Opioid Disposition in Human Sweat after Controlled Oral Codeine Administration

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Background: Characterization of opioid excretion in sweat is important for accurate interpretation of sweat tests in drug treatment, criminal justice, and workplace drug testing programs.

Methods: Participants (n = 20) received placebo, 3 low (60 mg/70 kg) or 3 high (120 mg/70 kg) codeine sulfate doses (used as a model for opioid excretion) within 1 week. Codeine and metabolites in sweat were collected with PharmChek® Sweat Patches; hourly patches were applied for 1 to 15 h (n = 775) and weekly patches for 7 days (n = 118). Patches were analyzed by solid-phase extraction and gas chromatography–mass spectrometry for codeine, norcodeine, morphine, normorphine, and 6-acetylmorphine. Limits of quantification were 2.5 ng/patch (codeine and morphine) and 5 ng/patch (other analytes).

Results: Codeine was the only analyte identified in 12.6% of hourly patches and 83.3% of weekly sweat patches worn during dosing. Weekly patch concentrations (SD) were 38.6 (59.9) ng/patch [median (range), 15.9 (0–225.1) ng/patch] for low and 34.1 (32.7) ng/patch [24.0 (0–96.2) ng/patch] for high codeine doses. Codeine detected 1 week after dosing was 4.6 (5.3) ng/patch [median (range), 4.0 (0–17.1) ng/patch; n = 11] after low and 7.7 (7.1) ng/patch [6.9 (0–20.5) ng/patch; n = 10] after high doses. In total, 2.6% of hourly, 38.5% of low-dose, and 45.5% of high-dose weekly patches contained codeine at the proposed Substance Abuse and Mental Health Services Administration cutoff.

Conclusions: Codeine was the only analyte detected, at highly variable concentrations, up to 2 weeks after dosing. These results are consistent, considering the complex processes of codeine deposition in sweat. Sweat testing is a useful alternative technique for qualitative monitoring of opioid use.

Drug monitoring in treatment, criminal justice, and workplace programs provides objective data on drug exposure and verification of self-reported use. Since the invention of the PharmChek® sweat patch, sweat has been considered as an alternative matrix for drug testing. Sweat has a longer drug detection window than urine or plasma for most illicit drugs, its collection is noninvasive, and patches are relatively tamper resistant (1, 2).

The sweat patch is applied to the skin for several days to allow sufficient absorption of excreted drugs. Deposition of drugs into sweat depends on molecular mass, pKa, extent of protein binding, and lipophilicity (2). Nonionized basic drugs in blood diffuse into sweat and become ionized, leading to ion trapping in sweat because of its lower pH (3). Drugs in sweat on the skin’s surface may contribute to drug incorporation into hair (4). PharmChek sweat patches have been used to detect codeine (5–7), nicotine (8), cocaine (9, 10), heroin (11), cannabis (12), and methamphetamine (13, 14).

There are limited data on the excretion of opioids in sweat after controlled drug administration. Significant variability in codeine concentrations was observed in patches applied to various locations on the upper body (6). Codeine (2–127 ng/patch) was detected within 1 h and peaked within 24 h, and no metabolites were detected. Additionally, in a study showing good agreement between Drugwipe® (Securtec) and PharmChek sweat patch results (5), sweat patch codeine concentrations ranged from 3 to 124 ng/patch. In a different study, sweat patches worn for 2 days after codeine phosphate administration (15) had a mean codeine concentration <20 ng/patch. Another study examined excretion of heroin and metabolites after controlled administration of heroin (16). In sweat patches worn for 1 to 5 days, heroin

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administration, with at least 48 h between doses. After opioid self-administration, a small proportion of sweat patches from heroin abusers in a buprenorphine substitution program contained 67 to 4018 ng of codeine (7). Codeine concentrations of 13 to 900 ng/patch were noted in 206 of 925 patches collected from patients in a methadone maintenance program (17).

