Trial@home for children: novel non-invasive methodology for the pediatric clinical trial of the future
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PART IV

NON-INVASIVE PHARMACOKINETICS

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Abstract

BACKGROUND Historically, pharmacokinetic studies and therapeutic drug monitoring (TDM) have relied on plasma as sampling matrix. Non–invasive sampling matrices, such as saliva, could reduce the burden for pediatric patients. The variable plasma–saliva relationship can be quantified using population PK models (non–linear mixed effect models (NLMEM)). However, criteria regarding acceptable levels of variability in such models are unclear. This simulation study aimed to propose a saliva TDM evaluation framework and to evaluate model requirements in the context of TDM, using gentamicin and lamotrigine as model compounds.

METHODS Two population pharmacokinetic models for gentamicin in neonates and lamotrigine in pediatrics were extended with a saliva compartment which included a delay constant (K_{SALIVA}), a saliva:plasma ratio and between–subject–variability (BSV) on both parameters. Subjects were simulated with a realistic covariate distribution. Bayesian maximum a posteriori TDM was applied to assess the performance of an increasing number of TDM saliva samples, varying levels of BSV and varying levels of residual variability. Saliva TDM performance was compared to plasma TDM performance. The framework was applied to a known voriconazole saliva model as case study.

RESULTS TDM with saliva resulted in higher target attainment compared to no TDM, and a residual proportional error <25% on saliva observations led to saliva TDM performance comparable to plasma TDM. BSV on K_{SALIVA} did not impact performance, whereas increasing BSV on saliva:plasma ratio >25% for gentamicin and >50% for lamotrigine caused a lower performance. Simulated target attainment for voriconazole saliva TDM was > 90%.

CONCLUSION Saliva as alternative matrix for non–invasive TDM is possible using NLMEM combined with Bayesian optimization. This paper provides a workflow to explore TDM performance for compounds measured in saliva and can be used as evaluation during model building.

Introduction

Historically, pharmacokinetic (PK) studies and therapeutic drug monitoring (TDM) have relied on plasma as the primary sampling matrix.[1] Plasma samples are reliable, reproducible, well–known and easy to obtain from most patients, but pose a hurdle for PK studies and TDM in vulnerable populations such as children and subjects with intellectual disability.[2] Although plasma sampling is possible in these populations when necessary, for example for gentamicin TDM or PK in pivotal studies in rare diseases, the burden is high, which leads to lower recruitment rates.[3] Therefore, alternative non–invasive sampling matrices, such as saliva, would be highly beneficial. Besides the non–invasive nature of saliva as a sampling matrix, advantages are the possibilities of obtaining multiple samples over time and sampling by subjects themselves in a home–setting.

An example of a compound where non–invasive TDM could provide added value is gentamicin. Gentamicin is one of the medications that is most often prescribed to neonates and has a narrow therapeutic range with risks of oto– and nephrotoxicity.[4] Additionally, implementation of non–invasive TDM for several anti–epileptic drugs (AEDS), such as lamotrigine, could have added value as well.[5] Patients with epilepsy often use multiple AEDS, and unpredictable drug–drug interactions between AEDS means TDM can increase the proportion of patients with plasma concentrations within the target range. Currently, TDM is usually performed using commercial software, such as MwPharm or InsightRx, which estimate individual PK parameters using Bayesian methods, incorporating available information about a drugs' population PK, individual patient variables, and measured plasma concentrations.[6]

TDM with saliva samples is relatively straightforward in the case of a low variability and a constant ratio between the plasma and saliva concentrations, for example in the case of morphine or fluconazole.[7] If a non–linear relationship is present due to a delay or a non–linear penetration or when there are multiple sources of inter–individual variability, concentrations in saliva are more difficult to interpret. The development of a non–linear mixed effects population PK model (NLMEM) can solve this problem.[8,9] These models can be used to characterize the distribution kinetics of the drug in plasma and correlate this with the distribution in saliva, and to identify linear or non–linear relationships, including rate constants or interindividual variability on the saliva:plasma ratio.[10] However, there has been sparse published data about the application of this methodology for TDM with alternative sampling matrices.[11,12] Furthermore, not all population PK models are suitable for use

in TDM. For example, if saliva concentrations are associated with multiple and high levels of variability, estimation of individual plasma concentrations based on saliva might not be possible. Therefore, it is important to evaluate the TDM performance of candidate models.

