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Review

Sweat testing for cocaine, codeine and metabolites by gas chromatography–mass spectrometry

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Abstract

Sweat testing for drugs of abuse provides a convenient and considerably less invasive method for monitoring drug exposure than blood or urine. Numerous devices have been developed for collection of sweat specimens. The most common device in current use is the PharmChek™ Sweat Patch, which usually is worn by an individual for five to ten days. This device has been utilized in several field trials comparing sweat test results to conventional urinalysis and the results have been favorable. Two new Fast Patch devices have been developed and tested that allow rapid collection of sweat specimens. The Hand-held Fast Patch was applied to the palm of the hand and the Torso Fast Patch was applied to the abdomen or the sides of the trunk (flanks) of volunteer subjects participating in a research study. Both patches employed heat-induced sweat stimulation and a larger cellulose pad for increased drug collection. Sweat specimens were collected for 30 min at various times following administration of cocaine or codeine in controlled dosing studies. After patch removal, the cellulose pad was extracted with sodium acetate buffer, followed by solid-phase extraction. Extracts were derivatized and analyzed by gas chromatography mass spectrometry (GC–MS) simultaneously for cocaine, codeine and metabolites. Cocaine and codeine were the primary analytes detected in sweat. Peak cocaine and codeine concentrations ranged from 33 to 3579 ng/patch and 11 to 1123 ng/patch, respectively, across all doses for the Hand-held Patch compared to 22–1463 ng/patch and 12–360 ng/patch, respectively, for the Torso Fast Patch. Peak concentrations generally occurred 4.5–24 h after dosing. Both drugs could be detected for at least 48 h after dosing. Considerably smaller concentrations of metabolites of cocaine and codeine were also present in some patches. Generally, concentrations of cocaine and codeine were higher in sweat specimens collected with the Hand-held Fast Patch than for the Torso Fast Patch. Drug concentrations were also considerably higher than those reported for the PharmChek™ Sweat Patch. The predominance of cocaine and codeine in sweat over metabolites is consistent with earlier studies of cocaine and codeine secretion in sweat. Multiple mechanisms appear to be operative in determining the amount of drug and metabolite secreted in sweat including passive diffusion from blood into sweat glands and outward transdermal migration of the drug. Additional important factors are the physico-chemical properties of the drug analyte, specific characteristics of the sweat collection device, site of sweat collection and, in this study, the application of heat to increase the amount of drug secreted. Published by Elsevier Science B.V.

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1. Introduction

Analysis of biological fluids and tissues provides the most objective method for documenting human drug exposure. Currently, urine is the principal specimen used in the workplace, criminal justice and treatment drug testing programs; blood and/or urine are primarily used in driving under the influence, post mortem and emergency toxicology applications. A major advantage of blood and urine testing for drugs is that considerable research has been conducted on the characterization of drug detection times and how drug concentrations relate to pharmacological effects. A primary disadvantage of testing blood and urine is that many drugs and metabolites can generally only be detected for a few hours to days following drug use. Urine drug testing must occur two to three times per week for reliable detection of drug use. Additionally, specimen collection procedures for both blood and urine are invasive, and there is some risk of infection or injury during blood drawing. Other biological matrices such as sweat may possess certain advantages as well as disadvantages over blood and urine testing. Currently, there is interest in characterizing the benefits and limitations of sweat testing for detection of drug use by individuals.

Sweat secretion is an important homeostatic mechanism for maintaining a constant core body temperature. Sweat is secreted from eccrine and apocrine glands originating deep within the skin dermis and terminating in secretory ducts that empty onto the skin surface and into hair follicles. Sweat is secreted onto the skin surface and evaporates causing convectional body heat loss. The amount of sweat secreted is highly variable and dependent upon daily activity, emotional state and environmental temperature [1]. The average sweat pH from resting individuals is 5.8 [2]; however, above 31°C and following exercise, human sweat production may increase to as much as 3 l/h over short periods of time [3]. With the increased flow rate, sweat pH has been found to increase to between 6.1 and 6.7 [4].

Investigators have been studying the secretion of endogenous and exogenous chemicals in sweat for more than sixty years. There are several potential mechanisms by which drugs may be secreted in sweat including passive diffusion from blood into sweat glands and transdermal migration of drugs across the skin. Non-ionized basic drugs diffuse into

sweat and become ionized as a result of the lower pH of sweat as compared to blood (pH approximately 7.4). Ion trapping of basic drugs in sweat may therefore occur due to these pH differences.

Methods to collect drugs in sweat have included the use of gauze, cotton or filter paper to absorb sweat and the collection of liquid sweat in rubber gloves or plastic body bags [5]. Application of heat or chemicals (e.g. pilocarpine) has also been used to increase sweat production. Specialized collection devices have been developed to improve sweat collection and the recovery of drug analytes. In 1977, Phillips [6] devised an occlusive adhesive patch that trapped solute and water components in sweat providing a possible means to monitor patient compliance with therapeutic regimens. The patch consisted of an absorbent pad impregnated with sodium chloride crystals under a waterproof dressing. The investigators reported that the concentration of ethanol in the sweat of individuals consuming alcoholic beverages varied with the amount of ethanol consumed and the mean concentration of ethanol in the blood over an eight-day period. However, the patch was time-consuming to apply, uncomfortably large, prone to detachment and yielded a small volume of sweat for analysis. An improved smaller patch was designed; however, the results of the earlier alcohol study could not be confirmed. This occlusive sweat patch design was found to alter the steady-state pH of the skin, the types of bacteria that colonize the skin and the transport characteristics of the skin, producing skin irritation after approximately 24 h. Conner et al. [7] developed a transcutaneous chemical collection device modeled after the Phillips occlusive patch but attempted to reduce the back diffusion of analyte into the skin with the inclusion of binding chemicals in the patch.

A non-occlusive sweat collection device (patch) was developed by a commercial firm (Sudormed, Santa Ana, CA, USA) in 1990. During wearing of the patch, sweat solutes are concentrated in an absorbent collection pad, while water evaporates from the patch. A disadvantage of the non-occlusive design is that concentrations of analytes in sweat cannot be determined because it is not possible to measure the volume of secreted sweat. However, an extended wear period (usually seven days) is reported to be well-tolerated, and a cumulative record of drug exposure can be obtained [8]. The device consists of an adhesive layer on a thin transparent film of surgical dressing to which a rectangular absorbent pad is attached. Attempts to remove the patch prematurely or tamper with the device are readily visible to personnel trained to monitor the sweat patch. This device, marketed as the PharmChek™ Sweat Patch, is FDA-approved in the United States for the detection of drugs in sweat and is currently used to monitor illicit drug use in criminal justice settings.

Diverse methods of sweat collection have identified the presence of licit and illicit drugs including alcohol [9], amphetamine [10], cocaine [8,11], heroin [8,12], morphine [13], methadone [14], methamphetamine [13,15,16] and phencyclidine [17]. Low nanogram concentrations of cocaine extracted from perspiration stains of an alleged sexual assault victim were submitted in a forensic proceeding to implicate use of cocaine [18]. Controlled drug administration studies indicate that a single episode of cocaine use of 50 mg may be detected for up to seven days after drug exposure when monitoring use with the PharmChek™ Sweat Patch [19]. In this study, 50 or 126 mg of cocaine hydrochloride were administered intranasally to 18 male cocaine users and sweat was collected with sweat patches for varying periods up to seven days. Cocaine was the primary analyte identified in the patches. Benzoylecgonine, a cocaine metabolite, was also detected in many patches at concentrations that were approximately 10% of the parent drug. Cocaine was detected in most patches following drug exposure, although inter-dose and inter-subject variability precluded determination of drug dose or time of drug exposure. Henderson et al. [5] reported a 6:1 ratio of deuterated cocaine to deuterated benzoylecgonine in the hair and sweat of subjects who were administered 0.3, 0.6 or 1.2 mg/kg of isotopically labeled cocaine intravenously or 0.4–11 mg/kg intranasally. Liquid sweat was collected using polyethylene shoulder length gloves after exercise. Deuterated cocaine levels in sweat as high as 50 μg/ml were found 1 h after intranasal administration of 0.6 mg/kg of D_5-cocaine. In another study, Henderson [20] reported cocaine concentrations greater than 100 ng/ml in sweat for up to 72 h after a single 2 mg/kg intranasal dose.

