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Detection of metabolites of lysergic acid diethylamide (LSD) in human urine specimens: 2-oxo-3-hydroxy-LSD, a prevalent metabolite of LSD

Gregory K. Poch*, Kevin L. Klette, Domingo A. Hallare, Marilyn G. Manglicmot, Robert J. Czarny, Lisa K. McWhorter, Cynthia J. Anderson

Navy Drug Screening Laboratory, 34425 Farenholt Avenue Suite 40, San Diego, CA 92134-7040 USA

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Abstract

Seventy-four urine specimens previously found to contain lysergic acid diethylamide (LSD) by gas chromatography–mass spectrometry (GC–MS) were analyzed by a new procedure for the LSD metabolite 2-oxo-3-hydroxy-LSD (O-H-LSD) using a Finnigan LC–MS–MS system. This procedure proved to be less complex, shorter to perform and provides cleaner chromatographic characteristics than the method currently utilized by the Navy Drug Screening Laboratories for the extraction of LSD from urine by GC–MS. All of the specimens used in the study screened positive for LSD by radioimmunoassay (Roche Abuscreen®). Analysis by GC–MS revealed detectable amounts of LSD in all of the specimens. In addition, isolysergic diethylamide (iso-LSD), a byproduct of LSD synthesis, was quantitated in 64 of the specimens. Utilizing the new LC–MS–MS method, low levels of *N*-desmethyl-LSD (nor-LSD), another identified LSD metabolite, were detected in some of the specimens. However, all 74 specimens contained O-H-LSD at significantly higher concentrations than LSD, iso-LSD, or nor-LSD alone. The O-H-LSD concentration ranged from 732 to 112 831 pg/ml (mean, 16 340 pg/ml) by quantification with an internal standard. The ratio of O-H-LSD to LSD ranged from 1.1 to 778.1 (mean, 42.9). The presence of O-H-LSD at substantially higher concentrations than LSD suggests that the analysis for O-H-LSD as the target analyte by employing LC–MS–MS will provide a much longer window of detection for the use of LSD than the analysis of the parent compound, LSD.

Keywords: 2-Oxo-3-hydroxy-LSD; *N*-Desmethyl-LSD

1. Introduction

Several factors contribute to the difficulties in developing a confirmatory method for the identification and quantitation of lysergic acid diethylamide (LSD) in urine specimens. LSD (Fig. 1A) is a highly potent hallucinogen; the typical dosage range is 25 to 150 μg, with amounts in excess of 20 μg being necessary to produce psychotropic effects [1]. The resulting concentrations of LSD in urine specimens are relatively low, ranging from 200–1000 pg/ml when compared to urinary concentrations in the ng/ml range for other drugs of abuse. Analysis is further complicated due to the extensive metabolism of LSD. Less than 1% of the ingested LSD dose is eliminated unchanged [2]. Additionally, LSD has a

*Corresponding author.

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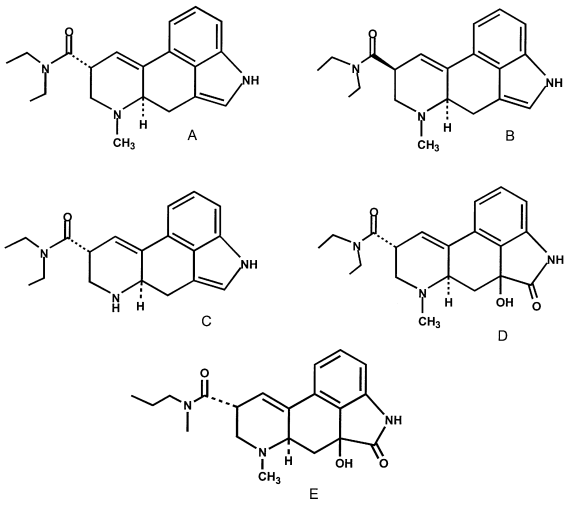

Fig. 1. Molecular structures of (A) LSD, (B) iso-LSD, (C) nor-LSD, (D) O-H-LSD and (E) O-H-LAMPA.

low volatility and a tendency to undergo absorptive losses during the extraction and gas chromatography–mass spectrometry (GC–MS) confirmation procedures. These factors contribute to an extremely short window of detection when using the parent drug as the target analyte.

The development of mass spectrometric methods capable of detecting the parent drug at pg/ml concentrations remains an analytical challenge. Recently, a unique approach aimed at increasing the LSD window of detection involved the conversion of isolysergic diethylamide (iso-LSD) (Fig. 1B), a synthetic byproduct of LSD synthesis found in some specimens, to LSD [3], thus increasing the total concentration of LSD.

Three recent review articles [4–6] summarize the current advances in the metabolism and pharmacokinetics of LSD. Additionally, these review articles highlight current advances in chromatographic methods for the detection and measurement of LSD and its known metabolites in physiological specimens. Interestingly, none of these review articles identify O-H-LSD as a LSD metabolite and, to the authors' knowledge, no chromatographic method for the detection and quantitation of O-H-LSD has been published in a refereed journal. Furthermore, none of the limited studies of the metabolism of LSD in rats, rabbits [7,8] and guinea pigs [9] identify O-H-LSD as a metabolite. Due to the ethical and legal restrictions on the administration of LSD to humans, there is limited literature on human metabolism. However, *N*-desmethyl-LSD (nor-LSD) (Fig. 1C) has been identified in the urine of LSD users [10].

