Correlation of Saliva Codeine Concentrations with Plasma Concentrations after Oral Codeine Administration

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Abstract

A clinical study was designed to determine if there was a predictable relationship between saliva and plasma codeine concentrations. Drug-free volunteers (n = 17) were administered a 30-mg dose of liquid codeine phosphate. Plasma and saliva specimens were collected at various times for 24 h after administration. Plasma and saliva were analyzed for codeine and morphine by positive-ion chemical ionization gas chromatography–mass spectrometry. The plasma codeine concentrations peaked between 30 min and 2 h after administration and ranged from 19 to 74 ng/mL with a mean of 46 ng/mL. Despite decontamination procedures, elevated saliva codeine concentrations were detected at the early collection times because of contamination of the oral cavity from the liquid codeine. Codeine concentrations in the 15-min specimens ranged from 690 ng/mL to over 15,000 ng/mL. After the initial 2-h period, the mean codeine saliva concentrations declined at a rate similar to that observed in the plasma, but remained 3 to 4 times greater than the plasma concentrations. During the elimination phase, half-life estimates for codeine in plasma and saliva were found to be equivalent, 2.6 and 2.9 h, respectively. However, the area under the curve (AUC) estimate for codeine in saliva was 13 times greater than the plasma AUC. Contamination of the saliva resulted in elevated saliva/plasma (S/P) concentration ratios for the first 1 to 2 h after drug administration. Consequently, S/P ratios in specimens collected in the first 15 to 30 min ranged from 75 to 2580. However, after the absorption phase, a significant correlation between saliva and plasma concentrations was observed (r = 0.809, p < 0.05) and mean S/P ratios remained constant (mean = 3.7). Although small changes in saliva pH were predicted to produce profound changes in the S/P ratios for codeine, this was not observed in the current study. Therefore, saliva codeine concentrations could be used to estimate plasma concentrations through the use of the S/P ratio once the oral contamination has been eliminated. However, these estimates should be made cautiously. One must ensure that oral contamination is not a factor. Also, as with blood-drug concentrations, considerable intersubject variability was observed.

Introduction

Recently, the use of biological specimens other than blood and urine for the detection and quantitation of drugs has been the focus of substantial scientific attention and research (1). For example, numerous protocols have been developed for the collection and detection of drugs in hair (2–5). The testing of drugs in sweat with commercially available absorbent patches, has been instituted in many criminal justice programs (6,7). Saliva is an additional biological specimen that has utility in drug testing. There are several potential advantages to saliva as a testing specimen. Saliva can be harvested by simple collection protocols that are noninvasive and can be collected under direct observation, eliminating concerns about sample adulteration and ensuring sample identity. Saliva is a blood filtrate and relatively free of blood constituents; therefore, it is easily processed for testing by conventional drug screening and confirmation methods.

Several studies have reported detecting therapeutic drugs in saliva (8–11). Examples of therapeutic drugs and drug classes that have been detected in saliva include ethosuximide, carbamazepine, phenobarbital, and other barbiturates, phenytoin, primidone, and theophylline (8); chlorpropamide, tolbutamide, and propranolol (9); benzodiazepines, ethanol, lithium, and methaqualone (10); antidepressants, salicylates, ibuprofen, cyclosporin, digoxin, lidocaine, quinidine, and many others (11). Drugs of abuse have also been detected in saliva. These include amphetamine(s), cannabinoids, cocaine, opioids, inhalants, lysergic acid diethylamide, and phencyclidine (12,13).
Much of the pharmacokinetic and pharmacodynamic research reported on therapeutic and abused drugs focuses on drugs in serum or plasma. Because saliva is a filtrate of the blood, saliva-drug concentrations may reflect blood-drug concentrations. If this is true, then saliva would be an extremely valuable specimen not only for the detection of drugs, but also for interpretative purposes. For example, it could be used in the criminal justice system, impaired-driving cases, postaccident testing, and for treatment compliance and therapeutic drug monitoring. Also, if saliva/plasma (S/P) concentration ratios were predictable, then the data bases of plasma pharmacokinetic, physiological, and behavioral data could be used to support interpretation of saliva drug concentrations.

