# Monitoring Opiate Use in Substance Abuse Treatment Patients With Sweat and Urine Drug Testing

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## Abstract

**Although urine testing remains the standard for drug use monitoring, sweat testing for drugs of abuse is increasing, especially in criminal justice programs. One reason for this increase is sweat testing may widen the detection window compared to urine testing. Drug metabolites are rapidly excreted in urine limiting the window of detection of a single use to a few days. In contrast, sweat collection devices can be worn for longer periods of time. This study was designed to compare the efficacy of sweat testing versus urine testing for detecting drug use. Paired sweat patches that were applied and removed weekly on Tuesdays were compared to 3–5 consecutive urine specimens collected Mondays, Wednesdays, and Fridays (355 matched sweat and urine specimen sets) from 44 patients in a methadone-maintenance outpatient treatment program. All patches ($N$ = 925) were extracted in 2.5 mL of solvent and analyzed by ELISA immunoassay for opiates (cutoff concentration 10 ng/mL). A subset ($N$ = 389) of patches was analyzed by gas chromatography–mass spectrometry (GC–MS). Urine specimens ($N$ = 1886) were subjected to qualitative analysis by EMIT (cutoff 300 ng/mL). Results were evaluated to (1) determine the identity and relative amounts of opiates in sweat; (2) assess replicability in duplicate patches; (3) compare ELISA and GC–MS results for opiates in sweat; and (4) compare the detection of opiate use by sweat and urine testing. Opiates were detected in 38.5% of the sweat patches with the ELISA screen. GC–MS analysis confirmed 83.4% of the screen-positive sweat patches for heroin, 6-acetylmorphine, morphine, and/or codeine (cutoff concentration 5 ng/mL) and 90.2% of the screen-negative patches. The sensitivity, specificity, and efficiency of ELISA opiate results as compared to GC–MS results in sweat were 96.7%, 72.2%, and 89.5%, respectively. Heroin and/or 6-acetylmorphine were detected in 78.1% of the GC–MS-positive sweat patches. Median concentrations of heroin, 6-acetylmorphine, morphine, and codeine in the positive sweat samples were 10.5, 13.6, 15.9, and 13.0 ng/mL, respectively. Agreement in paired sweat patch test results was 90.6% by ELISA analysis. For the purposes of this comparison of ELISA sweat patch to EMIT urine screening for opiates, the more commonly used urine test was considered to be the reference method. The sensitivity, specificity, and efficiency of sweat patch results to urine results for opiates were 68.6%, 86.1%, and 78.6%, respectively. There were 13.5% false-negative and 7.9% false-positive sweat results as compared to urine tests. Analysis of sweat patches provides an alternate method for objectively monitoring drug use and provides an advantage over urine drug testing by extending drug detection times to one week or longer. In addition, identification of heroin and/or 6-acetylmorphine in sweat patches confirmed the use of heroin in 78.1% of the positive cases and differentiated illicit heroin use from possible ingestion of codeine or opiate-containing foods. However, the percentage of false-negative results, at least in this treatment population, indicates that weekly sweat testing may be less sensitive than thrice weekly urine testing in detecting opiate use.**

## Introduction

The drug treatment, criminal justice, workplace, and military drug-testing programs have relied extensively on urine drug testing to monitor individuals' opiate use and to stem some of the problems associated with illicit drug use. Urine drug testing has become an established, reliable, standardized, relatively inexpensive, and widely available technology. One of the disadvantages of urine testing is the relatively short window of drug detection requiring frequent specimen collection to monitor drug use adequately. Furthermore, adulteration of urine specimens can be accomplished by adding a wide variety of chemical, and simply ingesting large quantities of water can lower drug concentrations below threshold limits. Careful monitoring of specimen collection, sometimes including direct observation, may be necessary to prevent specimen adulteration. In addition, the ingestion of opiate-containing foods (poppy seeds) or licit opioid analgesics can produce positive urine opiate tests. This has complicated the interpretation of positive opiate tests and contributed to the recent federally mandated increase in the opiate cutoff concentration from 300 ng/mL to 2000 ng/mL and the addition of 6-acetylmorphine confirmation to identify heroin abuse. In response to these issues, and because of the unique information provided from monitoring drugs in alternative biological matrices, testing of drugs of abuse in sweat, saliva, and hair has gained increased importance.

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Sweat is an alternative matrix for drug testing that may provide an additional tool for monitoring drug use. A number of drugs of abuse have been found to be secreted in sweat including methadone (1,2), amphetamines (3–7), methamphetamine (4,6,8–10), alcohol (8), morphine (2,8,11,12), heroin (7,13), cocaine (2,7,13–18,19), nicotine (11), and marijuana (7,11). In addition, sweat on clothing has been used to detect drugs for forensic purposes (8,12,20). A promising method for routine sweat collections appears to be the sweat patch (13,14,21). Our laboratory has recently demonstrated the utility of sweat patches for monitoring cocaine use in a treatment population. This paper reports the results of sweat testing for opiate use in the same population. The sweat patch device consists of an adhesive layer on a thin transparent film of surgical dressing and a rectangular, absorbent, cellulose pad (14 $cm^2$). The surgical dressing film allows oxygen, carbon dioxide, and water vapor to escape, whereas the nonvolatile constituents in sweat are retained in the absorbent pad. Sweat patches are applied to the torso or arm after cleansing of skin with an alcohol wipe to prevent contamination and improve adherence. The patches are tamper resistant; they have identifying serial numbers and once removed cannot be reapplied to the skin. Because the patches are worn for one week, the window of detection can be longer than that provided by urine testing.

Limited data are available on the identity and concentration of opiate analytes secreted in sweat following administration of heroin, morphine or codeine from controlled-dosing studies. An immunoassay for opiates was first used to document the presence of morphine in sweat after 10-mg oral doses of morphine (8). More than 15 years later, heroin and 6-acetylmorphine, but not morphine, were detected in all ($N = 6$) sweat patches collected up to 120 h after a single 20 mg intravenous dose of heroin to two human subjects (13). Heroin was the primary analyte detected in sweat in the first 24-h patch, but concentrations decreased in sweat patches worn for longer periods of time, suggesting heroin hydrolysis in the patch. In another study, codeine (90 mg) was orally administered to six subjects and sweat was collected with the PharmChek™ Sweat Patch over the following six days (22). Codeine was detected in sweat within 1 h, peak secretion occurred between 12 to 24 h, and concentrations remained relatively stable from 48 to 144 h. A fivefold variation in peak codeine concentration was noted between subjects and up to a threefold variation in patches worn by the same subject on different areas of the body. Morphine was not detected in any patch (limit of detection = 0.5 ng/patch). Codeine secretion in sweat measured for up to 24 h in six subjects after oral administration of 60 mg codeine sulfate confirmed the early appearance of codeine in sweat (1 h) with peak concentrations between 4 and 24 h (23).

Sweat patches have also been used to monitor opiate use in outpatient drug-treatment settings. Heroin, 6-acetylmorphine, and morphine were detected in 17 sweat patches collected from known heroin users admitted to the Haight Ashbury Free Clinic in San Francisco (13). Heroin concentrations were greater than 6-acetylmorphine concentrations in approximately half of the patches; there was no consistent ratio between the analytes. Furthermore, morphine concentrations exceeded 6-acetylmorphine levels in about one-third of the patches. In a study of 20 heroin users in a detoxification clinic, sweat patches worn for five days were analyzed for heroin, 6-acetylmorphine, morphine, and codeine by GC–MS or LC–MS (7). In the eight cases where heroin use was confirmed, 6-acetylmorphine was the primary analyte, with 6-acetylmorphine concentrations exceeding those of heroin and morphine, except in one instance. Codeine use was noted in four cases; codeine concentrations were 10 to 100 times greater than morphine concentrations in the sweat. In another study of methadone-maintenance patients, 6-acetylmorphine, morphine, and codeine, but not heroin, were detected in sweat patches worn for seven days by individuals abusing heroin (24).

The present study evaluated the use of sweat patches for monitoring opiate use in a drug-abuse treatment population (19,25). Duplicate patches were applied to methadone-maintenance patients participating in a clinical trial of a behavioral treatment for drug abuse. Patches were worn for one week, removed, and analyzed by ELISA immunoassay and GC–MS for the presence of opiates. Urine specimens collected over a similar timeframe were analyzed for opiates by EMIT immunoassay. Results were evaluated to (1) determine the identity and relative amount of opiates in sweat; (2) assess replicability in duplicate patches; (3) compare two methods (ELISA and GC–MS) of assaying opiates in sweat; and (4) compare the detection of opiate use by sweat and urine drug testing.

