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Gas Chromatographic/Mass Spectrometric Analysis of Morphine and Codeine in Human Urine of Poppy Seed Eaters

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ABSTRACT: In this study, poppy seeds were examined for a natural constituent that might serve as a marker for the seeds' ingestion as opposed to opiate abuse. Thebaine was selected as possible marker, since it was found to be a component of all poppy seeds examined and was not a natural component of different heroin samples. During the course of this investigation, a new extraction and cleanup procedure was developed for the gas chromatographic/nitrogen phosphorus detection (GC/NPD) and gas chromatographic/mass spectrometric (GC/MS) analysis of morphine and codeine in urine. A linear response, over a concentration range of 25 to 600 ng/mL, was obtained for codeine and morphine ($r = 0.9982$ and 0.9947, respectively). The minimum detectable level (LOD) and limit of quantitation (LOQ) for morphine were 10 and 30 ng/mL, respectively; whereas LOD and LOQ for codeine were 2 and 8 ng/mL, respectively. The coefficients of variance (CV, $n = 6$) for morphine and codeine analyses at the 100-ng/mL level were 13.3 and 4.6%, respectively.

This procedure was used for the analysis of urine samples from five poppy seed eaters who each ingested 200 g of poppy seed cake. Results indicated that significant amounts of morphine and codeine are excreted in urine and that in all subjects, at least at one point in time, the apparent morphine concentration as determined by radioimmunoassay (RIA) analysis exceeded the cutoff value (300 ng/mL) established for screening. Thebaine was not detected in urine specimens collected following poppy seeds ingestion and thus could not be used as a marker.

KEYWORDS: toxicology, chemical analysis, poppy seeds, urine, morphine, codeine

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Early work carried out on the seeds of *Papaver somniferum* indicated that they were devoid of alkaloids [*1-4*]. A later investigation on Turkish seeds showed that they contained trace amount of narcotine, together with small amounts of morphine and papaverine [*5*]. Using thin-layer chromatography (TLC) and paper chromatography, Preininger et al. [*6*] found that poppy seeds contained morphine, codeine, thebaine, papaverine, and narcotine (see Fig. 1).

Grove et al. [*7*] analyzed the seeds for "free" and "bound" morphine and codeine by gas chromatography/mass spectrometry (GC/MS) of their trimethylsilyl ether derivatives. Results showed that the amount of the "bound" form of these two alkaloids was higher than the "free" form.

Subsequent to these studies, Bjerver et al. [*8*] determined the morphine content of commercially available poppy seeds and poppy seed cake using a GC/MS procedure in which the pentafluoropropionate derivative of morphine was formed. This procedure was also used to determine morphine levels in urine samples from healthy adults collected 3 to 15 h after ingestion of two poppy seed cakes.

Recently, Fritschi and Prescott [*9*] determined urine morphine levels after poppy seed consumption using radioimmunoassay (RIA), enzyme multiple immunoassay technique