Based on the sensitivity limitations of GC–MS for the detection of LSD and evidence presented at the 1997 Society of Forensic Toxicologists Meeting [11] indicating that 2-oxo-3-hydroxy-LSD (Fig. 1D) is a human LSD metabolite, this laboratory developed a procedure that was capable of identifying and quantitating nor-LSD and O-H-LSD in human urine specimens.

2. Experimental

2.1. Reagents

All solvents and reagents were of analytical or HPLC grade. LSD and lysergic acid methylpropylamide (LAMPA), which was used as an internal standard (I.S.), were purchased from Alltech, (Deerfield, IL, USA). Nor-LSD, O-H-LSD and 2-oxo-3-hydroxy-LAMPA (O-H-LAMPA) (I.S.) were obtained from Radian (Austin, TX, USA). The derivatizing reagent bis(trimethylsilyl)trifluoroacetamide (BSTFA) was purchased from Pierce (Rockford, IL, USA). Certified drug-free, negative urine, preserved with sodium azide (0.1%, w/v) and purchased from Utak (Valencia, CA, USA) was utilized to prepare standards and controls.

2.2. Specimen acquisition

Urine specimens collected under forensic conditions from active-duty United States Navy and Marine Corps personnel were used for the study. Seventy-four specimens were previously screened for LSD using the Roche Abuscreen® radioimmunoassay at a cutoff concentration of 500 pg/ml and then confirmed for LSD by GC–MS at a cutoff concentration of 200 pg/ml. The specimens were frozen after testing for at least one year. Twelve of the specimens used in the study initially failed to confirm by GC–MS at or above the LSD cutoff. These specimens were stored frozen for no longer than three months.

2.3. Specimen analysis

Urine specimens containing detectable amounts of LSD were removed from frozen storage, thawed and re-analyzed for the following analytes: LSD and iso-LSD by GC–MS and nor-LSD and O-H-LSD by LC–MS–MS. Differences in the method for the preliminary and definitive study for nor-LSD and O-H-LSD are reported in Section 3.

2.4. Extraction and GC–MS analysis for LSD and iso-LSD

The urine specimens, controls and standards were extracted using the method of Paul et al. [12]. Briefly, 10 ml specimens were extracted using a one-step basic extraction of the urine into *n*-butyl chloride followed by solid-phase extraction (SPE) using Clean Screen® CSDAU203 (United Chemical Technologies, Bristol, PA, USA) solid-phase cartridges.

A Hewlett-Packard (HP) (Palo Alto, CA, USA) 5890 gas chromatograph, coupled to a 5970 mass selective detector (MSD) was used for the analysis of LSD and iso-LSD. Helium was the carrier gas and was used at a flow-rate of 30 ml/min. The injector temperature was 245°C and the transfer line was maintained at 293°C. A HP 5 capillary column (12 m×0.25 mm I.D., 0.25 mm film thickness) provided analytical separation. The retention times for iso-LSD, LSD and LAMPA (I.S.) were 7.1, 7.3 min and 7.5 min, respectively. The oven temperature program began at 193°C (held for 0.5 min), ramped to 293°C at 20°C/min and held for 5 min. The mass spectrometer was operated in the electron impact selected ion mode with the following ions being monitored: *m/z* 395, 293 and 253 for iso-LSD, LSD and LAMPA. The quantitation ratio (LSD/LAMPA) was *m/z* 395/395 and the qualifiers for identification for each compound were the *m/z* 293/395 and *m/z* 253/395 ratios. LSD concentrations for specimens and controls were determined by single-point calibration against the 200-pg/ml standard using the *m/z* 395/395 (LSD)/(LAMPA) ion ratio. The spiked urine LSD control concentrations were 0, 100, 250, 400 and 800 pg/ml. iso-LSD concentrations for specimens were determined empirically by comparison of the iso-LSD peak height to the peak height of the internal standard LAMPA. The limit of detection (LOD) and limit of quantitation (LOQ) for LSD and iso-LSD were 100 and 200 pg/ml, respectively.

2.5. Extraction and LC–MS–MS analysis for nor-LSD and O-H-LSD

Aliquots of each specimen (5 ml) containing 4000 pg/ml of internal standard (definitive study only) and 0.5 g of NaCl in a 150×20 mm extraction tube were extracted using a one-step basic extraction of the urine into a 95:5 (v/v) solution of methylene chloride–isopropanol. The tubes were sealed using PTFE-lined caps, shaken at 55 cycles/min for 30 min followed by centrifugation at 1350 *g* for 20 min. The organic layer was removed, evaporated under nitrogen gas and reconstituted with 2 ml of 0.05 *M* phosphate buffer (pH 6.0) followed by SPE using Clean Screen® ZSDAU020 (United Chemical Technologies). The column was conditioned with 3 ml of methanol, 3 ml of deionized water and 1 ml of 100 m*M* phosphate buffer (pH 6.0). The specimens were applied and the column washed with 3 ml of deionized water, 1 ml of 100 m*M* acetic acid and 3 ml of methanol–water (60:40, v/v) and aspirated to dryness. O-H-LSD was eluted with 3 ml of methylene chloride–isopropanol–NH_4OH (78:20:2, v/v) and evaporated under a stream of nitrogen.