## Methods

### Participants

The participants were 44 patients (29 male, 15 female; 20 African American, 24 Caucasian) who were recruited from among participants in a clinical trial of a behavioral treatment for cocaine and heroin abuse (25). Individuals were eligible for the primary treatment study if they were between the ages of 18 and 65, if they qualified for methadone maintenance according to the Food and Drug Administration guidelines, and if they reported histories of intravenous opiate use. All patients received standard methadone-maintenance drug-abuse treatment throughout the study that included daily methadone (50 to 80 mg/day, oral) and weekly individual counseling. The NIDA Institutional Review Board for human research approved this study. All volunteers gave informed written consent prior to study participation and were paid $10/week for wearing sweat patches. Details of the experimental treatment procedures have been described (25).

### Specimen collection and analysis

Volunteers could participate for a maximum of 18 weeks. Participants visited the clinic seven days per week to receive methadone. Urine specimens were collected on Monday, Wednesday, and Friday under direct observation by trained staff. Each specimen was analyzed for opiates (EMIT d.a.u.™, Behring Diagnostics, San Jose, CA) with a cutoff concentration of 300 ng/mL within 24 h of collection.

Sweat patches were applied each Tuesday to the subject's lower abdomen and back after the skin was cleaned with an alcohol wipe. The study number, the subject's identification code number, patch code number, and the date of application were recorded on a 3 × 5-in. index card. The following Tuesday, prior to removing each sweat patch, technicians examined the patch to

determine its condition. Patch condition was rated according to the following categories: I = intact patch; C = curling (edges); E = exposed patch edge; and M = missing patch. To remove patches, the technicians pulled the adhesive edge along the side of the patch. Once the adhesive along the side of the patch was away from the skin, the patch was pulled outward from both top corners equally on both sides of the patch. Technicians were instructed to wear gloves and to prevent contamination of the absorbent pad by not touching it. Technicians placed the patch adhesive-side down in the center of the index card, recorded the date the patch was removed and the condition of the patch, and placed the card in a resealable bag. The bag was sealed and stored in a refrigerator until transferred to a freezer at the end of the day.

At the conclusion of the study, patches were sent to PharmChem Laboratories, Inc. (Menlo Park, CA) for analysis. The patches were coded, randomized, and analyzed as blind specimens by the laboratory. The absorbent pad was removed from the adhesive layer, placed in a 5-mL screw-cap plastic tube with 2.5 mL of a sweat extraction buffer, 75% methanol/25% 0.2M sodium acetate (pH 5.0), and shaken for 30 min to extract the opiates. The eluent was then analyzed according to package directions by competitive enzyme immunoassay (ELISA) with the STC Opiate Micro-Plate EIA (STC Diagnostics, Bethlehem, PA). ELISA sweat results were reported as nanograms per milliliter of sweat extraction buffer according to the standardized reporting format. A 10-ng/mL cutoff was established and validated by STC Diagnostics and was used in this study. Because 2.5 mL of buffer was used to extract the patch, the 10-ng/mL cutoff concentration is equivalent to a concentration of 25 ng/patch. Both PharmChem Laboratories, Inc., which holds the license for PharmChek sweat patch distribution and which provides the analysis of these patches for treatment, criminal justice, and workplace drug-testing programs, and STC Diagnostics, manufacturer of the reagents, report results as nanograms per milliliter of elution solvent. The percent cross-reactivity at 10 ng/mL for each analyte was 100% for morphine, 28% for heroin, 30% for 6-acetylmorphine, 588% for codeine, 143% for hydrocodone, 16% for hydromorphone, and 30% for oxymorphone (26). A subset of sweat specimens (389 patches) was confirmed by GC–MS analysis operated in the selected ion monitoring mode (Hewlett-Packard 5890 GC interfaced to a Hewlett-Packard mass selective detector, Hewlett-Packard, Little Falls, DE) according to the laboratory's standard procedures. Limit of detection was 3 ng/mL for heroin, 6-acetylmorphine, morphine, and codeine. Limits of quantitation were 5 ng/mL for heroin and 3 ng/mL for 6-acetylmorphine, morphine, and codeine. Cutoff concentrations for positive specimens were 10 ng/mL for ELISA and 5 ng/mL for GC–MS.

**Table I. Opiate Analytes Identified by GC–MS in Positive Sweat Patches**

| Opiate analytes | % of Positive patches |
|---|---|
| 6-AM*, Morphine, and Codeine | 37.6% |
| Heroin, 6-AM, Morphine, and Codeine | 16.1% |
| Codeine | 9.5% |
| Morphine and Codeine | 6.9% |
| 6-AM and Morphine | 6.6% |
| Morphine | 5.5% |
| 6-AM | 4.7% |
| 6-AM and Codeine | 4.7% |
| Heroin and 6-AM | 4.0% |
| Heroin, 6-AM, and Morphine | 3.3% |
| All other analyte combinations | < 1% |

* 6-AM, 6-acetylmorphine.

### Data analysis

Four main analyses were conducted: (1) identification and quantitation of opiates in sweat; (2) comparison of replicate patch ELISA results; (3) comparison of opiate detection in sweat by ELISA and GC–MS; and (4) comparison of sweat test results to results from different combinations of urine collection periods. Median and maximum concentrations of heroin, 6-acetylmorphine, morphine, and codeine as determined by GC–MS were calculated for opiate-positive sweat patches. In patches positive for opiates by GC–MS, the percent positive for specific analytes and for important combinations of analytes were determined. Results of paired patches (abdomen and back) were compared to identify those with discrepant ELISA results (i.e., one positive and one negative).

For comparison of GC–MS and ELISA sweat results, a patch was considered positive by GC–MS if heroin, 6-acetylmorphine, morphine, or codeine were detected at or above 5 ng/mL and positive by ELISA if results were greater than or equal to 10 ng/mL. A true positive (TP) was defined as positive by both ELISA and GC–MS; a true negative (TN) was defined as negative by both ELISA and GC–MS; a false positive (FP) was defined as a positive ELISA result and negative GC–MS result; and a false negative (FN) was defined as negative ELISA result and positive GC–MS result. Sensitivity of the assay was calculated as TP/(TP + FN). Specificity was calculated as TN/TN + FP). Efficiency was calculated as (TP + TN)/N where N = the total number of analyzed patches. All ratios were multiplied by 100 and reported as percentages.

The results of opiate sweat tests (ELISA) of patches worn for 7 days were compared to the results of urine opiate immunoassay tests (EMIT) for four different monitoring intervals with the urine results as the reference method. Sensitivity, specificity and efficiency were determined as described above for four urine collection intervals: (1) Wednesday, Friday, and Monday (WFM) urine collections after the Tuesday sweat patch application; (2) Monday before and Wednesday, Friday, and Monday (MWFM) after the Tuesday patch application; (3) Wednesday, Friday, Monday, and Wednesday (WFMW) after the Tuesday patch application; and (4) Monday before and Wednesday, Friday, Monday, and Wednesday (MWFMW) after the Tuesday patch application (Figure 1). Comparisons were made only for those patch specimens in which all urine specimens collected during the comparison intervals were included. Actual opiate use was assumed if any urine specimen collected during the interval tested positive for opiates by EMIT; if all urine specimens were negative, drug abstinence was assumed. Sweat was determined to be positive if at least one of the two paired patches was positive for opiates by ELISA (cutoff concentration 10 ng/mL). In addition, 7-day ELISA sweat patch results were compared to EMIT urine test results from single weekly urine collections on the Wednesday, Friday, or Monday following patch application to evaluate the differences in once or

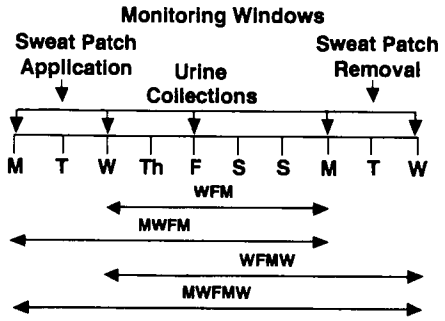


**Figure 1.** Diagram of sweat patch and urine specimen collections. Sweat patch results (patch applied on Tuesdays for seven days) were compared to opiate urine tests of specimens collected over the four time intervals as indicated by the horizontal lines. M, Monday; W, Wednesday; F, Friday.

thrice-weekly urine collection. For the purpose of these comparisons only, urine EMIT testing for opiates was used as the reference method and sweat patch ELISA results were compared to the urine results. Therefore, a TP was assigned if at least one patch and one urine specimen were positive; an FP was assigned if at least one patch was positive, but all urine specimens were negative; a TN was assigned if both patches and all urine specimens were negative; and an FN was assigned if both patches were negative and at least one urine specimen was positive.