Following administration of single smoked, in-

travenous and intranasal doses of heroin and cocaine to humans, Cone et al. [8] identified heroin and cocaine as the primary analytes secreted in sweat collected on PharmChek™ Sweat Patches. Cocaine appeared in sweat within 1–2 h and peaked within 24 h in an apparent dose-dependent manner. Analysis of duplicate adjacent patches from individual subjects suggested that intra-subject variability was relatively low, whereas inter-subject variability was high. Trace amounts of cocaine could be detected in patches following intravenous dosing of as little as 1 mg. Lower concentrations of ecgonine methyl ester and benzoylecgonine were also identified, although only following larger doses. Heroin and 6-acetylmorphine (6AM) were detected in patches after intravenous heroin administration. Increasing 6AM concentrations and decreasing heroin concentrations in patches removed at later time points indicated that heroin may undergo hydrolysis in the patch. High inter-subject variability for opiate secretion in sweat was also documented following heroin administration.

Additional field studies with the PharmChek™ Sweat Patch have been conducted comparing the effectiveness of monitoring drug use by sweat and urine drug testing [21,22]. In two recent reports, the efficiency of sweat and urine testing for monitoring drug use in an outpatient methadone maintenance treatment program for opiate abuse was compared [23,24]. The results of thrice weekly urine drug tests (EIA cocaine and opiate cutoffs 300 ng/ml; gas chromatography mass spectrometry (GC–MS) cutoffs 150 ng/ml for benzoylecgonine, 300 ng/ml for morphine and codeine) were compared to seven day sweat patch test results (ELISA immunoassay cocaine and opiates cutoffs 10 ng/ml and GC–MS cutoffs 5 ng/ml for parent drug and metabolites). In 180 cases of matched sweat and urine specimens from 25 patients, the sweat immunoassay results for cocaine and opiates were found to be 92.2 and 75.6% accurate as compared to urine results. Sensitivities and specificities for cocaine detection were 98.4 and 76.9% and for opiate detection were 73.8 and 78.1%. The accuracy, sensitivity and specificity of sweat patch ELISA immunoassay results as compared to GC–MS results were 91.9, 91.4 and 94.9% for cocaine and 91.9, 92.6 and 88.9% for opiates. Cocaine was detected in over 99% of positive sweat patches with a mean GC–MS cocaine concentration of 823 ng/ml. In contrast, the mean benzoylecgonine and ecgonine methyl ester concentrations were 88 and 71 ng/ml. Lower mean opiate concentrations were found in sweat: heroin 4 ng/ml, 6-acetylmorphine (6AM) 12 ng/ml, morphine 11 ng/ml and codeine 12 ng/ml. Heroin was detected in one-quarter of all positive specimens, while 6AM, morphine and codeine were detected in more than three-quarters of all positive specimens. Analysis of sweat patches was found to provide an alternative method for objectively monitoring drug use and evaluating behavioral interventions in drug treatment programs.

In the present study, two new sweat collection devices recently developed by the Sudormed Corporation were evaluated in a controlled, clinical study to evaluate the disposition of cocaine, codeine and their metabolites in sweat. These new Fast Patches require only 30 min for sweat collection because they employ heat-induced sweat stimulation and a larger cellulose pad for increased drug collection. In this study, Torso Fast Patches were applied to the abdomen or flank, and Hand-held Fast Patches were affixed to the palm of the non-dominant hand. Sweat was collected periodically for 48 h following subcutaneous administration of 75 or 150 mg of cocaine hydrochloride/70 kg and oral administration of 60 or 120 mg of codeine sulfate/70 kg. A sensitive and specific dual derivatization (GC–MS) method was employed to simultaneously measure the concentration of cocaine and codeine analytes in sweat. This study is the first to evaluate the use of the Torso and Hand-held Fast Patches as drug collection devices following controlled cocaine and codeine administration in humans. This information should improve the interpretation of sweat drug test results and our understanding of the unique chemical and pharmacological information provided by the analysis of drugs in sweat.

2. Experimental

2.1. Study population

Three Africoid males and one Africoid female participated in a ten week inpatient study conducted at the Intramural Research Program, National Insti-

Table 1
Subject characteristics and self-reported drug use

Subject	Age (years)	Weight (Kg)	Drugs used in last 30 days	Duration of	
				longest cocaine use (years)	longest opiate use (years)
K	35	79.5	Cocaine, heroin, alcohol	5	14
M	40	65.0	Cocaine, heroin, marijuana, alcohol, nicotine	24	22
N	36	59.5	Cocaine, heroin, alcohol, nicotine	14	14
P	29	84.1	Cocaine, heroin, alcohol, nicotine	3	Single use

tute on Drug Abuse. All subjects provided written informed consent and were paid for their participation. Table 1 lists subject characteristics. All subjects had a history of cocaine and opioid use and were required to test positive for cocaine use by urinalysis prior to admission to the clinical ward. Detailed physical and psychological screening was performed to ensure subjects were healthy and without psychological abnormalities. Subjects were not physically dependent on drugs or medications with the possible exception of nicotine and caffeine. During the study, subjects resided on a secure ward, and urine drug testing was conducted to ensure compliance with study guidelines which forbade self-administration of drugs and over the counter medications. Urine testing was performed by immunoassay with EMIT II reagents (Behring Diagnostics, San Jose, CA, USA) for cocaine metabolite, amphetamines, opiates, cannabinoids, phencyclidine, barbiturates and benzodiazepines.

2.2. Drug administration

Cocaine hydrochloride for human administration was obtained from Mallinkrodt (St. Louis, MO, USA) and was prepared in saline for subcutaneous injection. Codeine sulfate for oral human administration was obtained from Roxane Laboratories (Columbus, OH, USA) and was prepared in polished lactose capsules (Amend Drug and Chemical Co., Irvington, NJ, USA). Subjects resided on the research unit for twenty days prior to the first scheduled drug administration to permit previously self-administered drugs to be cleared from the body. Three low doses of cocaine hydrochloride (75 mg/70 kg) and codeine sulfate (60 mg/70 kg) were administered in week four on alternating days according to the timeline illustrated in Fig. 1. Three high doses of cocaine hydrochloride (150 mg/70 kg) and codeine sulfate (120 mg/70 kg) were administered in week eight. Sweat specimens were collected for 30 min with the Torso and Hand-held Fast Patches for intervals up to 48 h after each drug administration. Subject P participated in only the low dose cocaine and codeine administrations.

2.3. Sweat collection

Sweat was collected from the palm with Sudormed Hand-held Fast Patches and from the torso (abdomen and flank) with Sudormed Torso Fast Patches. Briefly, the Hand-held (Fig. 2A) and Torso devices (Fig. 2B) consist of a co-laminate nylon, polyester (bi-ax) bag (Prism Technologies, San Antonio, TX, USA) prepared with food grade sodium acetate, a metallic activation disk in the bag and 0.003 mm thick medical grade, one ply cellulose pad attached to the bag by adhesive (3M Health Care, St. Paul, MN, USA) in the Torso Fast Patch and by dot labels (Avery Dennison Corp.) in the Hand-held Fast Patch. Prior to applying patches to study participants, 300 μl of deionized water was evenly applied to the cellulose pad to promote solubilization and absorption of drug. Patches were activated by flexing the metallic activation disk between the fingers. This generates a pressure wave which initiates sodium acetate crystallization. Patches were immediately applied to isopropanol-cleansed skin with the cellulose pad oriented adjacent to the skin. The Torso Fast Patch was affixed to the skin by adhesive located on the perimeter surface of the bag; the Hand-held Patch was placed on the palm, wrapped in polyethylene, and a hand brace (Bauer and Black, Becton Dickinson Consumer Products, Franklin