The Substance Abuse and Mental Health Services Administration (SAMHSA) recommends a confirmation cutoff of 25 ng/patch for codeine, morphine, and 6-AM in patches worn for 1 week (18). Whether patches applied weekly after last drug administration will be positive at the proposed SAMHSA cutoff remains unanswered. Data on the disposition of drugs into sweat after controlled administration provide a scientific basis for interpretation of sweat test results. However, the duration of opioid excretion in sweat is unknown, a critical factor for differentiating new drug use from residual drug excretion. Additionally, to date, only single-dose studies have been conducted, whereas multiple opioid self-administrations are characteristic of abuse of opioids. Finally, excretion data used as the scientific basis for the interpretation of sweat test results should be collected in a controlled environment to preclude self-administration of drugs. We addressed these issues, using codeine as a model for opioid excretion in sweat. During a 10-week study period, we administered 3 low (60 mg/70 kg) and 3 high (120 mg/70 kg) oral codeine doses to 20 human opiate users who resided continuously on a secure research unit. To characterize multiple aspects of codeine disposition in sweat, patches were applied weekly during the first and second weeks after the last codeine administration to determine the duration of codeine excretion in sweat. Duplicate patches were examined to determine reproducibility of codeine excretion in sweat.

**Materials and Methods**

**HUMAN PARTICIPANTS**

Twenty participants (14 male, 6 female; 70% African American, 20% Caucasian, 10% Hispanic; mean age, 34.1 years; range, 23–43 years) provided written informed consent for this within-subject, single-blind, placebo-controlled, Institutional Review Board-approved study. Participants underwent physical and psychologic examinations, and self-reported a history of opioid use. Participants resided on the closed clinical unit for 10 weeks and received 60 mg/70 kg (low), and 120 mg/70 kg (high) oral codeine sulfate, 3 times within weeks 4 and 8, respectively (Fig. 1A), with at least 48 h between codeine doses. Placebo was administered 3 times during week 6.

**SWEAT COLLECTION**

Duplicate patches, applied weekly to the abdomen or back, were worn during each week. Single hourly patches were worn for 1, 2, 4, or 15 h after each codeine administration according to the schedule described in Fig. 1B. After removal, patches were sealed in plastic bags and stored at −20 °C until analysis.

**CHEMICALS, REAGENTS, AND MATERIALS**

Codeine sulfate was obtained from Roxane Laboratories and was encapsulated in polished capsules, provided by Amend Drug and Chemical. Methanol, acetonitrile, methylene chloride, 2-propanol, hydrochloric acid, ammonium hydroxide, and sodium acetate were obtained from J.T. Baker. Organic solvents were HPLC grade. N,O-bis(trimethyl)trifluoroacetamide with 1% trimethylchlorosilane; MTBSTFA +1% TBDMCS, N-methyl-N-(tert-butyldimethylsilyl)trifluoroacetamide with 1% tert-butyldimethylchlorosilane; LOD, limit of detection; and LOQ, limit of quantification.

![Fig. 1. Codeine dosing timeline (A), and hourly sweat patch application schedule (B).](image)

(A) codeine sulfate (60 mg/70 kg) was orally administered on Tuesday (T), Thursday (Th), and Monday (M) during week 4. Placebo was administered during week 6 and 120 mg/70 kg codeine sulfate was administered on Tuesday, Thursday, and Monday of week 8. (B) sweat patches were applied for 1, 2, 4, or 15 h after each low and high codeine administration, with at least 48 h between doses.
were then loosely capped and incubated for 15 min at

ness. The drugs were reconstituted in 20

mixed, and the samples were again evaporated to dry-

the eluate was evaporated to dryness. Acetonitrile (0.5

TBDMCS, after which the tubes were vortex-mixed, and

min to 310 °C, and held for 3 min. Inlet temperature was

morphine, morphine-d3, normorphine, 6-AM-d3, and

mol/L sodium acetate buffer (pH 4.0) and 100

patches we added 2.5, 5, 10, 25, 50, 100, 250, or 500 ng of
codine, norcodeine, morphine, normorphine, and 6-AM.