## Results

### Analyte analysis in sweat

A total of 925 sweat patches were collected from 44 participants and analyzed by ELISA; 356 (38.5%) specimens tested positive for opiates at concentrations ≥ 10 ng/mL. A subset of 389 patches (297 screen-positive and 92 screen-negative patches) was analyzed by GC–MS for heroin, 6-acetylmorphine, morphine, and codeine. One or more of these opiates were detected at concentrations ≥ 5 ng/mL in 274 sweat patches. A total of 115 sweat patches were negative by GC–MS. Heroin was identified in 67 of 274 (24.5%) patches with a median concentration of 10.5 ng/mL (range 5 to 195 ng/mL). 6-Acetylmorphine was confirmed in the highest number of positive patches, 212 of 274 specimens (77.4%). The median 6-acetylmorphine concentration in sweat was close to that of heroin at 13.6 ng/mL (range 5 to 181 ng/mL). Similar numbers of patches contained morphine and codeine, 208 and 206 patches, respectively. The median and range of concentrations of these opiates in the positive patches were 15.9 ng/mL (range 5 to 112 ng/mL) for morphine and 13.0 ng/mL (range 5 to 360 ng/mL) for codeine. As shown in Table I, 6-acetylmorphine, morphine, and codeine were identified concurrently in the largest percentage of GC–MS-positive patches (37.6%); 16.1% of the positive patches contained all four analytes. Heroin and/or 6-acetylmorphine were confirmed in 78.1% of the patches, with morphine and/or codeine only in 21.9%.

ELISA opiate results and GC–MS concentrations of heroin, 6-acetylmorphine, morphine, and codeine concentrations in sweat collected in patches applied to the abdomen and to the back across the course of the trial are illustrated for two representative patients in Figure 2. Most ELISA sweat tests were positive for Subject A with good agreement between abdomen and back patch results. Opiate concentrations increased during the later weeks of the study. However, the increases in opiate concentration were observed in patches collected during July and August and could be due to an increase in drug use or an increase in sweat secretion during the summer

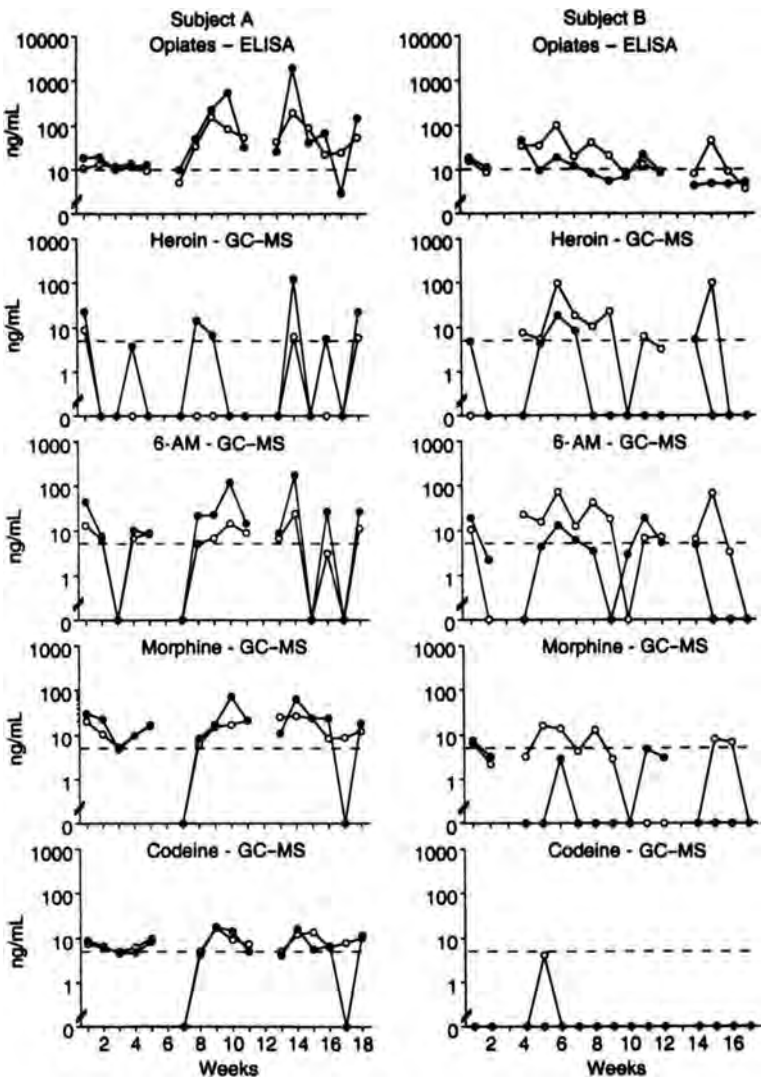


**Figure 2.** Semiquantitative results of sequential sweat patches collected from individual treatment patients over 18 weeks. Opiate (ELISA), and GC–MS concentrations of heroin, 6-acetylmorphine, morphine, and codeine were determined in replicate sweat patches applied to the abdomen (closed symbols) and back (open symbols) for one week. Horizontal dashed lines indicate cutoff concentrations for positive specimens (ELISA 10 ng/mL and GC–MS 5 ng/mL). Data points are not connected where specimen results are not available.

months. A good correlation (30 of 32 patches) was also noted between the ELISA and GC–MS results with only a single unconfirmed ELISA-positive and single unconfirmed ELISA-negative result. Heroin was found in fewer patches than 6-acetylmorphine, morphine, and codeine. In most positive ELISA patches, heroin and/or 6-acetylmorphine were confirmed in the patch substantiating heroin rather than morphine or codeine use. Approximately 50% of patches collected from Subject B were positive for opiates by ELISA with generally lower concentrations in the abdomen patches as compared to the back patches. There were three unconfirmed ELISA-positive results (6-acetylmorphine and morphine detected but below the LOQ) and five unconfirmed negative results. None of the patches were positive for codeine in this subject, with greater numbers of patches confirmed positive for heroin and 6-acetylmorphine than morphine.

### Comparison of paired sweat patches

The replicability of patch testing was evaluated by comparing paired patches placed on the abdomen and lower back. Semiquantitative ELISA results were available for 437 pairs of patches

