Saliva Sampling in Therapeutic Drug Monitoring and Physiologically Based Pharmacokinetic Modeling: Review

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ABSTRACT

Therapeutic drug monitoring investigations based on saliva samples can be utilized as an alternative to blood sampling for many advantages. Moreover, the development of physiologically based pharmacokinetic (PBPK) modeling tools can further help to estimate drug exposure from saliva. This review discusses the use of saliva samples and illustrates the applications and examples of PBPK modeling systems for estimating drug exposure from saliva.

Introduction

The efficacy and safety of treatments implemented play an important role in determining the overall health of populations. Many factors can affect drug pharmacokinetics such as physiological factors, coadministration of other medications and environmental variables; therefore, monitoring the administered drug's concentrations enhances treatment effectiveness and safety. Therapeutic drug monitoring (TDM) is detecting concentrations of a drug in a biological fluid at a single or several periods following a drug intake for adjusting and customizing drug dosage and administration. TDM helps to anticipate a patient's response and to choose the ideal drug dosage for initiating and sustaining a clinical response [1].

Drugs' efficacy and safety can be anticipated if the medication level maintains within the therapeutic range. Though not all medications need to be monitored, TDM is critical when assessing medications with a narrow therapeutic window between the lethal and the therapeutic dose. TDM is also essential for highly variable drugs to prevent toxic high concentration levels. Moreover, abnormal response to treatment, unusual adverse events, suspected misuse, and lack of adherence are among the most common TDM applications.TDM is also a significant practice for a specific population (such as pregnant women, children, elderly, and obese people) or some disease status that can affect the drug pharmacokinetics [2]. TDM involves measuring the drug concentration and/or its primary metabolites in body fluids (such as plasma, serum, saliva and urine).

This review provides an overview of TDM using saliva samples and shows the latest advanced applications of physiologically based pharmacokinetic modeling systems in estimating drug exposure from saliva.

TDM saliva-based sample

The main TDM applications for the majority of systemic drugs are performed in the blood (or plasma). TDM with blood sampling is well established and widely used approach. However, due to pain, anxiety, risk of infection, restricted blood supply and limited accessible veins in some populations, extensive blood sampling can be unpractical [3]. Saliva testing is a simple and safe procedure that can be used as an excellent substitute for serum testing to assess drug exposure as most substances identified in the blood are also present in saliva, including DNA, RNA, and protein. Because of its non-invasive nature, lack of expert training or equipment requirement, low cost, ease of analysis, and patient compliance it has become a valuable clinical approach to determining the drug's con-

centration and may have a stronger predictive value for toxicity and clinical prognosis [3]. Diabetes, cardiovascular disease, dental caries, inflammation and other oral disorders also have all been identified using saliva test biomarkers [4–7]. Saliva sampling can be used to monitor drugs for neonates, who usually show more variation in drug exposure, drug efficacy, and drug toxicity TDM [8]. Saliva sampling can be also valuable in a variety of settings and clinically challenging conditions such as elderly and anxious patients. Several studies in different age individuals have evaluated the usage of saliva sampling for TDM, and it has been demonstrated to be an effective method, especially for narrow therapeutic window drugs such as artemisinin, digoxin, lamotrigine, phenytoin, carbamazepine, phenobarbital, voriconazole, tacrolimus and lithium[8–13]. Published studies have described the relationships between saliva and plasma samplings for monitoring antiepileptic drugs levels such as clobazam, ethosuximide, gabapentin, lacosamide, levetiracetam, oxcarbazepine, primidone, topiramate, and zonisamide [14]. Measuring these drugs levels in the oral fluid of epileptic patients who use chronic medication gives a more accurate indication of the pharmacodynamically active, free quantities of these chemicals in serum [15]. TDM of antibiotics such as moxifloxacin, linezolid, gentamicin, and azithromycin using saliva-based samplings have also been also investigated and shown that the drug levels of these samples were comparable to serum [16–18].