To 4 control patches (3.75, 12.5, 125, and 375 ng), we

added a solution prepared independently of the calibra-
tor. Patches were placed in 15-mL fritted reservoirs with

closed stopcocks, which in turn were placed over a

vacuum manifold. To each reservoir we added 4 mL of 0.5

mol/L sodium acetate buffer (pH 4.0) and 100 µL of
deuteration-labeled internal standard solution (1 mg/L).

After 30 min, the solvent (4 mL) was collected. and 2

additional washes (2 mL) were performed. Columns were

conditioned with 1 mL of elution solvent (methylene

chloride–isopropanol–ammonium hydroxide; 80:20:2 by

volume), followed by water, methanol, and sodium ace-

cetate buffer. The samples were loaded, and the columns

were washed with water, 0.2 mol/L hydrochloric acid,

and methanol and dried under reduced pressure. Drugs

were eluted by addition of 1 mL of elution solvent 5 times.

To each tube we added 20 µL of MTBSTFA + 1%

TBDMCS, after which the tubes were vortex-mixed, and

the eluate was evaporated to dryness. Acetonitrile (0.5

mL) was added to each tube, the tubes were vortex-
mixed, and the samples were again evaporated to dry-

ness. The drugs were reconstituted in 20 µL of acetoni-

trile, vortex-mixed, and centrifuged. After centrifugation,

20 µL of MTBSTFA + 1% TBDMCS was added; the vials

were then loosely capped and incubated for 15 min at

80 °C. After cooling, 20 µL BSTFA + 1% TMCS was

added, and the vials were crimp-capped and incubated 45

min at 80 °C.

INSTRUMENTATION

Samples (2 µL) were injected into an Agilent 6890 Gas

Chromatograph/5973 Mass Selective Detector, equipped

with an HP-1 [30 m × 0.32 mm (i.d.); 0.25-µm df] column.

The initial oven temperature was 70 °C, which held for 1

min; the temperature was then increased at 30 °C/min to

175 °C, increased 23 °C/min to 250 °C, increased 18 °C/

min to 310 °C, and held for 3 min. Inlet temperature was

250 °C, pressure was 0.52 psi, and helium was the carrier

gas. In the selected-ion monitoring mode, the ions moni-
tored [target and qualifier(s) m/z] included codeine-d3

(m/z 374 and 237), codeine (m/z 371, 178, and 196),
norcodeine (m/z 429, 254, and 292), morphine-d3 (m/z 417

and 474), morphine (m/z 414, 471, and 278), normorphine

(m/z 472, 529, and 350), 6-AM-d3 (m/z 345 and 444),

and 6-AM (m/z 342, 441, and 384). The limits of detection

(LOD) and quantification (LOQ) were determined by

serial dilution of a calibrator solution. The LOD was

defined as the lowest concentration at which ions had a

signal-to-noise ratio ≥3/1, ion ratios were within 20% of

those of the calibrators, relative retention time was within

2%, and chromatography was acceptable. The LOQ crite-

ria included all the LOD criteria and quantification had to

be within 30% of the target. LOD and LOQ were 2.5

ng/patch for codeine, morphine, and 6-AM and 5.0 ng/

patch for norcodeine and normorphine. Two separate

calibration curves were constructed; a low curve from 2.5

to 50 ng/patch, and a high curve from 50 to 500 ng/patch.

Drugs were quantified by linear regression with equal

weighting. Quality-control samples were analyzed in each

batch (see Table 1 in the Data Supplement that accompa-
nies the online version of this article at http://www.
clinchem.org/content/vol52/issue8/).

STATISTICAL ANALYSIS

Concentration means, medians, and ranges were calcu-
lated from all patches analyzed in the group, unless

otherwise indicated. Statistical analyses were performed

with SPSS, Ver. 13.0 for Windows, release 13.0.1. A paired

t-test was used to compare sums of codeine concentra-
hions in hourly patches with codeine concentrations in

currently applied weekly patches. Spearman correla-
tion analysis was used to determine the correlation be-
tween duplicate patch positivity rates. A two-tailed P

value <0.05 was considered statistically significant.