**Table II. Comparisons of Paired Sweat Patches Applied to Abdomen and Back with Discrepant ELISA Opiate Results***

| Patch pair | Subject code | Abdomen ELISA Opiates† | Abdomen GC–MS HER‡ | Abdomen GC–MS 6-AM | Abdomen GC–MS MOR | Abdomen GC–MS COD | Back ELISA Opiates† | Back GC–MS HER | Back GC–MS 6-AM | Back GC–MS MOR | Back GC–MS COD |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | A | 12.7 | 0 | 8.1 | 16.7 | 8 | 9.3 | 0 | 8.6 | 15.9 | 9.9 |
| 2 | A | 2.9 | 0 | 0 | 0 | 0 | 23.8 | 0 | 0 | 8.5 | 7.9 |
| 3 | B | 11.1 | 0 | 2.1 | 3.1 | 0 | 8.5 | 0 | 0 | 2.1 | 0 |
| 4 | B | 9.4 | 4.1 | 4.2 | 0 | 0 | 32.8 | 5.3 | 15.3 | 15.9 | 3.9 |
| 5 | B | 7.9 | 0 | 3.4 | 0 | 0 | 40.0 | 10.1 | 42.2 | 13.2 | 0 |
| 6 | B | 5.2 | 0 | 0 | 0 | 0 | 20.9 | 22.5 | 18.3 | 2.9 | 0 |
| 7 | B | 4.7 | 0 | 0 | 0 | 0 | 45.7 | 101 | 67.8 | 7.7 | 0 |
| 8 | C | 9.0 | – | – | – | – | 21.9 | – | – | – | – |
| 9 | C | 19.9 | – | – | – | – | 6.4 | – | – | – | – |
| 10 | C | 2.1 | – | – | – | – | 12.8 | – | – | – | – |
| 11 | E | 7.4 | 0 | 3.2 | 0 | 4.8 | 45.3 | 10.2 | 13.8 | 0 | 9.6 |
| 12 | F | 4.9 | – | – | – | – | 12.4 | 0 | 1.1 | 0 | 4.0 |
| 13 | H | 12.4 | – | – | – | – | 5.1 | – | – | – | – |
| 14 | H | 10.4 | – | – | – | – | 9.2 | – | – | – | – |
| 15 | I | 14.9 | 0 | 5.2 | 8.1 | 1.8 | 2.8 | – | – | – | – |
| 16 | I | 15.9 | 9.7 | 12.1 | 0 | 0 | 1.8 | – | – | – | – |
| 17 | I | 62.4 | 4.2 | 8.1 | 10.5 | 5.4 | 2.3 | – | – | – | – |
| 18 | N | 8.2 | 0 | 0 | 0 | 0 | 10.5 | 0 | 0 | 0 | 0 |
| 19 | N | 10.6 | – | – | – | – | 4.6 | 0 | 0 | 0 | 0 |
| 20 | O | 7.6 | 0 | 0 | 0 | 0 | 11.2 | 0 | 0 | 6.2 | 0 |
| 21 | O | 7.7 | 0 | 0 | 1.2 | 2.8 | 21.7 | 0 | 0 | 0 | 6.2 |
| 22 | P | 14.8 | – | – | – | – | 8.0 | – | – | – | – |
| 23 | R | 7.4 | 0 | 0 | 0 | 3.5 | 35.3 | 0 | 2.3 | 6.0 | 7.6 |
| 24 | U | 4.3 | – | – | – | – | 13.6 | – | – | – | – |
| 25 | V | 23.7 | 0 | 6.7 | 0 | 5.1 | 8.1 | – | – | – | – |
| 26 | V | 25.3 | 0 | 5.1 | 0 | 4.2 | 5.1 | – | – | – | – |
| 27 | V | 23.4 | 0 | 0 | 0 | 7.3 | 6.1 | – | – | – | – |
| 28 | V | 33.2 | 0 | 0 | 0 | 9.0 | 5.4 | – | – | – | – |
| 29 | X | 11.2 | 0 | 3.9 | 0 | 0 | 5.7 | – | – | – | – |
| 30 | Y | 29.8 | 7.7 | 4.4 | 0 | 0 | 6.6 | – | – | – | – |
| 31 | Z | 22.9 | 8.5 | 7.7 | 0 | 0 | 7.7 | – | – | – | – |
| 32 | BB | 7.8 | 0 | 0 | 0 | 0 | 30.4 | 0 | 0 | 0 | 3 |
| 33 | BB | 6.0 | 0 | 0 | 0 | 0 | 113 | 0 | 5.9 | 0 | 15.3 |
| 34 | BB | 8.3 | 0 | 0 | 0 | 0 | 74.6 | 0 | 2.7 | 0 | 8.5 |
| 35 | EE | 6.3 | 0 | 0 | 0 | 0 | 15.9 | 0 | 0 | 0 | 4.6 |
| 36 | EE | 7.1 | 0 | 0 | 0 | 0 | 10.0 | 0 | 0 | 0 | 0 |
| 37 | HH | 10.3 | – | – | – | – | 3.4 | – | – | – | – |
| 38 | HH | 19.2 | 0 | 0 | 0 | 3 | 7.2 | – | – | – | – |
| 39 | OO | 8.5 | 18.4 | 57.1 | 34.6 | 8.2 | 262 | 142 | 160 | 48.8 | 7.5 |
| 40 | OO | 9.1 | 0 | 0 | 10.0 | 10.1 | 14.0 | 0 | 0 | 10.1 | 7.9 |
| 41 | MM | 9.0 | – | – | – | – | 10.4 | – | – | – | – |

* All values are nanograms per milliliter. All specimens were tested by ELISA. A subset was confirmed by GC–MS; these results are shown when available. Specimens not analyzed by GC–MS are indicated by dashes (–).
† Morphine equivalence concentrations.
‡ Abbreviations: HER, heroin; 6-AM, 6-acetylmorphine; MOR, morphine; COD, codeine.

with congruent positive or negative results in 396 pairs (90.6%) at the 10-ng/mL cutoff. There was no significant difference in ELISA opiate concentrations between sweat patches applied to the abdomen and to the back when using a two-tailed paired *t*-test ($p = 0.230$, $\alpha = 0.05$). As shown in Table II, discrepant results (one positive and one negative) occurred in 41 pairs (9.4%); 53.7% were negative in the back patch and 46.3% were negative in the abdomen patch. In more than half of the discrepant pairs (51.2%), the semiquantitative ELISA concentrations for the positive patch ranged from 10 to 20 ng/mL. In 14 (34%) of the positive patches, concentrations ranged from 20.1 and 40 ng/mL; four patches had concentrations from 40.1 to 80 ng/mL; and two positive patches produced results of 113 and 262 ng/mL. GC–MS analysis was performed on 51 of the 82 paired patches; 31 ELISA-positive specimens and 20 of the ELISA-negative specimens. GC–MS results are included in Table II where available. Among the 51 discrepant patches tested in the confirmation assay, 78.4% were confirmed by GC–MS; there were 23 TP, 17 TN, 8 FP, and 3 FN results.

**Table III. Concordance Between ELISA and GC–MS Analyses of Sweat Patches for Opiate Monitoring: False Positives and False Negatives***

| | Subject code | ELISA Opiates† | GC–MS HER‡ | 6-AM | MOR | COD |
|---|---|---|---|---|---|---|
| **False Positives** | | | | | | |
| 1 | EE | 10.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| 2 | A | 10.1 | 0.0 | 0.0 | 4.7 | 4.4 |
| 3 | N | 10.5 | 0.0 | 0.0 | 0.0 | 0.0 |
| 4 | HH | 10.5 | 0.0 | 0.0 | 0.0 | 0.0 |
| 5 | T | 10.9 | 0.0 | 0.0 | 0.0 | 0.0 |
| 6 | B | 11.1 | 0.0 | 2.1 | 3.1 | 0.0 |
| 7 | X | 11.2 | 0.0 | 3.9 | 0.0 | 0.0 |
| 8 | X | 12.0 | 0.0 | 2.9 | 0.0 | 0.0 |
| 9 | BB | 12.1 | 0.0 | 0.0 | 0.0 | 0.0 |
| 10 | F | 12.4 | 0.0 | 1.1 | 0.0 | 4.0 |
| 11 | GG | 12.4 | 0.0 | 0.0 | 0.0 | 0.0 |
| 12 | HH | 12.4 | 0.0 | 3.0 | 3.6 | 2.3 |
| 13 | I | 13.8 | 0.0 | 2.2 | 3.5 | 3.5 |
| 14 | Y | 14.0 | 2.2 | 2.9 | 3.6 | 2.1 |
| 15 | BB | 14.9 | 0.0 | 0.0 | 0.0 | 0.0 |
| 16 | E | 14.9 | 0.0 | 4.4 | 0.0 | 0.0 |
| 17 | EE | 15.9 | 0.0 | 0.0 | 0.0 | 4.6 |
| 18 | U | 16.0 | 0.0 | 0.6 | 2.1 | 2.0 |
| 19 | X | 16.8 | 0.0 | 2.8 | 0.0 | 3.4 |
| 20 | L | 17.0 | 0.0 | 4.4 | 3.3 | 1.8 |
| 21 | U | 17.3 | 0.0 | 0.0 | 1.1 | 1.4 |
| 22 | U | 17.8 | 0.0 | 1.0 | 2.3 | 2.1 |
| 23 | HH | 19.2 | 0.0 | 0.0 | 0.0 | 3.0 |
| 24 | R | 19.4 | 0.0 | 3.7 | 4.4 | 3.9 |
| 25 | U | 20.0 | 0.0 | 1.3 | 1.0 | 1.3 |
| 26 | BB | 23.9 | 0.0 | 0.0 | 0.0 | 0.0 |
| 27 | U | 28.1 | 0.0 | 1.0 | 1.5 | 1.4 |
| 28 | BB | 30.4 | 0.0 | 0.0 | 0.0 | 3.0 |
| 29 | B | 43.3 | 0.0 | 0.0 | 0.0 | 0.0 |
| 30 | U | 48.2 | 0.0 | 1.7 | 2.0 | 1.8 |
| 31 | U | 74.6 | 0.0 | 2.5 | 4.0 | 2.3 |
| 32 | U | 89.5 | 0.0 | 1.5 | 3.7 | 3.7 |
| **False Negatives** | | | | | | |
| 1 | B | 4.2 | 5.4 | 4.7 | 0.0 | 0.0 |
| 2 | B | 7.9 | 5.2 | 6.3 | 0.0 | 0.0 |
| 3 | B | 8.4 | 3.1 | 6.8 | 0.0 | 0.0 |
| 4 | OO | 8.5 | 18.4 | 57.1 | 34.6 | 8.2 |
| 5 | B | 8.8 | 0.0 | 3.1 | 6.4 | 0.0 |
| 6 | B | 9.0 | 0.0 | 5.4 | 3.0 | 0.0 |
| 7 | OO | 9.1 | 0.0 | 0.0 | 10.0 | 10.1 |
| 8 | A | 9.3 | 0.0 | 8.6 | 15.9 | 9.9 |
| 9 | X | 9.9 | 0.0 | 0.0 | 5.0 | 0.0 |

* All values are nanograms per milliliter.
† Morphine equivalents.
‡ Abbreviations: HER, heroin; 6-AM, 6-acetylmorphine; MOR, morphine; COD, codeine.

