residual standard error (RSE). Model robustness and internal validation of the final model were assessed using nonparametric bootstrap analysis (n = 1000) and visual predictive checks (VPC).

After establishing the plasma model, plasma PK parameters were fixed, and the saliva compartment was added using the ADVAN6 subroutine to construct the plasma–saliva joint model.[32] To characterize the drug transfer between plasma and saliva, both linear and nonlinear relationships were evaluated. The development of the joint model followed a similar procedure to that used for the plasma model, with selection of the appropriate transfer model and random effect structure based on OFV, RSE, and diagnostic plots, followed by covariate analysis and final model validation.

Model-Based Simulations

Monte Carlo simulations of the final model were conducted in R version 4.4.3. A simulated dataset (n = 1000) was generated based on the distribution of fat-free mass (FFM) in the modeled population. According to European and Chinese treatment guidelines for TD,[7,8] various oral dosing regimens of tiapride (50 mg bid, 50 mg tid, 66.6 mg bid, 66.6 mg tid, 75 mg bid, 75 mg tid, 100 mg bid, 100 mg tid) were simulated for 5 consecutive days, and plasma and saliva concentration were obtained over 0–12 h following the last dose. The proportion of simulated steady-state peak concentration (Cmax) within the therapeutic window of 560–2000 ng/mL was calculated to identify the optimal dosing regimen.[13]

Saliva sampling optimization was performed using the PopED package.[33] Under the optimal dosing regimen, 2–5 saliva samples were simulated at 1, 2, 3, 4, 5, 6, 7, and 8 h post-dose to determine the optimal sampling schedule. Based on simulated saliva concentration at these time points, individual pharmacokinetic parameters, including CL/F and Vd/F, were estimated using Bayesian maximum a posteriori (MAP) approach. Individual peak plasma concentration was predicted from the estimated CL/F and Vd/F. To account for residual estimation errors, a narrower target range (Cmax: 860–1700 ng/mL) was applied. Finally, the proportion of subjects achieving peak concentration within the target range after 5 days of dosing was calculated to evaluate the probability of target attainment (PTA).

Results

Demographic Characteristics and Correlation Analysis

A total of 38 patients aged 5–15 years were included in the analysis. The demographic and clinical characteristics of patients are summarized in Table 1. A total of 215 plasma samples and 205 saliva samples were collected, with a lower number of saliva samples due to insufficient volume and contamination. One plasma sample and one saliva sample below the LLOQ were excluded from analysis using M1 method.[34] Therefore, 214 plasma samples and 204 saliva samples were included in the final analysis. Linear regression analysis revealed a strong overall correlation between plasma and saliva concentration across the entire range (R = 0.87, $p < 0.01$). However, this relationship was concentration-dependent (Figure 1): a very strong correlation (R = 0.89, $p < 0.01$) was observed at plasma concentration below 700 ng/mL, which diminished significantly at higher concentration (≥ 700 ng/mL, R = 0.34).

PopPK Model Based on Plasma Concentration

Considering OFV, RSE, and Akaike information criterion (AIC), a one-compartment model was ultimately selected as the structural model for plasma concentration, incorporating a combined error model for residual variability. During covariate screening, potential influencing factors were preliminarily explored by plotting scatter plots of covariates versus the η values of individual pharmacokinetic parameters. Stepwise regression was then used to evaluate the effects of age, weight, height, BSA, FFM, and CLCR on CL. The final model included only FFM as a covariate on CL (ΔOFV = –25.1). Parameter estimates of the final plasma model are summarized in Table 2, and the model is described by Equations 5 to 7.

Table 1 Demographic Characteristics of the Study Population

Demographic	Median (IQR)/n
Males/Females	31/7
Age (yrs)	8 (7–10)
Weight (kg)	36.7 (31.0–42.5)
Height (cm)	135 (130–146.5)
BSA (cm^2)	1.18 (1.06–1.32)
BMI ($kg \cdot cm^2$)	19.1 (16.72–21.89)
FFM (kg)	30.62 (26.93–34.65)
CREAT (μmol/L)	47 (41–52)
CLCR (mL/min)	118.3 (106.77–136.79)
Number of combined medication cases	23
Disease duration (mo.)	11 (5–27)
Time since diagnosis (mo.)	8 (3–21)
Tiapride therapy duration prior to sampling (d)	72 (36–125)
Post-dose interval (h)	4.88 (2.17–13.81)
Tiapride daily dose (mg/day)	215 (150–300)