Ion chromatographic analysis was accomplished using a HP 1050 high-performance liquid chromatographic (HPLC) pump and a HP HPLC column [ODS-Hypersil® (preliminary study), with a particle size of 5 μm, 200×2 .1 mm or an Eclipse® XDB-C_{18} (definitive study), particle size 3.5 μm, 150×4.6 mm]. Instrument control and signal processing were performed using a HP HPLC 3D ChemStation and Finnigan Navigator software. The LC–MS–MS work was performed on a HP 1050 quaternary liquid chromatograph (LC) with an autosampler connected to a Finnigan LCQ (San Jose, CA, USA) ion trap using a Finnigan APCI interface. Nitrogen was used as the collision gas for the MS–MS. The instrument was set up to scan the mass range of 95.00–500.00 *m/z* using a collision offset of 20 eV. The specimens were reconstituted in 200 μl of the LC mobile phase [0.01 *M* ammonium acetate buffer (pH 8.0)–acetonitrile (80:20, v/v) and 0.02% triethylamine (TEA)]

and 90 μl injections were made for LC analysis. The flow-rates were 0.6 and 0.8 ml/min for the Hypersil and Eclipse columns, respectively. The product ions ($M+H^+$) were collected in the positive ion mode using *m/z* 310 (nor-LSD+H^+) and *m/z* 356 (O-H-LSD+H^+ and O-H-LAMPA+H^+). The interface was set for a spray voltage of 6 kV, a sheath gas pressure of 90 p.s.i. (1 p.s.i.=6894.76 Pa), and an auxiliary gas flow of 5 U. The interface capillary and vaporizer temperature were maintained at 220 and 550°C, respectively.

3. Results and discussion

3.1. Preliminary studies

Although LSD can be detected and quantitated by GC–MS using the parent drug as the target analyte and a cutoff of 200 pg/ml, the resulting window of detection in urine following LSD use is extremely short (12–22 h) [5]. Initially, we attempted to develop a GC–MS confirmatory method for the analysis of O-H-LSD, however, the design of the GC–MS instrumentation and derivatization resulted in low recovery and irreproducible chromatography due to the formation of multiple products. Therefore, a LC–MS–MS method was developed to investigate the occurrence and frequency of the LSD metabolites nor-LSD and O-H-LSD. The new solid-phase extraction procedure offers several advantages over the liquid–liquid extraction procedure that is currently being used [12]. Specifically, the extraction time is shorter and the procedure does not include a derivatization step. The combination of the solid-phase extraction and the LC–MS–MS procedure resulted in a considerable improvement in chromatographic characteristics.

When the preliminary study was conducted, no viable internal standards were available for nor-LSD and O-H-LSD. Thus, the concentration of nor-LSD for specimens and controls was determined by single-point calibration against the 400-pg/ml nor-LSD external standard (Radian) using the *m/z* 237/237 ion ratio of the specimen and nor-LSD external standard, respectively. The linear range of the nor-LSD assay was established by analyzing 0, 200, 400, 600, 800 and 1000 pg/ml controls. The assay was linear (r^2=0.9896) from 200 to 1000 pg/ml. The concentration of O-H-LSD for specimens and controls was determined by single-point calibration against the 2000-pg/ml O-H-LSD external standard using the *m/z* 338/338 ion ratio of the specimen and the O-H-LSD external standard, respectively. The linear range of the O-H-LSD assay was established by analyzing 0, 2000, 4000, 6000, 8000 and 10 000 pg/ml controls. The assay was linear (r^2=0.9983) from 2000 to 10 000 pg/ml.

The total ion chromatogram of a negative specimen and a specimen containing nor-LSD are shown in Fig. 2. Nor-LSD+H^+ was detected at a retention time of 10.95 min (Fig. 2B) by the LCQ utilizing MS–MS (ion trap); colliding the parent ion *m/z* 310 with an ionization energy of 20 eV. The resulting daughter ions are *m/z* 237, 209, and 183 (Fig. 2C). The same ions and the retention time were comparable with those found utilizing the nor-LSD standard (Fig. 3A and 3B).

The preliminary study specimen profile quantitation results are shown in Table 1. The mean LSD concentration was 240 pg/ml (median concentration, 143 pg/ml) with a range of values from 37 to 1156 pg/ml. The mean iso-LSD concentration was 309 pg/ml (median concentration, 200 pg/ml) with range values from 0 to 1000 pg/ml.

Eighteen specimens were analyzed for nor-LSD using LC–MS–MS as detailed in the Section 2. The mean nor-LSD concentration was 46 pg/ml with a range of values from 0 to 214 pg/ml. Since only two of the eighteen specimens contained nor-LSD greater than 200 pg/ml, no further efforts were made to detect nor-LSD in the remaining specimens.

The mean O-H-LSD concentration was 12 541 pg/ml (median concentration, 4160 pg/ml) with range values from 425–201,808 pg/ml. The mean ratio of O-H-LSD to LSD calculated for each specimen was 64. 1 (median ratio, 21.4) with a range of ratio values from 3.2 to 1040.2. Importantly, O-H-LSD was present in all specimens while the presence of nor-LSD was inconsistent and detected at a concentration greater than 200 pg/ml in only two of the 18 specimens.