Factors affect TDM in saliva

Age, sex, and food all have an impact on saliva volume and composition, which can vary from person to person. Patients' levels of hydration are hypothesized to affect parotid salivary flow rates, which in turn affect medication concentrations in saliva [19]. Since most of the saliva is water, it is assumed that a decrease in water volume caused by dehydration would result in a loss in salivary production. Moreover, several factors can influence the diffusion of a drug in saliva. The pH of saliva and the acid dissociation constant (pKa) of the drug can affect the drug level in saliva samples as presented for amphetamine saliva sampling where the paired saliva-to-serum concentrations of amphetamine can be very variable and greatly influenced by salivary pH [20]. The lipophilicity and protein binding affinity characterize of the drug can influence the TDM in saliva. The Salivary Excretion Classification System (SECS) was developed following the drug's physicochemical characteristics [18]. This method divides medications into four types based on intestinal permeability and protein binding. Using these two metrics as primary criteria, one can predict medications that are suitable to be monitored using saliva samples. According to SECS, class I and II medications with poor protein binding are subjected to salivary excretion. Class III medication with a high protein binding and high intestinal permeability, is susceptible to salivary excretion because of its low proportion of unbound and high permeability. Class IV medicines with high protein binding and limited intestinal permeability are not expected to be excreted in the saliva [18]. SCECS approach can be valuable using in-silico tools in the early stage of drug discovery, which can predict drug characters and expect drugs that can be monitored in salivary secretion.

Sample collection and analysis method

Saliva samples can be collected directly, passively through drooling, or with the aid of special equipment [11]. A few difficulties could arise with the method of sampling collection as variation in recovery depending on the kind of cotton rolls utilized has been documented, which can absorb the collected saliva samples. Therefore, it is important to standardize and tightly control the process of collecting saliva samples [10]. Also, it is highly advised to assess the matrix impact of collecting tubes as studies showed that serum separator gel-filled tubes can significantly impact the determination of some medications [10]. Additionally, samples taken by spitting have a higher bacterial content than samples taken by drooling, which may impact the results. The passive drooling technique is seen to be a promising substitute with significant amounts of saliva that may be gathered in a short time. For an immediate analysis, specimens can be kept at room temperature for a maximum of 30–90 minutes. To stop bacterial development and additional salivary molecule destruction, specimens can be kept at 4°C for no more than 6 hours. Moreover, the saliva samples following saliva collection can be preserved and maintained frozen at −20°C for years till the time of the drug analysis [4].

The method for obtaining a dried biological fluid is known as dried matrix spots (DMSs) sampling. It involves spotting the liquid specimen onto a collection card, allowing it to dry, and then transferring it to a tube with an extracting solvent [15, 21]. Likewise, Dried saliva spots (DSSs) are reported in the literature as an alternative to liquid oral fluid for TDM [22]. DSSs method offers many benefits, including simple transit and storage, cheap shipping costs, a tiny volume of greater analyte stability, a sample, and less chance of contamination because of an improperly handled sample [23]. Detecting and quantifying drugs of abuse in the toxicological analysis might be done more quickly and affordably by using DSSs [23].

The efficiency of saliva sample preparation and analysis is improved by combining the DSS method with a highly sensitive detection instrument [22, 24]. The assay protocols used for drug testing have been performed by applying a range of analytical techniques, including high-performance liquid chromatography (HPLC) techniques, solid-phase extraction (SPE), liquid-liquid extraction (LLE), and protein precipitation (PP) approaches[21]. Gas chromatography coupled to mass spectrometry (GC-MS) and ultra-high-performance liquid chromatography (UHPLC) coupled to MS/MS, liquid chromatography (LC) coupled to tandem mass spectrometry (MS/MS) have also been commonly used [19].

PBPK and saliva sampling

The physiologically based pharmacokinetic is one of the recognized modeling that has a significant aid in the optimal design of pharmaceuticals drug [25]. PBPK modeling and simulation is a tool for predicting drug pharmacokinetics and assessing the properties of intrinsic (e. g., organ dysfunction, age, genetics polymorphism, or disease state) and extrinsic (e. g., drug-drug interactions (DDI) and drug-food interactions) factors [25–27]. The processes of drug absorption, distribution, metabolism, and excretion are described by a set of differential equations in PBPK models, which reflect the physiology of the body compartments. Simulations range from a simple system with only a few critical compartments to full-body PBPK models with compartments connected by blood flow that

represent all main organs in the body. In this approach, physiochemical parameters from different sources such as in silico predictions, in vitro or in vivo experiments can be combined to predict drug absorption, disposition, and excretion of substances for various dosing regimens in different species, populations, or disease states [25, 27–29]. Thus, this approach can be valuable in individualized treatment as parameters can be computationally fitted in for specific disease/ population models to best describe in vivo drug concentrations and mechanistically understand the change in absorption. Moreover, this approach can predict the transporters' induction levels, inhibition, and the influence of DDI in each tissue, for example, glycoprotein (Pgp), cytochrome P450 (CYP), organic anion transporting polypeptide (OATP) and multidrug resistance protein transporters [30–32].