The aim of this study was to propose an evaluation framework, or blueprint, to evaluate the TDM performance of existing population PK models and to evaluate the requirements which a population PK model with an additional saliva compartment must fulfill to achieve adequate performance for the purpose of TDM. To this end, we evaluate two existing literature models describing the pharmacokinetics of gentamicin and lamotrigine in a pediatric population with an additional hypothetical, theoretical, saliva compartment. A combination of different levels of variability in the models was introduced and the performance of saliva TDM was compared to the standard of care using plasma samples. A case study of a recently developed voriconazole population PK model that described the relationship between plasma and saliva concentrations was included to demonstrate the applicability of the framework in practice.

Materials and methods

Plasma population PK models

Gentamicin and lamotrigine were chosen in this study for their frequency of use, known TDM applications and availability of existing population PK models.[13] The gentamicin population PK model from Fuchs *et al.* was used, which is based on data from 1449 neonates.[14] It concerns a 2-compartment model with between-subject variability (BSV) on clearance (CL, 28%) and central distribution volume (VC, 18%). Additionally, the covariates weight, postnatal age, and gestational age (GA) are included on clearance and weight and GA is included on VC. The proportional residual error of the model is 18%, with an additive residual error of 0.1 mg/L. The lamotrigine pediatric population model of He *et al.* is a 1-compartment model with BSV (26%) and comedication-based covariates on CL.[15] The proportional residual error of the model is 21% and no additive residual error was identified. The model was based on steady-state concentrations, and the absorption constant was fixed at $1\,h^{-1}$ by the authors.

R version 4.02[16] and the mrgsolve[17] package were used for simulation. During simulation, ω^2 was defined as $\ln(BSV^2+1)$ and σ^2 was defined as the square of the proportional residual error expressed as percentage.

Hypothetical saliva compartment

A hypothetical saliva compartment was included in both models to mimic the distribution from plasma to saliva. Since the expected absolute amount of drug in saliva is too low to influence the plasma PK, no mass transfer or reabsorption from the gastrointestinal tract was included in this model. A schematic representation of the model is displayed in *Figure 1A* and the ordinary differential equation of the saliva compartment is presented below.

Equation 1: $dSaliva/dt = c_{PLASMA} * k_{SALIVA} - Saliva * k_{SALIVA}$

Equation 2: $c_{SALIVA} = (Saliva * saliva{:}plasma\ ratio) * (1+\varepsilon^2)$

To describe the saliva concentrations, five additional parameters were implemented. First, a parameter representing the *saliva:plasma ratio* was included and fixed at 0.1 for gentamicin (based on unpublished clinical trial data) and 0.5 for lamotrigine.[13,18] Second, a constant k_{SALIVA}, representing delayed penetration to the saliva compartment was added and fixed at $0.4h^{-1}$ in order to mimic a moderate delay. BSV on the ratio (log-normal distributed with mean 0 and variance ω_{RATIO}^2) and the k_{SALIVA} (log-normal distributed with mean 0 and variance $\omega_{KSALIVA}^2$) was included to mimic the inter-individual variability present in the penetration to saliva. A proportional residual error (ε^2, normal distributed with mean 0 and variance σ^2_{SAL}) was included on the saliva observations.

Simulation populations

Four fictional simulation populations were prepared based on normative data for covariates and dosing guidelines for each population (*Figure 1B*). For gentamicin, simulation populations were divided in three groups of 1000 neonates each based on gestational age and corresponding dosing guidelines. Group 1 consisted of neonates with a gestational age (GA) < 32 weeks (dose 5mg/kg/48h iv in 30 minutes), group 2 included subjects with a GA 32-37 weeks (dose 5mg/kg/36h iv) and group 3 included subjects with a GA > 37 weeks (dose 4mg/kg/24h iv). For the lamotrigine simulation, a group consisting of 1000 subjects (dose 10mg/kg, initial maximum of 200mg po) was used with 100 subjects per age year from 6 through 16 years. Comedication was set at valproic acid, carbamazepine, phenobarbital, or none for 250 subjects each. For all cohorts, a uniform distribution of weights was simulated within the 10TH and 90TH percentile of normative data.[19,20]