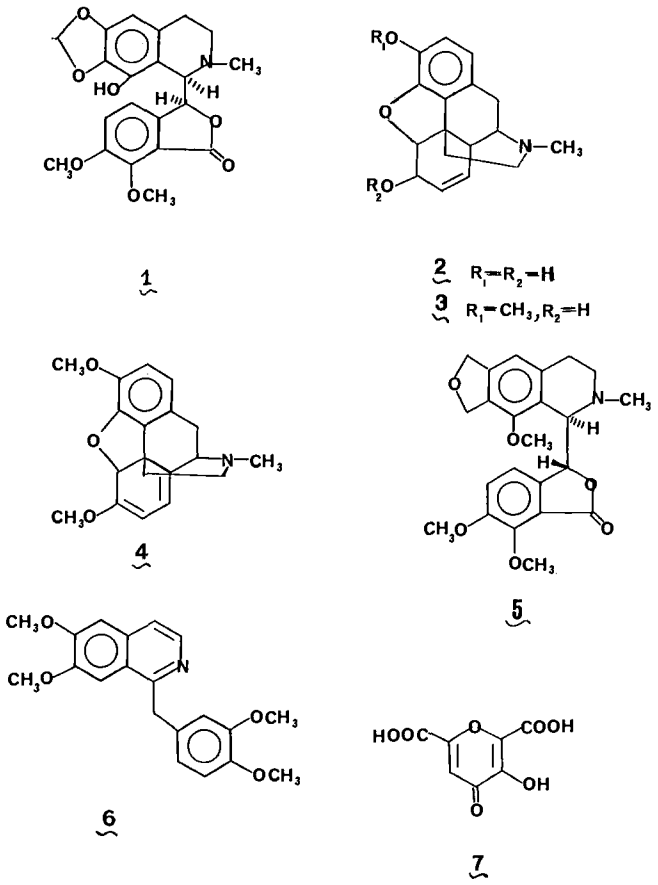

FIG. 1—*Chemical structures of selected compounds:* 1 = *narcotoline,* 2 = *morphine,* 3 = *codeine,* 4 = *thebaine,* 5 = *narcotine,* 6 = *papaverine, and* 7 = *meconic acid.*

(EMIT®-ST) and GC. They indicated also that narcotoline (see Fig. 1), a minor alkaloid of poppy seeds [*10*], could not be isolated from the most concentrated poppy seed urine and hence differentiation between poppy seed eaters and opiate abusers was not possible.

In this study, we attempted to examine poppy seeds for a natural constituent that might serve as a marker for the seeds' ingestion as opposed to opiate abuse. During the course of this investigation, a new extraction and cleanup procedure was developed for analysis of morphine and codeine. Seeds were acquired from different sources and examined for the most prevalent opium alkaloids. Heroin samples from different sources were also obtained and analyzed.

Thebaine (see Fig. 1) was selected as a possible markers and urine samples from five subjects who ingested poppy seed cake (200 g) were analyzed for thebaine. In addition, these urine specimens were analyzed by RIA for apparent morphine concentration and by GC/MS and gas chromatographic/nitrogen phosphorus detector (GC/NPD) for morphine and codeine following the newly developed procedure.

Material and Methods

Poppy Seeds

Seeds from Australian, Dutch, and Turkish varieties were obtained through the American Spice Trade Association, New York. These three varieties constitute about 94% of the total American market of poppy seeds.[6]

Poppy Seed Filling

Poppy seed paste used as cake filling was packaged by Sokol and Co. (Illinois).

Heroin

Illicit heroin samples were obtained through the Special Testing and Research Laboratory of the Drug Enforcement Administration (DEA). Three samples of heroin were received for analysis and were designated as: (a) heroin, Southeast Asia #4 (SEA #4); (b) heroin, Southwest Asia A (SWA/A); and (c) heroin, Mexican standard.

Standard Alkaloids

Morphine (NIDA), codeine (Sigma), papaverine (Sigma), and thebaine (Penick) were used as received from the suppliers. Dihydromorphine was prepared in house as follows: morphine HCl (100 mg) was dissolved in 95% ethanol (10 mL), 5% palladium on carbon (50 mg) was added, and hydrogenation allowed to proceed until the starting material was completely converted to one new product. The reaction product was filtered on a celite bed, evaporated to dryness (weight, 93 mg), and crystallized from methanol/ether (needles with melting point (m.p.) 163 to 170°C).

Preparation of Simulated Gastric Juice [11]

Pepsin (0.25 g) was triturated, in a mortar, with 1 g of sodium chloride until thoroughly mixed. To the resulting product was added acidified water (65 mL of 1*N* hydrochloric acid diluted with distilled water to 1 L) with trituration. The resulting solution was transferred to a 1-L measuring cylinder, and the mortar washed several times with acidified water until a volume of 1 L was reached.

[6]American Spice Trade Association, personal communication, 1985.

Reagents

All chemicals used were reagent grade.

Extraction of Poppy Seeds

Freshly crushed seeds (10 g) were defatted with hexane by maceration overnight. The defatted seeds were then extracted by percolation with 95% ethanol overnight (X2). The combined ethanol extracts were evaporated to dryness. The residue was partitioned between 0.5*N* hydrochloric acid (30 mL) and chloroform (30 mL). The acid extract was rendered alkaline with ammonium hydroxide (pH 9 to 9.5). The basic aqueous solution was applied over a dry column packed with acid-washed celite. The column was then eluted with a mixture of methylene chloride/isopropanol (9:1). The residue obtained after evaporation of the solvent was reconstituted in 1.0 mL of ethanol and examined by GC/NPD and GC/MS.

Extraction of Poppy Seed Paste

The paste was extracted by the same procedure described under poppy seeds but omitting the defatting step.