3.2. Definitive study

An internal standard O-H-LAMPA (Fig. 1E) was used in the definitive study for the quantitation of O-H-LSD . The following ions were monitored: *m/z*

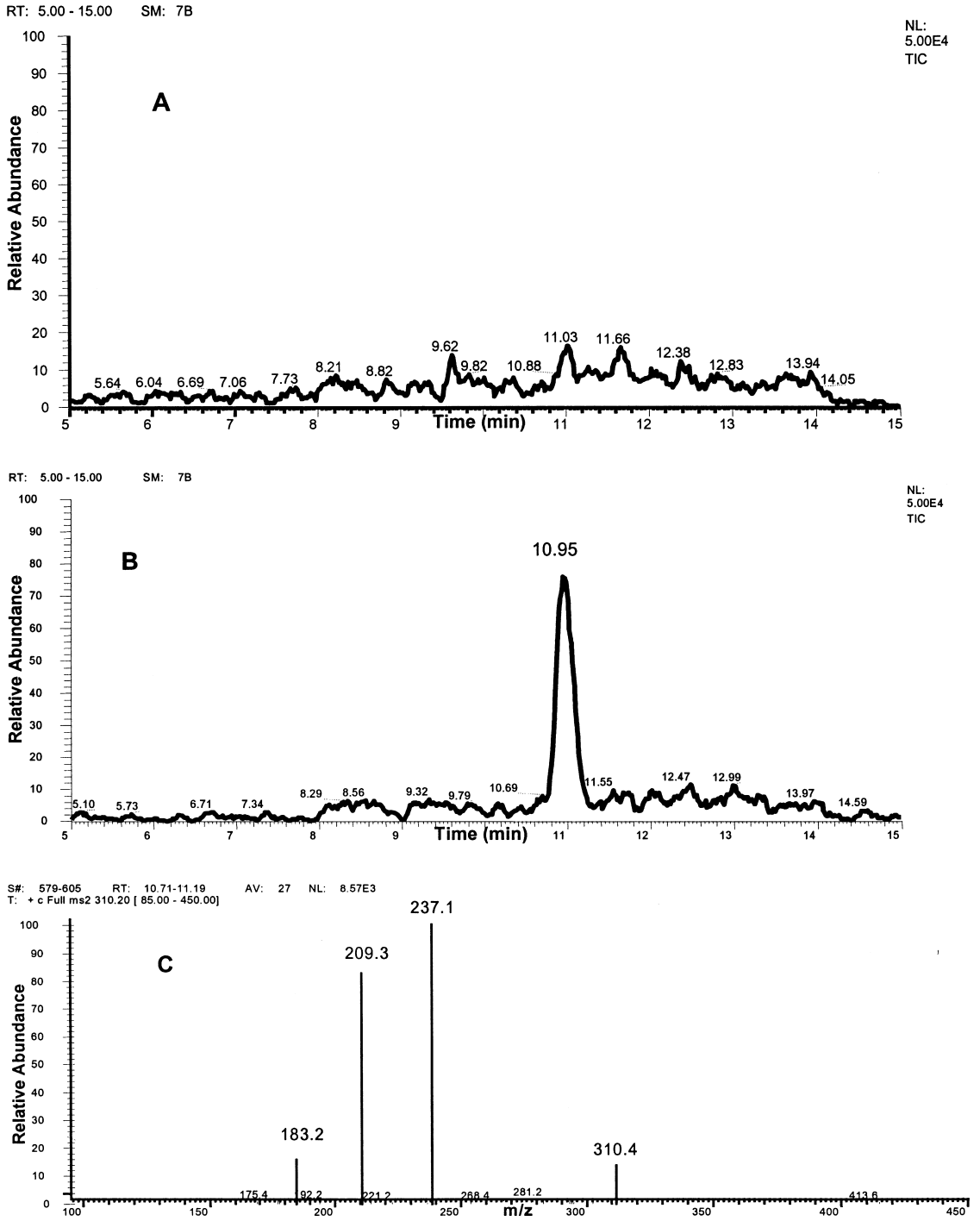

Fig. 2. Total ion chromatogram (TIC) of (A) negative urine extracted for nor-LSD, (B) an actual specimen (no. 3) and (C) the mass spectrum of nor-LSD found in the specimen as analyzed by LC–MS–MS.