Abbreviations: BSA, body surface area; BMI, body mass index; FFM, fat-free mass; CREAT, creatinine; CLCR, creatinine clearance.

$$Ka = 0.219 \times e^{\eta_{Ka}} \tag{5}$$

$$CL/F = 15.3 \times \left(\frac{\mathrm{FFM}}{30.62}\right)^{0.553} \times e^{\eta_{CL/F}} \tag{6}$$

$$Vd/F = 5.77 \times e^{\eta_{Vd/F}} \tag{7}$$

where Ka is the oral absorption rate constant, FFM is the fat-free mass, CL/F is the apparent clearance, Vd/F is the apparent volume of distribution.

The GOF plots for the final model demonstrated that the observed plasma concentration was in good agreement with model predictions. The majority of conditional weighted residuals (CWRES) were distributed within ± 2 standard deviations without obvious bias, indicating good predictive performance. Nonparametric bootstrap analysis (Table 2)

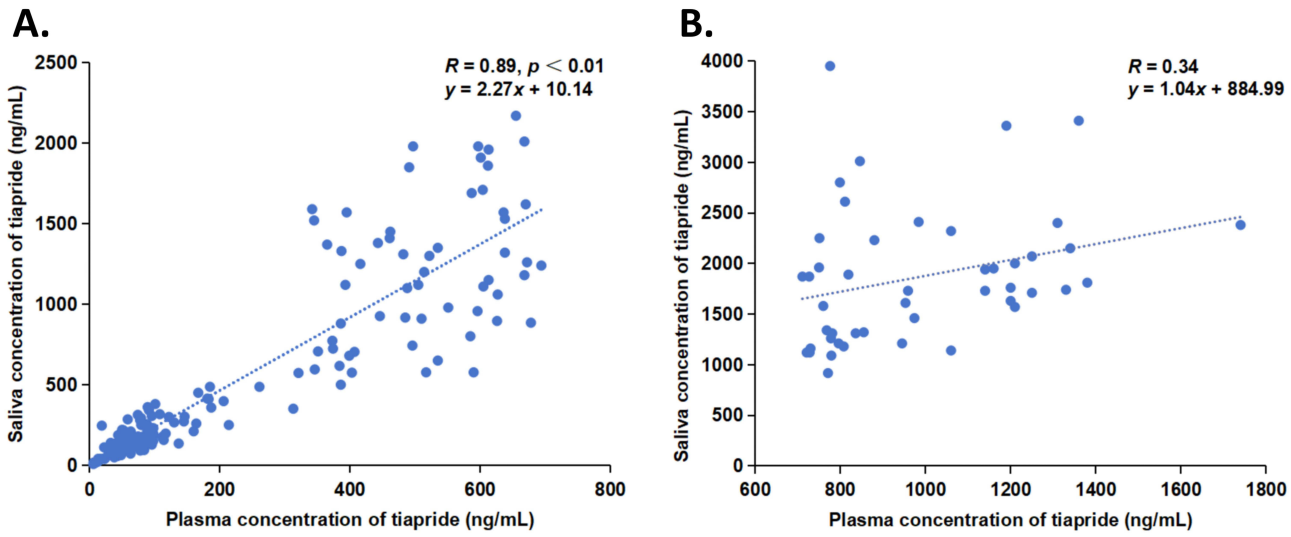

Figure 1 Linear regression between plasma concentration and saliva concentration of tiapride: (**A**) plasma concentration less than 700 ng/mL; (**B**) plasma concentration above 700 ng/mL.

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Table 2 Parameter Estimates of the Plasma Model and Bootstrap Results

Parameter	Final Model			Bootstrap Results (n = 1000)		
	Estimate	RSE (%)	Shrinkage (%)	Estimate	2.5th%	97.5th%
θ_{Ka} (h^{-1})	0.219	3	/	0.22	0.209	0.234
$\theta_{CL/F}$ (L/h)	15.3	3	/	15.4	14.5	16.3
$\theta_{Vd/F}$ (L)	5.77	16	/	7.25	1.99	11.6
$\theta_{FFM\text{-}CL/F}$	0.553	20	/	0.553	0.277	0.771
η_{Ka} (%)	17.6	13	31	16.5	9.9	21.8
$\eta_{CL/F}$ (%)	22.8	15	22	21.4	12.6	29.7
$\eta_{Vd/F}$ (%)	84.3	26	56	72.8	30.2	133.4
ε_{prop} (%)	15.6	25	43	15.2	9.1	21.3
ε_{add} (ng/mL)	87.9	57	43	81.4	15.3	294.9

