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Gas Chromatography-Mass Spectrometry (GC-MS) Analysis of Amphetamine, Methamphetamine, 3,4-Methylenedioxy-amphetamine and 3,4-Methylenedioxymethamphetamine in Human Hair and Hair Sections

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ABSTRACT

In this paper, the authors describe a sensitive method for simultaneous quantitation of amphetamine (AM), methamphetamine (MA), 3,4-methylenedioxyamphetamine (MDA) and 3,4-methylenedioxymethamphetamine (MDMA) in human hair by gas chromatography-mass spectrometry (GC-MS). Hair samples are initially cut into 0.5-cm sections, washed with methanol, and digested for 1 hr at 80°C in 2 N NaOH and deuterated internal standards. The resulting solutions are processed with a liquid-liquid extraction procedure and further derivatized with heptafluorobutyric anhydride (HFBA) before undergoing GC/MS analysis. The overall protocol achieves the following results when applied to the analysis of 50 mg drug-free hair specimens fortified with 2-40 ng/mg amphetamines: recovery: 77.45-86.86%; inter-day and intra-day precision ranges: 0.55-7.73% and 0.76-4.79%, respectively; linearity: $r^2 > 0.997$; detection limits: 0.05 ng/mg for AM, MA, and MDMA and 0.1 ng/mg for MDA; and quantitation limits: 0.1 ng/mg for AM, MA, and MDMA and 0.2 ng/mg for MDA. Data derived from our analysis of hair samples collected from 30 self-reported methamphetamine abusers range from 1.39 to 15.41 (mean ± S.D., 5.21 ± 3.25) ng/mg for amphetamine and 12.58 to 173.28 (mean ± S.D., 56.10 ± 36.85) ng/mg for methamphetamine. This method has also been utilized successfully to evaluate the deposition pattern of drugs in head hairs collected from six female methamphetamine abusers staying at a rehabilitation facility. We conclude that this relatively simple protocol can be used for routine and reliable identification and quantitation of AM, MA, MDA, and MDMA in hair.

Key words: hair analysis, amphetamines, drug deposition, drug abuse, GC-MS

INTRODUCTION

Urine drug testing has long been the standard method for detecting and identifying drug ingestions. Advantages of this approach include (a) the analytical procedure is relative simple and inexpensive and (b) test data can be intepreted with a high degree of accuracy due to the large volume of metabolism study data already published. This approach is, however, hindered by the relatively short detection window for drugs/metabolites of interest. For example, concentrations of amphetamines and their metabolites typically drop below commonly accepted "cutoff" values within 48-72 hr of parent drug ingestion[(1)]. This limitation and other concerns have led to the development of testing approaches utilizing non-urine specimens.

Testing human hair for traces of illicit drugs is still a relatively new science. While GC-MS has been cited in numerous reports as having been used successfully to detect amphetamine (AM)/methamphetamine (MA)[(2-6)] and 3,4-methylenedioxyamphetamine (MDA)/3,4-methylenedioxymethamphetamine (MDMA)[(7-14)] in hair, the process by which drug metabolites enter hair structures remain unclear. The prevalence of sulfydryl (-SH) groups of cystine in the protein-fiber network of the hair may provide the means by which drugs can form covalent bonds with hair proteins[(15)]. The proximity of arterial and venous blood vessels to actively growing hair follicles may facilitate the transfer of drugs from the circulatory system into hair shafts. Potential problems associated with the use of human hair to monitor drug use include the vulnerability of hair test data to complications from a variety of extraneous factors. For example, the use of hair dyes appear to affect drug deposition patterns and the treatment of hair with chemicals or other beauty aids may also affect the stability/retention of drugs deposited in hair follicles[(16,17)].

While true that the dose-quantity relationship has yet to be established, it is generally recognized that drug detection in hair reflects some form of drug exposure[(18)]. Furthermore, as scalp hair grows at a relatively constant rate (1.0-1.5 cm/month), it has been suggested that (a) drug

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concentration along the hair shaft reflects the degree of drug exposure and (b) the distance between the drug positive segment and the root can be used to calculate time elapsed since exposure[19].

The objectives of this study include (a) the development of a set of sample preparation and GC-MS protocols for quantitative analysis of AM, MA, MDA, and MDMA in hair samples; (b) the application of the method developed to analyze sections of hair samples collected from known methamphetamine users; and (c) comparison of hair sectional analysis data with information derived from personal interviews to assess the reliability of using this approach to estimate the date of drug exposure.

