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Monitoring Cocaine Use in Substance-Abuse-Treatment Patients by Sweat and Urine Testing

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Abstract

Sweat and urine specimens were collected from 44 methadone-maintenance patients to evaluate the use of sweat testing to monitor cocaine use. Paired sweat patches that were applied and removed weekly (on Tuesdays) were compared with 3–5 consecutive urine specimens collected Mondays, Wednesdays, and Fridays. All patches (N = 930) were extracted in 2.5 mL of solvent and analyzed by ELISA immunoassay (cutoff concentration 10 ng/mL); a subset of patches (N = 591) was also analyzed by gas chromatography–mass spectrometry (GC–MS) for cocaine, benzoylecgonine (BZE), and ecgonine methyl ester (EME) (cutoff concentration 5 ng/mL). Urine specimens were subjected to qualitative analysis by EMIT (cutoff 300 ng/mL) and subsets were analyzed by TDx (semiquantitative, LOD 30 ng/mL) and by GC–MS for cocaine (LOD 5 ng/mL). Results were evaluated to (1) determine the relative amounts of cocaine and its metabolites in sweat; (2) assess replicability in duplicate patches; (3) compare ELISA and GC–MS results for cocaine in sweat; and (4) compare the detection of cocaine use by sweat and urine testing. Cocaine was detected by GC–MS in 99% of ELISA-positive sweat patches; median concentrations of cocaine, BZE, and EME were 378, 78.7, and 74 ng/mL, respectively. Agreement in duplicate patches was approximately 90% by ELISA analysis. The sensitivity, specificity, and efficiency of sweat ELISA cocaine results as compared with sweat GC–MS results were 93.6%, 91.3%, and 93.2%, respectively. The sensitivity, specificity, and efficiency between ELISA sweat patch and EMIT urine results were 97.6%, 60.5%, and 77.7%, respectively. These results support the use of sweat patches for monitoring cocaine use, though further evaluation is needed.

Introduction

Cocaine use remains a significant public health problem in the United States with estimates of more than 3.5 million individuals using cocaine at least once in the past year and over 500,000 regular users (those who report use on 51 or more days in the past year) (1). Drug testing for cocaine use is employed in many situations, including drug treatment, employment screening, and the criminal justice system. The biological specimen most commonly used for drug testing is urine. Although urine testing is reliable, standardized, relatively inexpensive, and widely available, it does have some disadvantages. For example, the window of detection in urine is dependent on the half-life of the drug and can be relatively short. Because of the widespread use of urine testing, tactics for subverting test results are well known and products for adulteration are marketed for sale (2), necessitating close monitoring of specimen collection, sometimes including direct observation.

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 excreted in sweat, including methadone (3,4), amphetamines (5–9), methamphetamine (6,8,10–12), alcohol (10), morphine (4,10,13,14), heroin (9,15), cocaine (4,9,15–20), nicotine (13,21), and marijuana (9,13). In addition, sweat on clothing has been used to detect drugs for forensic purposes (10,14,22). A promising method for routine sweat collections appears to be the sweat patch (15,16,23). 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 while the nonvolatile constituents in sweat are retained in the absorbent pad. Sweat patches are applied to nonhairy portions of body (e.g., abdomen) after cleansing of skin with an alcohol wipe to avoid 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 up to one week, the window of detection can be longer than that provided by urine testing.

Earlier research showed that cocaine appeared on the sweat

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patch within 1–2 h of a single dose and that the concentration peaked within 24 h in an apparently dose-dependent manner (15). Parent cocaine was the primary analyte excreted in sweat with smaller amounts of metabolites, ecgonine methyl ester (EME) and benzoylecgonine (BZE), also detected. Gas chromatography–mass spectrometry (GC–MS) analysis of duplicate patches worn at the same time following controlled cocaine-dosing experiments provided similar cocaine concentrations (15). Burns and Baselt (16) also found that the patch content yielded cocaine concentrations that accurately reflected cocaine usage. However, the results from both studies (15,16) indicated high between-dose and between-subject variability, leading to the conclusion that the patch technology was best suited to detect drug usage and should not be used to determine dose or specific time of use.

The present study evaluated the use of sweat patches for monitoring cocaine use in a population of drug abuse treatment patients. 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 for the presence of cocaine and its metabolites. Urine specimens were collected three times per week and analyzed by immunoassay (cocaine metabolite) and GC–MS (cocaine). Results were evaluated to (1) determine the relative amounts of cocaine and its metabolites in sweat, (2) assess replicability in duplicate patches, (3) compare two methods (ELISA and GC–MS) of assaying cocaine in sweat, and (4) compare the detection of cocaine use by sweat and urine 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 (24). 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, which included daily methadone (50 to 80 mg/day orally) and weekly individual counseling, throughout the study. This study was approved by the local institutional review board for human research. All volunteers gave informed written consent prior to study participation and were paid $10 per week for wearing sweat patches. Details of the experimental treatment procedures have been described (24).