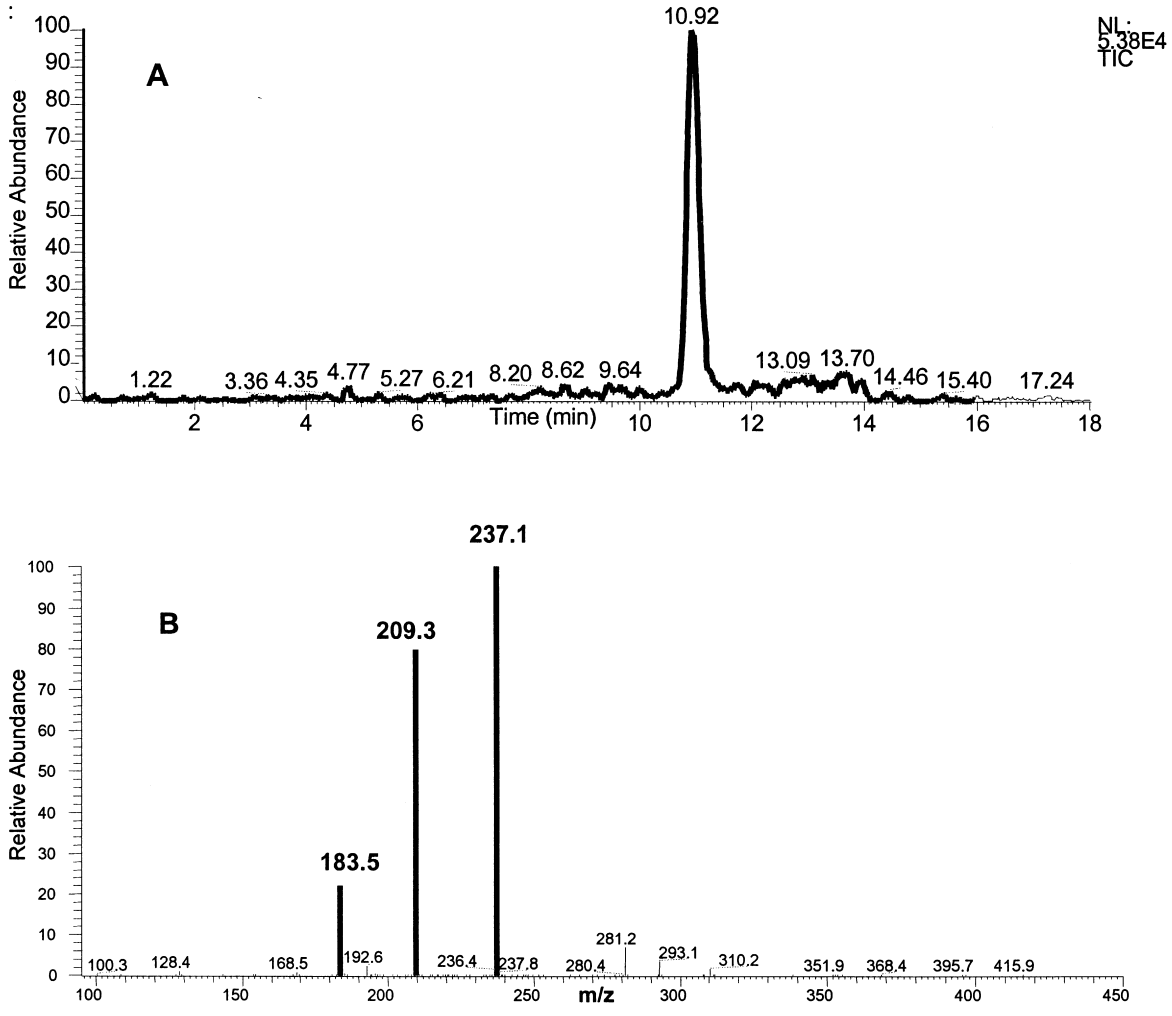

Fig. 3. TIC of (A) nor-LSD external standard (400 pg/ml) extracted from urine and (B) mass spectrum as analyzed by LC–MS–MS.

338, 265, and 237 for both O-H-LSD+H^+ and O-H-LAMPA+H^+. The quantitation ratio was based on the m/z 338 ion. The O-H-LSD control concentrations were 0, 1000, 2000, 4000, 6000 and 8000 pg/ml. O-H-LSD concentrations for specimens and controls were determined by single-point calibration against the 2000-pg/ml standard using the m/z 338/338 ion ratio for O-H-LSD+H^+ and O-H-LAMPA+H^+, respectively. The assay was linear (r^2=0.9805) from 1000 to 8000 pg/ml. The LOD and LOQ for O-H-LSD were 200 and 400 pg/ml, respectively. Subsequent studies were performed to determine the lower (r^2=0.9834) and upper (r^2=0.9760) limits of linearity for O-H-LSD. The assay was linear within ±20% of the target concentration from 400 to 200 000 pg/ml.

The total ion chromatogram of a negative specimen and a specimen containing O-H-LSD are shown in Fig. 4A and 4B, respectively. O-H-LSD and O-H-LAMPA were detected at retention times of 8.32 and 9.17 min, respectively, by the LCQ utilizing MS–MS. The parent ion m/z 356 was collided with the same ionization energy as above. The resulting daughter ions are m/z 338, 265 and 237 (Fig. 4C). The same ions and the retention times were comparable with those observed for an O-H-LSD standard

Table 1
Specimen profile of preliminary experiment (all amounts in pg/ml)

Specimen	LSD	O-H-LSD	O-H-LSD:LSD	Nor-LSD	Iso-LSD
1	132	425	3.2	0	30
2	68	448	6.6	0	0
3	1005	15498	15.4	213	600
4	245	10969	44.8	0	30
5	1156	15731	13.6	0	1000
6	362	7520	20.8	0	700
7	436	28696	65.8	214	0
8	236	5168	21.9	0	400
9	397	6675	16.8	34	50
10	273	16837	61.7	39	100
11	86	14469	168.2	0	400
12	196	2203	11.3	52	400
13	260	6117	23.5	0	NA
14	677	21690	32	173	135
15	320	4666	14.6	75	258
16	229	2098	9.2	34	200
17	60	1573	26	0	387
18	139	1383	9.9	0	800
19	68	1284	18.9	NA	40
20	99	1903	19.2	NA	NA
21	46	4284	93.1	NA	200
22	129	7237	56.1	NA	700
23	40	1122	28.1	NA	NA
24	116	7360	63.4	NA	50
25	113	942	8.3	NA	90
26	82	2272	27.7	NA	50
27	75	1538	20.5	NA	900
28	95	1001	10.5	NA	NA
29	37	2152	58.2	NA	NA
30	160	2203	13.8	NA	500
31	194	201808	1040.2	NA	150
32[a]	146	4036	27.6	NA	180
Mean=	240	12541	64.1	46	309
Median=	143	4160	21.4	0.0	200
Range	37–1156	425–201808	3.2–1040.2	0–214	0–1000

[a] Those specimens less than one-year old.
NA, No analysis was performed.