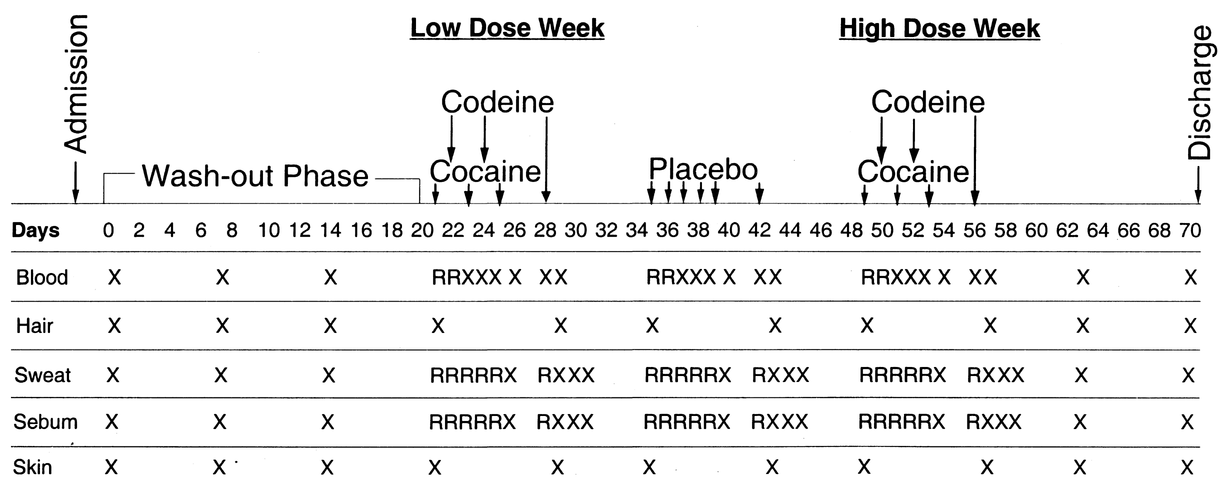

Fig. 1. Clinical study timeline for cocaine and codeine administration and sweat collection. X indicates a single specimen collection and R indicates multiple specimen collections during the day.

Lakes, NJ, USA) modified to fit the palm was applied. The crystallization process is exothermic, with patch heating element temperatures peaking (ca. 50.6°C) within 3–5 min. The temperature of the skin beneath the tissue reaches a maximum of ca. 39.4°C during the first 5 min that the patch is worn. This increase in skin temperature stimulates sweat production. After 5 min, the skin temperature gradually cools and is ca. 36.1°C 30 min after patch application. In this study, the patches were worn for 30 min to increase the amount of sweat collected and improve sensitivity. After removal of the patch, the cellulose pad was permitted to air-dry for 3–5 min and carefully removed from the patch with forceps. Cellulose pads were stored in labeled plastic bags at −30°C until analysis.

2.4. Chemicals and reagents

Chemicals were obtained from the following sources: cocaine hydrochloride (Mallinkrodt, St Louis, MO, USA); benzoylecgonine, norcocaine hydrochloride, benzoylnorecgonine·0.125 H_2O, *m*- and *p*-hydroxycocaine·0.5 H_2O, *m*-hydroxybenzoylecgonine·0.5 H_2O and *p*-hydroxybenzoylecgonine·0.7 H_2O (Research Biochemicals International, Natrick, MA, USA); ecgonine methyl ester hydrochloride, [$^2H_3$]-ecgonine methyl ester hydrochloride·H_2O, [$^2H_3$]-cocaine, [$^2H_3$]-benzoylecgonine·4H_2O, [$^2H_3$]-codeine hydrochloride·2H_2O, codeine·PO_4, [$^2H_3$]-morphine hydrochloride·3H_2O, morphine sulfate, norcodeine hydrochloride·3H_2O, normorphine hydrochloride·H_2O (Sigma Chemicals, St Louis, MO, USA); [$^2H_3$]-codeine, [$^2H_3$]-monoacetylmorphine, monoacetylmorphine (Radian, Austin, TX, USA); cocaethylene, norcocaethylene·fumarate (Research Triangle Institute, Research Triangle Park, NC, USA); anhydroecgonine methyl ester·oxalate, ecgonine ethyl ester (Intramural Research Program, NIDA, Baltimore, MD, USA); and *N*,*O*-*bis*(trimethyl)trifluoroacetamide (BSTFA) with 1% trimethylchlorosilane (TMCS), *N*-methyl-*N*-(*tert.*-butyldimethylsilyl) trifluoroacetamide (MTBSTFA) with 1% *tert.*-butyldimethylchlorosilane (TBDMCS) (Pierce Chemical, Rockford, IL, USA). Solid phase extraction (SPE) columns (Clean Screen DAU, 200 mg-10 ml) and 12 ml filtration columns were obtained from United Chemical Technologies (Bristol, PA, USA). Methanol, methylene chloride, 2-propanol and acetonitrile were HPLC grade chemicals. All other chemicals were reagent grade.

2.5. Calibrators and controls

Calibrators and controls were prepared with unused drug-free Torso and Hand-held Fast Patches.

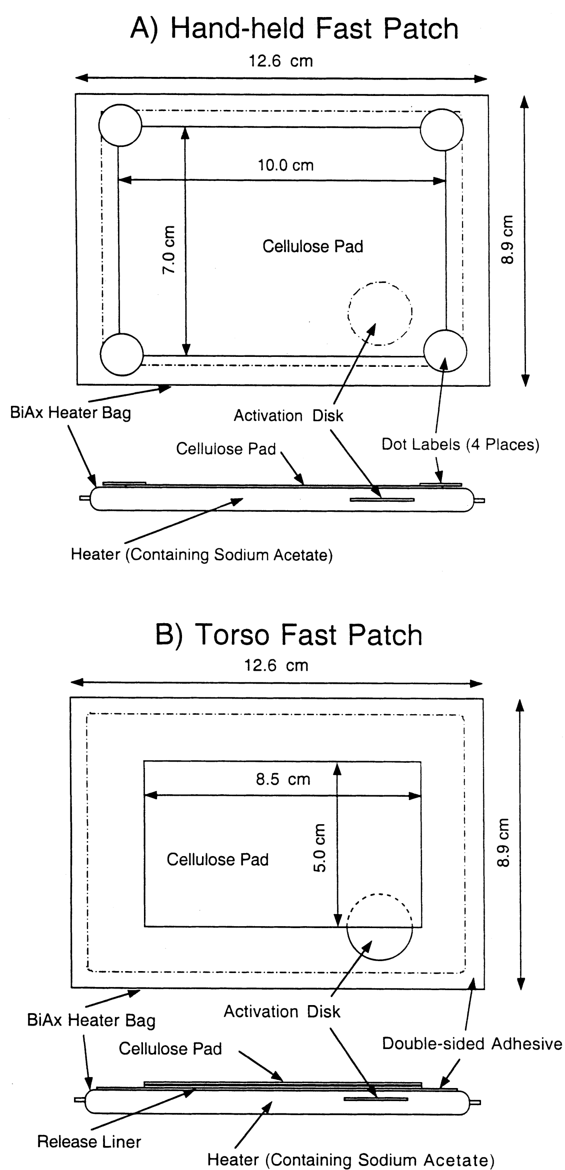

Fig. 2. Illustration of Hand-Held and Torso Fast Patches.

Deionized water (300 μl) was evenly aliquoted onto the cellulose pad of each patch, and the metallic disk in the heat pack was bent to initiate the heating process. At 3–5 min after patch activation, calibrator patches were prepared in duplicate at drug concentrations ranging from 0.5 to 1000 ng/patch for cocaine, codeine and their metabolites. The concentration of norcodeine, normorphine and 6-acetylmorphine in calibrators ranged from 1.0 to 500 ng/patch. Control patches were prepared from a different stock standard solution and spiked in duplicate at drug concentrations ranging from 0.5 to 500 ng/patch. Calibrators and controls were also prepared with internal standards (100 ng [$^{2}H_3$]-cocaine, [$^{2}H_3$]-benzoylecgonine, [$^{2}H_3$]-ecgonine methyl ester, [$^{2}H_3$]-codeine and [$^{2}H_3$]-morphine in 0.1 ml H_2O; 50 ng [$^{2}H_3$]-cocaethylene and [$^{2}H_3$]-6-acetylmorphine in 0.1 ml H_2O). After adding the drug solutions, the cellulose pads were allowed to dry.