Notes: θ_{Ka}, the oral absorption rate constant; $\theta_{CL/F}$, the apparent clearance of the central compartment; $\theta_{Vd/F}$, the apparent volume of distribution of the central compartment; $\theta_{FFM\text{-}CL/F}$, exponent for FFM as covariate for CL/F; η_{Ka}, IIV of Ka; $\eta_{CL/F}$, IIV of CL/F; $\eta_{Vd/F}$, IIV of Vd/F; ε_{prop}, proportional residual error; ε_{add}, additive residual error; "/", shrinkage (%) not calculated or not applicable.

showed that the final model parameter estimates were all within the 95% confidence interval obtained from bootstrap and close to the median estimates, suggesting good stability of the final model. Moreover, VPC based on 1000 simulations showed that nearly all observed concentration fell within the simulated 95% confidence intervals, further confirming the predictive performance of the model.

PopPK Model Based on Saliva Concentration

A saliva compartment was then added to the plasma model to describe the pharmacokinetics of tiapride in saliva. A nonlinear transport model between the plasma and saliva compartments outperformed a linear transport model. The saliva model, incorporating Michaelis-Menten nonlinear transport and first-order elimination from the saliva compartment (Figure 2), adequately described the concentration-time profiles of tiapride in saliva. Exploratory data analysis and initial model development indicated that the current data were insufficient to estimate the IIV of the Michaelis-Menten constant (Km) and the maximum transport rate (Vmax). Although Km could be estimated, its RSE% was unacceptably high; therefore, Km was fixed to ensure model stability.

Residuals of saliva concentration were described using a proportional error model, which could successfully estimate the Vmax of saturable transport and the first-order elimination rate from saliva (K30). Parameter estimates of the final saliva-based model are presented in Table 3, and the model is defined by Equations 8 to 10. Covariate analysis indicated that FFM influenced K30. The final model demonstrated satisfactory performance as evidenced by the GOF plots (Figure 3), nonparametric bootstrap results (Table 3), and VPC validation (Figure 4).

$$Vmax = 34.7 \tag{8}$$

$$Km = 762\,fixed \tag{9}$$

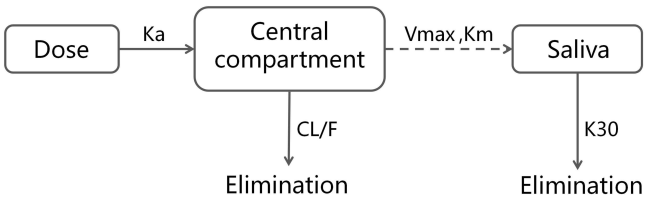

Figure 2 Conceptual PopPK model for tiapride in plasma and saliva. Ka: the oral absorption rate constant; CL/F: the apparent clearance of the central compartment; Km: the Michaelis-Menten constant for central-to-saliva compartment transport; Vmax: the maximum rate of saturate transport from the central compartment to the saliva compartment; K30: the elimination rate from saliva.

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Table 3 Parameter Estimates of the Saliva PopPK Model and Bootstrap Results

Parameter	Final Model			Bootstrap Results (n = 1000)		
	Estimate	RSE (%)	Shrinkage (%)	Estimate	2.5th%	97.5th%
θ_{Vmax} (mg/h)	34.7	13	/	35	27.3	46.9
θ_{Km} (ng/mL)	762 fixed	/	/	762 fixed	/	/
θ_{K30} (h^{-1})	6.24	4	/	6.22	5.72	6.8
$\theta_{FFM\text{-}K30}$	0.38	37	/	0.367	0.158	0.627
η_{K30} (%)	30	12	15	29.6	22.9	35.6
ε_{prop} (%)	28.4	15	18	28.3	24.5	32.6

Notes: θ_{Vmax}, the maximum reaction rate; θ_{Km}, the Michaelis-Menten constant; θ_{K30}, the clearance of the saliva compartment; $\theta_{FFM\text{-}K30}$, exponent for FFM as covariate for K30; η_{K30}, IIV of K30; ε_{prop}, proportional residual error; "/", shrinkage (%) not calculated or not applicable.

$$K30 = 6.24 \times \left(\frac{\mathrm{FFM}}{30.62}\right)^{0.38} \times e^{\eta} \tag{10}$$

where Vmax is the maximum reaction rate, Km is the Michaelis-Menten constant, FFM is the fat-free mass, K30 is the elimination rate from saliva.