### Comparison of ELISA and GC–MS sweat results

The presence of opiates was determined by both ELISA and GC–MS in 389 sweat patch specimens. A total of 297 (76.3%) of the 389 specimens screened positive by ELISA (≥ 10 ng/mL cutoff); of these, 265 (89.2%) were confirmed positive by GC–MS (≥ 5 ng/mL) for heroin, 6-acetylmorphine, morphine, and/or codeine. A similar rate of confirmation (90.2%) was achieved for the 92 screen-negative sweat specimens when analyzed by GC–MS. In the entire sample set, 265 were identified as TP (ELISA and GC–MS positive), 83 as TN (ELISA and GC–MS negative), 32 as FP (ELISA positive and GC–MS negative), and 9 as FN (ELISA negative and GC–MS positive) test results. FN specimens may be under-represented because of the small number of ELISA-negative specimens that were confirmed by GC–MS. The overall correlation (i.e., efficiency) of ELISA and GC–MS test results was 89.5%, with 96.7% sensitivity and 72.2% specificity.

ELISA sweat results for FP and FN specimens and respective GC–MS data are presented in Table III. Of the 32 FP tests, 25 had ELISA results < 20 ng/mL or close to the assay cutoff. One or more of the four opiate analytes were identified in 20 of these specimens by GC–MS, albeit below the ≥ 5-ng/mL cutoff. The number of FN results by GC–MS was low ($N = 9$), although a much smaller percentage of screen-negative specimens were analyzed. In all but two of the FN tests, the ELISA results were less than 20% below the cutoff of 10 ng/mL. In five of the FN patches, the total concentration of opiate analytes as determined by GC–MS was ≤ 10 ng/mL.

### Detection of opiate use by sweat and urine testing

Figure 3 illustrates six representative patients' patterns of opiate concentrations in sweat patches applied for one-week periods to the abdomen and back and qualitative urine results (positive or negative at 300 ng/mL) obtained from specimens collected three times weekly across the course of the

trial. Dashed lines indicate the 10-ng/mL cutoff concentration for the ELISA analysis in sweat. Semiquantitative opiate concentrations by ELISA are included for comparison. Urine EMIT results are either negative (< 300 ng/mL) or positive (≥ 300 ng/mL). Subject C had only a few positive opiate sweat and urine test results, primarily at the beginning of the treatment program. Opiate use declined significantly from days 12 through 51. Subject D had a similar pattern of results with consistent negative sweat and urine opiate tests from days 25 through 51, indicating decreased heroin use. Almost all sweat patches and most urine test results were positive for Subject E reflecting continued heroin use. Urine and sweat results for Subject F were concordant in almost all cases; the subject appeared to abstain from heroin use throughout most of the study with occasional heroin use documented in both urine and sweat test results. This participant had one sweat patch positive for opiates that was not accompanied by a positive urine specimen. Subject G is an interesting case with 23 positive urine tests throughout the study with no positive sweat patches. Subject H also had a large number of negative sweat patches with frequent single positive urine tests interspersed between negative urine results. Negative sweat patches with positive urine tests over the corresponding times occurred in only 13 of 44 subjects. Of these 13 subjects, 8 had only 1 or 2 negative sweat results. Three subjects had 7, 9, and 13 negative sweat patch results when a urine test was positive. A similar number of subjects (15 of 44) had positive sweat patches collected during weeks when all corresponding urine tests were negative. The majority (12 of 15) had only 1 or 2 inconsistent sweat and urine results; however, one individual had six positive sweat patch tests when the urine specimens were negative for opiates.

The relationship between urine and sweat drug tests was evaluated by comparing ELISA sweat results (10-ng/mL cutoff) from 355 patch pairs to EMIT results of urine specimens collected over four different time periods: WFM, WFMW, MWFM, and MWFMW (see Figure 1 for timeline). Concordance between sweat and urine was consistent across all four urine collection intervals (Table III), with sensitivity ranging from 63.4 to 68.6%, specificity

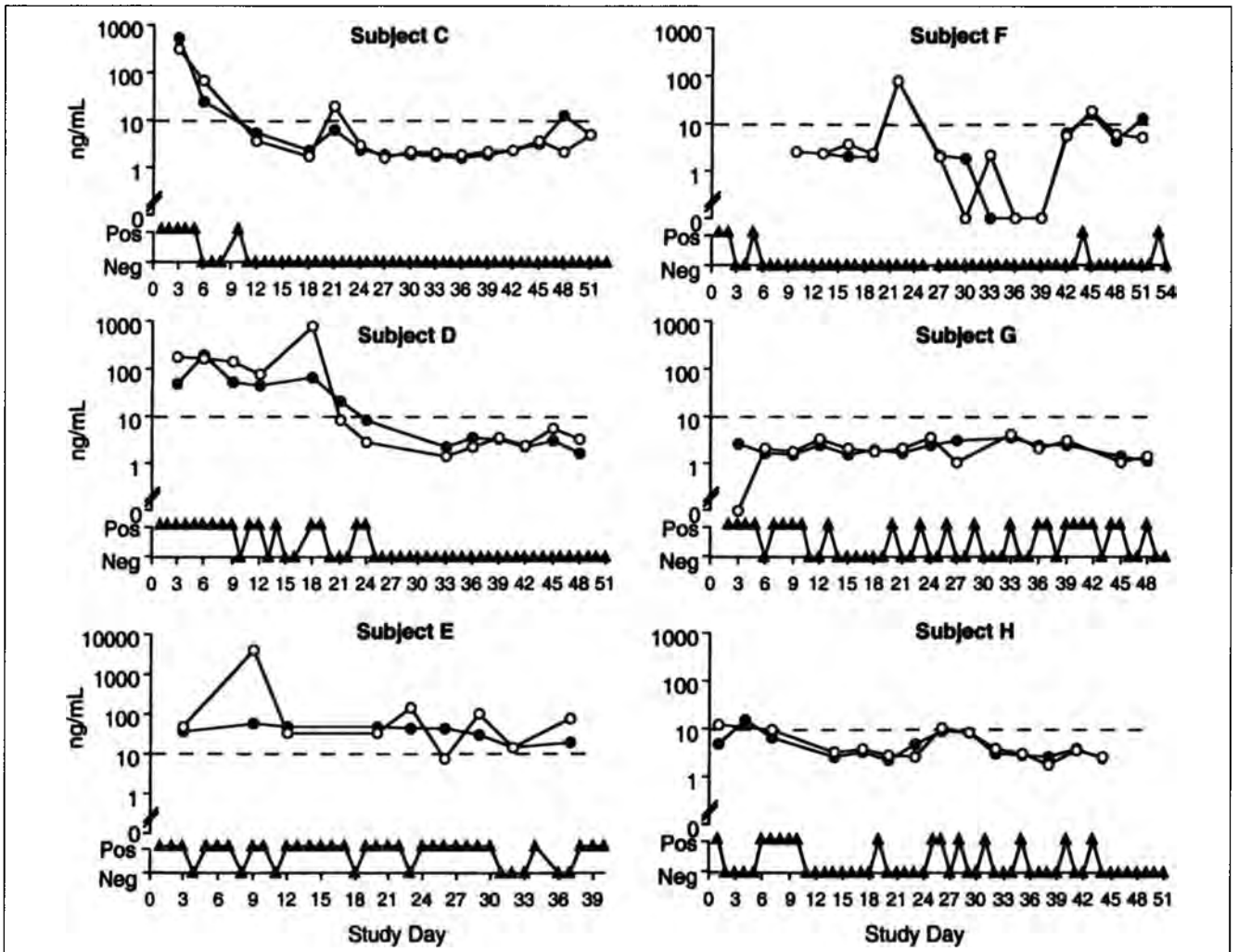


**Figure 3.** Semiquantitative results of sequential sweat patch (top panels) and urine specimens (bottom panels) collected from selected treatment patients over 18 weeks. Opiate (ELISA 300-ng/mL cutoff) concentrations were determined in replicate sweat patches applied to the abdomen (closed symbols) and back (open symbols) for one week. Horizontal dashed lines indicate cutoff concentrations for positive specimens (10 ng/mL for sweat patches). Qualitative opiate EMIT results (closed triangle symbols lower panel) were determined in urine specimens collected Mondays, Wednesdays, and Fridays. Data points are not connected where specimen results are not available.

ranging from 86.1 to 87.8%, and efficiency ranging from 75.8 to 78.6% at the 10-ng/mL ELISA cutoff. Concordance was reduced when a 5 ng/mL ELISA cutoff was applied: 33.0% TP; 37.5% TN; 19.4% FP; 10.1% FN; 76.5% sensitivity; 65.8% specificity; and 70.4% efficiency for the WFM urine collection interval.

