CASE REPORT

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Hmong Folk Remedies: Limited Acetylation of Opium by Aspirin and Acetaminophen

REFERENCE: Smith, R. M. and Nelson, L. A., **"Hmong Folk Remedies: Limited Acetylation of Opium by Aspirin and Acetaminophen,"** *Journal of Forensic Sciences,* JFSCA, Vol. 36, No. 1, Jan. 1991, pp. 280–287.

ABSTRACT: The traditional folk medicine of the Hmong and other Southeast Asian refugees has accompanied them during their immigration to this country over the past two decades. In two recent cases involving Hmong defendants, unknown solids, resembling charcoal in consistency and purported to be "backache remedies," were analyzed and found to be complex mixtures of aspirin, acetaminophen, caffeine, and partly acetylated opium. In particular, significant amounts of acetylacetaminophen, 3-*O*-acetylmorphine, 6-*O*-acetylcodeine, 6-*O*-acetylmorphine, and heroin were identified by gas chromatography/mass spectrometry. Heating approximately equal weights of solid opium, aspirin, and acetaminophen at 130°C for several hours produced a mixture of compounds showing a similar acetylation pattern.

KEYWORDS: toxicology, opium, folk medicine

The Hmong are residents of small, isolated villages in Southeast Asia who believe that their health depends on the interplay of both physical and spiritual forces. The focus of their health care is a shaman, or medicine man, who ministers (often with considerable theatrics) to both of these needs, and on individuals of less specialized training who act as "possessors of medicine." The "possessors of medicine" usually provide patients with medicinal ingredients and with advice on how to use them. It is a role exercised by many adult Hmong over age 40 [*1*].

Hmong remedies come in a variety of forms and include many vegetable medicines (of which opium is common), as well as some traditional Western drugs. Many of these remedies, often administered by smoking or inhaling, treat symptoms with unnecessary vigor, and may themselves cause serious physical injury [*2*] or lead to opium addiction [*3*].

Such traditional health care has accompanied the Hmong and other Southeast Asian refugees during their immigration to this country over the past two decades [*2*]. This was dramatically illustrated by two unusual samples recently received by our laboratory which

Received for publication 29 Jan. 1990; revised manuscript received 6 March 1990; accepted for publication 5 April 1990.

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the defendants, all reportedly Hmong but from widely separated parts of our state, claimed to be "backache remedies."

Case Report

Case No. 1

Three Orientals—one a 78-year-old woman, the other two a couple in their midthirties—were found with a large cache of drug-related paraphernalia. Included were two vials of liquid opium suspension, a small quantity of hard, glassy opium, a large metal and wooden smoking device, and several items containing hard black solids (nearly 6 g in one item) which had the appearance and consistency of charcoal. Acid extraction of still other items in the case led to the identification of acetaminophen (APAP), caffeine, and phenetsal. A small amount of aspirin was identified along with the above drugs in yet another item.

Case No. 2

A suspicious package from Thailand was delivered to the house of an Oriental female (age not given). The primary contents of the package consisted of a woody/dried mushroom-like material, but further investigation uncovered over ½ lb (250 g) of hard opium in a false bottom. This item was confiscated, along with part of a "hookah"-type smoking device and a metal cup with 12 g of a hard black solid similar to that described in Case No. 1.

Materials and Methods

Combined gas chromatography/mass spectrometry (GC/MS) was performed on a Hewlett-Packard Model 5970B mass selective detector controlled by a 59940A MS Chemstation (HP-UX series) and coupled to a Hewlett-Packard 5890 gas chromatograph (GC) equipped with a 10-m HP-1 methyl silicone capillary column. The GC oven was programed to go from 100 to 280°C at 20° per min and then hold at 280°C for 3 min.

Opiate Extraction

The case samples were extracted using traditional acid/base extraction techniques, but even with the pHs closely monitored, the opiate recovery was poor and complicated by concomitant extraction of the more abundant acid and neutral compounds. As a result, Bond-Elut Certify columns (Analytichem International, Harbor City, California) were used for opiate extraction.

