Cocaine Levels in Sweat Collection Patches Vary by Location of Patch Placement and Decline Over Time

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Abstract

Sweat collection patches are used for drug abuse monitoring. We investigated the effect of sweat patch location (back and shoulder) on cocaine levels after controlled intravenous cocaine exposure (210 mg/70 kg) in 12 subjects (Experiment 1). Gas chromatographic–mass spectrometric analyses show cocaine and metabolites levels in Pharmcheck™ patches were eightfold higher on the back than those on the shoulders. To assess the mechanisms for possible loss of cocaine from patches during wear, 48 sweat patches with a small amount of cocaine-d5 (100 ng as base/patch) were placed on the backs of eight cocaine-naïve volunteers for up to 72 h (Experiment 2). Drug-free patches were applied over eight of the cocaine-d5 (100 ng) containing patches to measure loss through the patch. Cocaine levels in spiked patches declined over time (p = 0.002), with levels at 48 h postapplication 30% less than control, consistent with possible drug reabsorption. Cocaine was detectable (> 2 ng/patch, LOQ) in four of eight initially cocaine-free patches placed on top of the cocaine-containing patches, indicating transfer through the patch outer membrane. Conversion to benzoylecgonine was detectable but at low levels (< 2%). Reabsorption (back transfer), degradation or hydrolysis, and loss of cocaine to the environment may account for substantial loss of cocaine from skin sweat collection patches during patch wear.

Introduction

Ascertaining recent illicit drug use can sometimes be accomplished by simply obtaining a history. Unfortunately, many (most) patients are not truthful about their current use. Thus, more objective monitoring of drug use is useful. Analysis of biological fluids and tissues is an objective method for determining human drug exposure (1). Blood and urine samples have long been used to monitor drug use; however, they cannot be conveniently used to monitor drug intake over extended periods (1). Patches applied to the skin and designed to collect drugs excreted into sweat are commercially available and are widely used to monitor illicit drug use in the workplace and by law enforcement (1–3). Recent studies suggest that skin sweat patch testing may be a useful alternative to urine assays or patient self-reports as an outcome measure in clinical trials (4). Although skin sweat patch testing may be useful and offer advantages over blood or urine monitoring, the pharmacokinetics of absorption and disposition of most illicit drugs in sweat patches are not as well characterized.

A major advantage of patches is cumulative collection of drug over time. One marketed, FDA-cleared collection device claims to measure cumulative drug exposure; however, marked inter- and intra-subject variability exist in the results of sweat analysis for cocaine and heroin (2,3,5). If the amount of drug secreted in sweat varies, then cumulative patch levels will also vary. In theoretical models, Peck et al. (6) simulated decline in patch drug levels. The rate of both secretion and reabsorption (back transfer of drug in the patch back into the body) may increase the variability in sweat patch analysis. Recent reports show that drugs may travel from the outside environment into patches through the patch membrane under some in vitro experimental conditions (7,8). There are only limited published in vivo data on degradation or loss of drugs from collection patches applied on human skin (4,5). Together these findings suggest that drug levels measured in sweat patches may not be truly cumulative records of cocaine exposure, as one might expect, if the patch simply serves as a passive collection reservoir.

In two experiments, we examined some of the factors affecting the results of sweat cocaine analysis. In the first experiment, we assessed the utility of using patch levels as an end-
point to detect exposure to a measured dose of cocaine-d₅ administered in a laboratory setting during an experiment investigating the effects of 10 days exposure to transdermally administered selegiline on cocaine pharmacokinetics. Our use of a substantial intravenous dose of deuterium-labeled cocaine allowed us to be more certain of cocaine dose absorbed and the source of cocaine in the skin patches. We evaluated the effects of the anatomic site of patch placement (lower back or upper shoulder) on cocaine levels collected in the patch.

Loss of collected drug from a skin patch may be due to re-absorption (back transfer) into the skin and systemic circulation, metabolism of drug on the surface of the skin, degradation in the patch, or mechanical transfer through the outer polyurethane membrane covering the patch and subsequent loss to the environment. To test the relative contributions of these mechanisms of drug loss from patches, we performed a second experiment. Deuterium-labeled cocaine was added to patches placed on non-cocaine-using subjects, and the time-dependent elimination of cocaine and metabolites from the skin patch was measured.