**Table IV. Mean Percent Concordance of Detection of Opiate Use in Sweat and Urine from 44 Participants***

| | WMF | MWFM | WFMW | MWFMW |
|---|---|---|---|---|
| Sensitivity | 68.6% | 64.7% | 65.8% | 63.4% |
| Specificity | 86.1% | 87.6% | 86.1% | 87.8% |
| Efficiency | 78.6% | 76.6% | 76.9% | 75.8% |
| True Positive† | 29.6% | 31.0% | 29.9% | 31.3% |
| False Positive | 7.9% | 6.5% | 7.6% | 6.2% |
| False Negative | 13.5% | 16.9% | 15.5% | 18.0% |
| True Negative | 49.0% | 45.6% | 47.0% | 44.5% |

* Sweat specimens were analyzed by ELISA (10-ng/mL cutoff); urine specimens were analyzed by EMIT (300-ng/mL cutoff).
† True Positive, at least one patch and one urine specimen were positive; false positive, at least one patch was positive and all urine specimens were negative; false negative, if both patches were negative and at least one urine specimen was positive; true negative, both patches and all urine specimens were negative.

At least one urine specimen tested positive for opiates by EMIT at 300 ng/mL in 153 out of 355 sets of WFM urine specimens. This frequency of positives was higher than that found in the corresponding sweat patch specimens, in which 134 of 355 patch pairs were found to have ELISA opiate concentrations above 10 ng/mL. When ELISA sweat results were compared to EMIT urine results (reference method for this comparison), 29.6% TP, 49.0% TN, 7.9% FP, and 13.5% FN were found for the WFM urine comparison. As shown in Table IV, there were 28 cases that had a result ≥ 10 ng/mL in at least one of the ELISA sweat patches when the EMIT results were less than 300 ng/mL for all three urine specimens. Additional information was obtained to evaluate these 28 cases. In all but one case, duplicate sweat patches were analyzed by ELISA. In 15 of the 27 sweat patch pairs, the ELISA opiate concentration was < 10 ng/mL in one of the patches. GC–MS analyses are included in Table V for 29 of the 40 FP sweat patches. Twenty-three of the ELISA results were confirmed positive for heroin, 6-acetylmorphine, morphine, and/or codeine; 6 positive

**Table V. ELISA Opiate Concentrations In Positive Sweat Patches from Subjects with Opiate-Negative Urine***

| Specimen | Subject code | ELISA Opiates† | GC–MS HER‡ | 6-AM | MOR | COD | ELISA Opiates† | GC–MS HER | 6-AM | MOR | COD |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | B | 98.1 | 94.4 | 70.7 | 13.9 | 0.0 | 18.4 | 17.7 | 13.2 | 2.8 | 0.0 |
| 2 | B | 19.4 | 17.7 | 12.0 | 4.3 | 0.0 | 11.8 | 8.4 | 5.8 | 0.0 | 0.0 |
| 3 | B | 40.0 | 10.1 | 42.2 | 13.2 | 0.0 | 7.9 | 0.0 | 3.4 | 0.0 | 0.0 |
| 4 | B | 20.9 | 22.5 | 18.3 | 2.9 | 0.0 | 5.2 | 0.0 | 0.0 | 0.0 | 0.0 |
| 5 | B | 12.7 | 6.3 | 6.6 | 0.0 | 0.0 | 21.3 | 0.0 | 19.3 | 4.7 | 0.0 |
| 6 | B | 45.7 | 101.0 | 67.8 | 7.7 | 0.0 | 4.7 | 0.0 | 0.0 | 0.0 | 0.0 |
| 7 | C | 25.8 | – | – | – | – | 70.6 | – | – | – | – |
| 8 | C | 6.4 | – | – | – | – | 19.9 | – | – | – | – |
| 9 | C | 12.8 | – | – | – | – | 2.1 | – | – | – | – |
| 10 | F | 81.9 | 0.0 | 0.0 | 0.0 | 21.3 | 78.0 | 0.0 | 0.0 | 0.0 | 17.9 |
| 11 | F | 16.1 | 0.0 | 0.0 | 2.1 | 6.6 | 18.9 | 0.0 | 0.0 | 0.0 | 5.9 |
| 12 | I | 2.8 | – | – | – | – | 14.9 | 5.2 | 8.1 | 1.8 | 1.8 |
| 13 | I | 1.8 | – | – | – | – | 15.9 | 9.7 | 12.1 | 4.2 | 1.0 |
| 14 | N | 10.5 | 0.0 | 0.0 | 0.0 | 0.0 | 8.2 | 0.0 | 0.0 | 0.0 | 0.0 |
| 15 | N | 4.6 | 0.0 | 0.0 | 0.0 | 0.0 | 10.6 | – | – | – | – |
| 16 | O | 11.2 | – | – | – | – | 7.6 | – | – | – | – |
| 17 | P | 8.0 | – | – | – | – | 14.8 | – | – | – | – |
| 18 | P | 47.7 | – | – | – | – | 94.5 | – | – | – | – |
| 19 | T | 18.2 | – | – | – | – | – | – | – | – | – |
| 20 | U | 27.2 | – | – | – | – | 89.5 | 0.0 | 1.5 | 3.7 | 3.7 |
| 21 | X | 5.7 | – | – | – | – | 11.2 | 0.0 | 3.9 | 0.0 | 0.0 |
| 22 | AA | 191.3 | 0.0 | 13.6 | 9.5 | 16.9 | 125.5 | 0.0 | 7.2 | 7.2 | 12.9 |
| 23 | BB | 23.9 | 0.0 | 1.7 | 0.0 | 0.0 | 14.9 | 26.8 | 51.6 | 0.0 | 0.0 |
| 24 | EE | 10.0 | 0.0 | 0.0 | 0.0 | 0.0 | 7.1 | 0.0 | 0.0 | 0.0 | 0.0 |
| 25 | EE | 17.8 | 0.0 | 6.3 | 0.0 | 0.0 | 13.2 | 0.0 | 10.9 | 0.0 | 0.0 |
| 26 | EE | 75.2 | 53.6 | 34.8 | 8.1 | 0.0 | 57.3 | 33.9 | 34.4 | 6.9 | 0.0 |
| 27 | HH | 7.2 | – | – | – | – | 19.2 | 0.0 | 0.0 | 0.0 | 3.0 |
| 28 | OO | 14.0 | 0.0 | 0.0 | 10.1 | 7.9 | 9.1 | 0.0 | 0.0 | 10.0 | 10.1 |

* All values are nanograms per milliliter. All specimens tested by ELISA; a subset was confirmed by GC–MS; these results are shown where available. Specimens not analyzed by GC–MS are indicated by dashes (–).
† Morphine equivalents.
‡ Abbreviations: HER, heroin; 6-AM, 6-acetylmorphine; MOR, morphine; COD, codeine.

ELISA results were not confirmed by GC–MS. Seven discrepant patches that tested negative in the screening assay were also tested by GC–MS; six were confirmed as negative and one was confirmed as a FN specimen.

Not all treatment, criminal justice, or workplace testing programs collect three urine specimens each week for drug monitoring. Therefore, we also compared ELISA sweat patch results to single urine specimens collected the Wednesday, Friday, or Monday following patch application. The sensitivity, specificity, efficiency, TP, FP, TN, and FN percentages of these comparisons are included in Table VI. The number of false negative sweat results decreased significantly, resulting in a substantial increase in sensitivity to greater than 90% as compared to urine testing. However, greater numbers of false-positive sweat results decreased specificity from 86% when compared to the thrice-weekly urine collections to approximately 75% when sweat was compared to the single Wednesday, Friday, or Monday urine collection. Overall, the efficiency of opiate sweat testing as compared to urine opiate testing remained about 78%.