Many of the disadvantages of saliva as a drug-testing specimen are attributable to our lack of scientific understanding of the pharmacokinetics and disposition of drugs into saliva. Much remains to be learned about how drugs and their metabolites are transferred from the blood into saliva, and a better understanding of mechanism(s) of this disposition is needed. Reported here is a controlled clinical study of 17 subjects designed to determine if codeine and morphine can be detected in saliva following single-dose administration and to determine the relationship between codeine concentrations in plasma and saliva.

Materials and Methods

Chemicals and reagents

Codeine, codeine-d₃, morphine, and morphine-d₃ reference solutions (1 mg/mL in methanol) were obtained from Radian Corp. (Austin, TX). Codeine phosphoric acid monohydrate were obtained from Alltech-Applied Science (State College, PA). Codeine phosphate oral liquid (30 mg/10 mL) was prepared by the Pharmacy Department of the University of Utah Health Sciences Center for administration to human subjects. Bond Elut Certify™ extraction columns were obtained from Varian (Harbor City, CA). Clean Screen® ZSDAU020 extraction columns were purchased from United Chemical Technologies, Inc. (Bristol, PA). Trifluoroacetic anhydride (TFAA) was obtained from Pierce Chemical (Rockford, IL); acetone, methanol, methylene chloride, and isopropanol (high performance liquid chromatographic [HPLC] grade) were obtained from Burdick & Jackson (Muskegon, MI); and ultra-high-purity helium was obtained from Mountain Airgas (Salt Lake City, UT). All other chemicals were reagent-grade and were obtained from Mallinckrodt Chemical Works (St. Louis, MO). All drug solutions were prepared in HPLC-grade methanol or distilled water as indicated.

Human subjects and study protocol

Seventeen human subjects were recruited by advertisement and by word-of-mouth at the University of Utah Health Sciences Center to participate in a study approved by the Institutional Review Board. Subjects were required to sign informed consent and be drug free prior to entering the study. To ensure that the subjects were drug free, urinalysis drug tests were performed for the following drugs: amphetamines, opiates, benzoylcodeine, cocaine, 9-carboxy-∆₉-tetrahydrocannabinol, benzodiazepines, and phencyclidine using EMIT® (Syva Corp., Palo Alto, CA). Subjects were excluded if they had taken any medications containing opiates during the preceding six months or if they had a history of acute or chronic illnesses.

Part of this comprehensive clinical study was designed to assess codeine incorporation in hair following chronic dosing. During that part of the study, subjects were administered codeine phosphate in oral liquid doses of 30 mg 3 times daily for 5 days (total dose, 450 mg). For the portion of the study reported here, the subjects were admitted to the Clinical Research Center at the University of Utah Health Sciences Center on the evening of the sixth study day for the pharmacokinetic study. The following morning, the subjects were given a single 30-mg dose of liquid codeine phosphate. The codeine dose was administered under direct supervision. The subjects brushed their teeth with toothpaste and/or vigorously rinsed their mouths following drug administration and prior to saliva collection. Blood (10 mL) was collected in heparinized tubes at the following times: predose; 15, 30, and 60 min; and 2, 4, 6, 8, 10, 12, and 24 h. Plasma was separated from the blood by centrifugation and stored at -20°C until analysis. Saliva was collected at the same time points by having the subjects "spit" into 5-mL inert polyethylene tubes. The pH of the saliva was recorded at the time of collection, and the samples were then stored at -20°C until analysis.

Calibrator and control preparation

Reference solutions of codeine and morphine were combined and diluted with methanol to obtain stock solutions containing 10 ng/µL and 1.0 ng/µL. These stock solutions were used to prepare calibrators. Saliva calibration curves were prepared and contained the following concentrations of codeine and morphine: 0.0, 5.0, 10.0, 25.0, 50.0, 100.0, 200.0, 400.0, and 500.0 ng/mL. A similar procedure was used to make separate stock solutions of codeine and morphine for preparation of quality-control (QC) samples. Batches of QC samples were prepared in saliva at 5.0 and 250.0 ng/mL, aliquoted into silanized glass tubes in 0.5 mL volumes, and stored at -20°C until analysis. For the plasma analysis, QC samples were prepared in plasma at 50.0 and 100.0 ng/mL, aliquoted in 2.0 mL volumes, and stored at -20°C until analysis. Concentrated internal standard solutions were combined and diluted in methanol to achieve a final concentration of 1.0 ng/µL of codeine-d₃ and morphine-d₃.