Monte Carlo Simulations

Plasma and saliva concentration of tiapride were simulated in a virtual cohort of 1000 individuals. PTA of the plasma Cmax were similar for the dosing regimens of 100 mg bid, 75 mg tid and 100 mg tid (98.2%, 97.1% and 97.3%, respectively) (Figure 5). However, the proportion of Cmax exceeding the therapeutic reference range was higher in the former two regimens, potentially increasing the risk of adverse events. Considering both efficacy and safety, the dosing regimen of 75 mg tid was identified as the optimal dosing strategy.

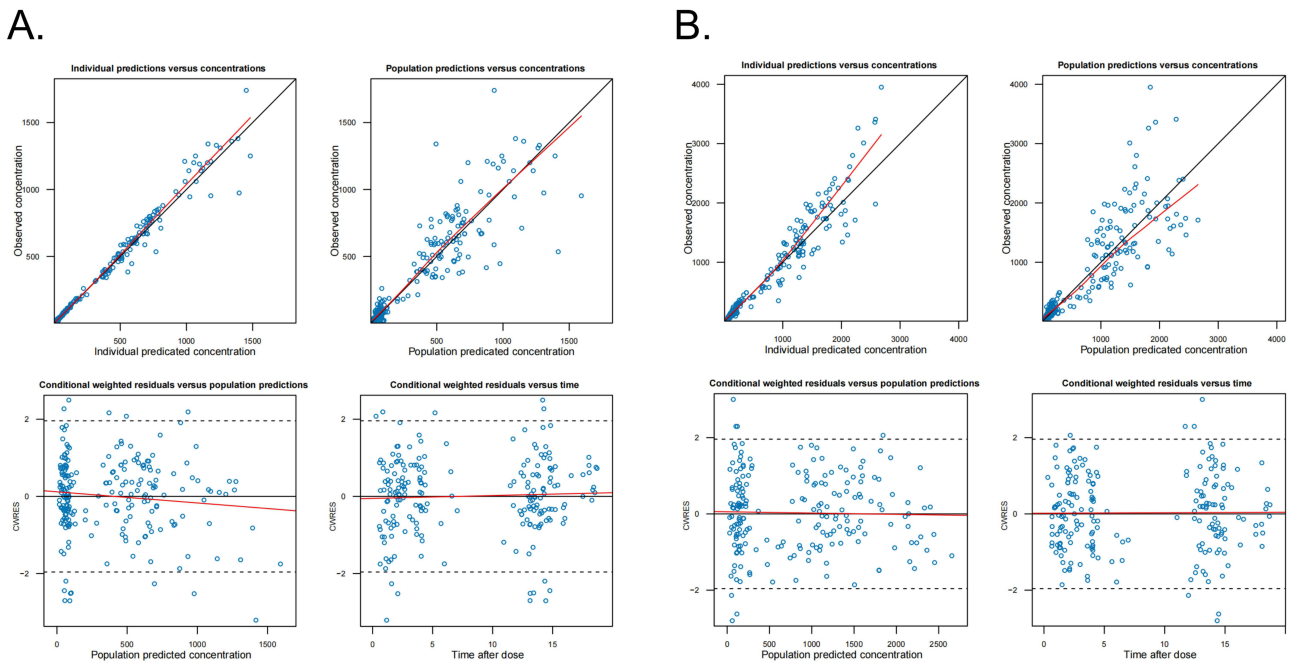

Figure 3 Goodness-of-fit plots of the final model: (**A**) plasma concentration and (**B**) saliva concentration. From top to bottom and left to right, the plots are observations against individual predictions (IPRED), observations against population predictions (PRED), conditional weighted residuals (CWRES) against PRED, and CWRES against time, respectively.