Figure 1. Visual clarification of the analysis. A. Gentamicin model schematic, green represents the published model, blue represents the hypothetical addition of a saliva compartment with two additional parameters (k_{SALIVA} and S:P ratio). * Gentamicin model only. B. Simulation cohorts were developed with realistic distribution of covariates (GA: Gestational age). C: Simulations performed with model and simulation cohorts. Black line and shaded area represent population median and 80% prediction interval in plasma. Blue line and shaded area's represent population median and 80% prediction interval in saliva. Red lines indicate the target ranges. D. Schematic view of simulation runs and parameter of interest within each simulation run. E. Examples of individual TDM (left: gentamicin, middle: gentamicin, right: lamotrigine) using Bayesian MAP methodology. Purple dots represent simulated TDM samples. Dotted gray and black lines represent the population average concentration-time profile for saliva and plasma, respectively. The dark blue and red lines represent the predicted saliva and plasma concentration-time profile, which is based on the simulated TDM samples. The dotted light blue and green lines represent the 'true' concentration-time profile of these individuals. Ideally, the predicted and 'true' concentration-time profiles overlap completely. Residual or between-subject variability leads to predictions closer to the population average and further from the true concentration-time profile.
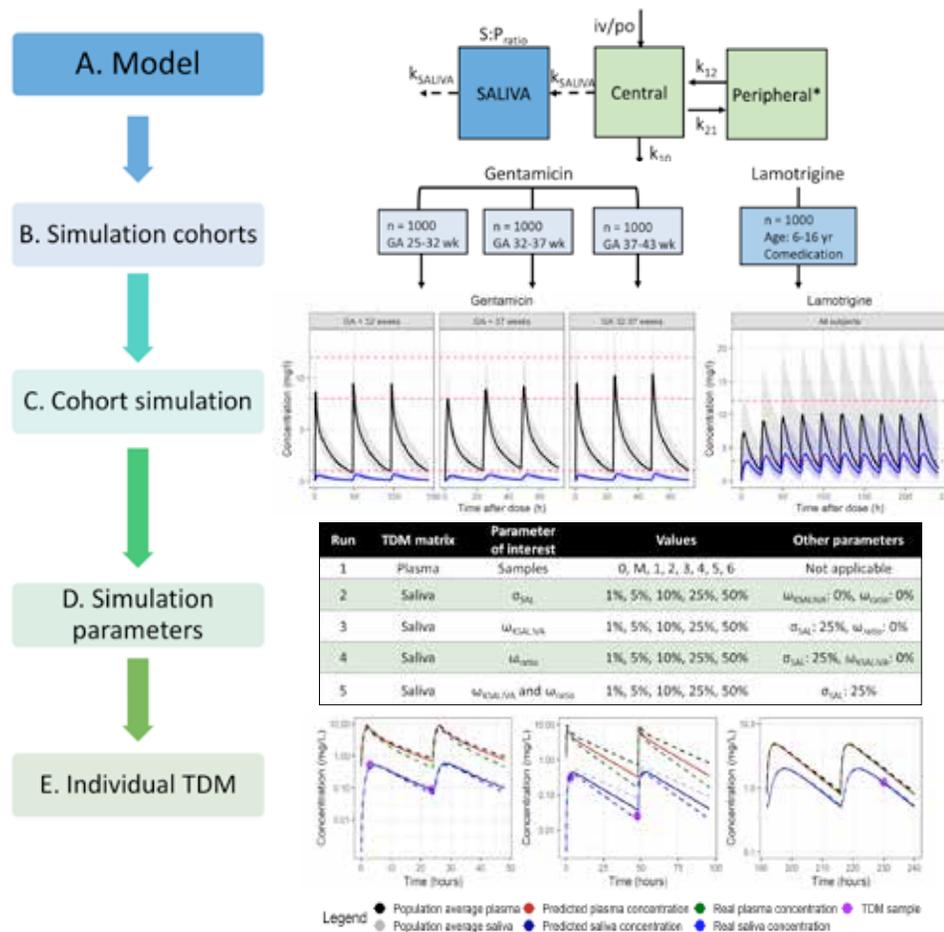
TDM sampling schedule and procedure

Population predictions and the 80% prediction interval of plasma- and saliva concentrations of the models are visualized in *Figure 1C*. For the simulation of realistic TDM scenario's, samples were simulated at different timepoints. In the case of one sample, an intermediate (14h post dose) sample was simulated. In the case of two samples, peak (1h post-dose for gentamicin in plasma and 3h post-dose for gentamicin saliva and lamotrigine samples) and trough (0.5h before next dose) samples were simulated after the first dose and compared to an intermediate (14h post-dose) level. Additionally, the combination of the three samples was evaluated. Finally, the effect of additional samples (at 7h, 7h+18h, and at 0.5h+7h+18h, to reach 4, 5 and 6 samples per subject, respectively) was evaluated. For gentamicin, samples were obtained after dose 1. For lamotrigine, samples were obtained after dose 10, to realistically account for the outpatient nature of TDM with anti-epileptics.