Sample preparation and analysis

Saliva. Drug-free saliva was collected from healthy volunteers and stored at -4°C until use. Aliquots (0.5 mL) of calibrators, controls and samples were transferred to labeled and silanized glass tubes. Twenty-five microliters of codeine-d₃ and morphine-d₃ (25 ng) were added to each tube. Four milliliters of distilled water, and then 2 mL of 0.1M phosphate buffer (pH 6.0) were added. The specimens were mixed and then centrifuged at 2000 x g for 10 min. Clean Screen ZSDAU020 solid-phase extraction columns were conditioned with methanol (3 mL), distilled water (3 mL), and phosphate buffer (1 mL). Supernatants

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of the specimens were added to the appropriately labeled SPE column. The columns were washed with distilled water (2 mL), 0.1 M acetate buffer (pH 4.5, 2 mL), and methanol (3 mL). Codeine and morphine were eluted with 3 mL methylene chloride/isopropanol (80:20) containing 3% ammonium hydroxide. The eluates were evaporated to dryness at < 40°C under a stream of nitrogen. The dried extracts were reconstituted in 100 μL chloroform, derivatized with TFAA (100 μL) for 30 min at 70°C, and evaporated to dryness at < 40°C under a stream of nitrogen. Derivatized extracts were reconstituted in 50 μL of ethyl acetate and analyzed on a Finnigan Mat 4500 gas chromatograph–mass spectrometer (GC–MS) (Finnigan Mat, San Jose, CA) using positive-ion chemical ionization. One microliter of reconstituted residue was injected onto the column, and the instrument was operated in the splitless mode. Methane–ammonia was used as the reagent gas, and helium as the carrier gas. The column was a DB-1 (15 m × 0.32 mm × 0.25 μm) capillary column (J&W Scientific, Folsom, CA). The initial column temperature of 135°C was held for 0.5 min and then programmed to 300°C at the rate of 18°C/min. The final temperature was held for 1 min. Temperatures of the injection port, interface, and ionizer were 250°C, 250°C, and 130°C, respectively. The MH+ ion for each analyte was monitored with masses at m/z 396, 399, 478, and 481 for trifluoroacetyl derivatives of codeine, codeine-d3, morphine, and morphine-d3, respectively. Peak-height ratios of codeine and morphine to their respective internal standards were calculated and the concentration of each analyte in the subject samples was determined by comparing the analyte response ratio to the least-squares equations generated from peak-height ratios of the calibrators. The standard curves were linear from 5 to 1500 ng/mL (r > 0.98) for codeine and morphine. The limits of detection (LOD) and quantitation (LOQ) were determined using serial dilutions of each injection (n = 5). The LOQ was the lowest concentration with a signal-to-noise (S/N) ratio of 3 or greater for each calibration data point after 2 h. The terminal half-life (t1/2) was estimated from 0.693/k.

Results and Discussion

Several oral fluids combine to constitute what is commonly referred to as “saliva,” “whole saliva,” or “oral fluids” (16). These fluids are excreted by the major salivary glands with some contribution from minor glands and gingival crevices. Saliva is an ultrafiltrate of blood; therefore, the matrix is less

![Figure 1](https://example.com/figure1.png)
complex than blood or plasma and easily prepared for drug screening and confirmation. With decreased interferences from endogenous constituents found in other matrices such as blood, smaller specimen volumes and lower LODs and LOQs can be achieved for drugs in saliva. Only 0.5 mL of saliva was needed for the saliva GC-MS assay, and a LOQ of 5 ng/mL and a LOD of 1 ng/mL were routinely achieved. Figure 1 shows a GC–MS chromatogram of a saliva specimen containing 5 ng/mL of codeine.