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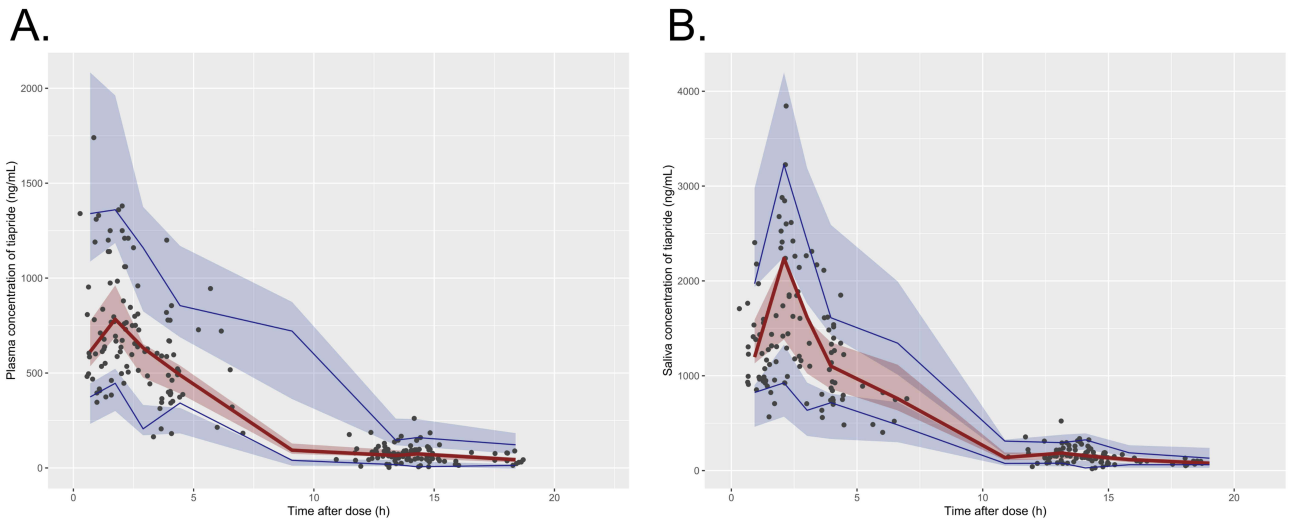

Figure 4 Visual predictive check of the final model (n = 1000): (**A**) plasma concentration and (**B**) saliva concentration. Black circles: observed tiapride concentration; red line: the 50th percentiles of the observed concentration; blue lines: the 5th and 95th percentiles of the observed concentration; red shadow: 95% confidence interval of the median prediction; blue shadow: 95% confidence intervals of the 5th and 95th percentiles of the predictions.