2.6. Analysis of cocaine, codeine and metabolites in sweat

Calibrator, control and clinical samples were processed by placing the cellulose pads in 12 ml filtration columns that were sealed with polypropylene luer caps. Internal standards were added to columns containing clinical samples at the same concentration as that added to calibrators and controls. A 3 ml aliquot of 0.5 *M* sodium acetate buffer (pH 4.0) was added, the cellulose pad was allowed to remain immersed in this solution for 2 h at room temperature, and the buffer was eluted into 6 ml centrifuge tubes. This step was repeated twice using 1.5 ml of buffer and 30 min incubation intervals. Eluates were combined and processed by SPE according to a previously published method [25]. Following SPE, samples were evaporated to dryness under nitrogen in a water bath at 40°C. A 500 μl aliquot of acetonitrile was added and the tubes were vortex mixed. Samples were evaporated again under nitrogen in a water bath at 40°C, and a 20 μl aliquot of acetonitrile was added. The tubes were vortex mixed followed by centrifugation at 1500 rpm for 5 min. Samples were transferred to autosampler vials, and a 20 μl aliquot of MTBSTFA+1% TBDMCS was added. The vials were capped and placed in a heat block at 80°C for 15–20 min. The caps were removed and a 20 μl aliquot of BSTFA+1% TMCS was added. The vials were then re-capped and heated again at 80°C for 45 min.

The samples were analyzed by GC–MS in selected ion monitoring mode. The quantitating or target *m/z* ion selected for each analyte was as follows:

[$^2H_3$]-cocaine (185), [$^2H_3$]-benzoylecgonine (285), [$^2H_3$]-ecgonine methyl ester (185), [$^2H_3$]-cocaethylene (199), [$^2H_3$]-codeine (374), [$^2H_3$]-morphine (417), [$^2H_3$]-6-acetylmorphine (345), cocaine (182), benzoylecgonine (282), ecgonine methyl ester (182), codeine (371 or 178), morphine (414), anhydroecgonine methyl ester (152), ecgonine ethyl ester (282), cocaethylene (196), norcocaine (140), norcocaethylene (254), benzoylnorecgonine (446), *m*- and *p*-hydroxycocaine (182), *m*-and *p*-hydroxybenzoylecgonine (282), norcodeine (429), normorphine (529), and 6-monoacetyl morphine (342). (The quantitating ion employed for codeine analysis was m/z 371 for all specimens with the exception of one subject set in which there was an interfering coelutant identified. In this set m/z 178 was employed for quantitative analysis of codeine. The criteria for the limit of detection (LOD) and the limit of quantitation (LOQ) measurements were also met for this ion). A minimum of two qualifying ions were also selected for each internal standard and analyte. Fig. 3 illustrates a typical ion chromatogram for an extracted calibration patch containing 250 ng or 500 ng of analyte (Panel A), negative calibrator (Panel B), Hand-held Patch specimen (Panel C) and Torso Fast Patch (Panel D). Controls were analyzed in quadruplicate at a concentration range of 0.5–25 ng/patch to determine the LOD for each analyte. The LOD was defined as the concentration at which the analyte quantitating ion signal-to-noise ratio (determined by peak height) was >3/1 and 75% of controls had ion ratios within ±20% of those observed for 1.25–10 ng calibration standards. For cocaine, benzoylecgonine and ecgonine methyl ester, the LOD was ca. 1.25 ng/patch. The LOD for all other analytes ranged from 1.25–5.0 ng/patch. The

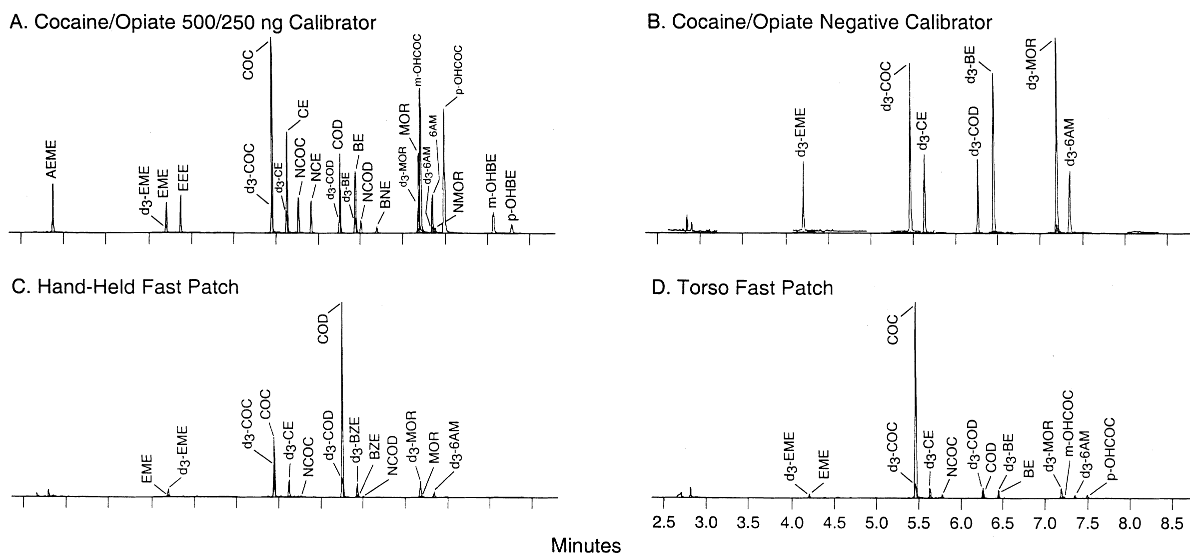

Fig. 3. GC–MS SIM recordings (superimposed) of a standard cocaine–codeine sweat patch extract, a drug-free control, a Hand-held Fast Patch and a Torso Fast Patch collected after cocaine and codeine administration. Panel A represents the responses for anhydroecgonine methyl ester (AEME, 250 ng), ecgonine methyl ester (EME, 500 ng), ecgonine ethyl ester (EEE, 250 ng), cocaine (COC, 500 ng), cocaethylene (CE, 250 ng), norcocaine (NCOC, 250 ng), norcocaethylene (NCE, 250 ng), codeine (COD, 500 ng), benzoylecgonine (BE, 500 ng), norcodeine (NCOD, 250 ng), benzoylnorecgonine (BNE, 250 ng), morphine (MOR, 500 ng), *m*-hydroxycocaine (*m*-OHCOC, 250 ng), 6-acetylmorphine (6AM, 250 ng), normorphine (NMOR, 250 ng), *p*-hydroxycocaine (*p*-OHCOC, 250 ng), *m*-hydroxybenzoylecgonine (*m*-OHBE, 250 ng), and *p*-hydroxybenzoylecgonine (*p*-OHBE, 250 ng) extracted from an unused patch. d_3-Ecgonine methyl ester (d_3-EME, 100 ng), d_3-cocaine (d_3-COC, 100 ng), d_3-cocaethylene (d_3-CE, 50 ng), d_3-codeine (d_3-COD, 100 ng), d_3-benzoylecgonine (d_3-BE, 100 ng), d_3-morphine (d_3-MOR, 100 ng) and d_3-6-acetylmorphine (d_3-6AM, 50 ng) were used as internal standards. Panel B represents the response for an extract from an unused sweat patch with a drug-free control. No cocaine or metabolites were detected. Panel C is an extract from a Hand-held Fast Patch collected 28.5 h after a 150 mg cocaine hydrochloride/70 kg subcutaneous dose and 4.5 h after a 120 mg codeine phosphate/70 kg oral dose. Panel D is an extract from a Torso Fast Patch collected 4.5 h after a 150 mg cocaine hydrochloride/70 kg subcutaneous dose and 28.5 h after a 120 mg codeine phosphate/70 kg oral dose.

LOQ definition included LOD criteria plus the requirement that 75% of the controls at a specific concentration quantitate was within ±25% of the target or expected concentration. One set of intra-assay precision and accuracy data for cocaine, codeine and major metabolites is listed in Table 2. For these analytes, the LOQ was ca. 2.5 ng/patch. The inter-assay CV values (*N*=6 runs X 2–4 replicates) for analytes were as follows: cocaine (10 ng/patch), 16.0%; benzoylecgonine (10 ng/patch), 15.0%; ecgonine methyl ester (10 ng/patch), 20.0%; ecgonine ethyl ester (5 ng/patch), 34.3%; anhydroecgonine methyl ester (10 ng/patch), 19.1%; cocaethylene (10 ng/patch), 11.1%; norcocaine (5 ng/patch), 19.0%; norcocaethylene (10 ng/patch), 15.0%; benzoylnorecgonine (10 ng/patch), 29.3%; *m*-hydroxycocaine (10 ng/patch), 12.5%; *p*-hydroxycocaine (10 ng/patch), 14.0%; *m*-hydroxybenzoylecgonine (10 ng/patch), 21.1%; *p*-hydroxybenzoylecgonine (10 ng/patch), 18.3%; codeine (12.5 ng/patch), 20.6%; morphine (12.5 ng/patch), 21.4%; norcodeine (12.5 ng/patch), 12.7%; normorphine (12.5 ng/patch), 27.0%; and monoacetylmorphine (12.5 ng/patch), 14.9%.