Methods

Subjects

Experiment 1. Twelve subjects (1 female and 11 males), 22 to 43 years of age (32.9 ± 6.5 years) were recruited by newspaper advertisements. Subjects were nondependent cocaine users. All were in good health as judged by medical, laboratory, and psychiatric evaluations and were not dependent on any illicit drugs or alcohol as assessed by DSM-IV criteria. Those who had a history of adverse reaction from cocaine or any type of dermatitis or skin sensitivity that may be worsened by wearing the sweat patches were excluded.

Experiment 2. Eight subjects (2 females and 6 males), 23 to 37 years of age (26.8 ± 4.8 years), were recruited by advertisements posted in the UCSF Medical Center. Subjects had never used cocaine as judged by medical history and absence of cocaine or metabolites in their urine. We assumed there was no likelihood of systemic effects from the cocaine in this experiment because of the extremely low amounts of cocaine added to the patches. All volunteers were in good health as judged by medical history and examination.

Protection of human subjects. Studies were approved by the Committee on Human Research (IRB) of the University of California, San Francisco (UCSF). All subjects gave informed consent prior to study participation.

Deuterated cocaine

Deuterium-labeled (d₅) cocaine was synthesized, purified from USP-grade cocaine hydrochloride under sterile conditions (9), and stored in a designated area apart from the drug testing rooms of the Drug Dependence Research Center (DDRC). Cocaine-d₅ was prepared for each dose by the UCSF Pharmacy and brought to the DDRC just prior to drug administration to avoid possible environmental contamination.

Selegiline

In Experiment 1, an investigational selegiline transdermal patch with selegiline as an amine base in an acrylic polymer adhesive matrix was supplied by the National Institute on Drug Abuse and manufactured by Somerset Pharmaceuticals. The formulation contains 18.3 mg of selegiline in a 15 cm² disc; the surface area of the drug-containing portion of the patch was 10 cm² yielding a selegiline concentration of 1.83 mg/cm².

Sweat patches

Commercially available sweat patches (Pharmchem, Menlo Park, CA) were used. The sweat patch is composed of three components: an outer polyurethane adhesive layer, a release liner, and a cellulose collection pad. The release liner is a thin cellulose tissue that prevents all but two opposing edges of the collection pad from sticking to the adhesive. This allows convenient removal of the collection pad after patch removal. The collection pad has an area of 14 cm². Patches were supplied by the manufacturer (Pharmchem). Researchers wore new latex gloves and opened new sweat patches just prior to patch applications. To remove the patches, researchers wore new gloves and used clean disposable forceps for each patch. Drug-free control patches were included in each batch of samples as an additional control for possible external contamination during the application and removal procedure.

Experiment 1: The effects of patch location on cocaine levels

Procedures. This study was conducted as a part of clinical trial testing selegiline for cocaine dependence (10). Cocaine-d₅ (2.5 mg/kg) was intravenously administered to 12 healthy, nondependent (by DSM-IV criteria) cocaine users the day before and the day after 10-days exposure to transdermal selegiline (one patch/day).

Cocaine dose. A 0.5 mg/kg intravenous loading dose of deuterium-labeled (d₅) cocaine injected by infusion pump over 10 min was followed by a continuous constant rate 4 h infusion of 2.0 mg/kg in an unblinded fashion. Plasma samples for cocaine and cocaine metabolites were collected for 45 h to confirm that there was no significant drug interaction with selegiline (10).

Sweat patch application and collection. Four patches were applied to the subject's skin just prior to the first cocaine infusion (first phase of the experiment, the cocaine kinetics study beginning on the day before the selegiline exposure) and then sequentially removed at 24, 72, 120, and 168 h after the end of the cocaine infusion. Two patches were applied just prior to the second (post selegiline exposure) cocaine infusion and sequentially removed at 24 and 72 h after the cocaine infusion. Because our initial interests did not include investigation of patch location as a factor affecting sweat cocaine analysis, each patch location (either back or shoulder) was randomly selected by the investigators but was not fully balanced as to location. In Experiment 1, 72 patches were applied. Thirty-one (43%) were placed on the back (16 on the right and 15 on the left), and 41 (57%) were placed on the shoulder (20 on the right and
3 mL deionized water, then eluted with 4.4 mL methanol, then allowed to dry. Cocaine-ds and BE-ds were extracted by solid-phase extraction as described.

