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Original Research Article

A Novel Chronic Opioid Monitoring Tool to Assess Prescription Drug Steady State Levels in Oral Fluid

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Abstract

Objective. Interpretation limitations of urine drug testing and the invasiveness of blood toxicology have motivated the desire for the development of simpler methods to assess biologically active drug levels on an individualized patient basis. Oral fluid is a matrix well-suited for the challenge because collections are based on simple noninvasive procedures and drug concentrations better correlate to blood drug levels as oral fluid is a filtrate of the blood. Well-established pharmacokinetic models were utilized to generate oral fluid steady state concentration ranges to assess the interpretive value of the alternative matrix to monitor steady state plasma oxycodone levels.

Methods. Paired oral fluid and plasma samples were collected from patients chronically prescribed oxycodone and quantitatively analyzed by liquid chromatography tandem mass spectrometry. Steady state plasma concentration ranges were calculated for each donor and converted to an equivalent range in oral fluid. Measured plasma and oral fluid oxycodone concentrations were compared with respective matrix-matched steady state ranges, using each plasma steady state classification as the control.

Results. A high degree of correlation was observed between matrices when classifying donors according to expected steady state oxycodone concentration. Agreement between plasma and oral fluid steady state classifications was observed in 75.6% of paired samples. This study supports novel application of basic pharmacokinetic knowledge to the pain management industry, simplifying and improving individualized drug monitoring and risk assessment through the use of oral fluid drug testing. Many benefits of established therapeutic drug monitoring in plasma can be realized in oral fluid for patients chronically prescribed oxycodone at steady state.

Key Words. Oral Fluid; Urine Drug Testing; Steady State Medication Monitoring; Prescription Regimen Adherence; Pharmacokinetics; Oxycodone

Introduction

Controlled substance abuse is on the rise in the United States, largely fueled by the escalating use of opioid analgesics. Unintentional deaths due to drug overdose have skyrocketed in recent years. A greater percentage of these deaths have involved opioid pain medications than heroin and cocaine combined. Since 2000, there

has been a 137% increase in the drug overdose death rate, along with a 200% increase when opioids, either pain killers or heroin, were involved [1,2]. In addition to the growing rate of unintentional overdose deaths related to opioid analgesics, many more individuals are admitted to substance abuse clinics, visit emergency rooms, admit to drug misuse or addiction, or abuse pain medications for recreational nonprescribed purposes [3]. Implementing better interventional approaches aimed at those individuals at greatest risk for opioid use disorder is important to help support patient compliance with controlled substance prescribing. This intensifying opioid epidemic is complicated by the fact that despite the multitude of problems surrounding prescribing controlled substances, conflicting arguments of undertreatment of pain are concurrently growing [4]. Thus, to help combat the heightening prevalence of opioid abuse and misuse, closer monitoring of prescription regimen adherence is imperative.

Prescribing controlled substances is focused upon the desired goal of maintaining patient access to appropriate pain management and treatment while mitigating and balancing the associated risks. Opioid abuse and aberrant medication-taking behavior is not uncommon in patients actively receiving chronic opioid therapy. A reported 22% of chronic pain patients use controlled substances in combination with illicit drugs. However, also noted, increased patient compliance monitoring protocols lowered this percentage to 16% in the same patient population. Furthermore, controlled substance abuse in the absence of illicit drugs has been reported in 14–16% of patients undergoing treatment for chronic pain. Controlled substance abuse and illicit drug use was reported in over double the patients (34%) in the same setting. In addition, the prevalence of current substance abuse disorders was estimated in greater than 40% of patients receiving opioid therapy for chronic back pain [5–7]. Safe and effective utilization of controlled substances is impacted by patient compliance to prescribed dosing regimen, as well as other clinical considerations, such as a person's genetic predisposition, metabolism, drug-drug interactions, tolerance, and health status (e.g., kidney and liver function), all of which can impact drug levels, toxicity, and efficacy [8–11]. In addition to the aforementioned considerations, drug testing is an important component in the assessment of patient adherence to the prescribed dosing regimen.