MATERIALS AND METHODS

I. *Reagents, Standards, and Test Specimens*

All solvents and reagents used in this study were of HPLC grade and purchased from J. T. Baker Inc. (Phillipsburg, NJ, USA). Heptafluorobutyric anhydride (HFBA) was obtained from Aldrich Chemical (Milwaukee, WI, USA). AM, AM-d_8, MA, MA-d_8, MDA, MDA-d_5, MDMA and MDMA-d_5 were provided by Cerilliant Corporation (Austin, TX, USA).

Analytical standards and controls were prepared using drug-free hair samples provided by a volunteer. Hair samples from this volunteer were confirmed drug free by GC-MS. Test specimens came from the following three sources: (a) 42 self-reported methamphetamine users under detention in a correction facility; (b) six victims and the accused involved in two high-profile criminal drug cases; and (c) six consenting female drug users confined in an rehabilitation clinic. All hair samples were black in color with unknown cosmetic/hygienic treatment histories.

II. *Sample Preparation*

Hair samples, each weighing at least 75 mg, were carefully cut into small segments (less than 5 mm), placed into a beaker, and decontaminated. The decontamination procedure involved three consecutive 1-min rinsings with 1 mL of methanol. The solvent was then evaporated at 50˚C under a slow stream of nitrogen.

Test specimens, analytical standards and controls were prepared by first spiking 50 mg of cut and decontaminated hair with 50 μL of a 4-internal standard mixture (10 μg/mL each of AM-d_8, MA-d_8, MDA-d_5 and MDMA-d_5). Samples were then digested in 2 mL of 2 N NaOH at 80˚C for 1 hr and completely solubilized. The resulting solution was cooled to room temperature and extracted with 5 mL of ethylacetate on a horizontal shaker for 5 min. The mixture was then centrifuged for 5 min and the upper ethylacetate phase was transferred to a clean screw-cap test tube. Two milliliter of 0.5 N HCl were added, and the mixture was shaken for 5 min. After centrifugation, the acidic layer was transferred and made basic with 1 mL of 2 N NaOH. pH paper was used to check its basicity before it was extracted with 5 mL of ethylacetate for 5 min. After centrifugation, the upper ethylacetate phase was transferred to a clean screw-top tube and evaporated to dryness under a stream of nitrogen at 50˚C.

III. *Derivatization*

For derivatization, 50 μL of ethylacetate and 50 μL of HFBA were added to the residue in the screw-top tube as prepared above. The capped tube was vortexed for 20 sec and then heated at 70˚C for 25 min. The reaction mixture was evaporated to dryness under a stream of nitrogen at 50˚C and reconstituted with 100 μL of ethylacetate prior to GC/MS analysis.

IV. *Gas Chromatography-Mass Spectrometry (GC/MS) Analysis*

A Hewlett-Packard 6890N gas chromatograph/5973N MSD, operating at 70 eV with an ion source temperature of 230˚C, was used in this study. The gas chromatograph was equipped with a 30 m Hewlett-Packard (Andover, MA) HP-1MS fused silica capillary column (0.25 mm I.D., 0.25 μm film thickness). The injector and interface temperature were maintained at 260˚C and 280˚C, respectively. The inlet pressure was held at 5 psi for 1 min, then raised at 2 psi/min to 20 psi, and held for 4.5 min. Oven temperature was held at 60˚C for 1 min, then raised to 300˚C at 20˚C/min, and held at this final temperature for 1 min. The following parameters were used for injecting samples into the GC-MS system: sample size, 1 μL; injection mode, splitless; injector purge-off duration, 1 min.

The following ions were selected to monitor HFB-derivatives: *m/z* 240, 118 and 91 for AM; 243, 126 and 96 for AM-d_8; 254, 210 and 118 for MA; 261, 213 and 123 for MA-d_8; 162, 240 and 375 for MDA; 167, 244 and 380 for MDA-d_5; 254, 210 and 162 for MDMA; and 258, 213 and 164 for MDMA-d_5. The first ion listed for each compound was used for quantitation using a five-point (2.0, 5.0, 10, 20, 40 ng/mg) calibration protocol.