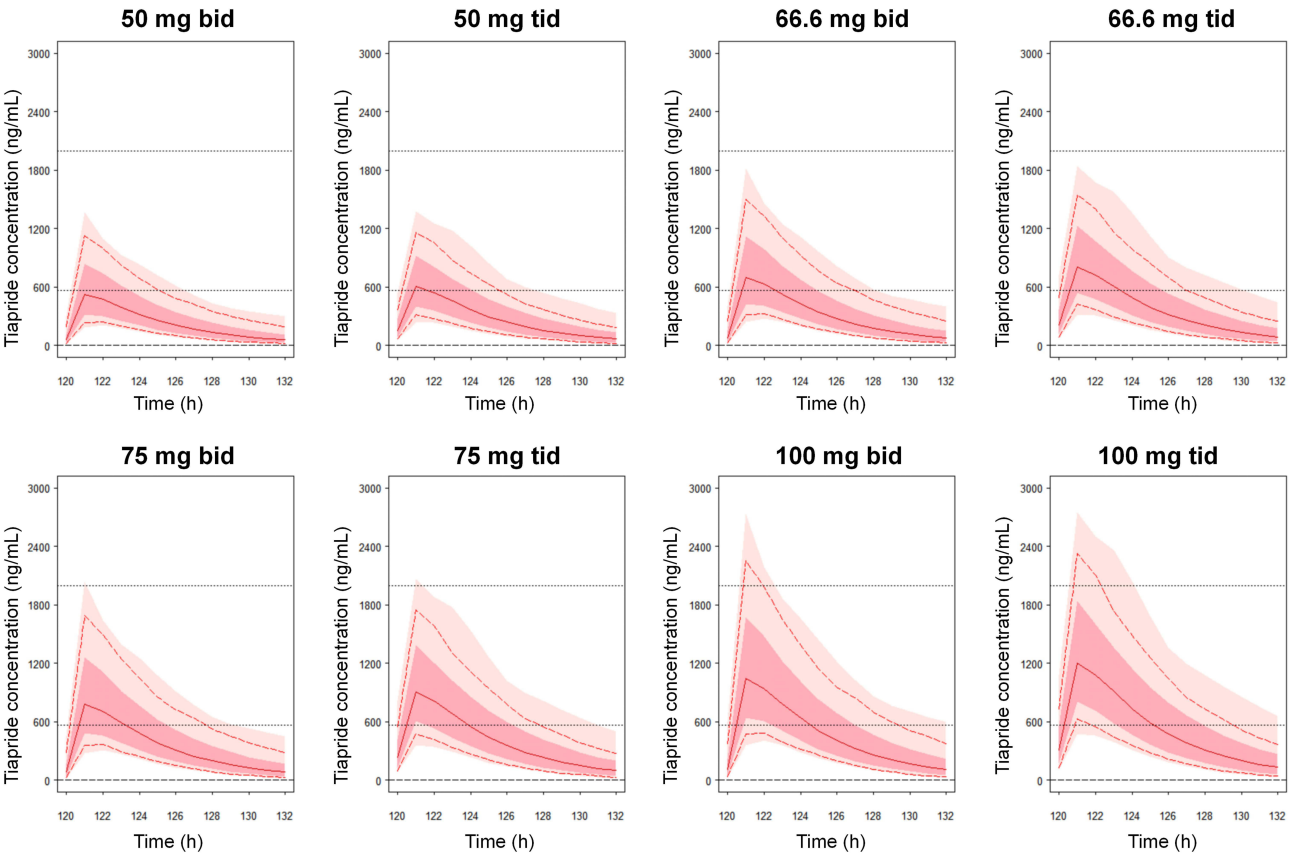

Figure 5 Monte Carlo simulations under different dosing regimens. Red solid line: Predicted median (50th percentile); Red dashed lines: Predicted 99.5th and 0.5th percentiles; Dark pink shading: Predicted 5th–95th percentile interval (main prediction interval); Light pink shading: Range between the maximum and 95th percentile, and between the minimum and 5th percentile; Black dashed lines: Horizontal reference values at 0, 560, and 2000 ng/mL.

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An optimal saliva sampling design was developed using PopED. Based on the dosing regimen (75 mg tid) derived from the above Monte Carlo simulations, the optimal sampling times were 1 h and 8 h post-dose. Based on simulated data, plasma Cmax predicted from saliva concentration at these times using the MAP method was within the target range (860–1700 ng/mL) in 84.9% of cases, supporting the feasibility of saliva as a surrogate for plasma in TDM.

Discussion

To the best of our knowledge, this is the first study to perform joint PopPK modeling of plasma and saliva concentration for oral tiapride in children and adolescents with TD. We identified FFM as the most influential covariate contributing to IIV in tiapride PK. Optimal dosing regimen of 75 mg bid was proposed by Monte carlo simulation, and MAP optimization further demonstrated the feasibility of TDM using saliva as a non-invasive, patient-friendly sampling matrix.

In paired samples, the concentration of tiapride in saliva consistently exceeded that in plasma (mean S/P ratio = 2.3). This phenomenon is likely attributable to the physicochemical properties of tiapride: its low plasma protein binding allows a substantial fraction to remain unbound, facilitating passive diffusion across the plasma–saliva barrier,[14] while its high hydrophilicity promotes accumulation in salivary fluid. Furthermore, drug translocation across membranes is primarily governed by the non-ionized fraction, implying that the S/P ratio is influenced by both the drug's acid dissociation constant (pKa) and salivary pH. As a weakly basic compound (pKa = 9.7), tiapride is partially ionized in plasma (pH = 7.35–7.45), enabling the non-ionized moiety to diffuse into saliva. Within the acidic-to-neutral salivary environment (pH = 5.8–7.8), the molecule undergoes protonation, leading to ion trapping and consequently higher salivary concentration (S/P > 1). Notably, a strong correlation between plasma and saliva concentration was observed at lower plasma levels, which diminished markedly at elevated concentration. This pattern suggests the involvement of a nonlinear transport mechanism during drug secretion from systemic circulation into saliva. Despite concentration-dependent variability, measurable levels of tiapride were consistently maintained in saliva, supporting its utility as a viable alternative matrix for pharmacokinetic assessments.