Extraction of Unconjugated and Conjugated Opium Alkaloids from Urine Specimens Collected from Individuals Following Poppy Seed Cake Ingestion

Five urine specimens (Specimens 1, 8, 14, 17, and 27) were extracted as follows: 10 mL of urine (pH 5.5) were made basic with ammonium hydroxide, then extracted (3 × 10 mL) with chloroform/isopropanol (9:1). The combined organic extracts were evaporated to dryness and the residue containing unconjugated alkaloids was analyzed for thebaine, morphine, and codeine using GC/NPD and GC/MS. The aqueous fraction was made acidic with concentrated hydrochloric acid and hydrolyzed by refluxing for 15 min. The hydrolysate was made alkaline (pH 9.0 to 9.5) and extracted with chloroform/isopropanol (9:1). The organic phase containing the conjugated alkaloids was analyzed for codeine and morphine using both GC/NPD and GC/MS. These extracts were also used to spike blank urine and the samples analyzed by RIA.

Analysis of urine specimens for morphine and codeine

Aliquots of 10 mL of urine (blank, spiked, or specimens to be analyzed) were transferred to a 50-mL screw-capped centrifuge tubes and 0.05 mL of internal standard solution (dihydromorphine, 0.1 mg/mL in methanol) was added to each tube.

Hydrolysis—To the urine sample was added 1.0 mL of concentrated hydrochloric acid. The sample was hydrolyzed in a household pressure cooker (120°C, 103 kPa [15 psi]) for 15 min, then allowed to cool to room temperature.

Extraction—One millilitre of 12*N* sodium hydroxide and one and one-half millilitres of 7.3*M* ammonium chloride were added to the sample and the pH adjusted to pH 9.0 using 12*N* sodium hydroxide. The compounds of interest were then extracted from the urine by adding 10 mL of chloroform/isopropanol (9:1) to the sample and the tube vortexed for 30 s. The tube was allowed to stand for 5 min and then placed in a sonicator bath briefly to achieve phase separation. The top aqueous layer was transferred to another tube and extracted again with 10 mL of chloroform/isopropanol (9:1). The two organic extracts were combined and passed through anhydrous sodium sulfate into a 25-mL conical flask. The solvent was then evaporated under vacuum at 50°C.

Cleanup—A champagne-style sample cleanup column (4 by 120 mm with a 30-mL reser-

voir) was prepared by plugging the tip with glass wool and loading with 0.5 g of silica gel 60 (70 to 230 mesh). The column was washed with 2 mL of methanol before proceeding. The sample residue was dissolved in 0.1 mL of methanol and transferred to the column. The sample flask was then washed with 0.1 mL of the eluting solvent (methanol/ammonium hydroxide—100:1.5) and the wash transferred to the column. After the solvent had been completely absorbed, this wash procedure was repeated three times, each time transferring the solvent only after the previously transferred solvent was absorbed.

The column was then eluted with 2.5 mL of the eluting solvent and the eluate discarded. The column was then eluted with 4.5 mL of the eluting solvent and the eluate was collected in a 15-mL test tube. The solvent from this fraction, containing the compounds of interest, was evaporated under nitrogen at 50°C. The residue was transferred quantitatively to a Reacti-Vial® using methanol. The solvent was evaporated and 0.2 mL of acetic anhydride and 0.2 mL of pyridine was added to the residue. The vial was capped with a septum and placed in an oven at 100°C for 1 h. When the vessel was removed from the oven it was allowed to stand for 5 min at room temperature before opening. The reagents were then evaporated under nitrogen at 50°C. The residue was dissolved in acetone and transferred to a 1-mL sample vial. The volume was adjusted to 0.1 mL with acetone for GC/MS analysis. This entire procedure is summarized in Fig. 2.