Although a valid prediction of population PK parameters requires very comprehensive pharmacokinetic data, this approach can identify patient-specific variables and personalized therapy. The applications of modeling and simulation approaches save huge time and resources in discovering and developing drug treatments [33]. As a result, scientists created powerful computer algorithms that can take these theories into account. Such software is used to forecast the pharmacokinetics of oral drugs and make medication candidate selection easier and assist with regulatory policy implementation. Examples are MATLAB, Stella, NONMEM, AcsLx, Phoenix, and Berkeley Madonna, R, Simbiology, Mathematica, Monolix, WinNonlin, ADAPT, NAPP, CMATRIX, PKQuest, MCSIM, and BioDMET, Simcyp Simulator, GastroPlus, and PKSim.

Reducing the expense, duration, and number of in vivo studies required for the discovery, development and approval of generic medicinal products globally is a goal shared by the pharmaceutical industry and regulators. Therefore, in silico, PBPK modelings are becoming more widely acknowledged by pharmaceutical industrial companies as they have adopted this approach in different stages of drug discovery and development. Moreover, the PBPK modeling and simulation are considered in regulatory agencies such as the United States Food and Drug Administration(US,FDA), the European Medicines Agency (EMA), and the Ministry of Health Labor and Welfare (MHLW) of Japan [34]. Additionally, FDA and EMA have released detailed guideline notes on conducting and reporting PBPK investigations (EMA, 2016; FDA, 2018). Therefore, the number of research studies incorporating PBPK modeling has risen dramatically in the last two decades, illustrating the broad use of this approach in the scientific community [35].

The use of saliva sampling in TDM to describe the time course in combination with PBPK modeling can constitute a unique strategy with broad applicability for assessing drug exposures [36]. This should be done considering the drug characteristics as plasma and saliva PK are expected to be comparable for some drugs [18, 37]. Utilizing simulations of bioequivalence studies can further aid in predicting drug exposure from saliva [38]. Published papers have illustrated examples of utilization and verification of this strategy using atomoxetine [39], gentamycin [40], lead [41, 42], mycophenolic acid [43], Linagliptin [44]. The computational models of the PBPK approach can extend in predicting and better understanding the mechanistic change of drug response in different populations or disease cases based on saliva samplings [39, 40]. Studies showed that sing saliva samples are a highly successful strategy for pharmacogenetics and pharmacokinetics studies [45]. Therefore, incorporating saliva samplings with PBPBK modelling may have potential in personalized medicine studies, which can optimize treatment and reduce the cost, time and resources.

Conclusion

Therapeutic drug concentration monitoring is a significant practice to adjust and maintain safety and efficacy. Using salivary-based sampling in TDM has many advantages. Linking the PBPK modelings, given their highly beneficial features, to the salivary TDM can further aid in predicting and optimizing in vivo drug response. This review discusses saliva-based sampling in TDM and shows how PBPK can maximize the benefits of using saliva samplings in drug monitoring.

Conflict of interest

The author declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

References

[1] Kang J-S, Lee M-H. Overview of Therapeutic Drug Monitoring. Korean J. Intern. Med., vol 24: p. 1 2009. doi:10.3904/kjim.2009.24.1.1

[2] Tuzimski T, Petruczynik A. Review of Chromatographic Methods Coupled with Modern Detection Techniques Applied in the Therapeutic Drugs Monitoring (TDM). Molecules, vol., vol 25: 2020. doi:10.3390/molecules25174026

[3] Ghareeb M, Akhlaghi F. Alternative matrices for therapeutic drug monitoring of immunosuppressive agents using LC-MS/MS. Bioanalysis, vol 7: pp. 1037–1058 2015. doi:10.4155/bio.15.35