The PK profile of tiapride was characterized by rapid absorption, with peak plasma concentration attained within 2 hours post-dose. The disposition phase exhibited biphasic kinetics, reflected by a distribution half-life ($t_{1/2\alpha}$) of 0.2 hours and a terminal elimination half-life ($t_{1/2\beta}$) of 3.23 hours (range: 2.19–4.55 hours).[35] Based on these characteristics, a two-compartment model incorporating first-order absorption and linear elimination was initially evaluated as the structural model for PopPK analysis.[35,36] Of the total collected samples, 45 (21%) were obtained during the absorption phase (0–2 hours), 18 (8%) around Tmax (2–2.5 hours), and 101 (49%) from the late elimination period (> 10 hours). Because the participants were outpatients, strict standardization of sampling times was not feasible due to variable clinic visit schedules and differences in medication adherence. Such variability is typical of opportunistic pharmacokinetic studies in paediatric clinical practice and reflects real-world clinical conditions. However, relatively limited data were available around the distribution–elimination transition and the early elimination phase (2.5–10 hours), which resulted in considerable instability in parameter estimates when a two-compartment model was evaluated. Therefore, a one-compartment structural model was ultimately selected for PopPK modeling.

In the plasma model, the typical population value of CL/F was 15.3 L/h, within the previously reported range (15–25 L/h),[37] and Ka was 0.219 h^{-1}, lower than the value of 0.615 h^{-1} reported in the adult study.[36] The enrolled population (adults vs. children), feeding status (fasted vs. fed), and different sampling times might contribute to the difference in the above values. Vd/F has not been reported. Only the terminal phase volume of distribution (Vz/F) has been previously described in adults, with values of 1.50 ± 0.5 L/kg reported by Roos et al[14] and 2.52 ± 0.45 L/kg reported by Norman et al[36] The estimate of Vd/F in the current study was 5.77 L (0.19 L/kg) using one-compartment model which assumed instantaneous distribution. In contrast, Vz/F derived from the β-phase reflects drug distribution into both plasma and deep tissues and is generally larger than Vd/F. Moreover, the robustness and precision of pharmacokinetic estimates in most previous studies could be limited by their sample sizes (eg, fewer than 10 subjects).

In the covariate screening, demographic factors (age, sex, body size index), CLCR, and concomitant medications were evaluated. Since tiapride is predominantly eliminated via the kidneys,[37] CLCR was initially anticipated to be the primary influential covariate. However, the final model indicated that the inclusion of FFM on CL/F yielded the greatest reduction in the OFV (ΔOFV) owing to its strong correlation with CLCR. FFM serves as a physiologically meaningful descriptor that closely reflects renal function and drug clearance, thus providing a sound basis for explaining inter-individual variability in the

clearance of renally excreted drugs.[38] Concomitant medications (aripiprazole, topiramate, clonidine, sodium valproate, and traditional Chinese medicine) and sex did not exhibit statistically significant effects on the pharmacokinetics of tiapride. These findings are consistent with previous reports involving adult patients with Huntington's disease and healthy volunteers.[35,36]

During the development of the joint model, both linear and nonlinear transfer mechanisms between the plasma and saliva compartment were evaluated. A model assuming linear transfer resulted in marked overprediction of saliva concentration in the high-concentration range, and GOF plots displayed higher systematic deviations between predicted and observed values. Therefore, a nonlinear transfer process from plasma to saliva, coupled with a first-order elimination from the saliva compartment, was incorporated into the final model. This structure provided a more accurate characterization of tiapride pharmacokinetics. The nonlinear behavior of tiapride during its transfer from plasma to saliva can be explained by several physicochemical and physiological constraints. As noted earlier, its pH-dependent distribution favors accumulation in saliva with an inherent upper-limit effect. In addition, saliva possesses intrinsic buffering capacity due to bicarbonate, phosphate, and protein components. When a substantial amount of weakly basic drug diffuses into saliva and undergoes protonation, the local microenvironment may experience slight pH elevation, and the availability of protons becomes limited, restricting further drug protonation. Under high-concentration conditions, this combination of buffering effects and limited proton supply reduces the efficiency of the ion-trapping mechanism, resulting in a slower increase of saliva concentration as plasma concentration rises. Furthermore, the low permeability and limited effective surface area of the salivary epithelium for diffusion progressively constrain trans-epithelial flux at higher concentration. The observed nonlinear transfer provides important insights for saliva-based TDM. Saliva concentration is not strictly proportional to plasma concentration due to variability in the S/P ratio. This nonlinearity should be considered in TDM interpretationin clinical practice.