Traditional urine drug testing (UDT) is a useful pain management tool that provides valuable information to assist clinicians in the decision-making surrounding diagnostic and therapeutic assessments. Currently, providers may focus on the presence of prescribed medications in the urine as evidence of usage and indication of compliance. The absence of a prescribed drug or the finding of nonprescribed or illicit substances in the urine would be an inconsistent test that merits further discussion [12,13]. While UDT may offer some interpretive boundaries, such as the lack of metabolites, potentially indicating that the medication is not being taken chronically, the principle outcome ultimately suggests previous exposure to a drug or lack thereof. Another drawback to UDT is that the matrix is the easiest to defeat. Adulteration, substitution, dilution/water-loading, and tampering with urine samples are commonly encountered in high-risk patient populations [14,15]. Precautions to avoid such manipulation require additional surveillance, testing, cost, and resources.

Oral fluid has been gaining recognition and momentum as an alternative matrix for prescription drug monitoring. Oral fluid drug testing is a simple and effective resource for clinicians to gain insight into a patient's recent medication usage. Like urine, oral fluid testing can identify whether prescribed medications are present in a patient's system or not, if the patient is refraining from use of illicit drugs and nonprescribed medications, and if the patient is overall complying with the rules of a treatment plan or mandated abstinence program. Despite oral fluid's slightly shorter window of detection in relation to urine, positivity rates in paired samples are highly comparable [16–19]. Additionally, oral fluid is an ideal matrix for testing patients who are at higher risk or those who have been involved in deviant drug-related behavior in the past as the observed collection provides greater reliable surrounding sample integrity. Oral fluid drug testing can highlight potentially harmful inconsistencies providing physicians with valuable information to assess best patient care [20].

A significant advantage of oral fluid as a testing matrix is that it is a filtrate of the blood and thus there is better correlation between blood and oral fluid drug concentrations [21,22]. Based upon this fact, as described in this study, it is now possible to monitor steady state drug ranges in oral fluid in a manner similar to traditional therapeutic drug monitoring. In this study, we describe the development of a novel prescription drug monitoring tool called Comprehensive Oral fluid Rx Evaluation (CORE). CORE correlates oral fluid drug concentrations to steady state blood plasma drug levels, providing additional clinical information beyond simply whether a drug is in a patient's system or not. CORE is an individualized patient screening tool that provides insight to aid clinician evaluation of patient compliance with prescription regimen, potential nonadherence, diversion, self-medication, tolerance, drug-drug interactions, health status considerations, or genetic or metabolic abnormalities that potentially warrant further clinical assessment and discussion with the patient.

Methods

Donor Selection

Individuals participating in the institutional review board–approved study included male and female chronic pain patients between the ages of 18 and 72 undergoing opioid treatment at pain management clinics. Patients were required to have documented daily treatment with oxycodone for a minimum of two months prior to

$PCss_{max} = (F \times D / 1\text{-}e^{-kt}) / dV_d$
$PCss_{min} = PCss_{max} \times e^{-kt}$

F = fractional oral bioavailability; **D** = medication dose; **k** = fractional rate constant; **t** = dosing frequency; $\mathbf{dV_d}$ = donor V_d

Figure 1 Pharmacokinetic models for calculating plasma steady state drug concentration range. D = medication dose; dVd = donor Vd; F = fractional oral bioavailability; k = fractional rate constant; t = dosing frequency.

enrollment in the study. Other select opioids actively under secondary investigation included morphine, hydrocodone, hydromorphone, oxymorphone, fentanyl, and tramadol, if chronic prescriptions were present. Individual donors were excluded from the study based on documented health issues such as impaired liver or renal function, prescriptions for multiple forms of the same opioid medication (extended release in combination with immediate release for breakthrough pain), simultaneous prescriptions for drugs known to influence opioid pharmacokinetics (CYP2D6, CYP3A4 inhibitors/inducers) or as needed (PRN) opioid medication use. Patient demographic information as well as comprehensive prescription drug lists, including drug dosing and frequency information, was collected from donors meeting the inclusion criteria. Written consent was obtained from applicable patients prior to the collection of paired samples and medication history. All samples and paperwork were de-identified by a generic specimen identification number to maintain donor anonymity throughout the study.