Specimen collection

Volunteers could participate for a maximum of 17 weeks. Participants visited the clinic seven days per week to receive methadone. Urine specimens were collected three days per week on Monday, Wednesday, and Friday under direct observation by trained staff. An aliquot of each specimen was immediately labeled and frozen at –30°C for later analyses; the remainder of the urine specimen was refrigerated for qualitative analysis within 24 h.

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 the sweat patch, a technician 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; 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 the sides of the patch. Technicians were instructed to wear gloves and not to contaminate the absorbent pad by 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 it was transferred to a freezer at the end of the day.

Urine specimen analyses

All urine specimens were analyzed qualitatively for cocaine metabolite (EMIT d.a.u.™, Behring Diagnostics, San Jose, CA) with a cutoff concentration of 300 ng/mL for cocaine metabolite. At the conclusion of the study, a subset of urine specimens were analyzed for BZE equivalents by fluorescence polarization immunoassay (FPIA) and for cocaine by GC–MS. Semiquantitative testing was conducted on freshly thawed aliquots. FPIA was performed with TDx® Cocaine Metabolite Assay reagents on a TDx instrument (Abbott Laboratories, Abbott Park, IL) according to manufacturer's recommended procedures. The cross-reactivity of this assay for BZE was 100% and < 1% for cocaine, EME, and ecgonine (25). The limit of detection of the assay was 30 ng/mL; the linear range for cocaine metabolite was 30 to 5000 ng/mL. Specimens that contained BZE equivalents greater than 5000 ng/mL were diluted with reagent buffer until results fell within the linear range of the assay. The 300-ng/mL cutoff concentration was also applied to the FPIA results. Urine cocaine concentrations were determined by a GC–MS procedure designed for rapid measurement of cocaine in urine specimens (26). The procedure consisted of a liquid–liquid extraction, followed by GC–MS analysis (Hewlett-Packard 5890 GC interfaced to a Hewlett-Packard model 5972 mass selective detector [MSD], Hewlett-Packard, Little Falls, DE) operated in the selected ion monitoring mode. Standard curves were prepared in blank urine with authentic drug standards in eight concentrations. The limit of detection was approximately 5 ng/mL, and the limit of quantitation was 25 ng/mL.

Sweat patch analyses

At the conclusion of the study, patches were sent to Pharmchem Laboratories, Inc. (Menlo Park, CA) for analysis. 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 cocaine and its metabolites. The eluent was then analyzed according to package directions by competitive enzyme immunoassay (ELISA) with the STC Cocaine Metabolite Micro-Plate EIA (STC Diagnostics, Bethlehem, PA). ELISA sweat results are reported as nanograms per milliliter of sweat extraction buffer according to the standardized reporting format. The cross-reactivity of this assay was 100% for BZE, 102% for cocaine, 18% for EME, 20% for ecgonine, and 143% for cocaethylene (25). A subset of sweat specimens (591 patches) was confirmed by GC–MS analysis operated in the selected ion monitoring mode (Hewlett-Packard 5890 GC interfaced to a Hewlett-Packard MSD). Limits of detection were 3 ng/mL for cocaine and 2 ng/mL for BZE and EME. Limits of quantitation were 4 ng/mL for cocaine and 2 ng/mL for BZE and EME. Cutoff concentrations for positive specimens were 10 ng/mL for ELISA and 5 ng/mL for GC–MS.

Data analysis

Four main analyses were conducted: identification and quantitation of cocaine analytes in sweat by GC–MS; comparison of replicate patch results; comparison of detection of cocaine use in sweat by ELISA and GC–MS; and comparison of sweat test results to results from different combinations of urine collection periods. Median and maximum concentrations of cocaine analytes by GC–MS were determined. In those patches that were positive for cocaine and/or its metabolites, the percent positive for each combination of analytes was determined. Results of paired patches (front and back) were compared as ratios of analyte concentrations in front and back patches and by identifying those with discrepant 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 cocaine, BZE, or EME 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 was defined as positive by both GC–MS and ELISA; a true negative was defined as negative by both GC–MS and ELISA. A false positive was defined as a positive ELISA result and negative GC–MS result; and a false negative was defined as negative ELISA result and positive GC–MS result. Sensitivity of the assay was calculated as true positives divided by true positives plus false negatives. Specificity was calculated as true negatives divided by true negatives plus false positives. Efficiency was calculated as true positives plus true negatives divided by the total number of analyzed patches. All ratios were multiplied by 100.