Experiment 1: The effects of patch location on cocaine levels

Sweat collection patches were well tolerated by all subjects. Seventy-two patches were applied. Five (6.9%) were lost by premature separation during patch wear. No patches were lost during the 0 to 24 h period. Two patches were lost from the back during the 0 to 72 h period and three patches were lost from the shoulder during the 72 to 120 h or 120 to 168 h periods. The sensitivity for detection of cocaine was 100%. As expected, all of the 67 collected sweat patches were positive for cocaine, regardless of selegeline exposure. Twelve of the 67 patches were negative for benzoylecgonine (BE), and 2 were negative for ecgonine methyl ester (EME). The sensitivity of the sweat test for BE and EME was 67.6% and 97.096%, respectively.

As might be expected because of regional differences in sweat gland density, the site of the sweat collection had a striking impact on cocaine levels. Levels in patches placed on the lower back during the 0 to 72 h period and three patches were lost from the shoulder during the 72 to 120 h or 120 to 168 h periods. The sensitivity for detection of cocaine was 100%. As expected, all of the 67 collected sweat patches were positive for cocaine, regardless of selegeline exposure. Twelve of the 67 patches were negative for benzoylecgonine (BE), and 2 were negative for ecgonine methyl ester (EME). The sensitivity of the sweat test for BE and EME was 67.6% and 97.096%, respectively.

As might be expected because of regional differences in sweat gland density, the site of the sweat collection had a striking impact on cocaine levels. Levels in patches placed on the lower
back were eightfold greater than those from the upper shoulder (Figure 1A). EME levels in patches from the back were also greater than those from the shoulder (Figure 1B), while BE levels showed a similar but blunted pattern with a greater variability (Figure 1C). Cocaine and metabolite levels were generally symmetric between the right and left sides of the back.

Correlation between levels of cocaine and its metabolites was high during the first 24 h (Figures 2A and 2B). Some unexpectedly high concentrations of BE were observed in three subjects from 72 to 168 h. Consequently, the correlation between cocaine and BE was lower because of the unexpected high amounts of BE in some patches, although the correlation between cocaine and EME remained relatively high (Figures 2C and 2D).

Ninety percent of patches had higher cocaine than metabolite (either BE or EME) levels. However, in eight patches, BE levels were higher than cocaine levels. In one patch, the BE level was 15-fold greater than the cocaine level.

Experiment 2: Mechanisms of loss of cocaine from patches

Figure 3 shows the time-dependent loss of cocaine-d5 from the sweat collection patches applied to the back of eight subjects. Cocaine was significantly (p < 0.0001) lost from patches during patch wear over time (Figure 3). Cocaine levels at 48 h post application were about 30% less than those at 1 h. Some conversion to BE was detectable but only at extremely low levels (<2%). Four of eight cocaine-free patches applied over cocaine-containing patches became positive (3.5–5.9 ng/patch) for cocaine during patch wear (Table 1). Although those levels would lead to a negative report based upon the manufacturer’s recommended cutoff (25 ng/patch), our data indicate that cocaine can travel outward through the patch membrane at low levels (0–6% of the spiked dose).

Discussion

Reliable methods to detect illicit drug use are important for evaluating compliance with treatment or with edicts of the criminal justice system. Objective biological drug testing may be more reliable than self-reports to detect drug abuse; hence, the interest in skin sweat collection patch analysis as an objective outcome measure in drug dependence treatment and clinical research. Previous studies have suggested that sweat testing could be used as a cumulative collection device for some drugs with relatively long half-lives (13,14). However, data variability seems to make quantitative analysis difficult.

Data from Experiment 1 show that the site of sweat collection could markedly impact the results of sweat analysis. Cocaine levels in patches from the lower back were eightfold greater than those from the upper shoulder. There is limited published data on how the site of sweat collection affects sweat analysis for drugs of abuse. Although the number of subjects was small (two), Kintz et al. (13) reported that codeine concentrations differed by a magnitude of 1 to 3 according to the site of sweat patch application: the upper arm, the back, and the ribs. The site of sweat collection seems to have a greater effect on cocaine sweat analysis than on codeine analysis. Preston et al. (5), in a study of patients in a treatment program using unknown doses of illicit cocaine, reported that a small portion (4%) of duplicated patches from different regions of the
body showed sixfold or greater differences in sweat cocaine levels. All of these data suggest that the site of collection should be more carefully considered when interpreting the results of sweat patch drug collection.