One objective of this study was to determine if codeine or morphine could be detected in saliva following a single oral dose. The time course for the appearance and disappearance of codeine in plasma and saliva is shown in Figure 2. The figure shows the mean codeine concentration for 17 subjects at each time point. No codeine or morphine was detected in the pre-dose plasma or saliva specimens for any of the subjects. Morphine was not detected in any of the plasma specimens. After the oral administration, the plasma codeine concentration peaked between 30 min and 2 h (mean = 30 min) at concentrations ranging from 19 to 74 ng/mL with a mean of 46 ng/mL. Plasma concentrations declined rapidly approaching the LOD for the assay (1 ng/mL) within 12 h. No codeine was detected in any of the plasma specimens collected 24 h after drug administration. In a previous study in which a similar dose of liquid codeine phosphate was administered, greater codeine and morphine plasma concentrations were observed (17). Both studies followed the same dosing protocol, except the pharmacokinetic portion was performed immediately following the last dose of chronic codeine administration in the previous study. In the current study, a one-day “wash-out” period was inserted between the chronic dosing protocol and the pharmacokinetic study to ensure that the plasma and saliva specimens were drug-free prior to the last dose of codeine. Because no wash-out period occurred in the Wilkins et al. (17) study, their reported codeine concentrations exceeded those reported here. The chronic codeine administration in this study was used as part of a related study on the incorporation of codeine into hair (unpublished data).

Codeine (13) reported that saliva heroin and its metabolites, 6-acetylmorphine (6-AM) and morphine, were “highly elevated” compared with plasma concentrations for the first hour after intranasal heroin administration. Figure 2 demonstrates that the same phenomenon was observed in this study. Elevated saliva codeine concentrations were detected at early collection times. Contamination of the oral cavity with codeine from the oral administration was evident in the saliva specimens collected for at least the first hour after administration. Codeine concentrations in the 15-min saliva specimens ranged from 690 ng/mL to over 15,000 ng/mL. The rapid decline in the mean saliva codeine concentration observed in the first 2 h following administration was the result of elimination of codeine from the oral cavity by “natural cleansing” and does not reflect metabolism or redistribution of the codeine. After the initial 2-h period, the mean codeine saliva concentration appeared to decline at a rate similar to that observed in the plasma (Figure 2). However, the mean saliva codeine concentrations remained 3–4 times greater than the plasma concentrations throughout the 24-h interval. Although subjects who brushed their teeth generally had lower saliva codeine concentrations, there was no significant difference in the concentrations between subjects who brushed their teeth and those who rinsed vigorously. Interferences from the toothpaste were not observed in the analysis of codeine or morphine in saliva.

Even though the slope of the decay curves for the plasma and saliva concentrations were similar, significant differences were observed in the detection times for codeine in the two specimens because of the greater saliva concentrations. Codeine was detected in the 24-h saliva specimens from 11 of the 17 subjects. The concentrations were below the LOQ for the assay (5 ng/mL). The saliva from one subject contained 5 ng/mL of codeine at 24 h. No codeine was detected at 24 h in any plasma samples. Morphine (< 5 ng/mL) was detected in three saliva specimens collected 15 or 30 min postadministration, but was not detected in any plasma samples.

Estimates of the elimination rate constant, $\text{t}_1/2$, and AUC for codeine in plasma and saliva are listed in Table I. Half-life estimates for codeine in plasma and saliva appear to be equivalent, 2.6 and 2.9 h, respectively. These estimates were consistent with those reported by Wilkins et al. (17) and Rollins et al. (18) for oral doses of codeine. In the study by Wilkins et al. (17) after a 30-mg dose, the plasma $\text{t}_1/2$ for males was reported to be 2.4 ± 0.76 h and 2.9 ± 0.32 h in females. Rollins et al. (18)

![Figure 2. The mean concentrations of codeine in saliva and plasma after oral codeine administration (n = 17).](image-url)
reported a plasma $t_{1/2}$ estimate of 2.36 h in male subjects administered 60 and 120 mg codeine. Studies involving administration of other drugs of abuse have reported variations in half-life estimates between saliva and plasma. Cone et al. (19) reported similar saliva and plasma $t_{1/2}$ estimates for cocaine administered intravenously (34.7 and 34.9 min, respectively). In contrast, Jenkins et al. (20) observed differing pharmacokinetic results with cocaine and heroin in saliva versus plasma. The saliva $t_{1/2}$ of heroin after smoking was reported to be approximately 14 to 60 times longer than blood and 2 to 208 times longer after intravenous administration, but only two subjects were included in the study. For cocaine ($n = 7$), Jenkins et al. (20) reported that the $t_{1/2}$ was shorter in saliva compared to plasma after smoking (52 versus 113 min).