The results of urine cocaine metabolite tests (EMIT) for four different monitoring intervals were compared to the results of sweat cocaine tests (ELISA) of patches worn for seven days. Sensitivity, specificity and efficiency were determined as described for four urine collection intervals: Wednesday, Friday, and Monday (WFM) urine collections after the Tuesday sweat patch application; Monday before and Wednesday, Friday, and Monday (MWFM) after the Tuesday patch application; Wednesday, Friday, Monday, and Wednesday (WFMW) after the Tuesday patch application; and Monday before and Wednesday, Friday, Monday, and Wednesday (MWFMW) after the Tuesday patch application (Figure 1). Comparisons were made only for those patch specimens for which all urine specimens collected during the comparison intervals were included. Actual cocaine use was assumed if any urine specimen collected in the interval tested positive for cocaine metabolite 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 cocaine by ELISA (cutoff concentration 10 ng/mL). For the purpose of this comparison, a true positive was assigned if at least one patch and one urine specimen were positive; a false positive was assigned if at least one patch was positive, but all urine specimens were negative; a true negative was assigned if both patches and all urine specimens were negative; and a false negative was assigned if both patches were negative and at least one urine specimen was positive.

Results

Analyte analysis in sweat

A total of 930 sweat patches was collected from 44 participants and analyzed by ELISA; 611 (66%) specimens tested positive for cocaine and/or metabolites at concentrations ≥ 10 ng/mL. A subset of 591 patches were analyzed by GC–MS for cocaine, BZE, and EME. Of the 591 sweat specimens, 499 (84.4%) tested positive (≥ 5 ng/mL) for one or more analytes and 92 were negative for all analytes. There were 362 specimens positive for all three analytes and 21 positive for both cocaine and BZE; 111 tested positive for cocaine only, and 5 tested positive for BZE only. No specimens were positive for EME only, for EME and BZE only, or for cocaine and EME only. In the cocaine-positive sweat specimens (N = 494), cocaine concentrations (plus or minus standard deviation) were as follows: mean 984.6 ± 1005.8 ng/mL; median 378 ng/mL; range 5–26,490 ng/mL. In the BZE-positive sweat specimens (N = 388), BZE concentrations were as follows: mean 133.7 ± 108.3 ng/mL;

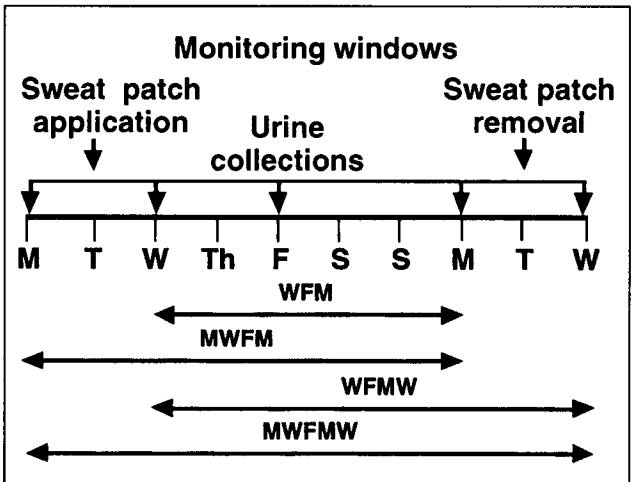

Figure 1. Diagram of sweat patch and urine specimen collections. Detection of cocaine in patches was compared with that detected in urine specimens collected over the four time intervals indicated by the horizontal lines. M, Monday; W, Wednesday; F, Friday.