In Experiment 1, the correlation between cocaine and BE levels was high during the first 24 h but declined during the following 72 to 168 h. In that experiment, BE was detected in concentrations similar to EME. Similar results were reported in controlled clinical studies (2,5,15). Cocaine seems to be the predominant moiety found in sweat patches after exposure to cocaine. (However, cocaine metabolites could be present in patches in higher concentrations.) Preston et al. (5) reported that 1% of the patches were identified as BE-positive without cocaine. In our Experiment 1, metabolite levels were higher than cocaine levels in some patches.

It is unclear why some patches show higher concentrations of cocaine metabolites than cocaine. The great inter- and intraindividual variability and poor dose-relationship previously reported for sweat cocaine and metabolites might be explained by the uncontrolled degradation (metabolism or non-enzymatic conversion) of cocaine to metabolites on the skin surface, which could possibly occur during patch wear (7). In Experiment 2 (which will be further discussed later), we demonstrated that metabolites found in the patches may have resulted from degradation of cocaine during patch wear. However, this degradation seems to be unpredictable and to occur at very low levels. In general, our data and the data of Winhusen et al. (4) suggest that spontaneous degradation from cocaine to BE may be a minor pathway for loss of cocaine during patch wear.

Data from Experiment 2 clearly show time-dependent loss of cocaine during patch wear over time. This cocaine loss from skin patches may be one of the factors limiting cumulative drug detection. Drugs such as codeine, phenobarbital,

![Figure 2](image)

*Figure 2. A: Correlation between cocaine-d₅ and benzoylecgonine-d₅ concentrations during the first 24 h (r = 0.864). Open squares, without selegiline; closed squares, with selegiline. B: Correlation between cocaine-d₅ and ecgonine methyl ester concentrations during the first 24 h (r = 0.743). C: Correlation between cocaine-d₅ and benzoylecgonine-d₅ concentrations for up to 168 h (7 days) (r = 0.252). Arrows indicate outliers. D: Correlation between cocaine-d₅ and ecgonine methyl ester concentrations for up to 168 h (7 days) (r = 0.738).*
and diazepam are reported to show cumulative increases in patch levels (13,14). Researchers have reported some cumulative increase in cocaine levels, but their data also exhibited a large variability and a possible decrease after long time. Burns et al. (3) showed that at the lower of the two doses (50 mg of intranasal cocaine) there was a decrease in mean concentrations after the first 72 h and at the higher dose (126 mg) a decrease in 10 of 15 subjects. Unlike codeine, phenobarbital, or diazepam, cocaine has a relatively short half-life (16). Excretion of a single dose of cocaine into sweat may occur for only a relatively short period. Cocaine may not be collected by the sweat patch cumulatively over an extended period; rather, cocaine may be gradually eliminated over time during patch wear after initially rapidly appearing in the patch.

The mechanisms by which the cocaine level is decreased over time are not clear. Few studies have examined the mechanisms by which cocaine is lost from patches. The present study suggests that 1. cocaine can be reabsorbed back to the skin from the patch, 2. cocaine can be metabolized or non-enzymatically degraded on the surface of the skin, and/or 3. the cocaine in the patch can transfer from the patch through the polyurethane adhesive layer.

Cocaine is probably transferred to the sweat patch pad via sweat. If reabsorption (back transfer) is very low, long term cumulative collection should theoretically be possible (6). With cumulative collection of drug, the levels should increase with time, if the drug is slowly excreted and such reabsorption is minimal. However, if the drug is reabsorbed, cocaine levels would be expected to decrease over time. The absorption is minimal. However, if the drug is reabsorbed, the patch should be equal to the sum of cocaine that 1. remained from patches, making quantitative cumulative collection should theoretically be possible (6).

In Experiment 2, the total amount of cocaine applied in the patch should be equal to the sum of cocaine that 1. remained in the patch, 2. was metabolized or non-enzymatically degraded in the patch, 3. was transferred to the outside of the patch, and 4. was absorbed through the skin. Therefore, the amount of cocaine lost by reabsorption can be approximately evaluated as the amount of cocaine lost during patch wear subtracted by the amount degraded (metabolized or non-enzymatically converted) in the patch and lost to the outside environment through the outer patch membrane. As already discussed, the data of Experiment 2 show that the amount degraded or lost to the environment was minimal, indirectly suggesting existence of substantial back-transfer.