Samples containing an equivalent of approximately 0.05 g or less of opiates (0.25 g or less of crude opium) were crushed in 5 mL of dilute hydrochloric acid (HCl) (1 drop of concentrated HCl in 5 mL of water) and allowed to stand for 5 to 10 min. These mixtures were neutralized to pH 5 to 7 using solid sodium bicarbonate and then centrifuged, and the liquid was decanted from the solid residue. The neutralized solutions were placed on Bond-Elut Certify columns (prewashed with 2 mL each of methanol and distilled water), then gently forced through the columns using a large rubber squeeze bulb or allowed to drip through by gravity, so as to allow an average of 4 to 5 min of contact between the solutions and the columns. After passage of the sample solutions, the columns were washed with 2 mL of distilled water, 1 mL of 0.1*M* acetate buffer (pH 4.0), and then 2 mL of methanol. At this point the receptacles under the columns were changed, and 2 mL of eluting solution (chloroform/isopropanol/ammonium hydroxide, 78.4:19.6:2)

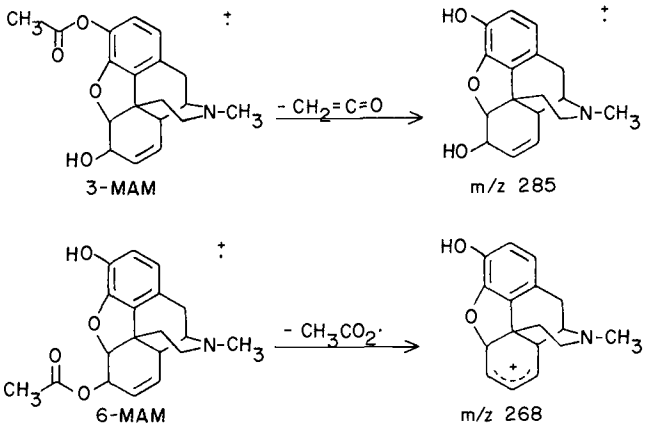
were passed through the columns. These solutions were evaporated to dryness under air and reconstituted with about ½ to 1 mL of a 3:1 chloroform/methanol mixture for GC and GC/MS analysis.

Opium Acetylation

Attempts to duplicate the acetylation pattern seen in the unknown samples were carried out under very simple conditions. Samples of solid opium from Case No. 2 (approximately 0.25 g per run) were finely pulverized and mixed with varying amounts of crushed aspirin (325 mg/tablet, Paddock Laboratories, Minneapolis, Minnesota), or acetaminophen tablets (325 mg/tablet, Henry Schein, Inc., Port Washington, New York), or both aspirin and acetaminophen together. The solids were placed in standard laboratory test tubes, vortexed briefly to mix them, and heated in an oil bath at temperatures ranging from 130 to 170°C for up to 6 h. After cooling to room temperature, the remaining solidified masses were tediously chipped out of the test tubes and extracted as described above.

Results and Discussion

Gas chromatography/mass spectrometry analyses of the opium from Case No. 2 and of the unknown solids from Cases No. 1 and 2 are compared in Fig. 1. The large diffuse thebaine peak in the opium chromatogram is due to rearrangement under GC conditions [*4*], providing several different MW 311 spectra under various portions of the peak. Thebaine is entirely absent from the unknown samples, whereas acetaminophen (APAP), caffeine, and several acetylation products of acetaminophen and of the opiates make their appearance. In addition to codeine and morphine, 3-*O*-acetylmorphine (3-MAM), 6-*O*-acetylcodeine (6-AC), 6-*O*-acetylmorphine (6-MAM), and diacetylmorphine (heroin) were identified (Figs. 2 and 3). Mass spectrometry easily distinguishes 3-MAM from 6-MAM in the loss of ketene (42 daltons), giving *m/z* 285 (compare this with a similar loss from the molecular ion of heroin), while 6-MAM loses 59 daltons as acetate to give *m/z* 268 (compare this with the fragmentation of 6-AC) [*5*].