## Discussion

Drug testing of biological matrices is an effective tool for the diagnosis of drug exposure; for the assessment of drug abstinence; and for deterrence of drug use in treatment, workplace, military, and criminal justice programs. No single analytical technique or single biological matrix can be expected to fulfill the needs and resolve the diverse issues posed by the goals of the different drug-monitoring programs. Additional methods for monitoring drug use are needed. This study is part of an ongoing program to develop improved biological monitoring procedures. In the present study, we compared sweat testing (ELISA and GC–MS) to urine testing (EMIT) for monitoring opiate use.

Heroin, 6-acetylmorphine, morphine, and codeine were measured by GC–MS in sweat collected from outpatient treatment patients. 6-Acetylmorphine, morphine, and codeine were detected concurrently in approximately 75% of all positive patches, with heroin identified in approximately 25% of positive patches. Thus, it appears that sweat testing for opiates is frequently useful for confirming heroin use as the source of the opiate positive rather than another form of opiate exposure. In the present study, the identification of heroin and/or 6-acetylmorphine in 78.1% of positive sweat patches identified heroin use, rather than licit codeine or morphine or the ingestion of food containing small concentrations of opiates. Confirmation of 6-acetylmorphine in urine also confirms heroin use; however, the short detection time of this analyte in urine is an important limiting factor. In controlled low-dose heroin-administration studies, 6-acetylmorphine was detected in urine only 2–4 h after 3 and 6 mg heroin administration (27). The patch may provide a longer window of detection, up to a week or more, after heroin administration because 6-acetylmorphine is collected and stored in the patch.

**Table VI. Mean Percent Concordance of Detection of Opiate Use in Sweat and Urine from 44 Participants***

| | W† | F | M |
|---|---|---|---|
| Sensitivity | 95.1% | 93.7% | 90.9% |
| Specificity | 75.9% | 74.8% | 75.7% |
| Efficiency | 76.7% | 77.4% | 78.3% |
| True Positive‡ | 21.1% | 22.0% | 22.3% |
| False Positive | 16.9% | 15.8% | 15.5% |
| False Negative | 6.8% | 6.2% | 8.2% |
| True Negative | 55.2% | 56.1% | 54.1% |

* Sweat specimens were analyzed by ELISA (10-ng/mL cutoff); urine specimens were analyzed by EMIT (300-ng/mL cutoff).
† Single weekly sweat patch compared to single urine specimen collected on Wednesday, Friday, or Monday following sweat patch application.
‡ True Positive, patch and urine results were positive; false positive, positive patch, and negative urine results; false negative, negative patch, and positive urine results; true negative, patch and urine results were negative.

The sweat patch may be less susceptible than urine to the production of positive test results due to the consumption of poppy seed containing foods (28–36). Fogerson et al. (26) reported that all sweat patches tested negative for opiates by ELISA (10-ng/mL cutoff) and GC–MS (5-ng/mL cutoff) following ingestion of up to 30 g of poppy seeds in bakery products. In contrast, urine specimens collected during the same time frame were positive (EMIT 300-ng/mL cutoff) on the first day after consuming three poppy seed bagels. Recently, the cutoff concentration for opiates in the federally mandated urine drug testing program was raised to 2000 ng/mL, in part because of the production of positive urine results from poppy-seed ingestion.

The results of the present study are generally consistent with other laboratory studies of opiate secretion in sweat. In the current study, median heroin, 6-acetylmorphine, morphine, and codeine concentrations in positive patches were 10.5, 13.6, 15.9, and 13.0 ng/mL, respectively. In a controlled intravenous administration of 20 mg heroin to two participants, maximum heroin concentrations of 48.7 and 53.3 ng/patch (equivalent to 19.5 and 21.3 ng/mL) were measured in the first 24 h patch (13). Heroin concentrations were decreased with stable or increasing 6-acetylmorphine concentrations in patches worn for five days compared to patches worn for shorter periods. Morphine was not detected in any patch. Heroin and 6-acetylmorphine sweat concentrations measured in the present study are consistent with those reported in the controlled dosing study; however, morphine and codeine were routinely identified in the positive sweat specimens collected from treatment patients. Codeine and morphine are frequent contaminants in illicit heroin and would not have been present in the pharmaceutical-grade heroin administered in the controlled study. The origin of the morphine identified in our positive sweat patches could have been from the metabolism of heroin and/or codeine and morphine in the illicit drug preparation or possibly from the breakdown of heroin or 6-acetylmorphine collected in the patch. In another laboratory study, the secretion of codeine in sweat over 24 h was measured following oral administration of 60 mg of codeine to six subjects (23). Codeine was detectable in the patch within 1 h; peak concentrations of 17 to 124 ng/patch occurred from 4 to 24 h after drug administration. If the 5-ng/mL GC–MS cutoff used in the present study had been used, 4 of the 24 patches would have been negative for codeine. In another codeine dosing study, analysis of sweat patches for codeine and morphine by GC–MS following oral administration of 30- and 60-mg doses of codeine were found to

reliably reflect codeine exposure (concentration data were not provided) (26). However, when 10 mg oral heroin or 13.9 mg of smoked heroin was administered in the same study, no sweat patches were positive for heroin, 6-acetylmorphine, or morphine. The authors (26) suggested that the minimum detectable dose of heroin was 20 mg by the intravenous route.

Reports of heroin, 6-acetylmorphine, morphine, and codeine concentrations in sweat collected in other treatment studies were also consistent with the results reported in this investigation. In a study of 17 heroin users who wore sweat patches for 3 to 7 days during outpatient drug treatment, heroin concentrations ranged from 0 to 400 ng/patch, 6-acetylmorphine concentrations ranged from 0 to 441 ng/patch, and morphine concentrations ranged from 0 to 156 ng/patch (13). Heroin concentrations exceeded 6-acetylmorphine concentrations in approximately half the patches; morphine concentrations were generally equivalent to or less than 6-acetylmorphine concentrations. In another study of 20 drug-treatment patients, heroin use was attributed to 8 patients and codeine use to 4 patients based on GC–MS analytical results from sweat patches worn for five days (7). Heroin, 6-acetylmorphine, and morphine concentrations ranged from 37 to 175 ng/patch, 60 to 2386 ng/patch, and 29 to 271 ng/patch, respectively, in the heroin abusers. The 6-acetylmorphine concentration always exceeded the heroin and usually the morphine concentration in the same patch. In the four codeine users, the morphine concentration was generally 10% or less of the parent drug concentration in sweat. Codeine concentrations ranged from 67 to 4018 ng/patch. 6-Acetylmorphine (up to 200 ng/patch) was the primary analyte detected in the sweat of two heroin abusers enrolled in a drug rehabilitation clinic. Lower concentrations of morphine (up to 50 ng/patch) and codeine (up to 25 ng/patch) were identified; however, heroin was not detected (24). In a single case study, sweat test results from one drug addict were reported as 234 ng/patch heroin, 1587 ng/patch 6-acetylmorphine, 59 ng/patch morphine, and 73 ng/patch codeine (21). The patch was also positive for desmethyldiazepam, oxazepam, and tetrahydrocannabinol.

Cocaine concentrations measured in the same sweat patches have been previously reported (19). In the positive sweat patches, median and maximum cocaine concentrations were found to be 378 and 26,490 ng/mL, respectively. Cocaine concentrations far exceeded opiate concentrations, and although the amounts of self-administered cocaine and opiate doses were unknown, these results are consistent with the finding of significantly greater concentrations of cocaine in sweat and hair, as compared to opiate concentrations in these alternative matrices.

Duplicate patches were applied to subjects in the current study to assess replicability of results from different regions of the body. The replicability of duplicate patches applied to the abdomen and lower back was high in the present study, with greater than 90% concordance. Although discrepant results (one positive and one negative) occurred in 9.4% of 437 pairs analyzed by ELISA, half of the discrepancies occurred in specimens with opiate concentrations (ELISA) close to the 10 ng/mL cutoff concentration. GC–MS confirmation of the two highest concentration discrepant patch results (pairs 34 and 39 in Table II) confirmed the presence of significant levels of opiates in the patches. In one case (pair 39), the positive and negative patches were found to be positive by GC–MS, and in the other case, only the positive patch was found to be positive. In addition, these opiate concentrations were well within the ranges documented in other published reports of opiate concentrations in sweat, reducing the probability of contamination of the patch. The high replicability of the patch pairs suggests that the placement of patches does not significantly affect the outcome and thus supports the utility of the procedure for monitoring drug use.

GC–MS confirmation of ELISA sweat results was 89.5% (348 of 389) with 10.8% unconfirmed-positive-screening results (32 of 297) and 9.8% unconfirmed-negative-screening results (9 of 92). Thus, the ELISA assay with a 10-ng/mL cutoff concentration appears to be a sensitive and specific screening assay for detecting opiates in sweat patches.