[4] Bhattarai KR, Kim H-R, Chae H-J. Compliance with Saliva Collection Protocol in Healthy Volunteers: Strategies for Managing Risk and Errors. Int. J. Med. Sci., vol 15: pp. 823–831 2018. doi:10.7150/ijms.25146

[5] Parkin G et al Associations between saliva and plasma cytokines and YKL-40 in cognitively-normal, older adults. Research Square 2022. doi:10.21203/rs.3.rs-1863157/v1

[6] Corey-Bloom J, Haque AS, Park S, Nathan AS, Baker RW, Thomas EA. Salivary levels of total huntingtin are elevated in Huntington's disease patients. Sci. Rep., vol 8: p. 7371 2018. doi:10.1038/s41598-018-25095-3

[7] Gutierrez A, Corey-Bloom J, Thomas EA, Desplats P. Evaluation of Biochemical and Epigenetic Measures of Peripheral Brain-Derived Neurotrophic Factor (BDNF) as a Biomarker in Huntington's Disease Patients. Front. Mol. Neurosci., vol 12: pp. 1–11 2020. doi:10.3389/fnmol.2019.00335

[8] De Rose DU et al. Therapeutic Drug Monitoring Is a Feasible Tool to Personalize Drug Administration in Neonates Using New Techniques: An Overview on the Pharmacokinetics and Pharmacodynamics in Neonatal Age. International Journal of Molecular Sciences, vol 21: 2020. doi:10.3390/ijms21165898

[9] Gordi T, Hai TN, Hoai NM, Thyberg M, Ashton M. Use of saliva and capillary blood samples as substitutes for venous blood sampling in pharmacokinetic investigations of artemisinin. Eur. J. Clin. Pharmacol., vol 56: pp. 561–566 2000. doi:10.1007/s002280000179

[10] Hutchinson L, Sinclair M, Reid B, Burnett K, Callan B. A descriptive systematic review of salivary therapeutic drug monitoring in neonates and infants. Br. J. Clin. Pharmacol., vol 84: pp. 1089–1108 2018. doi:10.1111/bcp.13553

[11] Avataneo V et al. A Non-Invasive Method for Detection of Antihypertensive Drugs in Biological Fluids: The Salivary Therapeutic Drug Monitoring. Front. Pharmacol., vol 12: pp. 1–9 2022. doi:10.3389/fphar.2021.755184

[12] Parkin GM et al. Saliva testing as a means to monitor therapeutic lithium levels in patients with psychiatric disorders: Identification of clinical and environmental covariates, and their incorporation into a prediction model. Bipolar Disord., vol 23: pp. 679–688 2021. doi:https://doi.org/10.1111/bdi.13128

[13] Kim HY et al. Saliva for Precision Dosing of Antifungal Drugs: Saliva Population PK Model for Voriconazole Based on a Systematic Review. Front. Pharmacol., vol 11: 2020. doi:10.3389/fphar.2020.00894

[14] Patsalos PN, Berry DJ. Therapeutic Drug Monitoring of Antiepileptic Drugs by Use of Saliva. Ther. Drug Monit., vol 35: 2013. doi:https://doi.org/10.1097/FTD.0b013e31827c11e7

[15] Carvalho J, Rosado T, Barroso M, Gallardo E. Determination of antiepileptic drugs using dried saliva spots. J. Anal. Toxicol., vol 43: pp. 61–71 2019. doi:10.1093/jat/bky064

[16] Van Den Elsen SHJ et al. Therapeutic drug monitoring using saliva as matrix: An opportunity for linezolid, but challenge for moxifloxacin. Eur. Respir. J., vol 55: 2020. doi:10.1183/13993003.01903-2019

[17] Hamadi S, Banna F, Al-awwa I, Al-ghazawi A, Idkaidek N. Saliva versus Blood Therapeutic Drug Monitoring of Tacrolimus in Jordanian Kidney Transplant Patients. pp. 1–5 2018. doi:10.19080/NAPDD.2018.04.555632

[18] Idkaidek N, Arafat T. Saliva versus Plasma Pharmacokinetics: Theory and Application of a Salivary Excretion Classification System. Mol. Pharm., vol 9: pp. 2358–2363 2012. doi:10.1021/mp300250r