Results

WEEKLY WASHOUT PATCHES

The 44 weekly washout patches from 13 participants,
applied during the 3 weeks before codeine administra-
tion, were all negative for codeine, norcodeine, morphine,
normorphine, and 6-AM, indicating that participants had

not recently self-administered opiates. Corresponding

plasma concentrations (19) also were negative for codeine

and metabolites (LOQ, 2.5 µg/L) during washout weeks.

PATCHES WORN FOR 1 TO 15 H

A total of 775 hourly patches from 20 participants were

applied before, and worn for 1 to 15 h during the first 48

h after drug. Codeine, the only analyte detected in any

patch, was found in 3 of 66 (4.5%) patches worn from 0 to

1 h after dosing (low and high doses combined). There

was large intra- and intersubject variability in codeine

concentrations in sweat during dosing weeks. Only

98 (12.6%) patches worn for 1 to 15 h (low and high
doses combined) contained codeine at or above the LOQ

(2.5 ng/patch), and 20 (2.6%) contained codeine at or above

the proposed SAMHSA cutoff (25 ng/patch).

Hourly patches worn for longer periods within the first

24 h after dosing were more likely to contain codeine

above the LOQ. Rates of positive hourly patches were
4.5% (n = 179), 13.3% (n = 75), 30.7% (n = 75), and 40% (n = 95) for patches worn 1, 2, 4, and 15 h, respectively. Detectability increased with wear duration, but codeine concentrations did not correlate with time worn or dose administered.

Codeine excretion occurred predominantly within the first 24 h after dosing (Fig. 2). Of the 15-h patches worn from hours 8 to 23 after low and high doses, 33.3% and 48.8%, respectively, had concentrations at or above the LOQ, compared with 2.5% (low), and 10.7% (high) of patches worn from hours 8 to 23 after low and high doses, respectively, were >25 ng/patch, whereas all 15-h patches worn from hours 32 to 47 were negative.

**WEEKLY PATCHES WORN DURING CODEINE ADMINISTRATION**

Weekly patches also were applied before the first of 3, and removed after the last of 3 codeine administrations (Table 2). Codeine was the only analyte detected in any patch, with no dose–concentration relationship.

**WEEKLY PATCHES WORN AFTER CODEINE ADMINISTRATION**

We examined the duration of codeine excretion in sweat, using duplicate weekly patches worn the first, second, and third weeks after the last of 3 low codeine administrations (weeks 5, 6, and 7), and the first and second weeks after the last of 3 high codeine administrations (weeks 9 and 10). Of the patches worn the first week after low and high doses, 63.6% and 70%, respectively, were positive for codeine above the LOQ, as were 2 of 8 patches worn the second week after the high doses. None were positive above the proposed SAMHSA cutoff.

### Table 1. Codeine concentrations and comparison between the number of positive sweat patches at the method LOQ and SAMHSA cutoffs in all 15-h patches worn from hours 8 to 23 (including negative patches) after codeine administration.

<table>
<thead>
<tr>
<th>Codeine dose</th>
<th>Dose 1</th>
<th>Dose 2</th>
<th>Dose 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (60 mg/70 kg) n = 19</td>
<td>n = 19</td>
<td>n = 16</td>
<td></td>
</tr>
<tr>
<td>Mean (SD), ng/patch</td>
<td>6.2 (11.4)</td>
<td>5.0 (9.0)</td>
<td>2.1 (3.8)</td>
</tr>
<tr>
<td>Percentage &gt;2.5 ng/patch</td>
<td>36.8</td>
<td>31.6</td>
<td>31.3</td>
</tr>
<tr>
<td>Range, ng/patch</td>
<td>3.9–37.2</td>
<td>3.1–32.1</td>
<td>3.2–12.4</td>
</tr>
<tr>
<td>Percentage &gt;25 ng/patch</td>
<td>10.5</td>
<td>5.3</td>
<td>0</td>
</tr>
<tr>
<td>Range, ng/patch</td>
<td>31.1–37.2</td>
<td>32.1</td>
<td></td>
</tr>
<tr>
<td>High (120 mg/70 kg) n = 14</td>
<td>n = 15</td>
<td>n = 12</td>
<td></td>
</tr>
<tr>
<td>Mean (SD), ng/patch</td>
<td>3.3 (5.5)</td>
<td>10.7 (13.7)</td>
<td>5.3 (10.4)</td>
</tr>
<tr>
<td>Percentage &gt;2.5 ng/patch</td>
<td>35.7</td>
<td>73.3</td>
<td>33.3</td>
</tr>
<tr>
<td>Range, ng/patch</td>
<td>3.1–16.0</td>
<td>2.8–40.2</td>
<td>2.9–34.1</td>
</tr>
<tr>
<td>Percentage &gt;25 ng/patch</td>
<td>0</td>
<td>20</td>
<td>8.3</td>
</tr>
<tr>
<td>Range</td>
<td>26.8–40.1</td>
<td>34.1</td>
<td></td>
</tr>
</tbody>
</table>