Study Design

To evaluate the feasibility of utilizing oral fluid as part of compliance drug monitoring, paired oral fluid and plasma specimens (N = 356) were collected from donors undergoing oxycodone treatment for chronic pain at multiple collection sites to obtain a wide variety of patients. In summary, blood samples were drawn into standard red top Vacutainer tubes (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) containing a clot activator. Following a wait period for proper clot formation, tubes were centrifuged and approximately three milliliters of separated plasma transferred to a secondary aliquot tube. Oral fluid specimens were collected using the Quantisal collection device (Immunalysis, Pomona, CA, USA). The collection device, consisting of an absorbent cellulose pad, was inserted under the tongue of the donor. Within approximately five minutes, an adequate volume of oral fluid was collected as indicated by the development of a blue dye in the visualization window. Following collection, the cellulose swab encompassing the oral fluid was inserted into a transport tube containing preservative buffer. A second aliquot of oral fluid was obtained by expectorating a small volume of saliva into a plastic cup. Expectorated oral fluid pH was measured with commercial pH paper and recorded (Micro Essential Laboratory, Brooklyn, NY, USA). The collected paired samples and associated paperwork were shipped to the laboratory for analysis.

Plasma steady state ranges for chronically prescribed opioids were determined for individual donors. Standard pharmacokinetic formulas utilizing published variables including drug clearance, half-life, volume of distribution, and fractional bioavailability were applied. Steady state maximum concentration ($PCss_{max}$) and steady state minimum concentration ($PCss_{min}$) were calculated using the formulas presented in Figure 1. A proprietary pharmacokinetic algorithm using measured oral fluid pH, published data on free drug fractions in plasma and oral fluid, plasma pH, and drug dissociation constants (pKa) was used to convert plasma steady state ranges into equivalent oral fluid steady state ranges ($OFCss_{max}$, $OFCss_{min}$).

These steady state ranges, both in plasma and oral fluid, served as the target ranges for measured drug concentration in matrix-matched specimens undergoing quantitative analysis by solid phase extraction (SPE) and liquid chromatography tandem mass spectrometry (LC-MS/MS). Comparing the measured drug concentration to the patient-specific matrix-matched expected steady state range served as an indicator of possible compliance with prescription drug regimen. Donor samples were classified as below range, within range, or above range accordingly. Comparison of the agreement between oral fluid classifications and paired plasma control classifications permitted the assessment of the feasibility to utilize oral fluid for steady state compliance monitoring.

Analytical Method

Analytical standards were obtained from Cerilliant Corp (Round Rock, TX, USA). Certified drug-free plasma was obtained from UTAK Laboratories (Valencia, CA, USA). Certified drug-free synthetic oral fluid was obtained from Immunalysis (Pomona, CA, USA). Chemical reagents including chlorobutane, isopropyl alcohol, methanol, water, formic acid, and sodium phosphate were purchased from VWR International (Bridgeport, NJ, USA). All solvents were HPLC grade or better.

Three working calibration standards were prepared in methanol from stock material at concentrations of 10,000 ng/mL, 1,000 ng/mL, and 100 ng/mL. Three working quality control standards were prepared in methanol

from separate stock material at concentrations of 10,000 ng/mL, 1,000 ng/mL, and 100 ng/mL. A deuterated internal standard was prepared in methanol from stock material at a concentration of 1,000 ng/mL. All working standards were stored at −20 °C when not in use. Calibration and quality control specimens were prepared by spiking aliquots of certified drug-free plasma or oral fluid with the appropriate volume of working calibration or quality control material. Calibration curves were generated over the range of 2.5–1,000 ng/mL. Quality control samples were included in each batch of analyzed specimens at concentrations of 10, 50, 100 ng/mL.

All specimens submitted for analysis underwent an SPE sample preparation procedure. Briefly, 500 uL aliquots of oral fluid or plasma were transferred to 3 cc mixed-mode cation exchange solid phase extraction cartridges (SPEware, Baldwin Park, CA, USA); 50 uL of an internal standard solution was added to each SPE column. The pH was then adjusted to 6.0 with 1 mL of 0.1 M sodium phosphate buffer. Samples were mixed and allowed to flow through the SPE columns. Columns were consecutively washed with water, 0.1 M sodium phosphate buffer (pH 6.0), and 25% methanol. Columns were dried under nitrogen gas, and analytes eluted with a mixture of dichloromethane:isopropanol:ammonium hydroxide (80:18:2). The solvent was transferred to clean autosampler vials, and the extracts were evaporated to dryness under nitrogen at 40 °C. Samples were reconstituted in 100 uL of 0.1% formic acid and thoroughly vortexed prior to LC-MS/MS analysis.