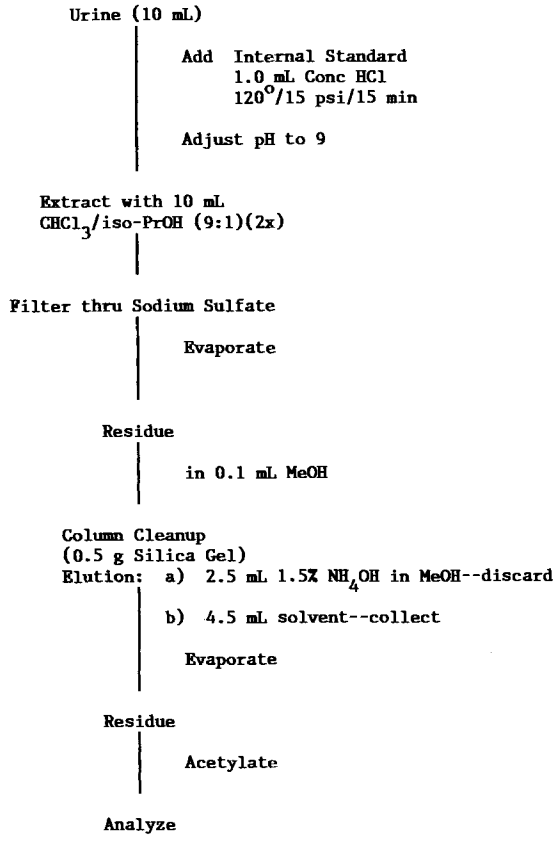

FIG. 2—*Extraction and cleanup of urine specimens before analysis for morphine and codeine.*

Calibration Curve Samples—In addition to the unknown samples assayed using this procedure, negative controls and calibration standards were prepared. These samples were blank urines to which both codeine and morphine were added in concentrations of 0, 25, 50, 100, 200, 300, 400, 500, and 600 ng/mL.

Gas Chromatographic Conditions (GC/NPD)

A Hewlett Packard Gas Chromatograph, Model 5710A, equipped with a NP detector was used with a capillary injector and a 0.25-mm by 15-m DB-5 capillary column. Analyses were performed isothermally at 250°C with helium carrier gas at a linear velocity of 33 cm/s.

GC/MS

A Hewlett Packard 5890 gas chromatograph interfaced to a Hewlett Packard 5970A mass selective detector was used for the analyses. A 0.25-mm by 15-m DB-1 column was operated isothermally at 230°C with helium carrier gas at a linear velocity of 45 cm/s. Using Hewlett Packard's Selected Ion Monitoring program, ions monitored were 282.05, 341.15, 327.10, 369.15, 329.10, and 371.15 AMU at dwell times of 100, 100, 100, 100, 50, and 50 ms, respectively. A 0.20-AMU window was set. For both GC/NPD and GC/MS analyses, split injection was used at a ratio of 50:1.

RIA of Urine Samples

The Abuscreen® Radioimmunoassay for Morphine (Roche Diagnostic Systems, Division of Hoffmann-LaRoche, Inc., Nutley, NJ) was used according to the manufacturer's protocol [*12*].

Results and Discussion

The question of whether poppy seeds on the American market contain sufficient opium alkaloids, especially morphine and codeine, to cause a positive test in a random drug testing program has significant forensic science implications. This study was designed to answer this question.

Poppy seeds from Dutch, Australian, and Turkish origin, which represent more than 90% of the American market,[6] were acquired and analyzed for morphine, codeine, thebaine, and papaverine. A sample of poppy seed cake filling was also analyzed for these alkaloids.

Extraction of the alkaloids was carried out through percolation of the defatted seeds with 95% ethanol. Although different extraction procedures were tried in our laboratory, the method reported here gave the highest yield of alkaloids including thebaine.

Table 1 shows the alkaloidal content of the different seeds and paste. Although all varieties tested did show morphine and codeine as the major alkaloids, the Turkish seeds had the lowest total alkaloidal content. Results published by Bjerver et al. [*8*] showed that the concentration of morphine in different poppy seeds brands ranged between 106 and 2.6 μg/g of seed. The morphine content of the poppy seed paste sample analyzed was reported to be 83 μg/g of paste. These values are in agreement with the present findings. The alkaloid thebaine which was identified in all preparations, was selected as a possible marker for poppy seed use.

Heroin samples acquired from different localities, for example, Southeast Asia, Southwest Asia, and Mexico, were analyzed by GC/NPD to establish whether or not thebaine was a component of crude heroin. Results are shown in Table 2.

The peaks shown at 3.92 and 3.91 min in SWA/A and Mexican heroin samples, respectively, have the same retention times as thebaine. However, when the samples were analyzed

TABLE 1—*Retention times and concentration of the major alkaloids in poppy seeds as determined by GC/NPD.*

Alkaloid	Retention Time[a]	Concentration, μg/g			
		Dutch	Australian	Turkish	Poppy Seed Paste (Filling)
Codeine	2.95	0.8	3.8	0.1	0.36
Morphine	3.28	19.0	106.0	5.1	24.00
Thebaine	3.94	1.5	14.0	0.3	0.46
Papaverine	8.09	trace	3.6	not detected	0.045

[a]Capillary DB-5 column (15-m by 0.25-mm ID) at 250°C and the helium flow rate at 33 cm/s.