Simulation runs

Simulation runs were performed for plasma- and saliva TDM. For plasma TDM, a simulation was performed for each TDM sampling schedule (1–6 samples in total). The outcome of plasma TDM was subsequently compared to the saliva TDM outcomes. For each saliva simulation run, BSV and residual error were varied to simulate different levels of variability. To explore the effect of a single level of variability, residual error was fixed at either 1%, 5%, 10%, 25% or 50%, while fixing BSV on k_{SALIVA} and saliva:plasma ratio at 0%. The BSV on k_{SALIVA} and saliva:plasma ratio or fixed at either 1%, 5%, 10%, 25% or 50% while fixing the other at 0%, and the proportional error at 25%. A residual error of this magnitude has been reported in a recent model incorporating saliva samples.[12] Finally, the combination of BSV on both k_{SALIVA} and saliva:plasma ratio simultaneously was assessed, where both were fixed at either 1%, 5%, 10%, 25% or 50%, with a proportional error of 25%. The various combinations are displayed in *Figure 1D*.

Individual TDM with Bayesian optimization

Bayesian maximum a posteriori (MAP) optimization was used to estimate the most likely CL, VD, k_{SALIVA} and saliva:plasma for each subject based on the obtained plasma- or saliva

samples (*Figure 1E*). Then, based on the estimated CL and VD, the peak and trough concentrations were simulated for each subject, who then entered a basic decision rule optimizing the concentrations by varying the dose and the dosing interval. For gentamicin, the goal was to obtain a peak concentration between 8-12 mg/L and a trough concentration < 1.0 mg/L.[21] Target ranges in the decision rule were deliberately set stricter (peak 9-11 mg/L, trough < 0.8) to account for residual error in the estimations. Optimal plasma concentrations for lamotrigine are a source of controversy.[22,23] For this analysis, trough concentrations between 3-14 mg/L for lamotrigine were targeted, with the decision rule set to optimize between 4-13 mg/L. The optimized dose for gentamicin and lamotrigine was given at dose 3 and 12, respectively, to account for the delay between analyzing the sample and adjusting the dose. For each individual subject, the true and predicted peak- and trough concentrations of gentamicin after the 3RD dose were simulated, as well as the trough concentration of lamotrigine after the 20TH dose to account for the inpatient- and outpatient nature of the TDM process, respectively. This allowed for the assessment of the result of the TDM process for each subject and to assess the accuracy of the model prediction.

Outcome

The proportion of subjects with target attainment after the final dose (plasma concentration within the target levels) was the primary outcome of each simulation run. These outcomes were compared to the proportion of subjects reaching target attainment after following the clinical dosing guidelines during the simulation without dose adjustment, and to the proportion of subjects reaching target attainment after dose adjustment solely based on covariates included in the population PK models, such as weight and comedication.

Case study Voriconazole

To assess whether the simulations with hypothetical saliva parameters are valid, we applied the methodology described above in a case study with the Voriconazole model of Kim *et al.*, which describes the relationship between plasma and saliva based on aggregated data from the literature.[12] The model concerns a one compartment model with a saliva:plasma ratio of 0.5, BSV on CL (36.9%) and a proportional residual error of 27% on

saliva concentrations and 24% on plasma concentrations, without any covariates. Thousand simulated subjects received a 4mg/kg twice daily dose. Target attainment was defined as a trough concentration between 1-4 mg/L, and the dose decision rule was programmed to optimize the dose to reach a trough between 1.5 and 3.5 mg/L. The proportion of subjects reaching target attainment was estimated for 0-3 plasma or saliva samples, using the same timepoints as in the analyses above.

Results

Performance of plasma TDM

To be able to compare the performance of saliva TDM to plasma TDM, the first simulation runs were performed with plasma sampling with the models as described in the literature. The proportion of subjects with plasma levels within the target range is displayed in *Figure 2A* (gentamicin) and *Figure 2B* (lamotrigine). For gentamicin, only 41% of subjects achieve plasma concentrations within the target range in our simulation if no TDM was applied and standard dosing guidelines were followed, whereas for lamotrigine this was the case in only 35% of subjects. Optimizing the dose based on the population PK model and covariates weight, age and comedication led to a 72% target attainment for both compounds. Obtaining a single plasma sample 14h post-dose led to 87% and 93% patients achieving sufficient plasma levels for gentamicin and lamotrigine, respectively. This proportion increased slightly for each additional sample taken. These numerical results will be used for comparison of the predictive performance of saliva.