Although the $t_{1/2}$ estimates for codeine were similar in saliva and plasma, the AUC estimate for codeine in saliva was 13 times greater than the plasma AUC. This was partially due to contamination of the oral cavity during the first 2 h after drug administration. In addition, codeine saliva concentrations exceeded plasma concentrations throughout the 24-h interval. However, this is an advantage of saliva as a specimen for drug testing because increased saliva concentrations resulted in longer detection times.

Another objective of the study was to determine if there was a predictable relationship between the saliva and plasma codeine concentrations. As shown in Figure 3, saliva codeine concentrations were correlated to plasma codeine concentrations for time $\geq$ 2 h ($r = 0.809, p < 0.05$). This correlation indicates that saliva codeine concentrations may be predictors of plasma codeine concentrations. However, because of the oral contamination, no correlation was observed for saliva and plasma codeine concentrations if the specimens collected in the first hour after drug administration were included in the evaluation ($r = 0.036$). The average time for elimination of oral contamination in the 17 subjects was approximately 2 h. As shown in Figure 3, higher codeine concentrations did not correlate as well because oral contamination remained in some of the subjects. Typically, saliva codeine concentrations greater than 100 ng/mL and plasma concentrations greater than 30 ng/mL were observed at the 2-h collection time. These data are consistent with other investigators who have reported a significant correlation between saliva and plasma drug concentrations. Thompson et al. (21) reported that plasma and saliva cocaine concentrations correlated significantly ($p < 0.001$) in a study in which three doses of cocaine were administered intravenously. Cone et al. (19) also reported a significant correlation between cocaine concentrations in saliva and plasma ($r = 0.89, p < 0.01$) after intravenous (IV) administration.

To further assess whether saliva codeine concentrations...
could be used to estimate plasma codeine concentrations, saliva/plasma concentration (S/P) ratios were calculated for the 17 subjects. Table II shows the mean plasma and saliva codeine concentrations with the corresponding S/P ratios. Contamination of the saliva from the liquid codeine produced elevated S/P ratios for at least the first hour after codeine administration. S/P ratios in specimens collected at 15 and 30 min ranged from 75 to 2580. At 1 h, the S/P ratios were still elevated because of oral contamination, but after 2 h, the contamination was not a factor in most subjects and the S/P remained constant with a mean ratio of 3.7 (Figure 4). These data are consistent with those of Sharp et al. (22) who administered 30-mg oral doses of codeine phosphate to study subjects. These investigators reported codeine S/P ratios ranged from 2.0 to 6.6 with a mean of 3.3. Other investigators have also demonstrated that there may be a predictable relationship between other drug concentration(s) in saliva and plasma. Wan et al. (23) reported a study in which 10 mg of amphetamine (as free base) was administered to four subjects. Following the absorption phase, the S/P ratio was 2.76. A number of articles have reported detecting cocaine or its metabolites in saliva (21,24,25). Saliva cocaine concentrations were found to parallel those found in the plasma (21). S/P ratios ranged from 0.5 to 2.96 with an overall mean of 1.25. Cone et al. (26) compared saliva cocaine concentrations following intravenous, intranasal and smoked administration. S/P ratios ranged from 1.3 to 10.1 following the IV administration. S/P ratios following the intranasal and smoked administration were generally higher than those after IV administration. Jenkins et al. (20) compared heroin concentrations in saliva and blood after administering the drug intravenously and by smoking (two subjects). Salivato-blood (S/B) concentration ratios were > 5 at all time points following smoked administration. Following IV administration, S/B ratios were always less than 2.