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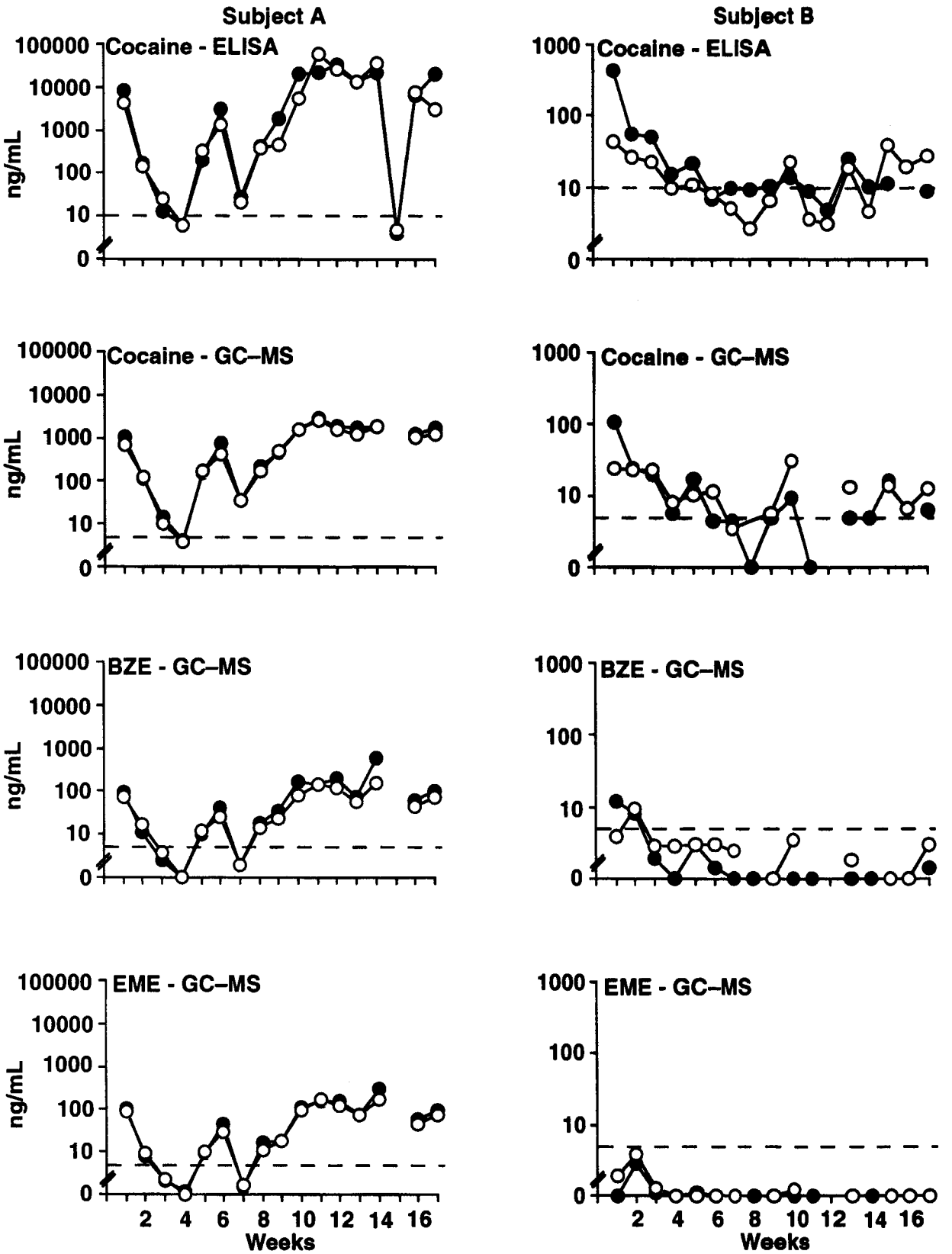

Figure 2. Quantitative results of sequential sweat patches collected from selected treatment patients over 17 weeks. Cocaine equivalent (ELISA), cocaine (GC–MS), BZE (GC–MS), and EME (GC–MS) concentrations were determined in replicate sweat patches applied to the front (closed symbols) and back (open symbols) abdomen for one week. Horizontal dashed lines indicate cutoff concentrations for positive specimens. Data points are not connected where specimen results were not available.

median 78.7 ng/mL; range 5–2150 ng/mL. In the EME-positive sweat specimens (N = 362), EME concentrations were as follows: mean 116.0 ± 90.3 ng/mL; median 74 ng/mL; range 5–774 ng/mL.

Patterns of cocaine, BZE, and EME concentrations in sweat collected in patches applied to the abdomen and to the back across the course of the 17-week trial are illustrated for two representative patients in Figure 2. Cutoff concentrations for positive specimens are indicated by dashed lines (ELISA 10 ng/mL; GC–MS 5 ng/mL). Subject A had generally high levels of cocaine use during the study, indicating frequent, heavy use of cocaine. Cocaine, BZE, and EME were present in concentrations well above the limit of quantitation in all but 1–3 specimens during this period. In contrast, Subject B had decreasing cocaine use in the first half of the treatment and a low level of use in the last half of treatment. After the first three weeks of treatment, patch cocaine concentrations remained close to the cutoff values for both ELISA and GC–MS. Cocaine, BZE, and EME (GC–MS) concentrations varied over time in patterns similar to one another, with cocaine present in the highest quantity and EME present in the the lowest quantity.

Table I. Comparison of Paired Sweat Patches Applied to Abdomen and Lower Back with Discrepant ELISA Results*

Patch pair	Abdomen ELISA COC†	Abdomen GC–MS COC	Abdomen GC–MS BZE	Abdomen GC–MS EME	Back ELISA COC†	Back GC–MS COC	Back GC–MS BZE	Back GC–MS EME
1	5	–	–	–	15	7	0	0
2	19	–	–	–	9	–	–	–
3	7	–	–	–	12	–	–	–
4	14	–	–	–	6	–	–	–
5	7	–	–	–	11	–	–	–
6	17	8	3	1	7	5	1	1
7	11	3	2	1	8	4	2	1
8	2	–	–	–	12	–	–	–
9	7	–	–	–	10	–	–	–
10	8	–	–	–	17	–	–	–
11	29	–	–	–	5	–	–	–
12	10	–	–	–	5	–	–	–
13	14	–	–	–	9	–	–	–
14	7	–	–	–	13	–	–	–
15	13	–	–	–	5	–	–	–
16	9	6	1	0	27	12	3	0
17	10	5	0	0	4	–	–	–
18	10	4	1	0	5	3	2	0
19	10	5	0	0	6	5	0	0
20	15	5	1	0	9	8	2	0
21	8	-	-	–	13	–	–	–
22	5	0	0	0	12	8	0	0
23	4	-	-	–	16	–	–	–
24	6	-	-	–	15	–	–	–
25	8	-	-	–	21	–	–	–
26	5	0	0	0	14	14	4	1
27	6	7	0	0	26	79	5	1
28	10	0	0	0	6	0	0	0
29	10	-	-	–	7	–	–	–
30	8	-	-	–	16	0	18	0
31	6	0	0	0	10	0	0	0
32	7	0	0	0	18	33	4	0
33	23	-	-	–	5	–	–	–
34	17	40	1	0	8	8	0	0
35	7000	2340	2150	132	3	–	–	–
36	10	-	-	–	7	–	–	–
37	5	7	0	2	241	298	229	159
38	10	18	2	0	4	5	0	0
39	17	53	5	3	5	7	0	0