Saliva TDM with increasing proportional residual error (σ_{SAL})

Figure 2C (gentamicin) and *Figure 2D* (lamotrigine) display the proportion of subjects with plasma levels within the target range after saliva TDM with a varying proportional residual error. In this analysis, no BSV on the saliva:plasma ratio and k_{SALIVA} was included. For gentamicin, assuming a TDM regimen with a peak and trough sample, 99% of subjects would reach plasma levels within the target range if σ_{SAL} was 1%, which decreases to 82% when σ_{SAL} is 25% and to 76% if σ_{SAL} is 50%. In the case of a residual error of 25% and 50%, each additional saliva sample taken led to an additional small percentage (0-4%) of subjects reaching plasma levels within the target range. For lamotrigine, similar effects of the

residual error on target attainment were observed, with 98–100% of subjects achieving target attainment with 2 saliva samples and a residual error of 1%–10%. With a 25% and 50% residual error, 91% and 84% achieved plasma concentrations within range.

Figure 2. Proportion of subjects with target attainment with varying residual error ($\sigma2$) but without BSV on saliva parameters. A/B: Heat map displaying the proportion of subjects who reach target attainment of gentamicin (A) and lamotrigine (B) after plasma TDM using an increasing number of plasma samples. C/D: Heat map displaying the proportion of subjects who reach target attainment of gentamicin (C) and lamotrigine (D) after saliva TDM using an increasing number of saliva samples and assuming an increasing residual error on each observation sample. No BSV on saliva parameters was incorporated in this analysis. Timepoints where samples were simulated: 0 : no samples, standard dosing according to guidelines; M: no samples, dosing optimized according to population model and individual covariates; 1: sample 14h post–dose; 2: peak sample at 3h post–dose for gentamicin saliva and lamotrigine samples) and trough sample 0.5h before next dose; 3: samples at peak, trough and 14h post–dose; 4: samples at peak, trough, 14h post–dose and 7h post–dose; 5: samples at peak, trough, 14h post–dose, 7h post–dose and 18h post–dose; 6: samples at peak, trough, 14h post–dose, 7h post–dose, 18h post–dose and 0.5h post–dose.
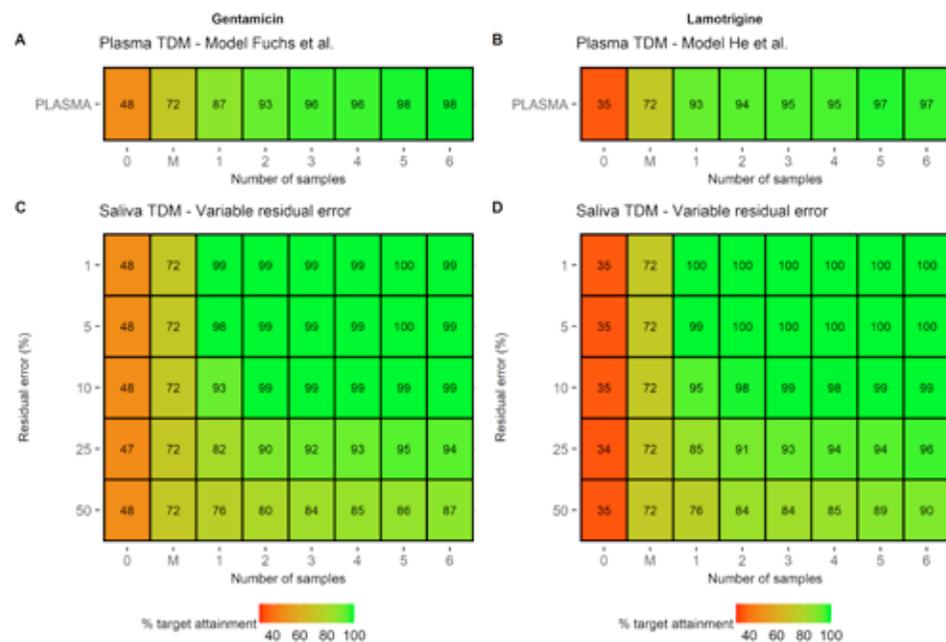