A wide variety of methods are used to collect saliva. Collection protocols may have an effect on saliva drug concentrations. We observed oral contamination even when subjects were instructed to cleanse their oral cavities by brushing their teeth or vigorous rinsing of their mouths. In addition, Cone (13) observed oral contamination from smoking and intranasal drug administration. Some collection methods involve stimulating saliva production, but others target collection of nonstimulated saliva. Nonstimulated saliva can be collected by "spitting" into containers or by the draining method. Draining is performed by allowing saliva to drip from the mouth into a collection container (27). Techniques to collect stimulated saliva include chewing paraffin wax, Teflon®, rubber bands, or gum (9,27-30). A lemon drop or citric acid crystals can also be placed in the mouth to provide a gustatory stimulus for saliva production (9,27,29). Saliva collected by stimulation may differ in composition from saliva collected by spitting because of changes in saliva flow rate. As saliva flow rate increases, the concentration of bicarbonate increases. Therefore, saliva pH increases, and this may affect the saliva drug concentration in a pH-dependent fashion. Salivary pH in normal individuals is usually between 6.2 and 7.4 (30). The pH of stimulated saliva is reported to fall within a narrow range around 7.4. The pH of nonstimulated saliva is reported to be more variable (22). An uncontrolled saliva collection method was used in this study in which subjects merely "spit" into an inert container without stimulating saliva production. The time needed for collection of the saliva specimen (1-2 mL) ranged from 3 to 5 min. Even under the uncontrolled collection conditions used in this study, a narrow range for the saliva pH was observed in most of the specimens. The pH of the specimens ranged from 6.0 to 8.0, but only eight specimens had a pH above 7.0.

As discussed, the pH of the saliva may be an important factor in the saliva-drug concentrations. For basic drugs, as the pH decreases, a greater concentration of drug will be ionized and the salivary concentration will increase. The theoretical S/P ratio for a particular drug can be estimated by the following mathematical model based on the Henderson-Hasselbach equation (31):

$$S/P = \frac{1 + 10^{(pK_a - pH_s)} * f_p}{1 + 10^{(pK_a - pH_p)} * f_s}$$

Eq. 1

where pHs and pHp are the pH of saliva and plasma, and fp and fs are the fraction of unbound drug in plasma and saliva. Therefore, small changes in saliva pH should result in profound changes in the S/P (22). For codeine (pK_a 8.2), the theoretical S/P at pH 6.0 is 20. However, at pH 7.0 it is only 2.1. In this study, the observed S/P ratios at pH 6.0 were not as high as the theoretical S/P ratios predicted by Eq. 1 (except within the first hour of drug administration when oral contamination was still present). The observed mean S/P was 4.7 at pH 6.0, 3.4 at pH 7.0, and 1.8 at pH 8.0. Although there was a large inter- and intrasubject variability observed for the S/P ratios (Figure 5), the mean S/P ratio decreased with increasing pH as predicted by Eq. 1. The decrease was not as dramatic as predicted by the model.

![Figure 5. Saliva/plasma (S/P) codeine concentration ratios as a function of pH. The mean S/P ratios were 4.7 at pH 6.0, 3.4 at pH 7.0, and 1.8 at pH 8.0.](image-url)
Conclusions

There are several advantages to the use of saliva as a specimen for drug testing. Saliva can be easily and noninvasively collected under direct observation. This eliminates the concerns about specimen integrity and identity often associated with urine collections. One to two milliliters of saliva can be collected in 3–5 min, and small specimen volumes can be used in the GC–MS analysis. In this study, peak plasma codeine concentrations ranged from 19 to 74 ng/mL and were < 1 ng/mL by 12 h. However, peak saliva codeine concentrations ranged from 690 to 15,000 ng/mL, and codeine was detected for 24 h in 12 of the 17 subjects. Therefore, the detection time for codeine in saliva was at least 12 h longer than in plasma. A major disadvantage of saliva drug testing is the potential for contamination of the oral cavity when the drug is administered orally, intranasally, or by smoking. Elevated S/P ratios have been reported for 1 h as blood-drug concentrations, there may be considerable intersubject variability even in controlled clinical settings. Additional methods (effective for all drugs) need to be investigated to remove oral contamination. Several collection devices are commercially available to harvest saliva. These may collect stimulated or nonstimulated oral fluids and may have unpredictable effects on the observed saliva-drug concentration. Therefore, the effect of the device on S/P ratios and our ability to estimate plasma-drug concentrations need to be investigated for each device and drug.

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