* All values are nanograms per milliliter. All specimens were 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 (–). Eight additional discrepant specimen pairs with cocaine equivalent concentrations (ELISA) within 10% of the 10-ng/mL cutoff (8 to 12 ng/mL) are not listed in the Table.
† Cocaine equivalent.

Comparison of duplicate sweat patches

The replicability of patch testing was evaluated by comparing paired patches placed on the abdomen and lower back. The concentrations of cocaine and its metabolites tended to be similar in patches applied to the abdomen and lower back, as illustrated for two subjects in Figure 2. ELISA results were available for 455 pairs of patches. At the 10-ng/mL cutoff, both patches were positive in 278 pairs and both were negative in 130 pairs. Discrepant results (one positive and one negative) occurred in 47 pairs (10.2%). ELISA results in eight of these pairs were within 20% of the 10-ng/mL cutoff (8 to 12 ng/mL). The quantitative results for the remaining 39 pairs are listed in Table I. All but two specimen pairs were in similar concentration ranges. Two specimen pairs (numbered 35 and 37) showed substantial differences in concentration between the front and back patches, suggesting the possibility of environmental contamination.

Among the 591 patches analyzed by GC–MS, there were 287 replicate pairs. The reproducibility of sweat patch results among these pairs was evaluated by comparing cocaine analyte concentrations. Discrepant results (one positive and one negative at the 5-ng/mL cutoff concentration) occurred in only six pairs (2%) of specimens (Table II). Sixfold or greater differences in cocaine concentration occurred in 12 pairs (4%) (Table II). Six of the 18 pairs listed in Table II were discrepant by ELISA analysis and are indicated by asterisks.

Comparison of ELISA and GC–MS sweat results

The presence of cocaine and/or its metabolites was determined by both ELISA and GC–MS in 591 sweat patch specimens. A total of 475 (79%) of the 591 specimens tested positive by ELISA (≥ 10 ng/mL cutoff); of these,

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Table II. Discrepant Sweat Patch Pairs and Pairs with Sixfold or Greater Differences in Cocaine Concentration Determined by GC–MS*

Patch pair	Abdomen Cocaine GC–MS	Abdomen BZE GC–MS	Abdomen EME GC–MS	Abdomen Cocaine† ELISA	Back Cocaine GC–MS	Back BZE GC–MS	Back EME GC–MS	Back Cocaine† ELISA	Ratio Abdomen/Back
Discrepant pairs									
1	5	0	0	8	0	0	0	5	
2	8	0	0	9	0	0	0	3	
3	8	0	0	5	0	0	0	7	
4†	0	0	0	5	8	0	0	12	
5†	0	0	0	5	14	4	1	14	
6†	0	0	0	7	33	4	0	18	
Sixfold differences									
1†	7	0	2	5	298	229	159	241	0.024
2	642	461	28	916	22160	575	257	10000	0.029
3†	7	0	0	6	79	5	1	26	0.092
4	128	7	11	58	1065	72	70	62	0.120
5	10	11	3	15	61	5	3	24	0.162
6	352	42	30	485	55	5	5	44	6.308
7†	53	5	3	17	7	0	0	5	7.026
8	1747	110	51	495	216	30	0	65	8.088
9	175	0	0	45	20	1	0	14	8.578
10	197	9	10	39	17	2	0	11	11.193
11	780	43	48	2619	22	2	1	28	35.470
12	26490	1661	264	7000	456	36	19	121	58.092

* All values are nanograms per milliliter.
† ELISA values discrepant.