An Agilent Technologies (Wilmington, DE, USA) 1290 liquid chromatograph equipped with a Zorbax Eclipse Plus C18 column (2.1 mm x 50 mm x 1.8 um), maintained at 50 °C, was utilized for chromatographic separation of opioid analytes. Mobile phases consisted of 0.1% formic acid in deionized water (A) and 100% methanol (B). The mobile phase flow rate was set to 0.7 mL/min. Table 1 depicts details on the gradients used in this analysis. The total chromatographic run time was 5.50 minutes. All analyte retention times were determined to be within +/- 2% of calibrator retention times. Drug identification and quantitation was performed with an Agilent Technologies 6460 triple quadrupole mass spectrometer with a Jetstream electrospray source operating in positive ion mode with the following common parameters: nitrogen drying gas temperature 350 °C, nitrogen sheath gas temperature 400 °C, nitrogen drying gas flow 10 L/min, nitrogen sheath gas flow 11 L/min, nebulizer pressure 50 psi, capillary voltage 4,000 V, and nozzle voltage 1,000 V. A dynamic multiple reaction monitoring (dMRM) method monitored ion transitions for the opioid analytes. Table 2 summarizes specific transitions, retention times, collision cell energies, and fragmentator voltages used for each drug and respective internal standard. One MRM transition served as a quantifier transition, and a second MRM transition served as a qualifier transition. Only one MRM transition was monitored for deuterated internal standards. All qualifier ion ratios were determined to be within +/- 20% of calibrator qualifier ion ratios. All analyte-specific parameters were optimized using individual methanolic standards and analyzed in either full scan or product ion monitoring modes.

Table 1 LC-MS/MS gradient

Time, min	% B composition
0	0
0.1	10
1	20
2	20
2.01	40
2.7	40
2.71	70
3.7	70
3.71	0

LC-MS/MS = liquid chromatography tandem mass spectrometry.

Results

Paired oral fluid and plasma samples collected from study participants were extracted and analyzed by LC-MS/MS. Tabulated analytical results were then compared with matrix-matched expected steady state ranges. An assessment of the results indicated that 75.6% (269) of the paired samples demonstrated agreement between plasma and oral fluid when classifying study participants as below range, within range, or above range according to expected steady state oxycodone concentration. Within the subset of oxycodone data demonstrating agreement between oral fluid and plasma, the majority of paired samples were classified as both within the expected steady state range, representing 73.2% (197). Additionally, 12.3% (33) and 14.5% (39) of paired samples were classified as both above range and both below range, respectively (Figure 2).

Disagreement between plasma and oral fluid steady state classification was observed in 24.4% (87) of the paired oxycodone samples. When plasma concentrations were found to be within range, a nearly equal distribution of oral fluid samples were below range (35) or above range (36). Also noted were much less frequently observed scenarios where neither plasma nor oral fluid was found to be within range, but did not agree with the other. This was recorded when plasma results fell above range while oral fluid results fell below range (3.9%, 3 paired samples) or when plasma results fell below range while oral fluid results fell above range (1.4%, 1 paired sample). Distribution of results is summarized in Figure 3.

Discussion

A pharmacokinetic-based mathematical model was applied to assess steady state oxycodone concentrations via oral fluid drug testing. This application in oral fluid is a