TABLE 2—*Analysis of heroin samples by GC/NPD.*

Sample	Retention Times[a] of Major Peaks, min
Heroin SEA #4	3.85, 5.07
Heroin SWA/A	3.82, 3.92, 5.06, 8.07
Mexican heroin	3.81, 3.91, 5.06, 8.05

[a]Retention times: 6-acetylcodeine, 3.83 min; diacetylmorphine, 5.06 min. Capillary DB-5 column (15-m by 0.25-mm ID) at 250°C and the helium flow rate at 33 cm/s.

by GC/MS for thebaine, there was no thebaine detected in any of the heroin samples. In addition, GC/MS analysis showed that there were only two major peaks, namely 6-acetylcodeine and diacetylmorphine, in all samples. Thebaine was therefore considered a possible marker for poppy seeds ingestion.

In view of the fact that thebaine possesses an enol ether function, a study was carried out to examine its stability in the presence of simulated gastric juice and hot acid treatment.

The results of this study revealed that thebaine was not affected by the acidity of gastric juice at physiological pH. On the other hand, hot acid hydrolysis (concentrated hydrochloric acid at 120°C under pressure) resulted in significant decomposition of thebaine as shown by at least seven major peaks on the GC/NPD chromatogram.

Thus, if thebaine is to be found in urine specimens it had to be extracted from urine before hydrolysis. Thebaine was recovered quantitatively from spiked urine samples upon basification of the urine and extraction with methylene chloride/isopropanol (9:1). Methylene chloride alone resulted in 57% recovery.

To investigate the effect of poppy seed ingestion on the urinalysis for opiates, six subjects were allowed to ingest two 100-g pieces of cake made with poppy seed filling. Urine specimens were collected from these individuals and total void volumes were measured. All urine specimens were subsequently analyzed for apparent morphine content by RIA and for morphine and codeine by GC/MS and GC/NPD. Five of these specimens were analyzed for free and conjugated morphine or codeine or both. These samples were extracted under basic conditions, with methylene chloride/isopropanol (9:1), then acidified, followed by hydrolysis and reextraction. The residues from the two extracts were dissolved in ethanol and the solutions used to spike normal urine for RIA analysis (Table 3).

The results shown in Table 3 indicated that there were no free alkaloids found in the urine samples examined. However, since we determined that thebaine had a cross-reactivity of

TABLE 3—*Summary of RIA results on poppy seed urines.*

Poppy Seed Urine No.	Apparent Morphine Concentration, ng/mL[a]		
	A	B	C
1	ND	ND	ND
8	66	ND	64
14	208	ND	194
17	>300	ND	>300
27	>300	ND	>300

[a]A—Neat urine. B—Residue from methylene chloride/isopropanol (9:1) extract of 10-mL urine, dissolved in 500-μL ethanol and 50 μL added to 1.0-mL blank urine. C—Residue from aqueous phase from B (hydrolyzed, cleaned on celite column, and extracted). The extract dissolved in 500-μL ethanol and 50 μL added to 1.0-mL blank urine. ND—Not detected.

only 3.8% with the morphine antibody, GC/MS analysis was required to determine the presence of thebaine in urine.

GC/MS analysis of the extract of unhydrolyzed urine for thebaine showed no detectable amounts of this alkaloid which could be attributed to the alkaloid's metabolism before urinary excretion. The conclusion, therefore, was that thebaine could not be used as a marker to differentiate poppy seed ingestion from opiate abuse.

All urine specimens collected from the five individuals who consumed poppy seed cake were subsequently analyzed by RIA for apparent morphine concentration and by GC/MS and GC/NPD for morphine and codeine. A new cleanup procedure was developed which resulted in no interfering substances for either GC/MS or GC/NPD analysis.

Nalorphine, which has been used as internal standard by other investigators [*13*] was not suitable for this analysis since it eluted along with the first fraction away from the compounds of interest. Dihydromorphine (prepared by catalytic hydrogenation of morphine) was used as an internal standard in this study. Under these experimental conditions the internal standard eluted with morphine and codeine from the silica gel column and had a GC retention time in between those of the two alkaloids. The acetate derivatives were made before GC analysis.