Figure 3. Proportion of subjects with target attainment with varying levels of between–subject variability. A/B. Estimated proportion of subjects within the target concentration range after saliva TDM without BSV. Here, residual error is 25% and no BSV is included on k_{SALIVA} or saliva:plasma ratio. Panel should be used for reference for other panels. C/D: Estimated proportion of subjects within the target concentration when a varying BSV on k_{SALIVA} is incorporated during simulations. E/F: Estimated proportion of subjects within the target concentration when a varying BSV on saliva:plasma ratio is used during simulations. G/H: Estimated proportion of subjects within the target concentration when a varying BSV on both k_{SALIVA} and saliva:plasma ratio is used during simulations (e.g., both 1%, both 5%, etc.).
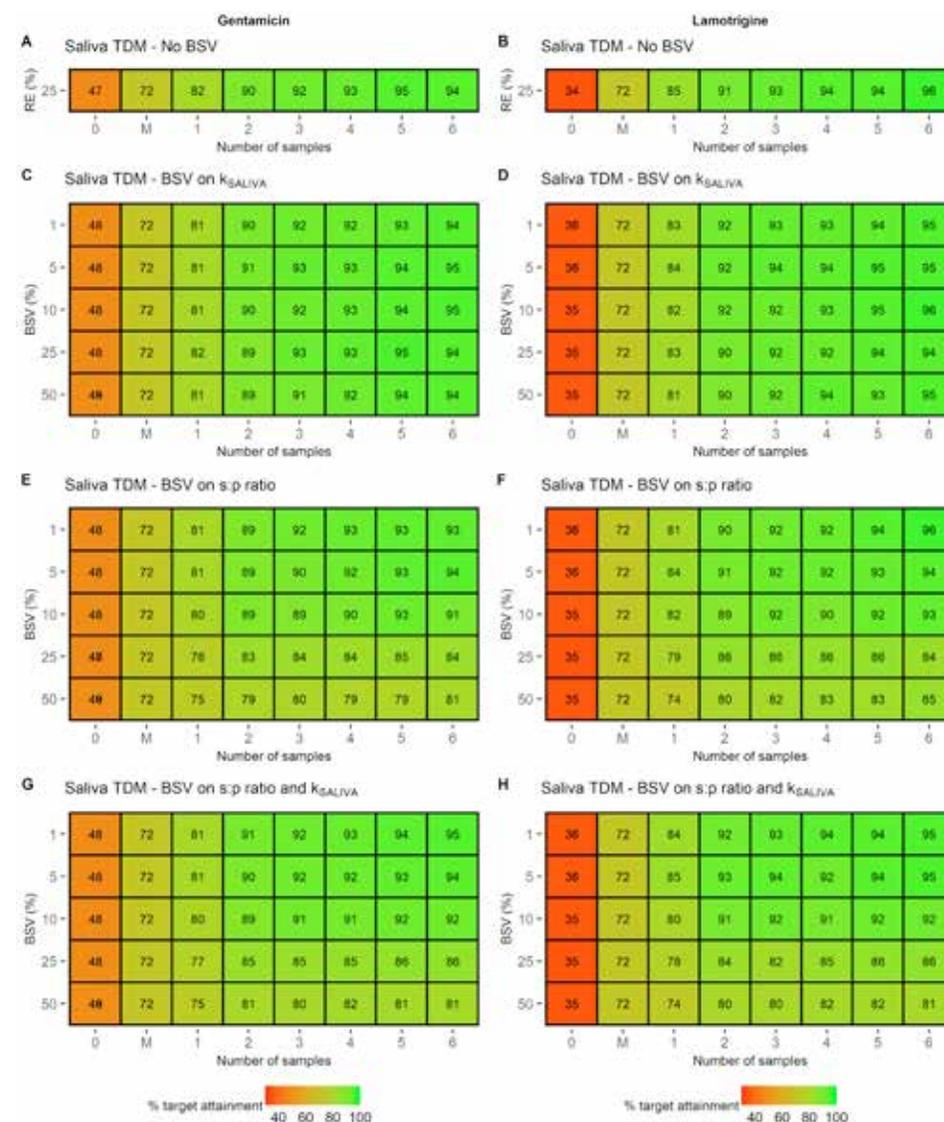
Saliva TDM with increasing BSV on saliva:plasma ratio (ω_{ratio}) and k_{saliva} ($\omega_{ksaliva}$)

Fitting a model that does not account for BSV in the saliva:plasma ratio and delayed penetration into the saliva compartment may lead to a high amount of unexplained variability, and as a result, lower TDM performance. On the other hand, incorporating BSV, for example on K_{SALIVA}, in a model poses an additional hurdle for the Bayesian optimization to consider, and could result in lower predictive performance of saliva samples to adequately isolate the CL and VD for each subject based on limited samples.