RESULTS AND DISCUSSION

Figures 1 and 2 show full-scan mass spectra of AM, AM-d_8, MA, MA-d_8, MDA, MDA-d_5, MDMA, and MDMA-d_5 obtained from analytical standards that were processed in accordance with the procedure described above. The evaluation of common analytical parameters and our application of the developed method to test specimens are described below.

I. *Evaluation of Common Analytical Parameters*

Extraction procedure recovery efficiencies for the four

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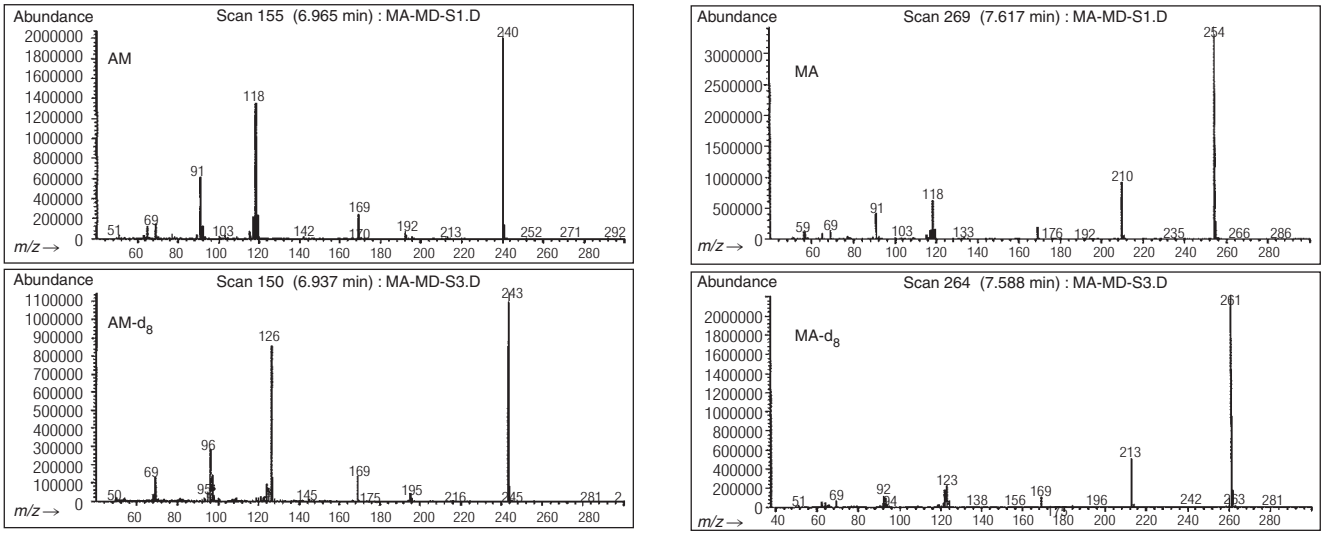

Figure 1. Mass spectra of analytes and internal standards: amphetamine (AM)/AM-d_8 and methamphetamine (MA)/MA-d_8 (all as HFB-derivatives).

