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Oral fluid cocaine and benzoylecgonine concentrations following controlled intravenous cocaine administration

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ABSTRACT

Limited oral fluid (OF) pharmacokinetic data collected with commercially available collection devices after controlled cocaine administration hinder OF result interpretations. Ten cocaine-using adults provided OF, collected with Oral-Eze® (OE) and StatSure Saliva Sampler™ (SS) devices, an hour prior to and up to 69 h after 25 mg intravenous (IV) cocaine administration. Cocaine and benzoylecgonine (BE) were quantified by a validated 2D-GC-MS method. Large inter-subject variability was observed. Cocaine was detected in OF in the first 0.17 h sample after IV administration, with much more rapid elimination than BE. OE observed C_{max} median (range) concentrations were 932 (394–1574) μg/L for cocaine and 248 (96.9–953) μg/L for BE. SS observed cocaine and BE C_{max} median (range) concentrations trended lower at 732 (83.3–1892) μg/L and 360 (77.2–836) μg/L, respectively. OE and SS cocaine OF detection times were 12.5 and 6.5 h and for BE 30.5 and 28.0 h, respectively at 1 μg/L. There were no significant pharmacokinetic differences between OE and SS OF collection devices, except cocaine half-life was significantly shorter in SS OF specimens. This difference could be attributed to differences in stabilizing buffers present in OF collection devices, which may affect cocaine stability in OF specimens, or decreased recovery from collection pads. Both OE and SS OF collection devices were effective in monitoring cocaine and metabolite concentrations with similar detection windows. Furthermore, we demonstrated that different confirmatory OF cutoffs can be selected to produce shorter or longer cocaine and metabolite detection windows to address specific needs of clinical and forensic drug testing programs.

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1. Introduction

Despite declining cocaine use prevalence in the general population, cocaine remains a widely used illicit drug in Europe (3.4 million users) [1] and the United States (1.5 million users) [2], behind only cannabis and methamphetamine [3]. Cocaine was the second most prevalent illicit drug (after cannabis) in the general driving population (0.42%), in Europe, [4] and the second most prevalent drug in nighttime drivers (1.4%) in the United States [5].

Alternative matrices, such as oral fluid (OF), are increasingly employed for detecting recent drug consumption due to non-invasive and observed collection, no need for same-sex collectors, and little potential for adulteration, dilution and substitution compared to urine [6–9]. OF cocaine concentrations were significantly correlated to those in plasma [10–13] and blood [14], making OF an attractive matrix for estimating cocaine-associated impairment and windows of detection. However, studies have demonstrated large inter- and intra-subject variability in OF to plasma ratios precluding calculating one concentration from the other [10,15]. Detection windows vary based on dose, analyte, administration route, drug intake frequency, cutoffs, and OF collection methods. Ideal drug detection windows differ depending upon the monitoring purpose. For driving under the influence of drugs (DUID) programs, detection windows should mirror the period of impairing effects; however, for workplace and pain management drug testing, longer detection windows are ideal due to widely separated specimen collections [16].

Cocaine pharmacokinetics are well studied in blood, plasma, and urine after various administration routes, but less is known about cocaine disposition in OF following controlled drug

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administration. Previous studies investigated OF cocaine and metabolite concentrations following controlled intravenous (IV) [12,13,17–21], smoking (SM) [18–21], intranasal (IN) [18,20,21], oral [21,22], and subcutaneous (SC) administration [10]; however, only three studies examined cocaine and metabolite OF pharmacokinetics [10,20,22], and none evaluated commercially available OF collection devices containing stabilizing and elution buffers. Furthermore, cocaine and metabolite detection windows are needed for recently published US Substance Abuse and Mental Health Services Administration (SAMHSA) National Laboratory Certification Program (NLCP) Mandatory Guidelines for federally-mandated oral fluid testing [23] and established Driving Under the Influence of Drugs, Alcohol and Medicines (DRUID) OF guidelines [24].

Cocaine was previously quantified in OF collected via citric-acid stimulated expectoration between 4.1–17.7 h following 25 mg IV, 32 mg IN, 42 mg SM, and 75 mg/70 kg and 150 mg/70 kg SC cocaine administration [10,21]. For benzoylecgonine (BE), the primary inactive cocaine metabolite, OF detection times ranged from 5.0–47 h. Following repeated oral cocaine administration (375–2000 mg), OF cocaine and BE were identified up to 21.2 and 50.0 h, respectively [21], indicating extended windows of detection with repeated dosing. It is unclear if OF collected with various commercially available devices, containing different elution and stabilization buffers, will exhibit similar cocaine concentration time profiles and kinetics over time. SAMHSA and DRUID proposed confirmatory OF cocaine cutoff concentrations of 8 and 10 μg/L, respectively [23,24], and 8 and 10 μg/L for BE. Eight μg/L also was recommended for suspected drug-impaired driving cases [25], and a 10 μg/L OF cocaine concentration was suggested by the Talloires recommendations [26].