This pattern of opiates is inconsistent in our experience with that arising from hydrolytic decomposition of a heroin sample containing significant amounts of 6-AC as an impurity, since 3-MAM is virtually unknown in illicit heroin samples.

Because the Hmong are known to mix Western medicines with opium and herbal medicines [*1*], and because these samples appeared to be "homemade" (that is, produced

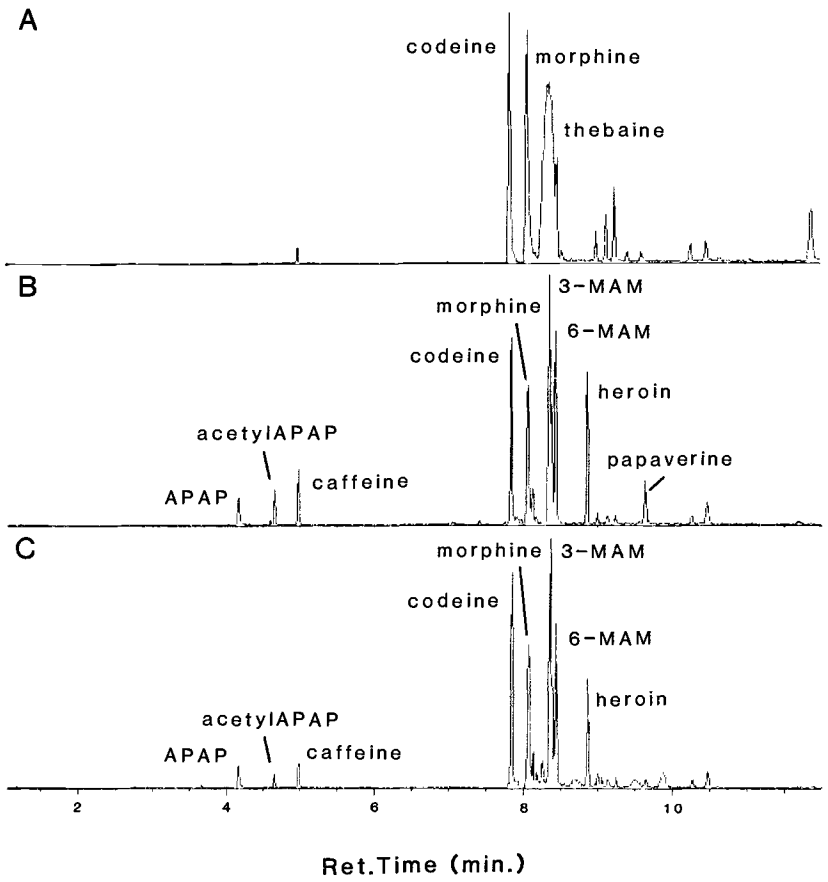


FIG. 1—*Total ion chromatograms from* (A) *opium from Case No. 2;* (B) *unknown solid sample No. 1; and* (C) *unknown solid sample No. 2.*

under unsophisticated laboratory conditions), it occurred to us that these mixtures might result from the possibly unintentional acetylation of the acetaminophen and the opiates by acetaminophen itself under sufficiently vigorous conditions. Indeed, heating a powdered mixture of opium and acetaminophen at 170°C (near the melting point of acetaminophen) produced some acetylation, but not the relative ratio of products seen in unknown samples Nos. 1 and 2 (Table 1 and *A* in Fig. 4). More vigorous conditions led to mixtures which were even further depleted in 3-MAM and heroin concentrations. Under no conditions was the self-acetylation of acetaminophen observed.