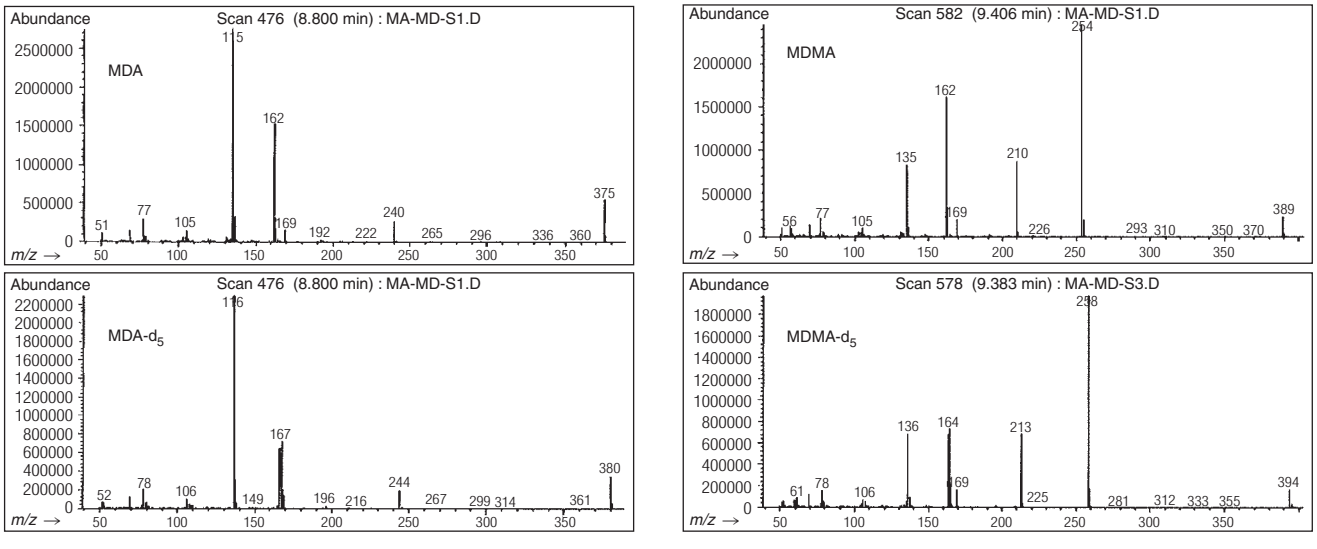

Figure 2. Mass spectra of analytes and internal standards: methylenedioxyamphetamine (MDA)/MDA-d_5 and methylenedioxymethamphetamine (MDMA)/MDMA-d_5 (all as HFB-derivatives).

analytes AM, MA, MDA, MDMA were evaluated using two sets (Set I and Set II) of standards at the five different concentration levels of 2.0, 5.0, 10, 20, and 40 ng/mg. For Set I, drug-free hair samples were spiked with the analytes and extracted without the internal standards. We then added internal standards (50 μL of 10 μg/mL solution each) to Set I extracts and Set II standards. Samples in both sets were then derivatized and analyzed by GC-MS protocol. Recovery efficiencies were calculated by dividing the quantity of each analyte in Set I by its equivalent in Set II. As shown in Table 1, the ranges, means, and standard deviations of extraction recoveries were: 78.6-85.8%, 82.5%, and 2.6% for AM; 82.0-86.2%, 83.9%, and 1.6% for MA; 77.5-82.5%, 80.6%, and 2.1% for MDA; and 80.4-86.9%, 83.9%, and 2.5% for MDMA.

We evaluated analytical protocol linearity using a set of standards containing all analytes at the following concentration levels: 2.0, 5.0, 10, 20, 40 ng/mg. Good linearity was demonstrated by plotting concentration against peak response values (Figure 3).

Intra- and inter-day precisions of the analytical procedure were also evaluated at five different levels of analyte concentration. Three sets of standards at these concentration levels were analyzed on the same day and after three days. Resultant data, noted in the last two columns of Table 2, show the following ranges: 0.55-4.72% for AM; 0.62-7.73% for MA; 0.60-4.79% for MDA; and 0.73-3.83% for MDMA.

To evaluate the assay's *limits of detection and quantitation* (LOD and LOQ), we prepared four sets of standard

solutions at the following levels of concentration: 4.0, 2.0, 1.0, 0.5, 0.4, 0.25, 0.2, 0.1, 0.05, 0.02 ng/mg. One set was used for calibration and three served as test specimens. All four were processed as one analytical batch. LOD and LOQ were defined using commonly accepted criteria (i.e., reasonable agreements with regard to retention time and ion ratio information as derived from standard and test specimens in the same analytical batch). Specifically, analyte retention time in test specimens was expected to be within ±2% of the standard; LOD was defined as the lowest concentration at which ion ratio pairs monitored for a particular analyte in the test specimen fell within ±20% of that observed in the standard; and LOQ was defined as the lowest concentration at which LOD requirements were met and in which the observed concentration fell within ±20% of the expected value.

Based on the criteria noted in the above paragraph, the LOQs for the protocol established in this study were 0.1 ng/mg for AM, MA, and MDMA and 0.2 ng/mg for MDA. LODs were 0.05 ng/mg for AM, MA and MDMA and 0.1 ng/mg for MDA.

II. *Applications*

The validated protocol was applied to the analysis of specimens collected from six alleged MDMA users involved in two high-profile criminal cases and 42 self-reported methamphetamine users incarcerated at a correction facility.