Table 2 Dynamic MRM details of LC-MS/MS method

Compound name	Precursor ion	Product ion	RT, min	Fragmentor	Collision energy	Cell accelerator voltage	Polarity
Fentanyl	337.3	188.1	3.14	140	20	7	Positive
Fentanyl	337.3	105.1	3.14	140	40	7	Positive
Fentanyl d5	342.4	188.1	3.13	130	20	7	Positive
Hydrocodone	300.3	199.1	1.96	155	28	7	Positive
Hydrocodone	300.3	128	1.96	155	60	7	Positive
Hydrocodone d3	303.3	199.1	1.95	150	28	7	Positive
Hydromorphone	286.3	185	1.03	150	28	7	Positive
Hydromorphone	286.3	128	1.03	150	68	7	Positive
Hydromorphone d3	289.3	185	1.01	155	28	7	Positive
Morphine	286.3	165	0.86	145	68	7	Positive
Morphine	286.3	152	0.86	145	44	7	Positive
Morphine d6	292.3	152	0.84	155	72	7	Positive
Oxycodone	316.3	298.1	1.8	120	16	7	Positive
Oxycodone	316.3	241.1	1.8	120	28	7	Positive
Oxycodone d6	322.4	218.1	1.76	130	48	7	Positive
Oxymorphone	302.3	284.1	0.91	130	16	7	Positive
Oxymorphone	302.3	227	0.91	130	24	7	Positive
Oxymorphone d3	305.3	201.1	0.91	125	48	7	Positive
Tramadol	264.2	58	2.59	80	12	7	Positive
Tramadol	264.2	42.5	2.59	80	40	7	Positive
Tramadol d3	268.3	58	2.58	95	12	7	Positive

LC-MS/MS = liquid chromatography tandem mass spectrometry; MRM = multiple reaction monitoring.

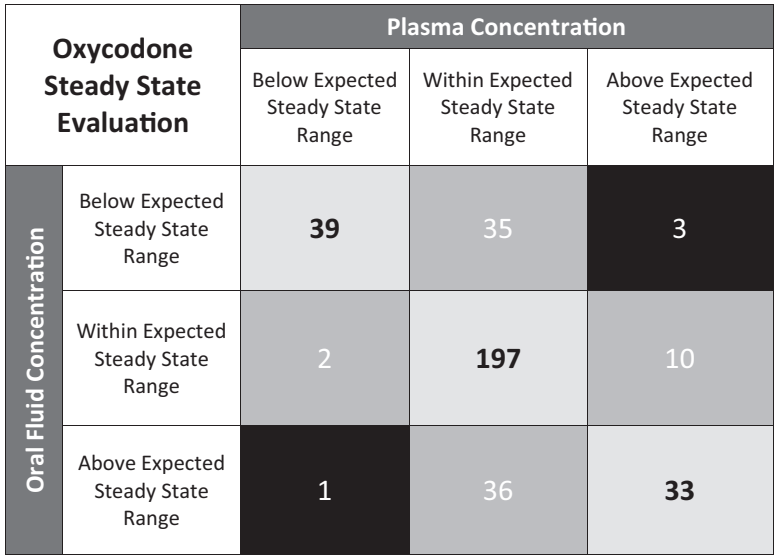

Figure 2 Distribution of oxycodone steady state range evaluation of paired plasma and oral fluid samples.

novel practice; however, the concept of steady state assessment is the foundation of therapeutic drug monitoring (TDM) in blood. TDM has been practiced and well accepted for many years by clinicians as a tool to help ensure patients are achieving analgesia without experiencing unwanted adverse effects or reaching toxic drug levels. Traditional TDM helps ensure that a patient maintains a consistent and targeted blood drug level that the clinician desires [23–26]. The use of oral fluid as a means of steady state evaluation can serve as a similar patient assessment tool, capable of providing oral fluid drug testing information that in many cases is reflective of what would be observed in blood TDM. This new medication monitoring approach, utilizing oral fluid as an alternative