Figure 3 displays the effects of including a varying ω_{RATIO} and $\omega_{KSALIVA}$ on TDM performance. Figure 3A–B repeats the outcome of a simulation with a residual error of 25% without additional BSV. Figure 3C–H displays the outcome of simulations with varying levels of BSV. Increasing $\omega_{KSALIVA}$ did not lead to a significant reduction of subjects achieving adequate plasma levels for either gentamicin or lamotrigine. Similarly, increasing the BSV on the S:P ratio to up to 10% did not cause a reduction in performance either. However, a ω_{RATIO} of 25% or 50% led to a 3–6% and 5–11% reduction in the proportion subjects achieving target attainment, depending on the number of samples. For lamotrigine, target trough attainment was achieved 2–6% (BSV 25%) and 6–11% (BSV 50%) less in those cases. The combination of both ω_{RATIO} and $\omega_{KSALIVA}$ led to similar performance compared to the simulation run that only included ω_{RATIO} for both gentamicin and lamotrigine.

Fig 4. Case study voriconazole-Proportion of subjects with plasma concentrations within target ranges with varying between-subject variability. Heat map with proportion of subjects with target attainment after TDM with 0–6 saliva- or plasma samples. Simulation based on the voriconazole model of Kim et. al.
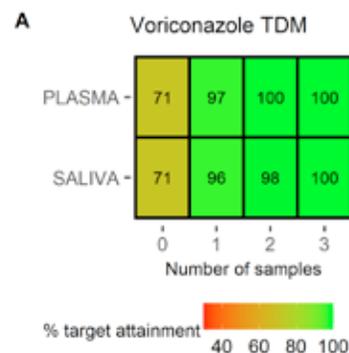
Case study with voriconazole saliva model

The estimated proportion of subjects with target attainment for the voriconazole saliva model of Kim *et al.* is displayed in *Figure 4* for several scenarios. Using the 4 mg/kg dosing guidelines, 70% of simulated subjects reached target attainment. Applying TDM with 1 sample led to 97 and 96% of subjects with adequate trough concentrations for plasma and saliva, respectively. Obtaining 3 samples led to 100% target attainment, for both plasma and saliva TDM.

Discussion

There have been many studies investigating the penetration of drugs into saliva and using saliva sampling for TDM has been recurrent subject of discussion in the field.[7,13] However, most papers investigating the potential of saliva sampling have focused on a constant ratio between saliva and plasma concentrations, which can vary over time. Non-linear mixed effect models are more flexible, can include covariates and BSV on parameters and, as a result, are better for prediction and estimation of an individual's PK profile. This analysis investigated the effect of several levels of variability structures for two commonly used drugs and this approach can assist pharmacometricians and clinicians when developing novel TDM techniques while assessing the use of saliva in clinical practice. In general, these results show that even with moderate to high levels of variability in the saliva–plasma relationship, TDM with saliva samples is feasible and leads to significantly higher target attainment compared to 'one size fits all' dosing guidelines or even model–based individualized dosing.

When estimating the CL and VD of each individual subject with either saliva or plasma samples, increasing the number of samples caused a small improvement in predictive capability for each additional sample. However, the largest improvement in performance was observed with 2 samples compared to 1 sample. Increasing the proportional error associated with the model increased the uncertainty around each individual estimation. As a result, the difference between the estimated– and true CL and VD was larger for each stepwise increase in the proportional error. If there are variables where incorporating BSV improves model fit, including this in the model will reduce the proportional error, which in turn may lead to increased performance of the model in the context of TDM. Our data demonstrates that including BSV on the delay constant towards the saliva compartment

($\omega_{KSALIVA}$) does not impact TDM performance in the models investigated here, independently of the size of the variability. It was expected this variable would cause uncertainty in the estimation of other parameters, especially VD. We hypothesize the correlation between CL and VD in the gentamicin model of Fuchs *et al.* and the lack of BSV on VD in the lamotrigine model allowed for this stable performance. BSV on the saliva:plasma ratio (ω_{RATIO}) only impacted TDM performance when the variability exceeded 25%.