Table 1. Percent recovery data (mean, standard deviation, relative standard deviation) of amphetamine, methamphetamine, MDA and MDMA spiked into drug-free hair

Concentration (ng/mg)	Replicate	Mean	S.D.	RSD
Amphetamine				
2.0	3	85.80	4.18	4.87
5.0	3	83.25	4.76	5.72
10.0	3	81.80	3.55	4.34
20.0	3	78.57	0.96	1.22
40.0	3	82.92	1.95	2.35
Methamphetamine				
2.0	3	86.17	4.48	5.20
5.0	3	83.97	1.26	1.50
10.0	3	82.81	2.21	2.67
20.0	3	81.97	0.92	1.12
40.0	3	84.49	0.93	1.10
MDA				
2.0	3	82.47	1.03	1.25
5.0	3	82.10	1.04	1.27
10.0	3	81.38	2.06	2.53
20.0	3	77.45	0.62	0.80
40.0	3	79.73	0.49	0.61
MDMA				
2.0	3	85.64	1.76	2.06
5.0	3	86.86	0.94	1.08
10.0	3	83.33	1.95	2.34
20.0	3	80.41	0.24	0.30
40.0	3	83.20	1.50	1.80

Table 2. Intra- and inter-day precision data (mean, standard deviation, relative standard deviation) for the analysis of amphetamine, methamphetamine, MDA and MDMA spiked into drug-free hair

Concentration	Intra-day				Inter-day		
(ng/mg)	Replicate	Mean	S.D.	RSD	Mean	S.D.	RSD
Amphetamine							
2.0	3	2.12	0.10	4.72	2.20	0.07	3.18
5.0	3	4.94	0.14	2.83	5.03	0.17	3.38
10.0	3	9.71	0.23	2.37	9.68	0.06	0.62
20.0	3	20.88	0.45	2.16	20.33	0.50	2.46
40.0	3	39.88	0.86	2.16	39.96	0.22	0.55
Methamphetamine							
2.0	3	2.00	0.09	4.50	2.20	0.17	7.73
5.0	3	5.10	0.18	3.53	5.08	0.17	3.35
10.0	3	9.80	0.31	3.16	9.74	0.06	0.62
20.0	3	20.72	0.63	3.04	20.17	0.48	2.38
40.0	3	39.86	1.19	2.99	40.03	0.28	0.70
MDA							
2.0	3	1.88	0.09	4.79	1.83	0.04	2.19
5.0	3	4.78	0.11	2.30	4.88	0.19	3.89
10.0	3	9.88	0.15	1.52	9.98	0.09	0.90
20.0	3	21.37	0.22	1.03	20.86	0.44	2.11
40.0	3	39.50	0.35	0.89	39.72	0.24	0.60
MDMA							
2.0	3	2.16	0.08	3.70	2.16	0.02	0.93
5.0	3	4.86	0.09	1.85	4.96	0.19	3.83
10.0	3	9.70	0.12	1.24	9.68	0.11	1.14
20.0	3	20.92	0.18	0.86	20.43	0.43	2.10
40.0	3	39.66	0.30	0.76	39.96	0.29	0.73

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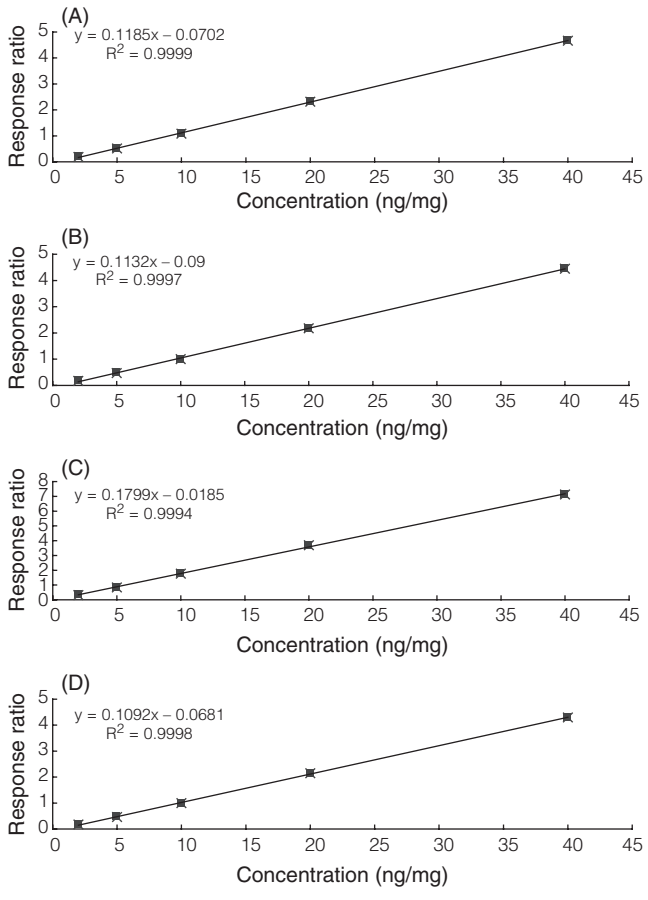