2.7. Instrumentation

Quantitative analyses were performed on a Hewlett–Packard 5890A gas chromatograph interfaced with a Hewlett–Packard 5972 mass selective detector or a Hewlett–Packard 6890 gas chromatograph interfaced with a Hewlett–Packard 5973 mass selective detector. A split-splitless capillary inlet system operated in the splitless mode and HP-1 fused-silica capillary columns (12 m×0.2 mm I.D., 0.33 μm film thickness) were utilized for the analyses. Chromatographic conditions have been previously published [26].

2.8. Recovery

Recovery studies were performed to determine the efficiency of the extraction assay (Table 2). Sample set A consisted of drug-free Torso Fast Patches (*N*=3) that were prepared with 25 ng of non-deuterated analytes (cocaine, benzoylecgonine, ecgonine methyl ester, ecgonine ethyl ester, anhydroecgonine methyl ester, norcocaine, *m*-hydroxycocaine, *p*-hydroxycocaine, *m*-hydroxybenzoylecgonine,

Table 2
Intra-assay accuracy and precision for cocaine, benzoylecgonine, ecgonine methyl ester, codeine and morphine[a]

Concentration	COC	EME	BZE	COD	MOR
1.25 ng/patch					
Mean	1.3	1.2	1.4	N.D.[c]	N.D.
Accuracy (%)	111.2	100.6	117.4	–	–
CV[b]	6.4	30.3	16.3	–	–
2.5 ng/patch					
Mean	2.5	2.4	2.2	1.7	1.8
Accuracy (%)	101.5	96.7	90.4	68.9	74.9
CV	2.6	6.6	10.7	22.5	25.2
5.0 ng/patch					
Mean	5.0	4.9	5.2	5.5	5.6
Accuracy (%)	101.0	98.4	105.0	111.1	112.5
CV	0.6	3.5	7.0	3.0	6.6
25 ng/patch					
Mean	25.0	24.5	25.1	22.1	22.1
Accuracy (%)	100.3	98.1	100.6	88.3	88.5
CV	0.3	4.4	0.7	5.1	2.8

COC=cocaine; EME=ecgonine methyl ester; BZE=benzoylecgonine; COD=codeine; MOR=morphine.
[a] Four replicate Fast Patches were prepared at each drug concentration.
[b] Coefficient of variation.
[c] Less than LOD.

p-hydroxybenzoylecgonine, benzoylnorecgonine, cocaethylene, norcocaethylene, codeine, norcodeine, morphine, normorphine and 6-monoacetylmorphine in 0.1 ml of H_2O) and 100 ng of internal standards ([$^2H_3$]-cocaine, [$^2H_3$]-benzoylecgonine, [$^2H_3$]-ecgonine methyl ester, [$^2H_3$]-codeine and [$^2H_3$]-morphine in 0.1 ml of H_2O; 50 ng [$^2H_3$]-cocaethylene and [$^2H_3$]-monoacetylmorphine in 0.1 ml of H_2O). The second set, B, of drug-free Torso Fast Patches ($N=3$) was prepared with 25 ng of non-deuterated analytes. All patches were extracted by adding 0.5 *M* sodium acetate buffer (pH 4.0) followed by SPE as described earlier. After SPE, internal standards were added to the elution solvent collected from sample set B. The elution solvent from all samples was evaporated followed by derivatization. Samples were then analyzed by GC–MS. The chromatographic peak area for each analyte and internal standard quantitating ion was determined. The analyte peak area divided by the internal standard peak area yielded a response ratio. The mean ratio for sample set B was divided by the mean ratio for set A to determine the recovery ratio. The recovery ratio was multiplied by 100 to calculate percentage recovery. Additional recovery studies were also performed by the same methods at the 50 ng non-deuterated analyte/patch level and are included in Table 3.

2.9. Linearity

Calibration curves for each analyte were constructed at two concentration ranges; 2.5–100 ng/patch and 100–1000 ng/patch. Linear regression analyses of clinical samples containing less than 100 ng of drug were performed employing the 2.5–100 ng/patch curves and those above 100 ng/patch were analyzed using the 100–1000 ng/patch curves. Linear regression analyses were also performed with calibration standards prepared with cocaine at concentrations ranging from 1000 to 3000 ng/patch. These calibration curves were used for quantitative analyses of clinical samples containing more than 1000 ng cocaine/patch. Correlation coefficients were typically greater than 0.99 with the exception of norcodeine and normorphine, where correlation coefficients ranged from 0.97 to 0.99.

3. Results

3.1. Cocaine secretion in sweat

3.1.1. Torso Fast Patches

Cocaine was the primary analyte detected in sweat collected with Torso Fast Patches, but no dose–

Table 3
Recovery of drug added to drug-free Fast Patch

Concentration (ng/patch)	Percentage recovery (Mean±SEM)					
	COC	*EME*	*BZE*	*EEE*	*NCOC*	*BNE*
25	91.5±8.8	55.7±2.9	89.8±5.7	63.3±2.8	90.3±9.6	84.0±19.8
50	103.6±4.7	63.1±4.3	95.7±4.0	60.1±6.4	79.7±3.5	87.6±22.5
	m-HOCOC	*p-HOCOC*	*m-HOBZE*	*p-HOBZE*	*AEME*	*CE*
25	82.5±10.9	101.9±7.2	63.3±2.3	79.4±7.6	48.3±1.0	106.6±4.0
50	75.1±12.0	96.6±18.0	52.8±4.0	63.1±36.8	46.2±1.2	98.8±13.1
	COD	*NCOD*	*MOR*	*NMOR*	*NCE*	*6AM*
25	90.3±14.5	82.4±26.3	72.2±8.9	57.7±9.3	102.8±3.6	100.2±0.9
50	99.6±1.3	91.5±24.3	93.3±10.6	50.1±11.1	83.8±13.0	95.1±11.6

COC=cocaine; EME=ecgonine methyl ester; BZE=benzoylecgonine; EEE=ecgonine ethyl ester; NCOC=norcocaine; BNE=benzoylnorecgonine; *m*-HOCOC=*m*-hydroxy cocaine; *p*-HOCOC=*p*-hydroxycocaine; AEME=anhydroecgonine methyl ester; CE=cocaethylene; NCE=norcocaethylene; MOR=morphine; NMOR=normorphine; COD=codeine; NCOD=norcodeine; 6AM=monoacetylmorphine.