Because patches were applied on Tuesdays and urine specimens were collected on a Wednesday-Friday-Monday schedule, and given that opiates reside in the body for several days, it was unclear which set of urine specimens should be compared to the patch data. Drug taken after the Monday urine specimen and before patch removal on Tuesday could be detectable in the patch. Comparison of sweat patch results to four different urine collection intervals produced approximate mean sensitivities, specificities, and efficiencies of 65%, 86%, and 77%, respectively, for all four sets of results (Table IV). Overall, sweat patches applied on Tuesday and removed the following Tuesday adequately reflected opiate use detected in the urine specimens collected on the Wednesday, Friday, and Monday while the patches were worn. More opiate use was detected by thrice-weekly urine testing than by duplicate sweat patch testing in this comparison. However, the majority of sweat patches found positive for opiates by ELISA in the absence of opiate positive urine were confirmed positive by GC–MS. This suggests that these patch results were true positives. Increased detection of opiate use with thrice-weekly urine testing may be due to higher drug concentrations in urine; collection of a small total amount of sweat and hence, low total amounts of drug in the patch; and/or higher cross-reactivity of the EMIT assay with the primary analyte found in urine as compared to the lower cross-reactivity of ELISA with 6-acetylmorphine, the primary analyte in sweat; and/or differences in analytical cutoffs. Sweat and urine opiate results agreed better using the 10-ng/mL ELISA cutoff concentration than using the lower 5-ng/mL sweat cutoff. Thus, lowering the screening cutoff concentration did not result in an improved correlation between the two methods.

Three other comparisons of sweat and urine monitoring of opiate use have been reported in the recent literature. Interpatch reliability and validity of patch results in comparison to urine tests collected at the beginning and end of patch application were evaluated in methadone-maintenance patients (37). Patches were worn for 5 to 10 days and were analyzed with an opiate immunoassay (Cozart Bioscience Ltd., Abingdon, U.K.; cutoff 7.5 ng/patch). Urine specimens were tested for opiates by EMIT immunoassay with a cutoff of 300 ng/mL. Duplicate patches worn on the side and arm had similar qualitative results for opiates in 96% of the patches. There was 100% agreement between the sweat and urine results with 28 positive and 3 negative test results. Patches were well tolerated by participants, although some patients reported minor skin irritation. There was no

evidence of reduction of illicit drug use during periods of sweat patch monitoring. The authors concluded that sweat patches were a reliable, albeit more expensive, means of monitoring drug use in the methadone-maintenance clinic.

A large study evaluating 2885 sweat patches and 10,080 urine specimens collected from 1054 subjects compared the efficiency of detection of opiate use by sweat and urine monitoring in a criminal justice population (38). Two distinct subject populations were studied. In a three-month comparison of sweat and urine monitoring of opiate use in subjects in the residential and electronic monitoring sites of the Michigan State Department of Correction Facilities, urine specimens were collected every three days and sweat patches were worn for 7 to 14 days. In a second component of the study conducted over six months with prison inmates, urine specimens were collected at the time of sweat patch application and at removal 7 to 14 days later. Urine specimens were screened for opiates by EMIT at 300 ng/mL and confirmed by GC–MS (cutoff not described). Sweat patches were analyzed for opiates with the same STC immunoassay as used in the present study with a 10 ng/mL cutoff and were confirmed by GC–MS (10 ng/mL). In this study, the percentages of total sweat patches and urine specimens found to be positive for opiates over the course of the study were compared to evaluate the efficiency of drug detection by sweat and urine testing. One percent of the total patches were positive for opiates as compared to 0.3% of the urine specimens. These data indicate that a single sweat patch worn for 7 to 14 days detects more opiate use than a single urine specimen collected during the time the patch is worn. In order to compare the results from the present study with these data, a similar comparison of total urine specimens to total sweat patch results was made. In our study population of methadone-maintenance treatment patients, 31.6% of the total number of urine specimens were found to be positive for opiates as compared to 37.7% of the total number of sweat patches collected over a four-month period.

The results of a pilot program of the Administrative Office of the U.S. Courts was presented at the Substance Abuse and Mental Health Services Administration meeting on the use of alternative matrices for drug testing. This program was designed to determine the usefulness of sweat patches for monitoring drug use in the Federal probation program. Sweat patches were applied for 7 to 14 days with urine collection at the time of patch application and removal. A total of 396 subjects provided 875 sweat patches and 782 urine specimens. ELISA screening and GC–MS confirmation of sweat patch results utilized a 10-ng/mL cutoff. EMIT screening and GC–MS confirmation of urine results used cutoffs of 300 ng/mL and 150 ng/mL, respectively. In this population, 0.5% (4 of 782) of the total sweat patches tested positive for opiates as compared to 1.4% (11 of 782) of the two urine specimens collected during/close to the time of sweat patch wear. It was interesting to note that almost all of the positive opiate tests indicated use of codeine rather than heroin. The authors concluded that in this population, urine testing was more sensitive than sweat testing for the detection of opiate use.

The concordance of sweat and urine tests in the detection of drug use is greatly affected by the cutoff concentrations of the immunoassay tests and by the frequency of urine collection. At the time this study was being conducted, the federally mandated immunoassay cutoff concentration for workplace monitoring of opiates was 300 ng/mL. Since this time, the federally mandated opiate cutoff concentration has been raised to 2000 ng/mL. It is expected that treatment drug testing programs will continue use of the 300-ng/mL cutoff concentration for opiates. However, in a comparison of sweat and urine testing in programs using the 2000-ng/mL urine cutoff, it would be expected that sweat testing would identify more cases of opiate exposure because of its much lower cutoff. In addition, the present study compared a weekly sweat patch with three weekly urine specimens. When we compared the sweat patch opiate results to urine specimens collected once a week on the Wednesday, Friday, or Monday after patch application, the number of false-negative patch results decreased and the number of false-positive results increased, with resultant increases in sensitivity and decreases in specificity. Therefore, if the frequency of urine collection is reduced to one urine specimen per week, sweat testing identified the same or slightly more opiate use as compared to urine testing.

Few problems were encountered in using the patches in the outpatient population. In one patient, patches did not reliably adhere over a seven-day period and participation in the study was terminated. This individual was moderately obese and worked in a position that required repetitive motion that caused rubbing of the patch against his clothing. With a second person, an allergic reaction developed at the site of the patch. The rash appeared to be due to the use of alcohol on the skin for cleansing; the rash resolved completely when the patch use was discontinued.

Potentially more problematic is the possible external contamination of patches during application to the skin and during the removal process. The rate of discrepant results of duplicate sweat patches was low in this study, indicating little problem with external contamination. Care was taken to ensure that patches were handled properly according to manufacturer's directions. False-positive sweat patches (compared to urine) were usually associated with low opiate sweat concentrations, suggesting a threshold phenomenon rather than environmental contamination. A recent report on the persistence of externally applied 1 μg alcoholic solutions of cocaine and tetrahydrocannabinol to the skin indicated that these drugs or metabolites may remain detectable for up to three days (39). Normal hygiene did not remove the drug. The authors suggest that cleaning of the skin with isopropanol, as required prior to patch application, may be insufficient to remove residual drug. This is the only report describing this phenomenon; further research is needed to resolve this important issue.

Advantages of sweat testing over urine testing include a wider drug detection window, easier specimen collection, reduced opportunity for adulteration, and the ability to more frequently differentiate illicit heroin use from licit codeine and opiate-containing food ingestion. Disadvantages of sweat testing include the lack of automation of sweat patch analysis, increased cost, minimal controlled drug administration data to interpret sweat test results, especially for drugs other than cocaine, and a qualitative rather than quantitative profile of drug use. It may be possible in the future to compare drug concentrations in sweat to a marker in sweat, such as lactic acid, thereby removing the effects of variable diaphoretic volume. Additional research is needed to determine if this is a feasible approach to obtaining more quantitative drug use

information. This would be analogous to the normalization of drug concentrations in urine to the urine creatinine concentration.

In summary, sweat testing provides a useful alternative for monitoring opiate usage. The patches were easy to apply and adhered appropriately to most participants. Heroin, 6-acetylmorphine, morphine, and codeine in sweat detected by ELISA at a 10-ng/mL cutoff concentration was reliably confirmed by GC–MS at a 5-ng/mL cutoff concentration. Finally, there was good correspondence in detection of opiate use between thrice-weekly urine monitoring and weekly sweat patch monitoring.

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