[19] Samiksha G et al. Evaluation of Saliva as a Potential Alternative Sampling Matrix for Therapeutic Drug Monitoring of Levofloxacin in Patients with Multidrug-Resistant Tuberculosis. Antimicrob. Agents Chemother., vol 63: pp. e02379–18 2019. doi:10.1128/AAC.02379-18

[20] Wohkittel C, Högger P, Fekete S, Romanos M, Gerlach M. Relationship Between Amphetamine Concentrations in Saliva and Serum in Children and Adolescents With Attention-Deficit/Hyperactivity Disorder. Ther. Drug Monit., vol 43: pp. 564–569 2021. doi:10.1097/FTD.0000000000000831

[21] Almeida E et al. Stability of Cocaine, Opiates, and Metabolites in Dried Saliva Spots. Molecules, vol 27: 2022. doi:10.3390/molecules27030641

[22] Han Y, Li X-L, Zhang M, Wang J, Zeng S, Min JZ. Potential use of a dried saliva spot (DSS) in therapeutic drug monitoring and disease diagnosis. J. Pharm. Anal. 2021. doi:10.1016/j.jpha.2021.11.001

[23] Jacques ALB, dos Santos MK, Limberger RP. Development and Validation of a Method Using Dried Oral Fluid Spot to Determine Drugs of Abuse. J. Forensic Sci., vol 64: pp. 1906–1912 2019. doi:10.1111/1556-4029.14112

[24] Ates HC, Roberts JA, Lipman J, Cass AEG, Urban GA, Dincer C. On-Site Therapeutic Drug Monitoring. Trends Biotechnol., vol 38: pp. 1262–1277 2020. doi:10.1016/j.tibtech.2020.03.001

[25] Almukainzi M, Jamali F, Aghazadeh-Habashi A, Löbenberg R. Disease specific modeling: Simulation of the pharmacokinetics of meloxicam and ibuprofen in disease state vs. healthy conditions. Eur. J. Pharm. Biopharm., vol 100: 2016. doi:10.1016/j.ejpb.2015.12.004

[26] Bolger MB, Macwan JS, Sarfraz M, Almukainzi M, Löbenberg R. The Irrelevance of In Vitro Dissolution in Setting Product Specifications for Drugs Like Dextromethorphan That are Subject to Lysosomal Trapping. J. Pharm. Sci., vol 108: 2019. doi:10.1016/j.xphs.2018.09.036

[27] Almukainzi M, Gabr R, Abdelhamid G, Löbenberg R. Mechanistic understanding of the effect of renal impairment on metformin oral absorption using computer simulations. J. Pharm. Investig., vol 47: 2017. doi:10.1007/s40005-017-0307-y

[28] Almukainzi M, Lukacova V, Löbenberg R. Modelling the Absorption of Metformin with Patients Post Gastric Bypass Surgery. J. Diabetes Metab., vol 05: 2014. doi:10.4172/2155-6156.1000353

[29] Almukainzi M. The application of computer simulation to investigate drug absorption and bioavailability in disease states. pp. 1–152 2016. doi:10.7939/R3QR4P28H

[30] Yang H, Yang L, Zhong X, Jiang X, Zheng L, Wang L. Physiologically based pharmacokinetic modeling of brivaracetam and its interactions with rifampin based on CYP2C19 phenotypes. Eur. J. Pharm. Sci. p. 106258 2022. doi:https://doi.org/10.1016/j.ejps.2022.106258

[31] Asaumi R, Nunoya K. ichi, Yamaura Y, Taskar KS, Sugiyama Y. Robust physiologically based pharmacokinetic model of rifampicin for predicting drug-drug interactions via P-glycoprotein induction and inhibition in the intestine, liver, and kidney. CPT Pharmacometrics Syst. Pharmacol., no. April pp. 919–933 2022. doi:10.1002/psp4.12807

[32] Fuhr LM, Marok FZ, Mees M, Mahfoud F, Selzer D, Lehr T. A Physiologically Based Pharmacokinetic and Pharmacodynamic Model of the CYP3A4 Substrate Felodipine for Drug–Drug Interaction Modeling. Pharmaceutics, vol 14: 2022. doi:10.3390/pharmaceutics14071474