Figure 3. Calibration plot for amphetamine (A), methamphetamine (B), MDA (C), and MDMA (D) -- each in hair fortified at concentrations of 2, 5, 10, 20, and 40 ng/mg.

It was also used for sectional analysis of hair samples collected from six consenting female drug users in a drug rehabilitation facility. Analytical data are discussed below.

(I) *Analysis of Specimens Collected from Alleged and Known Drug Users*

Analytical data for the alleged MDMA user group are shown in Table 3. The concentrations of MDA and MDMA found in these samples were 2.96-10.27 and 14.02-59.91 (ng/mg), respectively. As shown in Table 4, the ranges, means, and standard deviations of amphetamine and methamphetamine found in the 30 positive samples were 1.39-15.4, 5.21, 3.25 and 12.6-173, 56.1, 36.9 (ng/mg), respectively. It is interesting to note that, after analyzing specimens obtained from the 42 self-reported methamphetamine users participating in this study, we obtained positive drug-use results for only 30 individuals. This finding is consistent with the following position statement formulated by the Society of Hair Testing: "A positive result may be used to confirm if a person has used or was exposed to a drug but a negative result does not refute use or exposure to the drug[18]."

As different sample preparation (washing, digestion, and extraction) methods[20] are known to affect final analytical data differently, direct comparison of the analytical data resulting from this study against those reported in the literature may not be meaningful. However, it is comforting to note that the levels of methamphetamine concentration found in this study are comparable to (at the higher end) concentration levels reported by other researchers[4-6,9].

(II) *Analysis of Hair Sections*

The potential of applying sectional hair analysis data to estimate the time frame in which an individual was

Table 3. Concentrations (ng/mg) of MDA and MDMA in the hair of criminal case MDMA users

Subject	MDA	MDMA	MDA/MDMA
1	3.57	27.86	0.128
2	10.27	59.91	0.171
3	7.71	59.35	0.130
4	6.07	43.11	0.141
5	5.60	31.82	0.176
6	2.96	14.02	0.211

Table 4. Concentrations (ng/mg) of amphetamine and methamphetamine in the hair of self-reported methamphetamine users*

Subject	AM	MA	AM/MA
1	4.20	54.15	0.078
2	4.65	37.17	0.125
3	5.87	79.23	0.074
4	5.45	36.45	0.150
5	5.03	58.14	0.087
6	9.25	37.08	0.249
7	3.61	50.31	0.072
8	3.74	33.52	0.112
9	5.11	80.33	0.064
10	2.98	31.54	0.094
11	3.87	65.38	0.059
12	2.83	12.58	0.225
13	9.01	58.89	0.155
14	2.54	13.45	0.189
15	1.79	24.81	0.072
16	5.31	72.45	0.073
17	2.67	41.37	0.065
18	7.48	58.53	0.128
19	6.36	49.26	0.129
20	15.41	103.67	0.149
21	1.39	14.23	0.098
22	4.07	38.95	0.104
23	5.89	83.76	0.070
24	2.54	28.48	0.089
25	3.67	35.73	0.103
26	4.88	42.43	0.115
27	7.58	60.42	0.125
28	13.83	173.28	0.080
29	3.58	49.13	0.073
30	1.63	158.24	0.010
Conc. range	1.39-15.41	12.58-173.28	0.010-0.249
Mean ± S.D.	5.21 ± 3.25	56.10 ± 36.85	0.107 ± 0.050

*Among samples collected from 42 subjects, 30 were found positive and are hereby documented.