Of course, the acceptable level of the proportion of subjects reaching adequate plasma levels differs between each compound. Gentamicin has a narrow therapeutic range with potentially debilitating adverse events, which necessitates to aim for accurate TDM, especially when treating for extended periods.[24] On the other hand, lamotrigine has a wider therapeutic range with possible extreme effects of comedication on plasma concentration. In such cases, a larger prediction error could be accepted on the condition that such outliers would be identified reliably, and saliva samples can be used to identify these.

While this paper focuses on saliva, our methods can be applied to other alternative sampling matrices as well, such as dried blood spots, sweat, lacrimal fluid or others.[25-28] The potential applications of alternative sampling matrices are numerous. First, the fact that they are non-invasive allows for widespread application in vulnerable populations that are usually not represented in studies that determine general pharmacokinetic properties, such as children or the mentally impaired. Determining whether these patients obtain adequate plasma concentrations could improve their quality of care. Second, as demonstrated in this paper, increasing the amount of TDM samples obtained from patients leads to better estimations and more patients with plasma concentrations within the target range, and non-invasive sampling matrices make repeated sampling more accessible. Third, non-invasive sampling matrices usually do not require extensive training or supervision to perform. As a result, samples for the pediatric pharmacokinetic clinical trial of the future could be taken in a home-setting, stored in a domestic freezer, and eventually be retrieved by courier. This complements a general trend in clinical trials and-care which moves away from the clinic towards the home.[29]

The purpose of this paper was to propose an evaluation framework and to determine the influence of several model parameters on the performance of TDM with saliva. The saliva:plasma relationship is dependent on several factors, including polarity, molecule size and protein binding capacity.[30] In the end, compounds that reach saliva in too unpredictable or variable ways will be unsuitable for TDM on their own, as estimations based on saliva samples in such models would be driven purely by population effects, such as was observed with high levels of variability of 50% in the current analysis. In NLMEM, this can be quantified by the residual error and BSV. The models that were used during simulation in this study used fictional saliva compartments, and it is unclear whether saliva TDM is viable for the two compounds in the absence of clinical data about the saliva:plasma relationship. The included parameters model a delayed penetration of drug towards the saliva compartment with a given saliva:plasma ratio. This is likely a simplification of the underlying physiology, but there currently is little salivary data available for either gentamicin or lamotrigine. Even so, it is likely that this resembles true physiology more closely compared to the constant saliva:plasma ratio without a delay that is currently employed in most salivary PK studies. In the future, when more data becomes available, modelling may reveal other model structures or differing input and output constants for the saliva compartment. The proposed framework can then be applied on this newly developed model. Although a limitation of the current analysis is that it is not based on real salivary data, it allows to explore the impact of several levels of variability and to determine thresholds of variability that severely impact TDM performance when exceeded. The thresholds of variability around 25% found during simulation appear viable targets during model building. The potential of saliva TDM was confirmed in the simulations of a saliva model of voriconazole[12], with target attainment > 90% for all saliva simulation scenarios and highly comparable target attainment compared with plasma TDM. In the future, additional simulations of alternative sampling timepoints or different covariate distributions may lead to different proportions of subjects that achieve target attainment. However, since a large cohort was used that was identical during each simulation run, relative differences across simulations in the proportion of subject with target attainment should remain constant. Future studies should focus on confirming these simulations with real data. Furthermore, advanced modelling techniques such as physiologically based pharmacokinetic modelling (PBPK) of the penetration of the salivary compartment may lead to low levels of variability. Additionally, a hybrid approach combining both saliva- and plasma samples for TDM could also be investigated. For example, a first iteration of TDM could use plasma sampling to determine baseline CL and V, after which outpatient saliva samples could confirm a holding steady-state concentration or provide a warning sign indicative of a need for dose adjustment.

Conclusion

Saliva as alternative matrix for non-invasive TDM in pediatrics may be possible using non-linear mixed effects models combined with Bayesian optimization. Gentamicin or lamotrigine models with low- to moderate levels of variability below 50% on saliva observations achieve TDM performance comparable to TDM with plasma samples according to the simulations presented here. Additionally, this paper provides a workflow to explore the added value of TDM for compounds measured in saliva or other non-invasive sampling matrices.

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