(Fig. 5B). A total ion chromatogram of specimen 47, demonstrating the presence O-H-LSD, nor-LSD, LSD, iso-LSD and internal standards, is shown in Fig. 6.

The definitive study specimen profile quantitation results are shown in Table 2. The mean LSD concentration was 649 pg/ml (median concentration, 397 pg/ml) with a range of values from 40 to 2541 pg/ml. The mean concentration of iso-LSD was 1190 pg/ml (median concentration, 600 pg/ml) with range values from 0 to 7540 pg/ml. The mean concentration of O-H-LSD was 16 340 pg/ml (median concentration, 4826 pg/ml), with a range of values from 732–112 831 pg/ml. The mean ratio of O-H-LSD to LSD calculated for each specimen was 42.9 (median ratio, 16.1) with a range of values from 1.1 to 778.1. Every specimen that was analyzed was found to contain a significant level (ng/ml) of O-H-LSD. The presence of O-H-LSD is in agreement with ongoing studies where the metabolite was detected at similar concentrations in the urine of LSD users [13–15].

The presence of nor-LSD was found to be inconsistent and detected (>200 pg/ml) in only seven of

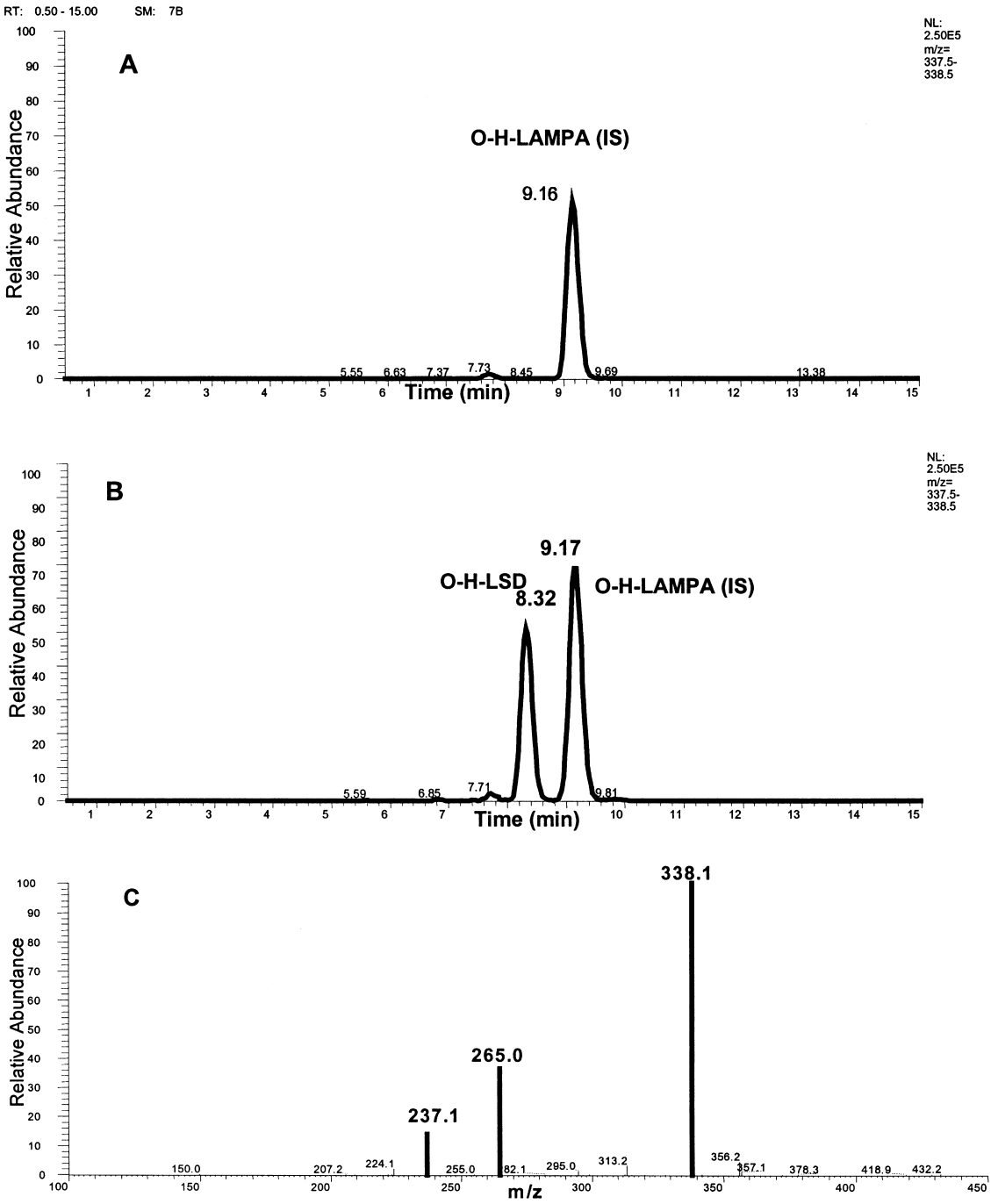

Fig. 4. TIC of (A) negative urine extracted for O-H-LSD, (B) an actual specimen (no. 65) and (C) mass spectrum of O-H-LSD found in the specimen as analyzed by LC–MS–MS.