After establishing the nonlinear plasma–saliva transfer, the inclusion of a first-order back-transfer from the saliva to the central compartment did not lead to any improvement in model fit. In the final model, Km was fixed due to its high RSE%, whereas Vmax was estimated with acceptable precision, confirming a quantifiable transfer process. The estimated K30 was 6.19 h^{-1} indicating rapid saliva turnover. An IIV of 31.3% in K30 may be attributed to differences in saliva flow rate, glandular function, or feeding status. The incorporation of FFM as a covariate on K30 successfully reduced the residual variability. This finding is indirectly supported by existing evidence that individual body composition can influence the profile of salivary proteins involved in secretion and metabolism (eg, CA-VI, SPLUNC2, Zn-α_2-glycoprotein),[39] suggesting that FFM may modulate drug clearance in saliva.

The simulated dosing regimens in this study (50 mg bid, 50 mg tid, 66.6 mg bid, 66.6 mg tid, 75 mg bid, 75 mg tid, 100 mg bid, and 100 mg tid) were within the recommended dosing range of 2–10 mg/kg/day across the body weight range and corresponded to practical tablet fractions, supporting clinical feasibility. Based on these commonly used and clinically relevant regimens, Monte Carlo simulations in a cohort of 1000 virtual patients revealed significant differences in tiapride exposure in both plasma and saliva across the evaluated dosing regimens. Higher doses increased the proportion of patients achieving the target Cmax but simultaneously raised the risk of surpassing safe exposure thresholds. Excessively high plasma concentration may increase the likelihood of extrapyramidal motor adverse effects.[13] Among the various regimens assessed, the dosing regimen of 75 mg tid demonstrated an optimal balance between exposure and safety, aligning with the "safety first" principle paramount in psychiatric pharmacotherapy. Furthermore, PopPK-based sampling optimization identified 1 h and 8 h post-dose as the most informative time points for saliva collection. This finding is consistent with the PK characteristics of tiapride and the dosing regimen employed. Tiapride is rapidly absorbed, reaching peak plasma concentration around 2 h after oral administration. Therefore, the 1 h sampling time captures the absorption phase and remains sensitive to the early concentration–time profile. Under the 75 mg tid dosing regimen used in this study, the 8 h sampling time occurs close to the trough concentration prior to the next dose and falls within the elimination phase, where the drug concentration is primarily governed by systemic clearance. At these time points, saliva tiapride concentration served as an accurate surrogate for predicting total plasma exposure, thereby establishing a robust methodological foundation for non-invasive TDM in clinical practice.

Limitations

Several limitations of the study should be noted. First, only two samples were collected per patient at each outpatient visit, which may limit the ability of the structural model to fully capture the true pharmacokinetics of tiapride. However,

PopPK studies are specifically designed to allow sparse sampling and particularly suitable for pediatric populations to minimize blood sampling burden. Previous work has shown that PK parameters can be reasonably estimated with two samples per subject, even with a very small sample size.[40] Thus, the sampling strategy employed is considered appropriate. Second, the limited study population may affect the precision of parameter estimates and the exploration of IIV, potentially reducing the robustness and external validity of the model. Third, when implemented in other research centers, the chromatographic method used in this study may require further evaluation of its analytical performance, including sensitivity and selectivity, to ensure accurate and reliable drug concentration measurements. Finally, the absence of efficacy-related endpoints precluded an assessment of potential concentration-response relationships. Future investigations should involve larger patient cohorts and incorporate systematic efficacy evaluations to better characterize the exposure-response profile of tiapride.

Conclusions

This is the first study to establish both a plasma-based and a joint plasma–saliva PopPK model for tiapride in patients with TD. Internal validation confirmed that the two models demonstrated good robustness and reliable predictive performance. Simulations based on the models suggested an optimal tiapride dosing regimen of 75 mg tid. Furthermore, our results support the feasibility and practical utility of saliva sampling for TDM of tiapride. Collectively, this work provides a theoretical foundation for individualized tiapride dosing and could help promote the wider adoption of non-invasive sampling approaches in special populations, particularly in pediatric settings. Nevertheless, further validation in larger cohorts and independent clinical settings is warranted.

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Disclosure

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