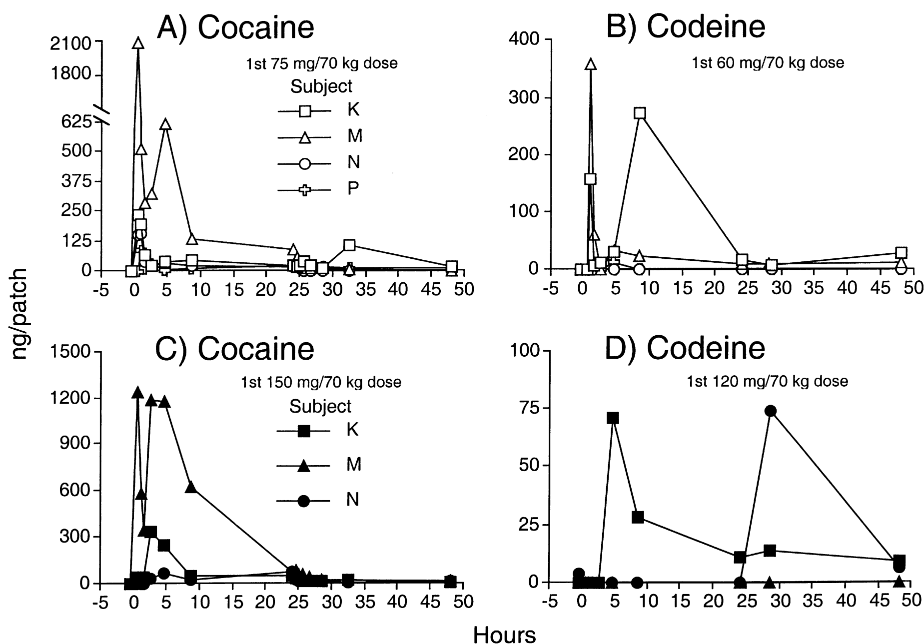

Fig. 4. Drug disposition in Torso Fast Patches following administration of three doses of cocaine hydrochloride at 75 mg/70 kg and at 150 mg/70 kg by the subcutaneous route and three doses of codeine sulfate at 60 mg/70 kg and at 120 mg/70 kg by the oral route to four volunteer subjects. Each drug administration was separated by a minimum of 48 h.

concentration relationship could be demonstrated. The time course of cocaine in sweat is illustrated in Fig. 4 (Panels A and C). Large intra- and inter-subject variability was also noted after both low and high doses. Ninety-one percent of the patches collected following cocaine administration were positive for cocaine and, in most cases, cocaine was detected in patches collected at 48 h post-dose. The time of the first detection of cocaine varied from 0.5 to 2.5 h. The highest concentrations of cocaine (as high as 2085 ng/patch after 75 mg/70 kg of cocaine hydrochloride was administered and 1463 ng/patch after the 150 mg/70 kg dose) were measured in patches collected up to 4.5 h after dosing. Peak cocaine concentrations for all subjects ranged from 22 to 2085 and 40 to 1463 ng/patch for the low and high doses respectively. Time to peak cocaine concentration was highly variable and ranged from 0.5 to 24 h following both doses.

Benzoylecgonine was detected in at least one patch collected from every subject following both low and high doses. However, it was detected in only 28% of the patches, at much lower concentrations and no correlation between cocaine concentrations and benzoylecgonine concentrations was observed. Peak benzoylecgonine concentration ranges were 3–44 ng/patch and 18–60 ng/patch for low and high doses respectively, and they occurred within the 24 h following drug administration.

Several minor metabolites were detected in torso patches collected from subjects M, N and P and included ecgonine methyl ester, norcocaine, *m*-hydroxycocaine, *p*-hydroxycocaine, benzoylnorecgonine and *m*- and *p*-hydroxybenzoylecgonine. With the exception of one patch, all patches positive for ecgonine methyl ester were collected from subject M. The majority of specimens positive for ecgonine methyl ester were collected following the 150 mg dose with a peak concentration of 171 ng/patch at 2.5 h after dosing. When ecgonine methyl ester was detected in sweat, it was generally in conjunction with high concentrations of cocaine (>282 ng/

patch), and ecgonine methyl ester concentrations were greater than benzoylecgonine concentrations. Norcocaine was detected in specimens collected from subjects M and N and was generally associated with peak or near-peak concentrations of cocaine. Concentrations did not exceed 60 ng/patch and were found to peak within 28.5 h. Low concentrations of other minor metabolites were detected as follows: *m*-hydroxycocaine (5–27 ng/patch, subjects M and N); *p*-hydroxycocaine (5–57 ng/patch, subjects M and N); benzoylnorecgonine (5–25 ng/patch, subject P); *m*-hydroxybenzoylecgonine (5–7 ng/patch, subject N); and *p*-hydroxybenzoylecgonine (30–33 ng/patch, subject N).

3.1.2. Hand-held Fast Patches

Cocaine was also the primary analyte detected in sweat collected with Hand-held Fast Patches. Again, there was no demonstrable correlation between drug concentration and dose. As seen in Fig. 5, intra- and inter-subject variability for sweat cocaine concentrations after the low and high doses were large. All patches collected during the 48 h following drug administration were positive for cocaine. The highest concentrations of cocaine (up to 739 ng/patch after 75 mg of cocaine hydrochloride/70 kg was administered and up to 3579 ng/patch after the 150 mg/70 kg dose) were measured in the first sweat patch collected 4.5 h after dosing. The mean peak cocaine concentrations after the first administration of the low and high doses in all subjects were 136 and 670 ng/patch, respectively. Peak cocaine concentrations following all drug administrations ranged from 33 to 739 ng/patch and from 150–3579 ng/patch for the low and high doses, respectively. Generally, peak cocaine concentrations were detected in the first or second patch collected after dosing (4.5 or 8.5 h).

Benzoylecgonine was detected in 69.4% of the patches and in specimens from all subjects. Specimens were also positive for benzoylecgonine following both the low and high doses. Peak benzoylecgonine concentrations ranged from 11 to 121 ng/patch and from 15 to 127 ng/patch for the low and high dose, respectively, and usually occurred within 24 h but occasionally 48 h after drug administration. Peak benzoylecgonine concentrations were generally detected in specimens containing peak cocaine concentrations or in the next specimen collected.

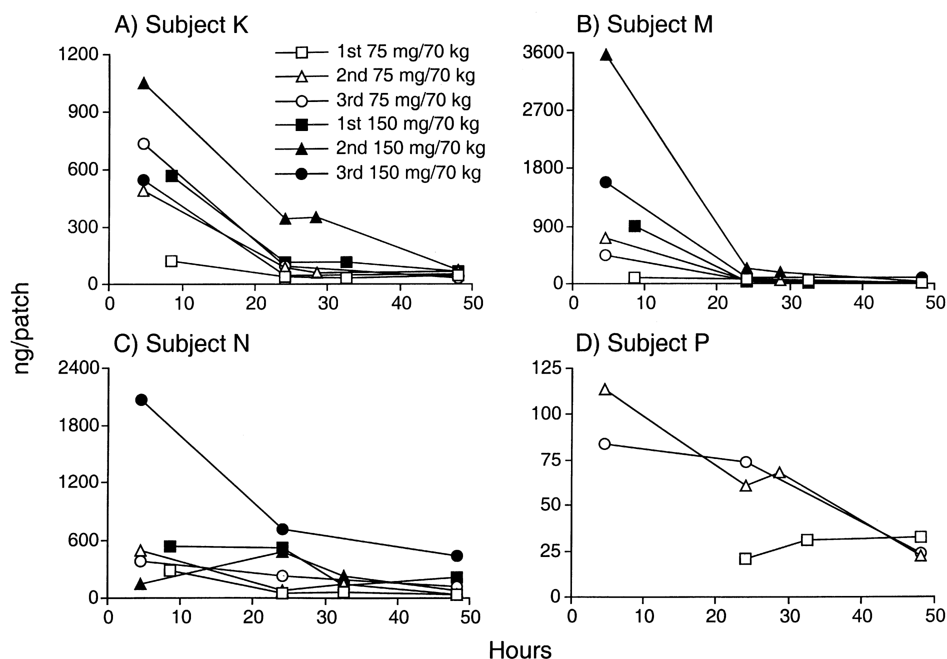

Fig. 5. Cocaine disposition in Hand-held Patches following administration of three doses of cocaine hydrochloride at 75 mg/70 kg and at 150 mg/70 kg by the subcutaneous route to four volunteer subjects. Each drug administration was separated by a minimum of 48 h.

Ecgonine methyl ester was detected in Fast Patches collected from subjects M and N only. Peak ecgonine methyl ester concentrations coincided with peak cocaine concentrations, ranging from 44 to 47 ng/patch (low dose) and from 40 to 595 ng/patch (high dose) and occurred within 24 h. However, unlike the case with the Torso Fast Patches, the ecgonine methyl ester concentrations did not always exceed the benzoylecgonine concentrations. Other minor metabolites were detected in specimens collected from subjects M, N and P. Norcocaine was detected following the low dose only in specimens collected from subject N and following the high dose in subjects M and N. Peak norcocaine concentrations generally occurred within 24 h of dosing, coincided with peak cocaine concentrations and ranged from 16 to 18 ng/patch after the low dose, and from 21 to 220 ng/patch after the high dose. Other minor metabolites detected in the Hand-held sweat patches included *m*-hydroxycocaine, *p*-hydroxycocaine, benzoylnorecgonine, *m*-hydroxybenzoylecgonine and *p*-hydroxybenzoylecgonine. Concentrations were generally less than 10% of the parent drug.