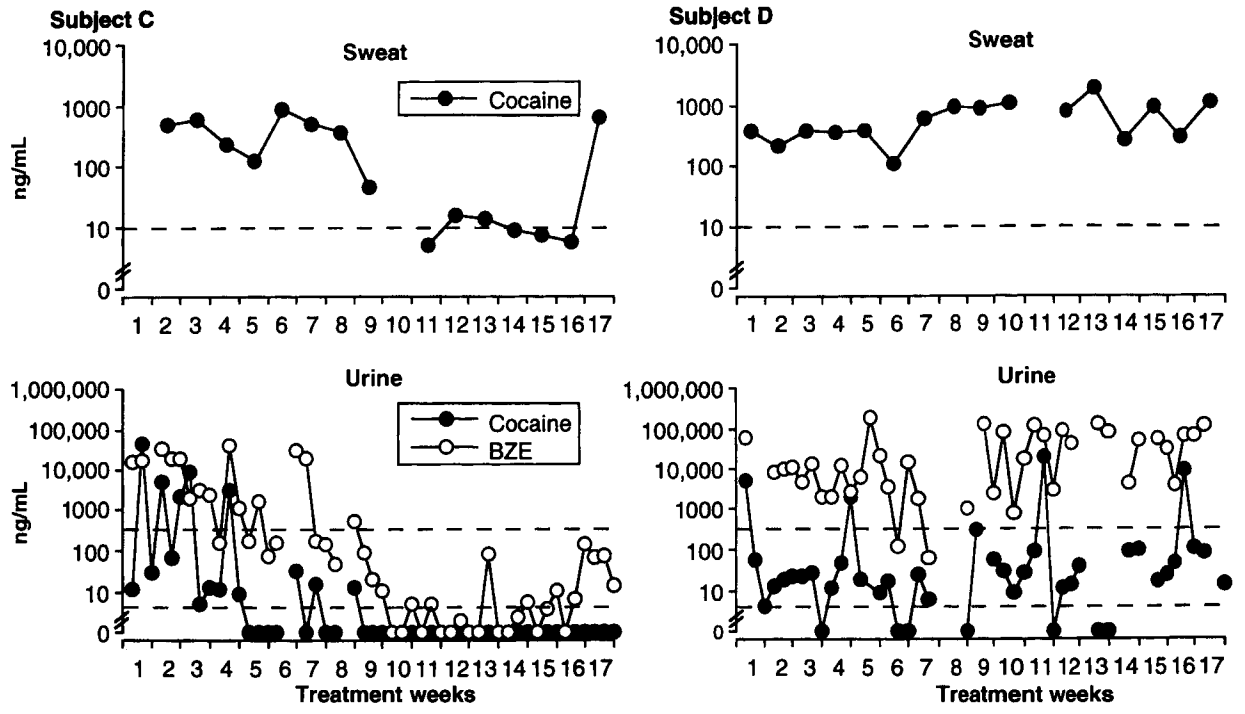

Figure 3. Quantitative results of sequential sweat patch (top panels) and urine specimens (bottom panels) collected from selected treatment patients over 17 weeks. Cocaine equivalent concentrations (ELISA) were determined in sweat patches applied for one week on Tuesdays. BZE equivalent (open symbols; FPIA) and cocaine concentrations (closed symbols; GC–MS) were determined in urine specimens collected Mondays, Wednesdays, and Fridays. Horizontal dashed lines indicate cutoff concentrations for positive specimens (10 ng/mL for sweat patches; 300 ng/mL for immunoassay analysis of urine specimens; 5 ng/mL for GC–MS analysis of urine specimens). Data points are not connected where specimen results were not available.

467 (98.3%) were positive by GC–MS (≥ 5 ng/mL). In the entire sample set (N = 591), 79% were identified as true positives (ELISA positive and GC–MS positive), 1.4% as false positives (ELISA positive and GC–MS negative), 5.4% as false negative (ELISA negative and GC–MS positive), 14.2% as true negative (ELISA negative and GC–MS negative). Overall, sensitivity was 93.6%, specificity was 91.3%, and efficiency was 93.2%.

The concentrations determined by ELISA (ascending order) and GC–MS for cocaine, BZE, and EME for the 32 specimens identified as false negatives and the eight specimens identified as false positives are listed in Table III. GC–MS-determined cocaine concentrations were greater than 10 ng/mL in only eight of the false-negative specimens. Three of the false-negative specimens were positive for BZE only, and 29 were positive for cocaine only. There were nine replicate pairs (i.e., paired front and back applied the same week to the same subject) among the 40 specimens identified as false negative or false positive. In all cases, the paired specimens were either both false positive (one pair) or both false negative (eight pairs). In 7 of the 8 false positive sweat tests, ELISA results were lower than 15 ng/mL.

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

Specimen	ELISA COC†	GC–MS COC	GC–MS BZE	GC–MS EME
False negatives				
1	3	35	1	0
2	3	5	0	1
3	4	6	0	1
4	4	12	3	3
5	4	5	0	0
6	4	5	0	0
7	5	5	0	1
8	5	8	0	0
9	5	8	0	0
10	5	7	0	0
11	5	7	0	2
12	6	7	0	0
13	6	9	0	0
14	6	5	0	0
15	7	4	5	0
16	7	12	1	0
17	7	5	1	1
18	7	20	0	0
19	7	9	1	1
20	7	6	1	1
21	8	5	0	0
22	8	11	3	0
23	8	11	1	0
24	8	0	5	0
25	8	8	0	0
26	9	6	1	0
27	9	6	0	0
28	9	8	0	0
29	9	12	0	0
30	9	13	1	0
31	9	4	8	0
32	9	8	2	0
False positives				
33	10	4	1	0
34	10	0	0	0
35	10	0	0	0
36	10	0	0	0
37	11	3	2	1
38	11	0	0	0
39	13	4	0	0
40	25	4	0	0

* All values are nanograms per milliliter.
† Cocaine equivalent concentrations.