*Participants received 60 mg/70 kg (low), and 120 mg/70 kg (high) codeine sulfate on Tuesday, Thursday, and Monday of weeks 4 and 8, respectively. The 15-h patches were applied 8 h after dosing, according to the schedule in Fig. 1B.*
ANALYSIS OF DUPLICATE PATCHES

Codeine concentrations in duplicate weekly patches were compared to determine reproducibility of codeine sweat excretion (Table 2 in the online Data Supplement). Patches were applied to the sides of the abdomen and worn the week of dosing or the first or second weeks after dosing. Twenty of 41 patch pairs were positive for codeine at the LOQ in at least one patch. Four pairs contained low concentrations of codeine (\( <12 \text{ ng/patch} \)) in only one patch and were not included in statistical calculations. The mean (SD) difference in codeine concentration between positive duplicate patches was 5.9 (7.0) ng/patch [median (range), 3.0 (0.3–28.8) ng/patch]. Nine of 16 pairs (56%) were within 20%, 6 of 16 (38%) were within 40%, and 1 pair (6%) had a difference of >40%. There was a significant correlation between codeine concentrations in positive duplicate sweat patches \((P < 0.01)\).

CUMULATIVE EXCRETION OF CODEINE

We examined cumulative codeine excretion in sweat by comparing the sum of codeine concentrations in hourly patches with those in weekly patches (Table 3). Sixteen sets of positive weekly and hourly patches (low and high doses combined) were available for comparison. The sum of hourly patch concentrations was greater than weekly patch concentration in 11 sets, with a mean (SD) difference of 25 (19.8) ng/patch [median (range), 17.4 (0.3–57.5) ng/patch]. The mean hourly patch sum was 57.9 (60.4) ng/patch [41.0 (5.4–240.3) ng/patch], which was significantly higher than the mean corresponding weekly patch concentration [44.0 (55.5) ng/patch; median (range), 20.6 (1.7–225.1) ng/patch; \( P < 0.05 \)].

Discussion

Metabolites of codeine were not detected in any sweat patch, which is partially explained by the physiochemical differences between plasma and sweat. Codeine, a lipophilic, basic compound, diffuses through membranes and becomes ionized in sweat at its lower pH (4–6), leading to accumulation and ion-trapping in this matrix. Norcodeine likely was not detected in sweat because it is present in much lower concentrations in blood and is less lipophilic than codeine. Morphine, a less lipophilic minor codeine metabolite, has a similar pKa of 8.1, but was not

| Table 2. Comparison between codeine concentrations in weekly sweat patches worn each week of the 10-week study.\(^a\) |
|-----------------|-----------------|----------------|-----------------|-----------------|
| Week(s)         | No.             | Mean\(^b\) (SD) ng/patch | Range, ng/patch | LOQ, SAMHSA     |
| Washout 1–3     | 44              | 0.0                     | 0.0             | 0.0             |
| Low dose (60 mg/70 kg) | 4              | 38.6 (59.9)             | 0–225.1         | 84.6            |
|                  | 5              | 4.6 (5.3)               | 0–17.1          | 63.6            |
| Placebo 6–7     | 21              | 0.0                     | 0.0             | 0.0             |
| High dose (120 mg/70 kg) | 8              | 34.1 (32.7)             | 0–96.2          | 81.8            |
|                  | 9              | 7.7 (7.1)               | 0–20.5          | 70.0            |
|                  | 10             | 0.6 (1.2)               | 0–3.1           | 25.0            |