3.2. Codeine secretion in sweat

3.2.1. Torso Fast Patches

Codeine was the only opiate analyte detected in sweat collected with Torso Fast Patches. The time course of codeine in sweat is illustrated in Fig. 4 (Panels B and D). As with cocaine, no dose–concentration relationship could be demonstrated for codeine. Large intra- and inter-subject variability was also noted in codeine concentrations after both low and high doses. Sixty-three percent of the patches collected over the 48 h following all drug administrations were positive for codeine. However, codeine was not detected in sweat from all subjects following both doses. Sweat patches collected from Subject N after the 60 mg/70 kg doses and Subject M after the 120 mg/70 kg doses did not contain detectable concentrations of codeine. Peak codeine concentrations for all other 60 and 120 mg/70 kg doses ranged from 12 to 360 ng/patch and from 21 to 289 ng/patch, respectively, and mean peak codeine concentrations following the first administration of the low and high doses were 177 and 48 ng/patch, respectively. Although usually occurring within 4.5 h, peak codeine concentrations did occur up to 48 h post-dose. In most cases, sweat tested positive for codeine throughout 48 h.

3.2.2. Hand-held Fast Patches

Codeine was the primary analyte detected in sweat collected with Hand-held Fast Patches. There was no correlation between codeine dose and sweat codeine concentration. As seen in Fig. 6, there was large intra- and inter-subject variability after both low and high doses. Eighty-two percent of Hand-held Fast Patches collected during 48 h were positive for codeine. Codeine was detected in at least one patch from all subjects following both the low and high doses. Peak codeine concentrations after the 60 and 120 mg of codeine sulfate/70 kg doses ranged from 11 to 681 ng/patch and from 46 to 1123 ng/patch respectively. Mean peak codeine concentrations following the first administration of the low and high doses were 134 ng/patch and 99 ng/patch, respectively. Peak concentrations were noted 1.0–28.5 h after dosing. In all cases, codeine could still be identified in Hand-held Fast Patches 48 h after dosing. Unlike Torso Fast Patches, the codeine metabolites, norcodeine and morphine, were detected in 8.3 and 7.1% of Hand-held Fast Patches, respectively. Norcodeine was occasionally detected in sweat from subjects K and M at concentrations from 11 to 26 ng/patch at 4.5 h post-dose. Morphine was found in Subject N sweat patches collected after the 120 mg/70 kg dose at a peak concentration of 2 ng/patch within 24 h after dosing.

4. Discussion

Disposition of drugs into biological fluids and tissues is dependent upon a combination of pharmacological and chemical processes. Absorption and distribution processes deliver the parent drug to different tissues throughout the body. Biotransformation and excretion processes alter, reduce or eliminate parent drug and produce new chemical species that are generally less lipophilic than the original chemical species. Appearance of drug and metabolite in different biological matrices is further determined by numerous processes including blood flow to host tissue from which the matrix arises, protein binding

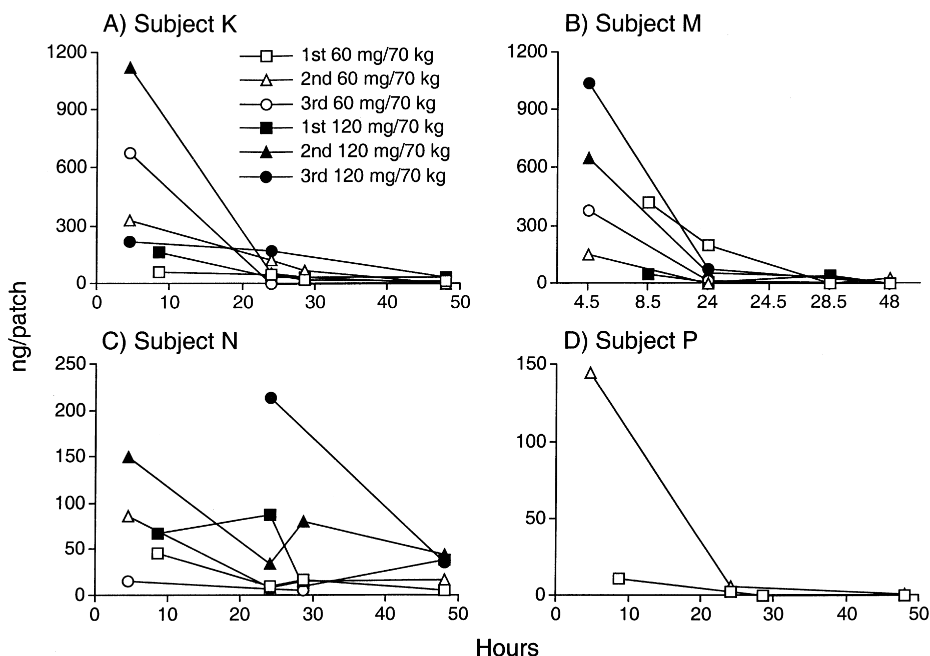

Fig. 6. Codeine disposition in Hand-held Patches following administration of three doses of codeine sulfate at 60 mg/70 kg and at 120 mg/70 kg by the oral route to four volunteer subjects. Each drug administration was separated by a minimum of 48 h.

and the chemical and physical properties of the drug and metabolite. For sweat, it appears that molecular mass, pK_a, degree of protein binding and lipophilicity primarily determine drug and metabolite disposition.

Blood flow to sweat glands, i.e., eccrine and apocrine glands, delivers the drug and the metabolite at their respective concentrations to these glands. Immediately following cocaine administration, the concentration of the parent drug in the blood is high, but declines rapidly as a result of cocaine's short half-life of approximately 1 h [27,28]. Cocaine is transformed primarily by hydrolysis to benzoylecgonine. Benzoylecgonine concentration in blood rises rapidly after drug administration and is sustained for a considerably longer period than that of the parent drug. Despite the longer half-life of benzoylecgonine (ca. 6–8 h) [28–30] and higher concentration, the primary analyte found in sweat is cocaine. Similarly, codeine, which is metabolized by a combination of oxidative pathways and conjugation, is the primary analyte in sweat. As a result of these considerations, it appears that the concentration of the drug in blood is not the major determinant of drug concentration in sweat. Passive diffusion from blood to tissues is commonly considered to be the major mechanism for appearance of drug in other tissues. The similar oil–water partition coefficients of cocaine and codeine (ca. 3 for octanol–water at 37°C (E. J. Cone, unpublished data)) and similar pK_a constants (8.6 for cocaine and 8.2 for codeine) [31] appear favorable for diffusion through the membranes surrounding the sweat glands.

Other mechanisms may also be operative in drug disposition processes that occur in sweat. The penetration of drug substances through the skin in both directions (from and to blood) has been studied. Skin is a protective physical barrier to the environment, thereby limiting exposure to many toxins. Also, skin has been demonstrated to be an active drug metabolizing organ [32–34] with multi-enzyme protein systems that are able to oxidize and conjugate drugs and endogenous compounds, albeit at a low rate of activity. The bilayer arrangement of polar lipids forms the basis for this effective barrier [35], although lipid soluble drugs can be transferred across skin and enter the general circulation, e.g., phencyclidine, nicotine and fentanyl. Drugs passively

diffuse through the skin based on the physico-chemical properties of the drug and the normal physiological and pathological conditions of the skin. The free base form of the drug is almost entirely responsible for permeation of the skin as shown in fentanyl and sufentanil studies [36]. Skin hydration, temperature, age, regional variations and pathological injuries affect skin permeability.