Calibration curves were prepared for codeine and morphine which showed a linear response over a concentration range of 25 to 600 ng/mL ($r^2 = 0.9982$ and 0.9947, respectively). The minimum detectable level (LOD) and limit of quantitative (LOQ) for morphine were 10 and 30 ng/mL, respectively, whereas the LOD and LOQ for codeine were 2 and 8 ng/mL, respectively. The coefficients of variance (CV, $n = 6$) for morphine and codeine analyses at the 100-ng/mL level were 13.3 and 4.6%, respectively.

This procedure was used for the analysis of urine samples from poppy seed eaters, and the results are shown in Table 4.

Examination of the data shows that significant amounts of morphine and codeine are excreted in urine and that in all subjects, at least at one point in time, the apparent morphine concentration as determined by RIA analysis exceeded the cutoff value (300 ng/mL) established for screening. Bjerver et al. [*8*] reported morphine concentrations between 150 and 400 ng/mL in urine samples obtained after poppy seed cake ingestion.

The data also show that, although morphine concentration was always higher than that of codeine, the morphine/codeine ratio varied from 1.20 to 19.60. There was also variation in morphine/codeine ratio within specimens from a given subject, depending upon the time of urine collection. Furthermore, there does not appear to be any correlation between any of the individual concentrations and the morphine/codeine ratios.

TABLE 4—*Analysis of poppy seed urines.*

Subject	Sample Number	Collection Time, h	Collection Vol., mL	RIA-1,[a] ng/mL	RIA-2,[b] ng/mL	Codeine, ng/mL	Morphine, ng/mL	Morphine: Codeine Ratio
A	1	0	196	0.8	0	ND	ND	ND
	2	2	148	363	268	26	223	13.94
	3	3.5	148	517	>300	31	278	8.97
	4	6	149	684	>300	39	411	10.54
	5	6.5	12	125		(sample not received by RIPS)		
	6	7.5	100	219	208	75	158	2.11
	7	10.5	97	186	169	26	127	4.89
	8	12.5	255	47	66	13	46	3.54
	9	14.5	250	80	81	35	62	1.77
	10	20.5	175	280	240	22	226	0.27
B	11	0	253	0	0	ND	ND	ND
	12	4	250	631	>300	33	504	15.27
	13	10	250	465	>300	28	346	12.36
	14	19	247	202	199	19	164	8.63
C	15	0	31	0	0	ND	ND	ND
	16	2.5	100	728	>300	42	823	19.60
	17	4.5	199	433	>300	22	306	13.91
	18	9	200	250	227	16	167	10.44
	19	12.25	507	73	80	18	72	4.00
	20	14.75	240	500	>300	60	659	10.98
D	21	0	177	0	46	ND	31	...
	22	2.5	171	298	254	32	240	7.50
	23	10	152	264	>300	83	168	2.02
E	24	0	71	0	0	ND	ND	ND
	25	3	100	982	>300	94	720	7.66
	26	6.5	100	868	>300	292	702	2.40
	27	9	150	711	>300	358	754	2.11
	28	12	150	780	>300	247	860	3.48
	29	21	504	262	196	39	106	2.72
F	30	0	206	0	0	ND	ND	ND
	31	2	197	188	185	86	127	1.48
	32	6	201	319	>300	139	291	2.09
	33	11	127	300	>300	69	83	1.20
	34	22	194	108	101	55	144	2.62

[a]Original RIA data supplied by Roche Diagnostic Systems.
[b]RIA data generated at University of Mississippi.

Note from the data that the concentration of morphine or codeine or both in urine was highest a few hours after use (2 to 12 h). However, another peak was observed about 20 h after ingestion. The second peak could be explained on the basis of the difference in excretion rates and metabolism for morphine and codeine (the latter being metabolized to morphine, at least in part) which exist together in the seeds. Alternatively, the second peak could be the result of urine concentration in the first void specimens collected at the 20-h time frame postingestion.

Meconic acid (see Fig. 1, structure 7), the natural organic acid which forms the salt of opium alkaloids, presents an alternative marker. A standard sample of the compound was unavailable for analysis and we are in the process of isolating the compound from fresh opium for further examination. Until such time when a marker is identified, interpretation of analytical data relative to opiate abuse versus poppy seed ingestion should be done with extreme caution.

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