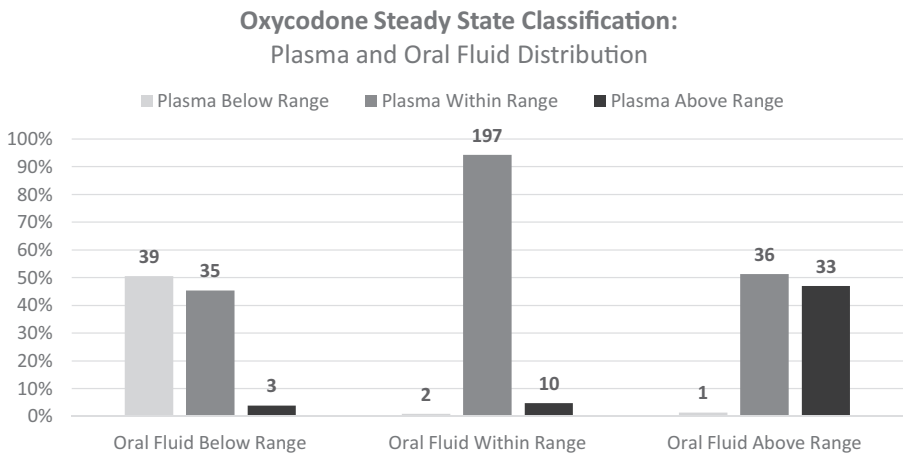

Figure 3 Distribution of steady state range classification between paired plasma and oral fluid samples.

matrix to correlate drug levels to expected steady state ranges, lessens the need for phlebotomists and invasive blood draws, highlighting oral fluid as a highly capable and promising matrix for clinical drug testing.

Inclusion parameters for the study were established to help ensure patients providing paired specimens were at steady state; however, the open study design does not guarantee consistent dosing. If a patient was not adhering to his or her dosing regimen exactly as directed, the measured drug concentration no longer has a predictable relationship with the expected steady state range, in blood or oral fluid. Thus, patients prescribed oxycodone PRN, along with patients prescribed multiple formulations of oxycodone for flare-ups, were not applicable for the study. Despite this open study design, 75.6% of donors resulted in the same oxycodone steady state classification regardless of whether plasma or oral fluid was evaluated. The majority of the agreement observed was due to oxycodone concentrations in both matrices falling within the respective expected steady state range, suggesting the population to be more compliant with chronic oxycodone prescription regimens than not. The 20.2% of samples (72) that fell outside the expected range in both matrices may have previously been considered consistent drug tests because chronically prescribed oxycodone was detected; however, assessment of steady state suggests otherwise.

Comparison of the results of the oral fluid steady state classifications with paired plasma classification controls permitted evaluation of the performance of this novel test [27]. A false positive result was defined as an oral fluid classification that did not agree with its paired plasma control classification. For example, the plasma samples fell within the expected plasma steady state range in 268 patients. One hundred ninety-seven corresponding oral fluid samples also fell within the expected oral fluid steady state range. The remaining 71 corresponding oral fluid samples fell outside range, either above the steady state maximum oral fluid concentration or below the steady state minimum oral fluid concentration. Plasma samples fell below the expected plasma steady state range in 42 patients, while 39 corresponding oral fluid samples agreed. Similarly, plasma samples fell above the expected plasma steady state range in 46 patients, while 33 corresponding oral fluid samples agreed. Thus, the positive predictive values, or the precision of oral fluid oxycodone steady state classification falling within, below, or above range, are 73.5%, 92.8%, and 71.7%, respectively. Summing the scenarios where the oral fluid classification agreed with the paired plasma control classification yields a total of 75.6% overall accuracy for oral fluid steady state analysis as 197 paired samples were both classified as within range in both matrices, 39 paired samples fell below range in both matrices, and 33 paired samples fell above range in both matrices.

The 24.4% overall disagreement observed between plasma and oral fluid steady state assessment can be a result of various contributing factors, including the patient not adhering to the dosing regimen, lack of steady state, inaccurate sample collection procedures, metabolic considerations, genetic differences, drug-drug interactions, or health status. Furthermore, the nearly equivalent distribution of disagreement due to oral fluid concentrations falling below range, while plasma fell within range (35) and oral fluid concentrations fell above range, while plasma fell within range (36), emphasizes the importance of proper oral fluid sample collection. Disagreement due to oral fluid concentrations falling below range may be a result of inadequate specimen volume collected, while inaccurate salivary pH determination can result in significant shifts, both higher and lower, in oral fluid drug concentration and steady state range. Emphasis on proper oral fluid collection technique, improved collection devices, and pH reading capabilities will help this discrepancy in future studies. Furthermore, a controlled dosing study to ensure steady state is achieved would likely improve the data as the