The aims of this study were to characterize for the first time cocaine and BE OF pharmacokinetics collected with the Oral-Eze® (OE) and StatSure Saliva Sampler™ (SS) devices (two of the most commonly used commercial devices) following controlled IV cocaine administration. Additionally, we investigated detection windows with different OF collection devices at the recommended SAMHSA and DRUID OF testing guidelines.

2. Materials and methods

2.1. Participants

Participants provided written informed consent for this NIDA Institutional Review Board and Food and Drug Administration-approved study. Eligibility criteria included healthy adults ages 18-50 years who smoked or used IV cocaine for at least six months and at least three times per month during the three months prior to screening. Exclusion criteria included pregnant or nursing women; current physical dependence on any drug other than cocaine, caffeine, or nicotine; current clinically significant medical or psychiatric disorder; hemoglobin less than 12.5 g/dL or blood donation within eight weeks of study entry; current hypertension or blood pressure readings consistently above 140 mm Hg systolic or 90 mm Hg diastolic while at rest; heart rate consistently above 90 or below 50 bpm while at rest; abnormal 12-lead ECG; history of clinically significant adverse reaction to cocaine, acetazolamide, or quinine; or interest in drug abuse treatment within three months of study screening.

2.2. Drug administration

Participants resided on a secure research unit for 13 days and 12 nights, and received a single dose of 25 mg IV cocaine through a peripheral venous catheter on three separate days (Days 1, 5, and 10). Cocaine was administered alone on Day 1, in combination with oral acetazolamide on Day 5, and with oral quinine on Day 10. The study's primary aims were to evaluate potential pharmacodynamic and pharmacokinetic interactions between cocaine and acetazolamide and quinine, as they are being considered as medication compliance markers for cocaine use disorder treatment pharmacotherapies, similar to a study performed with oxycodone and quinine by Babalonis et al. [27].

2.3. Oral fluid specimen collection

OF was collected with either the Oral-Eze® (Quest Diagnostics) or StatSure Saliva Sampler™ (StatSure Diagnostic Systems) devices by placing the absorptive pad under the tongue until the volume-adequacy indicator turned blue, indicating 1 mL OF was collected, or 5 min had elapsed, whichever occurred first. OF was collected with a single device type prior to and following each IV cocaine dose in each participant. All participants had OF collected with each device type. OE collection tubes contained 2 mL stabilizing buffer, yielding a 3-fold OF dilution, whereas SS tubes contained 1 mL buffer for a 2-fold dilution. Following manufacturer's recommendations, the pad was removed and placed in the stabilizing buffer and left at room temperature (OE) or 4 °C (SS) for ≥ 12 h for drug elution. Serum separators depressed into the collection tube were utilized to facilitate decanting into a 3.6 mL Nunc® CryoTube®, with samples stored refrigerated at 4 °C prior to analysis. The majority of OF specimens were analyzed within 4 months, although all specimen analysis was complete within 8 months. No oral intake or smoking was permitted 10 min before OF collection at −1.0, 0.17, 0.5, 1, 1.5, 2, 3, 4, 6.5, 9.5, 12.5 and 21 h from dosing. Additional collections were obtained at 28 (Day 10 only), 33 (Day 1 only), 45 and 69 h (Days 1 and 5) post-administration.

2.4. Quantification of cocaine and benzoylecgonine in oral fluid

Cocaine and BE OF were quantified with modifications of a previously validated venous blood analytical method [28]. Calibrators were prepared at drug concentrations from 1–100 μg/L in 0.75 mL (OE: 0.25 mL blank OF + 0.5 mL OE stabilizing buffer) or 0.5 mL (SS: 0.25 mL blank OF + 0.25 mL SS buffer) solutions at the same dilutions as authentic specimens, therefore, accounting for the dilution factor. Quality controls (QCs) were prepared at 3, 25, and 75 μg/L in the same manner as calibrators, although from different standard ampoules. Briefly, 25 μL internal standard (IS) (250 μg/L D_3-cocaine and D_8-BE) were added to either 0.75 or 0.5 mL OF with 2 mL phosphate buffer (pH 6). After vortexing and centrifugation, the filtrate was decanted onto preconditioned UCT Clean Screen DAU 200 mg 10 mL SPE cartridges. Columns were washed (water, 0.1 M hydrochloric acid, methanol), dried for 20 min, and eluted into conical glass centrifuge tubes with dichloromethane:isopropanol (80:20, v/v prepared for 100 mL) mixed with 2 mL ammonium hydroxide. After evaporating to dryness, samples were derivatized with 20 μL ethyl acetate:MTBSTFA + 1% t-BDMS (50:50 v/v) for 40 min at 70 °C. The derivatized extracts (2 μL) were analyzed by an electron impact two-dimensional (2D) GC-MS method [28] with oven temperature program modifications for a total run time of 18.05 min (Supplemental Table 1). Instrument parameters were described in detail previously [28] and are outlined in Supplemental Table 1. The upper limit of linearity was 100 μg/L; specimens exceeding this limit were diluted with oral fluid and buffer mixture (2:1, v/v; 1:1 v/v), re-extracted and analyzed.

2.5. Method validation

OF methods were validated in accordance with the Scientific Working Group for Forensic Toxicology recommendations [29].