In order to directly confirm the transdermal back-transfer of cocaine from patches to the body, cocaine should be detectable in skin or plasma after the skin is exposed to cocaine. However, this may be difficult. We have recently reported that the skin is not a reservoir for cocaine after systemic administration, that cocaine follows a similar disposition pattern in the skin compared to the plasma, and disappears from the skin as rapidly as it does from the plasma (16). Therefore, prolonged disposition of cocaine in the plasma or the skin is unlikely after transdermal absorption. A nonpharmacologically active amount of cocaine may be transdermally absorbed, but is unlikely to be detectable in the skin or plasma. It is technically difficult to directly evaluate the back-transfer of the small amount of cocaine found in sweat cocaine testing.

There were limitations in this study. First, Experiment 1 was primarily designed to demonstrate the usefulness of patches to detect a controlled cocaine exposure, but not specifically designed to investigate the effect of patch location and wear time on the sweat cocaine analysis. Although we clearly showed the high sensitivity of the sweat patch analysis to detect cocaine exposure, the great variability in data led us to consider how patch location and wear time affect the analysis. Patch locations in Experiment 1, for instance, were not well-balanced or randomized. Some other possible factors besides patch location and patch wear time may have a significant effect on sweat cocaine analysis. For example, local sweat pH, rate of sweating, and sweat gland distribution may play a role in the patch analysis variability, but Experiment 1 lacks controls for those data.

Second, we did not measure the local sweat rate or amount of sweat independent of cocaine at collection sites. The data are expressed as mean values ± SD. *p < 0.001 (ANOVAs). **p < 0.05. ***p < 0.01.

![Figure 3. Time-dependent loss of cocaine-d5 from the sweat patches spiked with cocaine-d5 and applied to the back of subjects (N = 8/condition). Data are expressed as mean values ± SD.](https://example.com/figure3)

<table>
<thead>
<tr>
<th>Subject #</th>
<th>Time after application (h)</th>
<th>Cocaine-d5 levels (ng/patch)</th>
</tr>
</thead>
<tbody>
<tr>
<td>01</td>
<td>8</td>
<td>n.d.</td>
</tr>
<tr>
<td>02</td>
<td>8</td>
<td>5.1</td>
</tr>
<tr>
<td>03</td>
<td>72</td>
<td>3.5</td>
</tr>
<tr>
<td>04</td>
<td>72</td>
<td>n.d.</td>
</tr>
<tr>
<td>05</td>
<td>72</td>
<td>5.9</td>
</tr>
<tr>
<td>06</td>
<td>48</td>
<td>n.d.</td>
</tr>
<tr>
<td>07</td>
<td>48</td>
<td>n.d.</td>
</tr>
<tr>
<td>08</td>
<td>48</td>
<td>3.5</td>
</tr>
</tbody>
</table>

* Four of the cocaine-free patches placed on patches spiked with cocaine-d5 became positive for cocaine.
degree to which the rate of cocaine excretion into sweat is proportional to the sweat flow and pH is not fully understood. Future studies need to develop a reliable method to directly determine the local sweat rate and correlate that rate with the amount of drugs secreted in sweat in order to answer that question. The commercial patches used in this study do not lend themselves to measures of total sweat collected. The semi-permeable membrane and resulting evaporation of sweat collected make quantitation impossible.

Third, the number of patches may be too small for both experiments to finally confirm the precise degradation of cocaine to metabolites.

Fourth, Experiment 2 lacks direct evidence for reabsorption. Instead, we inferred the possibility of some reabsorption because of loss of cocaine from patches. As we considered only one potential metabolic pathway (BE formation) for the evaluation of reabsorption, in Experiment 2 we have not accounted for other metabolites that can potentially be formed (EME, N-demethyl, ring hydroxylation products, etc.). EME was not included in the analyses because the d6 label would be lost. Presence of EME could either be from previous use and/or administration of cocaine-d6. As already discussed, reabsorption of very small, nonpharmacologically active amounts of cocaine on the skin is not likely to result in detectable levels in plasma; therefore, we did not measure cocaine in the skin by biopsy or in blood after patches spiked with cocaine were placed on the skin.

Fifth, Experiment 2 investigated the decline in cocaine levels in patches placed on the back, but not on other body areas. The anatomical location may have a significant effect on the disappearance (the rate of reabsorption) of cocaine from patches. This needs further investigation.

Conclusions

Sweat analysis is a sensitive method for detecting cocaine use. The results may be affected by the collection period and by the site of sweat collection. Loss of cocaine may occur from skin collection patches. Researchers using sweat cocaine techniques should take these factors into consideration.

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References


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