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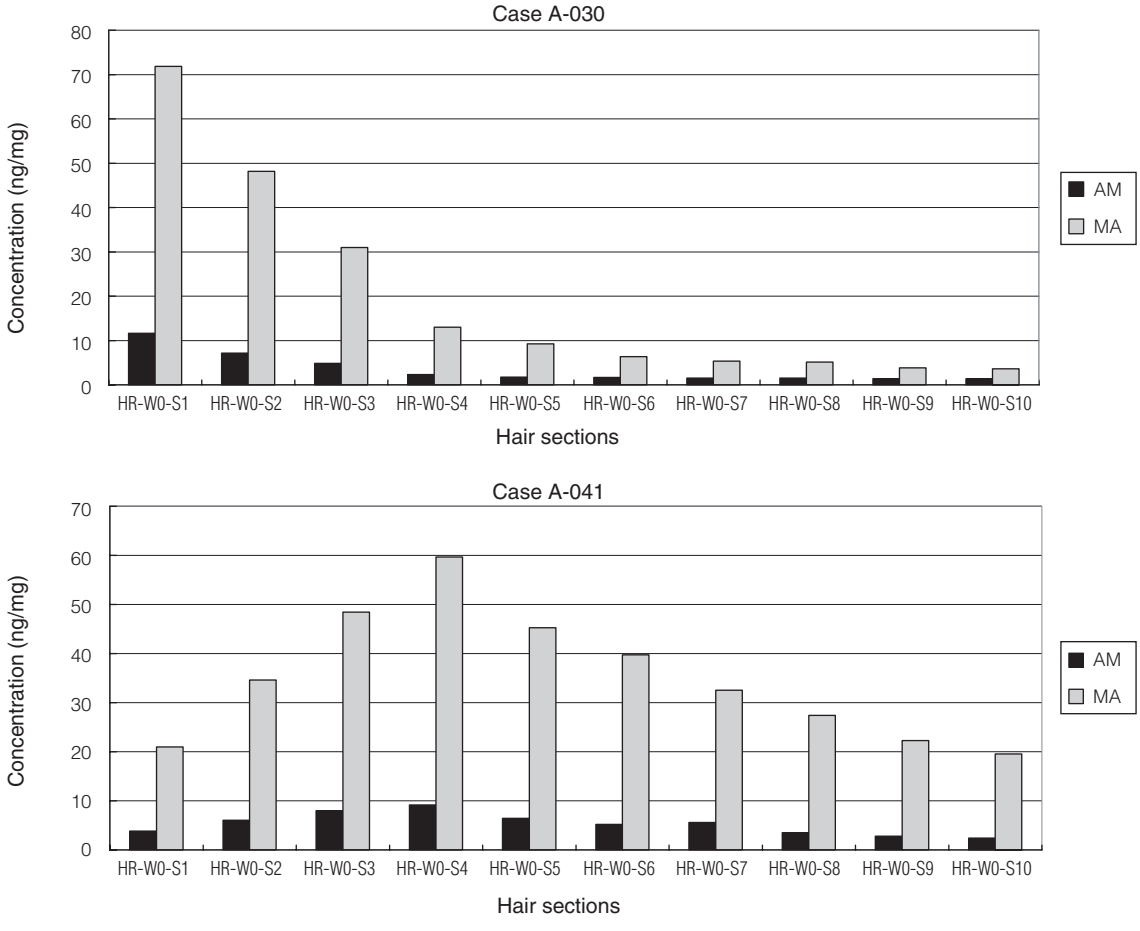

Figure 4. Exemplar distribution profiles of methamphetamine/amphetamine in 1.5-cm hair specimen sections collected from six consenting female methamphetamine users.

exposed to a drug has been advocated as an advantage of using hair as the test specimen in drug tests[19]. To further assess the potential for this application, we also applied our developed analytical protocol to conduct sectional analyses of samples of hair from six consenting females who had admitted to using methamphetamine. Hair samples measuring 15 cm or longer were collected, cut into 10 1.5-cm sections, and numbered in a progressive manner such that the lower the number, the closer the relative position of that section to the hair follicle. Analytical data derived from sectional analyses of these samples are shown in Table 5. For subjects A-024 and A-030, analyte concentrations peak at approximately 3 and 1 cm from the root, respectively (See an exemplar profile shown in the upper section of Figure 4). Analyte concentrations for subjects A-008, A-013, A-027, and A-041 peak at approximately 4-7 cm from the root (See an exemplar profile shown in the lower section of Figure 4). Different analysis results likely indicate that the two subject groups were exposed to the highest drug concentrations at different times.