[33] Bouzom F, Ball K, Perdaems N, Walther B. Physiologically based pharmacokinetic (PBPK) modelling tools: how to fit with our needs? Biopharm. Drug Dispos., vol 33: pp. 55–71 2012. doi:https://doi.org/10.1002/bdd.1767

[34] Jones HM et al. Physiologically Based Pharmacokinetic Modeling in Drug Discovery and Development: A Pharmaceutical Industry Perspective," vol 97: 2015. doi:10.1002/cpt.37

[35] El-Khateeb E, Burkhill S, Murby S, Amirat H, Rostami-Hodjegan A, Ahmad A. Physiological-based pharmacokinetic modeling trends in pharmaceutical drug development over the last 20-years; in-depth analysis of applications, organizations, and platforms. Biopharm. Drug Dispos., vol 42: pp. 107–117 2021. doi:10.1002/bdd.2257

[36] Arabyat M et al. Therapeutic Drug Monitoring of Vancomycin in Jordanian Patients. Development of Physiologically-Based Pharmacokinetic (PBPK) Model and Validation of Class II Drugs of Salivary Excretion Classification System (SECS). Drug Res, no. EFirst 2022. doi:10.1055/a-1852-5391

[37] Dobson NR et al. Salivary caffeine concentrations are comparable to plasma concentrations in preterm infants receiving extended caffeine therapy. Br. J. Clin. Pharmacol., vol 82: pp. 754–761 2016. doi:https://doi.org/10.1111/bcp.13001

[38] Idkaidek N, Agha H, Arafat T Saliva versus Plasma Bioequivalence of Valsartan/Hydrochlorothiazide in Humans: Validation of Classes II and IV Drugs of the Salivary Excretion Classification System. Drug Res. (Stuttg)., vol 68: pp. 54–59 2018. doi:10.1055/s-0043-117775

[39] Alsmadi MM, AL Eitan NL, Idkaidek MN, Alzoubi HK. The Development of a PBPK Model for Atomoxetine Using Levels in Plasma, Saliva and Brain Extracellular Fluid in Patients with Normal and Deteriorated Kidney Function. CNS & Neurological Disorders – Drug Targets, vol 21: pp. 704–716 2022. doi:http://dx.doi.org/10.2174/1871527320666210621102437

[40] Idkaidek N et al. Saliva versus Plasma Therapeutic Drug Monitoring of Gentamicin in Jordanian Preterm Infants. Development of a Physiologically-Based Pharmacokinetic (PBPK) Model and Validation of Class II Drugs of Salivary Excretion Classification System. Drug Res, vol 70: pp. 455–462 2020. doi:10.1055/a-1233-358

[41] Timchalk C, Poet TS, Lin Y, Weitz KK, Zhao R, Thrall KD. Development of an Integrated Microanalytical System for Analysis of Lead in Saliva and Linkage to a Physiologically Based Pharmacokinetic Model Describing Lead Saliva Secretion. AIHAJ – Am. Ind. Hyg. Assoc., vol 62: pp. 295–302 2001. doi:10.1080/15298660108984631

[42] Timchalk C, Poet TS, Kousba AA, Campbell JA, Lin Y. Noninvasive Biomonitoring Approaches to Determine Dosimetry and Risk Following Acute Chemical Exposure: Analysis of Lead or Organophosphate Insecticide in Saliva. J. Toxicol. Environ. Heal. Part A, vol 67: pp. 635–650 2004. doi:10.1080/15287390490428035

[43] Alsmadi MM et al. The development of a population physiologically based pharmacokinetic model for mycophenolic mofetil and mycophenolic acid in humans using data from plasma, saliva, and kidney tissue. Biopharm. Drug Dispos., vol 40: pp. 325–340 2019. doi:https://doi.org/10.1002/bdd.2206

[44] Wu N, An G. Incorporating Pharmacological Target-Mediated Drug Disposition (TMDD) in a Whole-Body Physiologically Based Pharmacokinetic (PBPK) Model of Linagliptin in Rat and Scale-up to Human. AAPS J., vol 22: p. 125 2020. doi:10.1208/s12248-020-00481-w

[45] Bolani B et al. Pharmacogenetic and pharmacokinetic assays from saliva samples can guarantee personalized drug prescription. Braz. Dent. J., vol 32: pp. 3–8 2021. doi:10.1590/0103-6440202104059