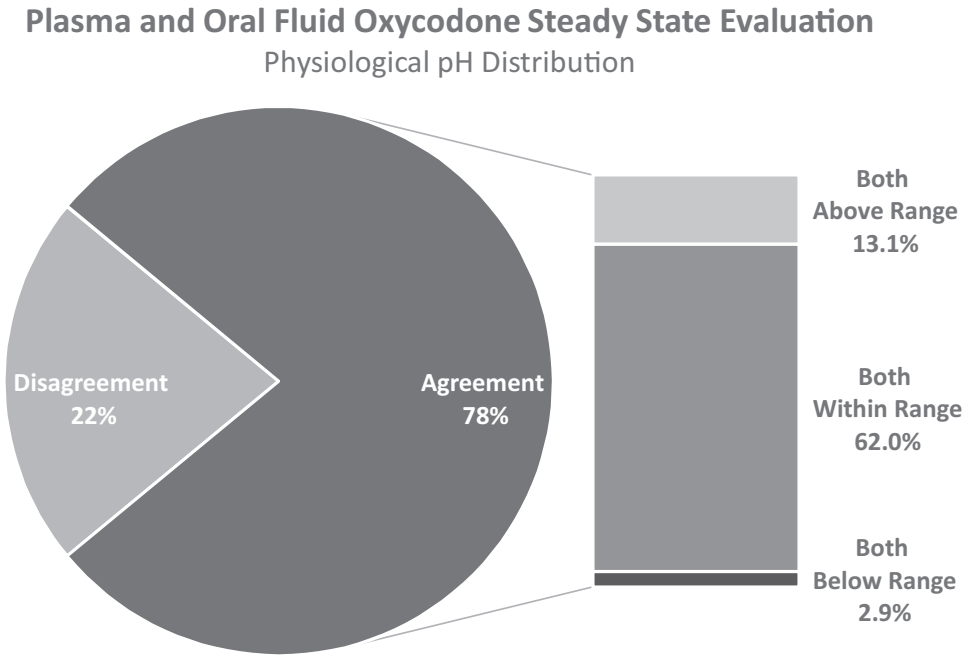

Figure 4 Distribution of agreement observed between oral fluid and plasma steady state classification within expected physiological salivary pH range.

true pain population tested in this study introduces variability in the interpretation of steady state pharmacokinetics with even slightly inconsistent dosing.

Interestingly, 65.5% (57) of the disagreeing samples had salivary pH measurements recorded outside the normal human salivary pH range. Salivary pH typically ranges from 6.2–7.6, with 6.7 being the average pH in healthy individuals. As the oral cavity maintains a near neutral pH range of 6.7–7.3 [28], the salivary pH measurements falling far outside this typical physiological range were likely a result of collection issues, including but not limited to collector error, inadequate waiting period after consumption of foods or drinks, or inaccurate pH measurement. As salivary pH plays a major role in drug transfer into oral fluid, accurate salivary pH measurement at the time of sample collection and proper oral fluid collection protocol is of great importance. Isolation of the 137 paired samples with salivary pH measurements falling within the normal expected salivary pH range revealed an increased 78.1% agreement (107 paired samples) between the two matrices and respective steady state ranges (Figure 4).

Proof of concept studies expanding the use of this algorithm are underway applying the same model for patients chronically prescribed morphine, hydrocodone, hydromorphone, oxymorphone, fentanyl, and tramadol. Preliminary results reveal similar correlation between plasma and oral fluid steady state classifications. Extension of the algorithm to further support these opioids, as well as to evaluate other commonly chronically prescribed pain medications, is ongoing with potentially broad application.

Conclusions

In this study, we describe the development of a novel prescription drug monitoring tool called Comprehensive Oral fluid Rx Evaluation. CORE is the first drug monitoring method to correlate oral fluid drug concentrations to steady state blood plasma drug levels, providing patient-specific insight surrounding chronic dosing. This novel application of pharmacokinetic principles expands the utility of oral fluid drug testing by providing a mechanism to help monitor steady state drug levels without requiring invasive blood collection. The agreement observed between the paired samples in this study establishes oral fluid as a viable alternative for steady state oxycodone prescription monitoring. As an individualized medication monitoring tool, CORE provides clinicians with additional knowledge to help assess prescription regimen adherence, open patient dialogue, and enhance clinical assessment in effort to combat the escalating opioid epidemic.

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