Data presented in Table 5 and Figure 4 is derived from analyses of hair samples that were collected immediately following the admission of their donors to the rehabilitation facility. In a follow-up study to the one reported in this paper, we continued to collect and analyze hair samples at 2-week intervals, with resultant data and findings published elsewhere[21]. This follow-up study found that peak analyte concentrations did migrate to higher sections with the passage of time.

Attempts to obtain a positive correlattion between sectional analyses and data obtained from personal interviews have not been as productive. Difficulties are believed related to the general nature of the questions posed by the interviewers and, perhaps, exacerbated by subject drug use patterns (continuous use). For example, information obtained from interviews included only type of drug(s) used, number of years used, and quantity and frequency of drug use. Future studies on long-term drug use history and hair sectional analysis should target subjects who have a history of intermittent drug use and should incorporate more specific interview questions.

CONCLUSIONS

Using hair specimens to evaluate an individual's drug use status provides several potential advantages. First, it permits assessment of an individual's longer-term drug use

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Table 5. Amphetamine and methamphetamine concentrations in the first ten 1.5-cm hair sample sections collected from six consenting female methamphetamine users

Subjects	Drugs	H_{S-1}*	H_{S-2}	H_{S-3}	H_{S-4}	H_{S-5}	H_{S-6}	H_{S-7}	H_{S-8}	H_{S-9}	H_{S-10}
A-008	Amphetamine	4.17	8.40	12.57	12.52	10.63	10.33	8.43	7.07	5.69	5.51
	Methamphetamine	18.27	40.35	59.11	58.00	50.82	55.75	41.81	31.13	31.82	27.78
	Am/Metham (in %)	22.8	20.8	21.3	21.6	20.9	18.5	20.2	22.7	17.9	19.8
A-013	Amphetamine	1.92	2.27	1.98	2.50	2.30	1.78	2.09	1.89	2.05	1.84
	Methamphetamine	22.53	28.13	26.44	33.66	29.51	25.52	30.26	26.74	28.52	21.44
	Am/Metham (in %)	8.52	8.07	7.49	7.43	7.79	6.97	6.91	7.07	7.19	8.58
A-024	Amphetamine	25.40	32.19	29.77	16.25	10.00	8.57	4.54	3.37	2.39	1.63
	Methamphetamine	176.2	222.6	224.1	133.3	86.05	78.24	40.99	29.55	22.11	16.03
	Am/Metham (in %)	14.4	14.5	13.3	12.2	11.6	11.0	11.1	11.4	10.8	10.2
A-027	Amphetamine	2.34	5.20	6.28	7.09	6.56	4.09	3.04	2.18	1.92	2.15
	Methamphetamine	8.67	24.92	32.91	37.71	32.84	17.91	12.26	9.20	7.95	7.64
	Am/Metham (in %)	27.0	20.9	19.1	18.8	20.0	22.8	24.8	23.7	24.2	28.1
A-030	Amphetamine	11.68	9.62	5.43	3.12	2.35	1.68	1.28	1.25	1.24	1.26
	Methamphetamine	75.55	65.10	33.64	16.20	11.49	7.94	5.44	4.80	4.51	4.12
	Am/Metham (in %)	15.5	14.8	16.1	19.3	20.5	21.2	23.5	26.0	27.5	30.6
A-041	Amphetamine	4.03	7.45	9.33	9.42	6.82	6.40	4.06	3.93	2.91	2.57
	Methamphetamine	20.19	41.47	56.85	63.07	46.71	48.04	30.52	33.33	25.82	24.53
	Am/Metham (in %)	20.0	18.0	16.4	14.9	14.6	13.3	13.3	11.8	11.3	10.5

*H_{S-1}: H = hair; $_{S-1}$ = section 1.

history, particularly if the subject has long hair. Secondly, the potential for adulteration is significantly less in hair samples than urine samples and, if results are called into question, a second sampling can be readily taken. In contrast to urine, hair samples can be obtained easily in a minimally intrusive manner. The sample preparation process required for hair analysis is undoubtedly more labor-intensive than that required for urinalysis. With this in mind, the method developed in this paper proposes the minimum level of complexity for each analytical step, while still ensuring test integrity and effectiveness. For our study, we completed the assays for a 20-specimen batch within 4 hr. The developed method has been proven effective for analysis AM, MA, MDA, and MDMA in case samples. Further studies on the interpretation of hair sectional analysis data are needed.

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