Detection of cocaine use by sweat versus urine testing

Figure 3 illustrates two representative patients' patterns of cocaine concentrations in sweat collected in patches applied for one-week periods to the abdomen and cocaine and BZE concentrations in urine specimens collected three times weekly over the course of the 17-week trial. Dashed lines indicate the 10- and 300-ng/mL cutoff concentrations for the ELISA analyses in sweat and FPIA analyses in urine, respectively. Semiquantitative cocaine concentrations by ELISA are included for comparison. Subject C used cocaine frequently in the first half of treatment and very infrequently in the last half of treatment. After the first eight weeks of treatment, patch cocaine concentrations remained close to the cutoff values, and all urine specimens were negative for cocaine use. Sweat contained cocaine above cutoff concentrations in at least three weeks during which no urine specimens tested positive for cocaine use. Subject D had generally high concentrations of cocaine metabolites and/or cocaine in both urine and sweat throughout the study, indicating frequent, heavy use of cocaine. Only two urine specimens tested below the 300-ng/mL cutoff concentration for BZE, and cocaine was above the 5-ng/mL limit of detection in many urine specimens. Cocaine was present in concentrations well above the 10-ng/mL ELISA cutoff concentration in all sweat specimens during this period.

The relationship between the urine results and sweat results was evaluated by comparing ELISA sweat results (10-ng/mL cutoff) from 355 patch pairs to EMIT results of urine

Table IV. Mean Concordance of Cocaine Use Detection in Sweat and Urine in 44 Participants*

	WFM	MWFM	WFMW	MWFMW
Sensitivity	97.6%	96.5%	97.0%	96.0%
Specificity	60.5%	62.1%	61.3%	62.9%
Efficiency	77.7%	78.9%	78.3%	79.4%
True Positive†	45.4%	47.0%	46.2%	47.9%
False Positive	21.1%	19.4%	20.3%	18.6%
False Negative	1.1%	1.7%	1.4%	2.0%
True Negative	32.4%	31.8%	32.1%	31.5%

* 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.

specimens collected over four different time periods: WFM, WFMW, MWFM, and MWFMW (see Figure 1 for timeline). Concordance between sweat and urine was acceptable and consistent across all four urine collection intervals (Table IV) with sensitivity ranging from 96.0 to 97.6%, specificity ranging from 60.5 to 62.9%, and efficiency ranging from 77.7 to 79.4% at the 10-ng/mL ELISA cutoff. Concordance was reduced when a 5-ng/mL ELISA cutoff was applied: 45.4% true positive; 40.3% false positive; 0.6% false negative; 13.2% true negative; 98.8% sensitivity; 24.7% specificity; and 58.9% efficiency for the WFM urine collection interval.

At least one urine specimen tested positive for cocaine by EMIT at 300 ng/mL in 165 out of 355 sets of WFM urine specimens. This frequency of positives was lower than that found in the corresponding sweat patch specimens in which 236 of 355 patch pairs were found to have ELISA cocaine concentrations above 10 ng/mL. Comparison of ELISA sweat results to EMIT urine results gave a 45.4% true-positive rate, a 21.1% false-positive rate, a 1.1% false-negative rate, and a 32.4% true-negative rate for the WFM urine comparison. In 75 cases, at least one of the ELISA sweat patches had a result greater than 10 ng/mL when the EMIT results were less than 300 ng/mL for all three urine specimens. Additional information was obtained to evaluate these 75 cases. In 73 of the 75 cases, duplicate sweat patches were analyzed by ELISA. In only half of these 73 sweat patch pairs, the ELISA cocaine concentration was found to be greater than the 10-ng/mL cutoff concentration indicating low sweat cocaine concentrations in the patches. Urine FPIA test results were available for 33% (25 of 75) of the false positive cases; 40% (10 of 25) of these had at least one of three urine specimens with a concentration greater than 30 ng/mL, which is above the limit of detection but below the federally mandated cutoff of 300 ng/mL, indicating low level cocaine metabolite concentrations in the urine. GC–MS sweat analyses were available for 56% (42 of 75) of the false-positive cases; 93% (39 of 42) were confirmed positive for cocaine, BZE, and/or EME above 5 ng/mL, substantiating the ELISA sweat results.

Discussion

Biological monitoring (drug testing) is needed in treatment to assess patient outcome. Urine testing is the current, standard method for monitoring drug use, but it suffers from some disadvantages such as short detection time and difficulties in collection of unadulterated specimens. Thus, better 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, FPIA, and GC–MS) for monitoring cocaine use.