Passage of drugs through the skin in the opposite direction, outward transdermal migration, has also been studied in a few cases [37,38] and appears to be slow. In one study, Conner et al. [7] administered caffeine to human volunteers. Transcutaneous chemical collection devices were employed to study transcutaneous chemical migration. The amount of caffeine collected was linearly related to the plasma concentration–time curve (AUC). Sweating had a large contribution (40%) to transdermal collection in the early period (5.5 h) but much less (14%) at longer collection times (10 h). The multiple barriers that must be transversed by drugs undergoing outward diffusion (subcutaneous fat, dermis, epidermis and stratum corneum) are major impediments that serve to limit transdermal migration of drugs to the skin surface. In addition, the stratum corneum contains structures that may function as diffusion shunts, thus rendering three potentially distinct routes of penetration through the stratum corneum: hair follicles, sweat ducts and the unbroken stratum corneum [39]. Most studies on steady state drug transport through the skin support the contention that bulk diffusion pathway through the intact stratum corneum predominates over diffusion shunts [39]. However, shunt diffusion predominates until the steady state is reached. Delivery of high concentrations of the drug to the skin surface by sebum and sweat could produce a deposition on the stratum corneum and allow the skin to serve as a shallow drug depot. Leaching of the drug from sebum and skin could provide an additional pathway for drug entry into sweat.

The concentration of drug in sweat is also likely to be highly dependent upon the method, the site of collection and the type of device employed. In the present study, sweat collection with the Torso Fast Patches and the Hand-held Fast Patches resulted in peak cocaine concentrations that were several-fold greater than those reported for the PharmChek™ Sweat Patches [8,19], but were somewhat similar to those collected for liquid sweat [20,40]. The use of heat in the Fast Patches to stimulate sweat production can produce changes in liquid sweat volume, pH and electrolyte composition [41]. Sweat solute concentrations are determined by the amount of solute secreted into the secretory coil and by the subsequent ductal modification-absorption or secretion. These are influenced by the sweat rate due to the effect of the rate of absorption on the efficiency of ductal modification [42]. Clearly these changes could affect rates of cocaine and metabolite secretion in sweat.

Changing the site of collection also produced differences in cocaine secretion in sweat. Cocaine concentrations in sweat collected from the Hand-held Fast Patches were more than two-fold greater than found in the Torso Fast Patch. The ratio of cocaine to metabolites in the Fast Patches were similar to earlier reports in that cocaine concentration consistently predominated over metabolite concentrations. Ecgonine methyl ester concentrations in sweat consistently exceeded benzoylecgonine concentrations in the Torso Fast Patch, with benzoylecgonine being detected in only 28% of the patches. Benzoylecgonine was detected in higher concentrations and more frequently in the Hand-held Fast Patches compared to the Torso Fast Patches. These differences in cocaine and metabolite disposition for the two Fast Patches are likely to be due to differences in the anatomy and physiology of the skin on the palm of the hand compared to the torso skin. The skin on the palm is thicker and contains an abundance of sweat glands. The density of sweat glands on the palm of the hand is at least twice as great as that found on the torso of the body [43]. The thicker skin on the palm and the absence of sebaceous glands on the palm may also affect drug disposition in Hand-held and Torso Fast Patches.

The disposition of cocaine in sweat collected by the Fast Patches is generally consistent with earlier studies [5,8,19,40,44–51]. Cocaine predominates in concentration followed by ecgonine methyl ester and benzoylecgonine. The high concentration of cocaine relative to benzoylecgonine is distinctly different than that found in urine specimens following cocaine administration. Cone et al. [52] reported that benzoylecgonine excretion in urine accounted for 16–

39% of the administered dose followed in abundance by ecgonine methyl ester, which accounted for 7-15%. Cocaine excretion in urine accounted for only 0.5–1% of the dose. The predominance of cocaine in sweat necessitated development of new screening methods for sweat that were targeted for cocaine rather than benzoylecgonine. Spiehler et al. [46] reported the development of an enzyme immunoassay (EIA) involving microtiter plates for the analysis of cocaine in sweat. The assay demonstrated a cross-reactivity for cocaine of 102%, relative to 100% for benzoylecgonine and 148% for cocaethylene, a metabolite of cocaine produced when users ingest alcohol with cocaine. Combination of the EIA with GC–MS confirmation provided a sensitivity of 86% and specificity of 97% for specimens collected with the PharmChek™ Sweat Patch from volunteers who were dosed with known amounts of cocaine in a research study. The authors concluded that the combination of EIA and GC–MS analysis of the patch was sufficiently sensitive to detect cocaine in sweat after minimal cocaine use.

Codeine concentrations measured by the Fast Patches tended to be higher than those reported by Kintz et al. [53] for the PharmChek™ Sweat Patch following oral administration of a single 90 mg dose of codeine. Kintz et al. reported concentrations in the range of 2–127 ng/patch with peak concentrations occurring during the 12–24 h period. In addition, they found that concentrations varied by a magnitude of 1–3 in sweat collections from different parts of the torso. They also noted high inter-subject variability, concluding that the PharmChek™ Sweat Patch is more suitable for qualitative than quantitative testing. In the present study, large inter-subject variability was also found for codeine with the Fast Patches. In a separate study, Kintz et al. [54] attempted to compare results of the PharmChek™ Sweat Patch to sweat testing with the Drugwipe, a non instrument-based immunodiagnostic assay for the detection of drugs on surfaces. Following administration of 60 mg of codeine sulfate, sweat samples were collected with Drugwipe and PharmChek™ Sweat Patches at similar times. The sweat patches tested positive for codeine by GC–MS in the range of 3–124 ng/patch. The Drugwipe assay appeared to be less sensitive with several negative test results at times when the patch tested positive.

Sweat testing for other opioids has also provided variable results in analyte concentration. Henderson and Wilson attempted to determine optimal methadone dosage by monitoring the concentration of methadone in sweat [14]. Intra- and inter-subject variability was found to be too high to predict the required methadone dosage from the methadone concentration in sweat. Cone et al. [8] used the PharmChek™ Sweat Patch to test for opiates following single administrations of heroin. The heroin metabolite, 6AM, appeared rapidly after heroin administration and continued to increase while heroin concentrations decreased suggesting that heroin was undergoing hydrolysis during its residence in the patch. Kintz et al. [48] applied the PharmChek™ Sweat Patch to 20 known heroin abusers and monitored use of a variety of drugs including opiates. Heroin was always present in lower concentration than 6AM, which was the major analyte detected. In addition, buprenorphine, which was administered as pharmacotherapy, was detected in the range of 1.3–153.3 ng/patch. No relationship between buprenorphine concentration and the daily dose was found. Recently, Taylor et al. [21] attempted to evaluate the use of the PharmChek™ Sweat Patch in outpatients of a methadone maintenance clinic. Duplicate patches were worn on the arm and on the side of the torso for a period of five to ten days, removed and analyzed by immunoassay. Urine specimens were also collected and analyzed. There was a good inter-patch reliability between the duplicate patches for methadone and opiates, but only moderate agreement for benzoylecgonine. There was also a good agreement between the sweat patch results and the urine tests for methadone and opiates, but again only moderate agreement for benzoylecgonine.

5. Summary

Sweat testing provides a less invasive method for monitoring drug exposure than blood or urine. The wearing of sweat patches over a period of five to ten days by individuals undergoing drug monitoring provides a convenient alternative to urine testing. Studies comparing sweat patch results for cocaine and opiates to urine results have generally been

favorable. The PharmChek™ Sweat Patch device is the most commonly used device for collection of sweat. Current studies with other types of sweat collection devices are underway. The present report details results from a new type of sweat collection device that allows rapid collection of sweat samples. These new Fast Patches employ heat-induced sweat stimulation and a larger cellulose pad for increased sweat collection. Two body collection sites were studied with the new patches. The Hand-held Fast Patch was applied to the palm of the hand and the Torso Fast Patch was applied to the torso (abdomen and flank areas) for 30 min. Sweat patches collected following controlled dosing studies with cocaine and codeine were analyzed by GC–MS and were positive for up to 48 h following dosing. Drug concentrations were generally two-fold or greater than concentrations reported for the PharmChek™ Sweat Patch. The higher drug concentrations in sweat collected by the Fast Patches was almost certainly produced as a result of the heat-induced stimulation, however, drug disposition processes in sweat are incompletely understood. There appears to be multiple mechanisms involved in the disposition of drugs into secreted sweat. Passive diffusion from blood into sweat glands and transdermal migration across the skin are likely to be most important, but the physicochemical properties of the drug analyte appear to be equally important. This study also demonstrated that drug disposition can change as a result of differences in the collection device and the site of collection. Further improvements in sweat testing technology can be expected to arise from development of new collection devices and elucidation of the mechanisms involved in drug disposition into sweat.

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