\(^a\) At the beginning of each week, new duplicate sweat patches were applied to the back or abdomen of participants, and the previous week's patches were removed. Three low (60 mg/70 kg) and 3 high (120 mg/70 kg) doses of codeine sulfate were administered on Tuesday, Thursday, and Monday of weeks 4 and 8, respectively. Rates of positive patches are compared between the method LOQ (2.5 ng/patch) and the proposed SAMHSA cutoff (25 ng/patch for codeine, morphine, and 6-AM). \(^b\) Mean codeine concentration of all (including negative) weekly sweat patches collected during the respective week.

<table>
<thead>
<tr>
<th>Weekly patch concentrations, 60 mg/70 kg (3 doses)</th>
<th>Sum of hourly patch concentration, ng/patch</th>
<th>Difference, ng/patch</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 mg/70 kg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24.3</td>
<td>29.8</td>
<td>5.5</td>
</tr>
<tr>
<td>50.0</td>
<td>31.0</td>
<td>−19.0</td>
</tr>
<tr>
<td>1.7</td>
<td>8.4</td>
<td>6.8</td>
</tr>
<tr>
<td>225.1</td>
<td>240.3</td>
<td>15.2</td>
</tr>
<tr>
<td>14.4</td>
<td>5.4</td>
<td>−9.0</td>
</tr>
<tr>
<td>11.1</td>
<td>6.9</td>
<td>−4.2</td>
</tr>
<tr>
<td>15.9</td>
<td>59.3</td>
<td>43.4</td>
</tr>
<tr>
<td>15.9</td>
<td>6.9</td>
<td>−9.0</td>
</tr>
</tbody>
</table>

\(^a\) Codeine concentrations (ng/patch) in hourly patches were summed and compared with codeine concentrations (ng/patch) in weekly patches. Sixteen complete weekly sets were available for comparison. When available, the mean of 2 duplicate weekly patches was compared with the sum of hourly patches. Three low (60 mg/70 kg) and 3 high (120 mg/70 kg) administrations of oral codeine sulfate occurred on Tuesday, Thursday, and Monday during weeks 4 and 8 of the 10-week study. Hourly patches were applied according to the schedule in Fig. 1B, after each of 3 low or high codeine administrations. Weekly patches were applied before dosing and worn for 1 week during 3 low or 3 high codeine administrations.
detected in any patch. The area under the curve for nonconjugated morphine in plasma was reported as 4.4% of the area under the curve for codeine after controlled codeine phosphate administration (19). Therefore, little free morphine is available for transfer into sweat.

Detection of codeine in the absence of its more polar metabolites also has been reported in other controlled codeine administration studies (5, 6); however, minor metabolites were detected in low concentrations in sweat under heat-stimulated conditions (2). Sudormed Fast Patches, a unique type of heat-activated sweat patch containing a metallic activation disc and food-grade sodium acetate, were applied to the torso and palms of the hands according to the same codeine dosing schedule as in the present study (2). Torso Fast Patches were positive for codeine and negative for metabolites; however, 8.3% of hand-held Fast Patches contained norcodeine at 11–26 ng/patch, and 7.1% contained trace quantities of morphine at ≤2 ng/patch. Differences in the skin anatomy and physiology of the torso and palms of the hands may have been responsible for observed differences in codeine and metabolite kinetics in sweat.

The time course of codeine excretion in sweat was evaluated with 1 to 15 h patches. Codeine detection depended on the duration of patch wear and when the patch was applied and removed relative to dosing. Codeine in hourly patches worn within the first 24 h after dosing increased from 4.5% in 1-h patches (n = 179) to 40% in 15-h patches (n = 95). Only 4.5% of 15-h patches were positive when worn 24 h after dosing (n = 67). Using a similar technique, Kintz et al. (6) observed peak codeine concentrations in the 12- to 24-h patch with lower concentrations from 72 to 98 h.