High concentrations of cocaine and metabolites were detected in sweat by GC–MS collected from outpatient-treatment patients. The major analyte present was cocaine; similar results were found following acute administration of cocaine in controlled-clinical studies (15). Of the positive sweat specimens analyzed by GC–MS, only five specimens (1%) were identified as containing BZE without cocaine. BZE was frequently present in concentrations similar to or higher than those of EME. No specimens that contained EME in the absence of cocaine were identified. BZE was also found in higher concentrations than EME in routine specimens from criminal justice and treatment settings (27). However, two earlier studies reported that EME was present in sweat in greater concentrations than BZE (15,23). The reason for this difference is not clear. All three studies used sweat patches manufactured by the same company. The participants in the study by Kintz (23) were drawn from a population of intravenous heroin abusers in a detoxification center; the cocaine detected in sweat patches was apparently from street use, as was true in our study. In the study reported by Cone et al. (15), only single doses of cocaine were administered. It is possible that the frequency of cocaine use in the current study was higher than either of these studies. With a higher frequency of use, BZE might selectively accumulate relative to EME because of its longer half-life. There may also have been greater degradation of cocaine to BZE in the present study than in the cocaine-administration study because degradation could have occurred while patients were wearing the sweat patches as well as during storage.

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, which is consistent with the finding of relatively low intrasubject variability in quantitative assessment of duplicate patches in participants who received acute administration of cocaine in a laboratory setting (15). Although discrepant results (one positive and one negative) occurred in about 10% of 455 pairs analyzed by ELISA, the discrepancies tended to occur for specimens with cocaine concentrations (ELISA) close to the 10-ng/mL cutoff concentration. Out of 47 discrepant pairs, eight pairs were within 20% of the 10-ng/mL cutoff (8–12 ng/mL) in both specimens, and only two pairs showed evidence that the discrepancy might have been due to contamination. Sixfold or greater differences in cocaine concentration occurred in only 4% of 287 pairs analyzed by GC–MS. The high replicability of the patch pairs suggests that the placement of patches does not significantly affect the outcome and therefore supports the utility of the procedure for monitoring drug use.

GC–MS confirmation of ELISA sweat results was 93.2% with low percentages of false-positive (5.4%) and false-negative (1.4%) screening results. Therefore, the ELISA assay with a 10-ng/mL cutoff concentration appears to be a sensitive and specific screening assay for detecting cocaine and metabolites in sweat patches

Because patches were applied on Tuesdays and urine specimens were collected on a Wednesday-Friday-Monday schedule, and given that cocaine and/or its metabolites reside in the body for several days, it was unclear which set of urine specimens should be compared with the patch data. Drugs 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 intervals of urine monitoring results showed high sensitivity, specificity, and efficiency for all four sets of results. Overall, sweat patches applied on Tuesday

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and removed the following Tuesday adequately reflected cocaine use detected in the urine specimens collected on the Wednesday, Friday, and Monday while the patches were worn. Comparison of detection of cocaine use in sweat (ELISA, 10 ng/mL) to urine (EMIT, 300 ng/mL) resulted in an 80% concordance. More cocaine use was detected by sweat patch testing than by urine testing. The majority of sweat patches found positive for cocaine by ELISA in the absence of a cocaine-positive urine were confirmed positive by GC–MS, suggesting that the occasions of drug use detected with sweat but not urine testing were true positives. Also supportive of some cocaine use was the finding that urine BZE concentrations (FPIA) were between the 30-ng/mL limit of detection and 300-ng/mL cutoff concentration for a substantial proportion of the false-positive sweat patches. Increased detection of cocaine use with sweat testing may be due to higher sensitivity, external contamination of the patch during application or removal, and/or differences in analytical cutoffs. The correlation between sweat and urine cocaine results was higher with a 10-ng/mL ELISA cutoff concentration than with a 5-ng/mL cutoff.

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 subject, a skin reaction developed at the site of the patch. The rash appeared to be due to the use of the alcohol on the skin for cleansing; the rash resolved completely when the patch use was discontinued.

Potentially more problematic was the possible external contamination of patches during application to the skin and removal. However, rates of discrepant results were quite low when handled properly according to manufacturer's directions. False-positive sweat patches (compared to urine) were usually associated with low BZE urine concentrations, suggesting a threshold phenomenon rather than contamination. Only 12 out of 287 sweat patch pairs analyzed by GC–MS had greater than sixfold differences in cocaine concentration.

In summary, sweat testing provides a useful alternative for monitoring drug usage. The patches were easy to apply and adhered appropriately to most participants. Cocaine 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 cocaine use between thrice-weekly urine monitoring and weekly sweat patch monitoring. In fact, sweat patches appeared to detect more cocaine use than the frequent urine monitoring. Thus, sweat patch testing required fewer patient visits while having a higher detection rate than urine monitoring.

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