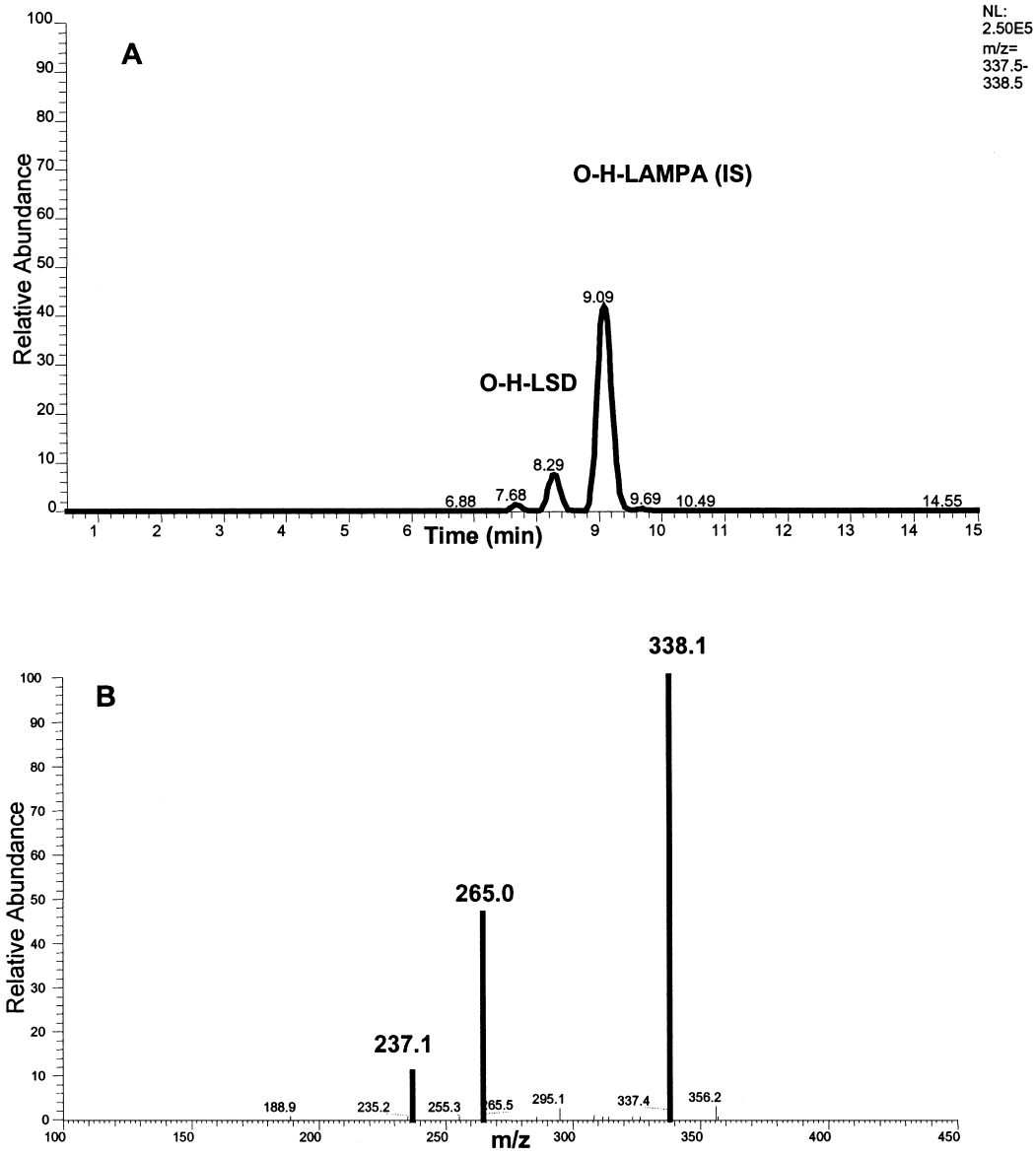

Fig. 5. TIC of (A) O-H-LAMPA (4000 pg/ml) and O-H-LSD (400 pg/ml) extracted from urine and (B) mass spectrum as analyzed by LC–MS–MS.

the 42 specimens. The resulting nor-LSD mean concentration was 934 pg/ml (median concentration, 761 pg/ml) with a range of values from 388 to 2185 pg/ml.