Participants in the present study received 3 codeine doses of 60 mg/70 kg within 1 week, followed 3 weeks later by 3 codeine doses of 120 mg/70 kg. Administration of multiple doses permitted evaluation of the dose–concentration relationship and more closely approximated drug usage patterns. To our knowledge, this is the first multiple-dose controlled opioid administration study that addresses dose–concentration relationships and stability of drug on the patch.

A possible mechanism of codeine deposition in sweat patches applied several days after last drug administration is release of the drug from adipose and cutaneous depots. Previous studies suggested that drugs may be present for long periods in the stratum corneum (20, 21) and in adipose tissue beneath the skin’s dermal layer (22). Hygienic washing with isopropanol did not completely remove externally applied cocaine, methamphetamine, and heroin, indicating that drugs are tightly bound in skin (1). In the present study, codeine remained detectable in plasma for only ~24 h (23). This demonstrates that codeine found in sweat patches applied up to 2 weeks after last codeine administration was the result of deposition from sources other than passive diffusion from blood.

Codeine concentrations in sweat patches were highly variable within and between participants. In 2 participants, all weekly patches applied during dosing were negative for codeine, whereas 3 hourly patches had concentrations < 8.0 ng/patch. In a third participant, codeine was detected in weekly patches applied during dosing, the week after dosing, and in multiple hourly patches.

Data from this and other research suggest that the large intra- and intersubject variability is the result of multiple complex and dynamic metabolic processes. For example, the site of patch application on the body influences codeine concentrations in sweat (16, 24). Other sources of variability include differences in sweat output between individuals and potential loss or dynamic exchange of codeine between the patch and the skin (1, 24).

In this study, we also examined the reproducibility of codeine excretion in sweat. Duplicate patches were applied for 1 week during and 1 week after codeine administration. Four of 20 pairs contained codeine in only 1 patch. Overall, results of the present study indicated that codeine concentrations in duplicate sweat patches after controlled codeine administration were generally consistent at the method LOQ of 2.5 ng/patch and the proposed SAMHSA cutoff.

We examined the cumulative excretion of codeine in sweat by comparing codeine concentrations in weekly sweat patches with the sums of codeine concentrations in hourly patches. It was thought that the sweat patch acts as a passive reservoir for drug accumulation; however, there is evidence of loss or dynamic exchange of drugs between skin and the patch (22, 24). Our results indicated that the sum of codeine concentrations in hourly patches were generally higher than in patches worn for 1 week, indicating possible loss from patches applied for longer periods and/or dynamic exchange between the skin and the patch. Possible mechanisms include loss of codeine through the acrylate backing, and reabsorption of codeine into the stratum corneum (24). Alteration of codeine structure through metabolism or chemical degradation on the skin’s surface was not detected at the method LOQ.

Excretion of codeine in sweat occurred up to 2 weeks after the last dose. Of the weekly sweat patches worn the week after the last low and high doses, 63.6% and 70%, respectively, were positive for codeine at the method LOQ. In addition, 2 of 8 weekly sweat patches worn the second week after the last high dose contained codeine below the SAMHSA cutoff. These data provide critical information about the duration of opioid detection in sweat, an important parameter for interpreting sweat test results.

In another of our studies determining concordance between opioid excretion in urine and sweat, 28 positive weekly sweat patch results were found in the absence of a positive urine (17), 5 of which contained 6-AM above the proposed cutoff. Similarly, we examined cocaine and its metabolites in methadone maintenance patients and...
found discrepancies between sweat patch results and urinalyses in ~20% of cases (25).

The proposed Mandatory Guidelines for Federal Workplace Drug Testing Programs (18) indicated that sweat testing may be used for return to duty and follow-up testing because of its large window of detection and tamper-evident patch design. Sweat testing enables continuous determination of drug use outside the work environment and serves as a deterrent to future drug use. The present study comprehensively evaluated hourly and weekly sweat patches to characterize the duration, accumulation, reproducibility, time of first appearance, and dose–concentration relationship of codeine excretion in sweat, which are valuable guides for interpretation of opioid sweat results. Sweat testing is a useful alternative technique for qualitative monitoring of opioid use.

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References