3.2.1. Conclusion

All seventy-four specimens used in the study were positive for LSD using a cutoff concentration of 500 pg/ml by the Roche Abuscreen® radioimmunoassay, and contained detectable (≥37 pg/ml) amounts of LSD by GC–MS. iso-LSD was quantitated in 64 of these specimens. Only nine of the 60 specimens analyzed for nor-LSD contained this metabolite in an amount greater than 200 pg/ml, while all of the 74 specimens contained significant levels of O-H-LSD by LC–MS–MS. The inconsistency in the presence

Table 2
Specimen profile of definitive experiment (all amounts in pg/ml)

Specimen	LSD	O-H-LSD	O-H-LSD:LSD	Nor-LSD	iso-LSD
33	1310	4107	3.1	ND	2000
34	1153	4158	3.6	ND	1400
35	151	4732	31.3	ND	150
36	135	5709	42.3	ND	1200
37	40	3035	75.9	ND	700
38	236	3980	16.9	ND	240
39	1824	14792	8.1	ND	3500
40	404	732	1.8	ND	300
41	592	4920	8.3	ND	800
42	442	1452	3.3	ND	1100
43	2541	2707	1.1	ND	7540
44[a]	122	828	6.8	ND	250
45[a]	184	3182	17.3	ND	1500
46	439	3045	6.9	ND	0
47	785	100057	127.5	592	2500
48	2233	69686	31.2	546	5000
49	907	56429	62.2	ND	2500
50	993	18279	18.4	ND	0
51	936	8786	9.4	ND	0
52	667	49275	73.9	761	600
53	1605	67935	42.3	835	5000
54	1058	16315	15.4	ND	200
55	225	9343	72.5	ND	700
56[a]	145	112831	778.1	2185	1500
57	1856	24030	12.9	ND	600
58	474	31918	6.7	ND	300
59	453	11051	24.4	ND	4000
60	207	5981	28.9	ND	950
61	1892	7334	3.9	ND	100
62	390	8132	20.9	ND	900
63	356	1860	5.2	ND	100
64	349	6926	19.8	ND	100
65	739	3588	4.9	388	250
66	257	28322	110.2	1229	100
67[a]	146	2465	16.9	ND	180
68[a]	122	1096	9.0	ND	250
69[a]	196	1321	6.7	ND	40
70[a]	156	7595	48.7	ND	300
71[a]	147	1071	7.3	ND	150
72[a]	115	2655	23.1	ND	200
73[a]	175	1797	10.3	ND	1500
74[a]	103	1545	15.0	ND	80
Mean=	649	16340	42.9	934	1190
Median=	397	4826	16.1	761	600
Range	40–2541	732–112831	1.1–778.1	388–2185	0–7540

[a] Specimens less than one-year old.
ND, not detected or <200 pg/ml.

of nor-LSD analyzed in these specimens suggests that this metabolite is a less suitable analytical marker than O-H-LSD for identification of LSD use.

At present, there appears to be no obvious correlation between the levels of LSD and that of the O-H-LSD metabolite ($r^2=0.0623$). However, 34 specimens, which were reported as negative for LSD (i.e. contained less than 200 pg/ml of LSD by

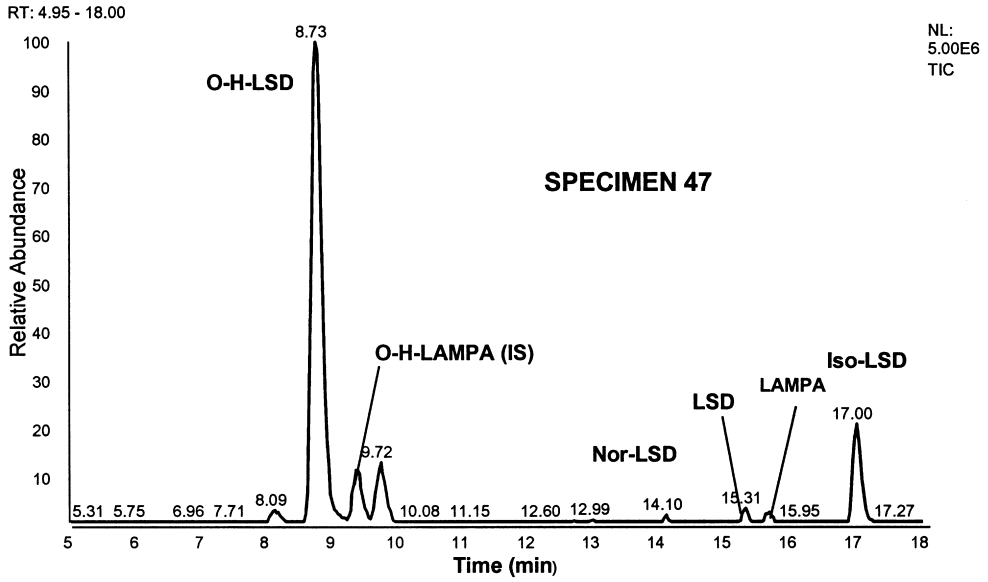

Fig. 6. TIC of a typical extracted urine specimen (no. 47) analyzed by LC–MS–MS demonstrating the presence of all of the LSD metabolites studied.

GC–MS; mean=118 pg/ml), contained appreciable amounts of O-H-LSD (mean=12 044 pg/ml). The ratio of O-H-LSD to LSD was 82.3 (data not shown).

In summary, this study indicates that the detection and quantitation of the LSD metabolite O-H-LSD can easily identify the use of LSD. The consistent and relatively large concentration of O-H-LSD present in all specimens investigated (at ng/ml levels versus pg/ml levels for LSD), shows great promise for detecting the use of LSD for a much longer period of time, possibly days versus hours.

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