Even though it was not detected in either of the unknowns, the presence of a small amount of aspirin [acetylsalicylic acid (ASA)] in a minor item in one of these two cases led us to consider the possibility of aspirin as the acetylating agent. Aspirin is known to acetylate other compounds under fairly mild conditions [*6*].

Various mixtures of opium, aspirin, and acetaminophen were heated. The results are shown in Table 1. The only conditions that came close to duplicating the product distribution seen in unknown samples Nos. 1 and 2 were those involving all three reactants heated to temperatures near the decomposition point of aspirin (about 120 to 130°C). Heating to 170°C appeared to deacetylate the 3-*O* position of 3-MAM and heroin, as these compounds were produced only in minor amounts at this temperature, even after

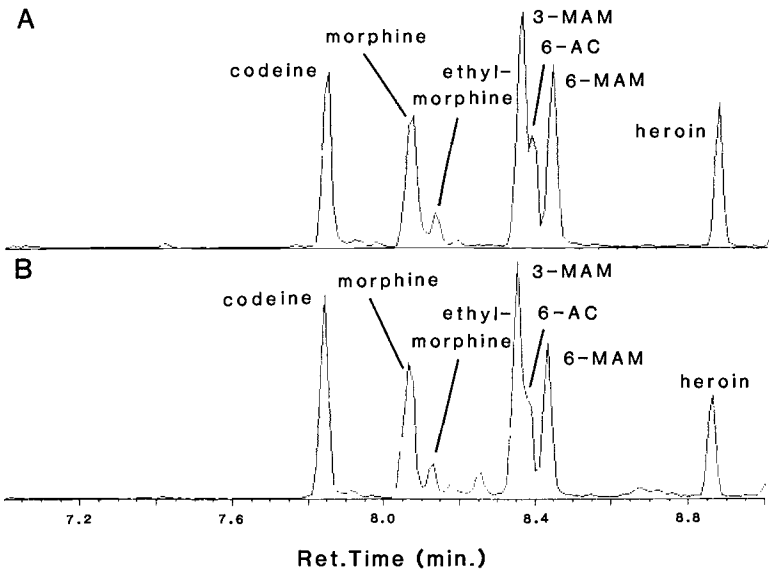


FIG. 2—*Enlarged portion of the chromatograms from unknown sample No. 1* (A) *and unknown No. 2* (B), *showing opium acetylation products.*

previous acetylation at 130°C. Varying the amounts of aspirin and acetaminophen in the reaction mixtures indicated an upper limit for the probable ASA/opium ratio in the original case samples at approximately 1:1 (*B* in Fig. 4). Higher ASA/opium ratios led to more complete acetylation [over 80% in the 4:1 mixture (*C* in Fig. 4)]. The relative amount of acetaminophen in the reaction mixture seemed to have less effect; in fact, at low temperatures acetaminophen competes with the opiates for the available aspirin (compare Runs 9 and 5 in Table 1).

The other drugs present in the unknown samples were assumed to be inert under the reaction conditions. Acetylation of thebaine did not contribute substantially to the product mixture. Under typical reaction conditions pure thebaine disappeared, but it produced only minor amounts of characterizable products. A feeling that the phenetsal found in unknown sample No. 1 might be formed from aspirin and acetaminophen under conditions leading to the acetylated products was not substantiated either by our own results or by its absence in sample No. 2. That aspirin was not detected, even in the acidic fraction, of either unknown sample is not surprising, since under our conditions it decomposed and sublimed from the reaction mixture as salicylic acid crystals. These collected on the walls of the test tube and were identified by infrared spectrometry.

Conclusions

The relatively facile approximation of the acetylation product ratios obtained by heating solid opium at fairly low temperatures with readily available drugs indicates the likelihood that the unknown samples were produced under reasonably crude laboratory conditions. That, coupled with the little information received with the cases, lends credence to the probability that both of these cases represent examples of Hmong folk medicine. Unfortunately, the suspects in these cases spoke little or no English, and were reluctant to discuss their situations with law enforcement people.

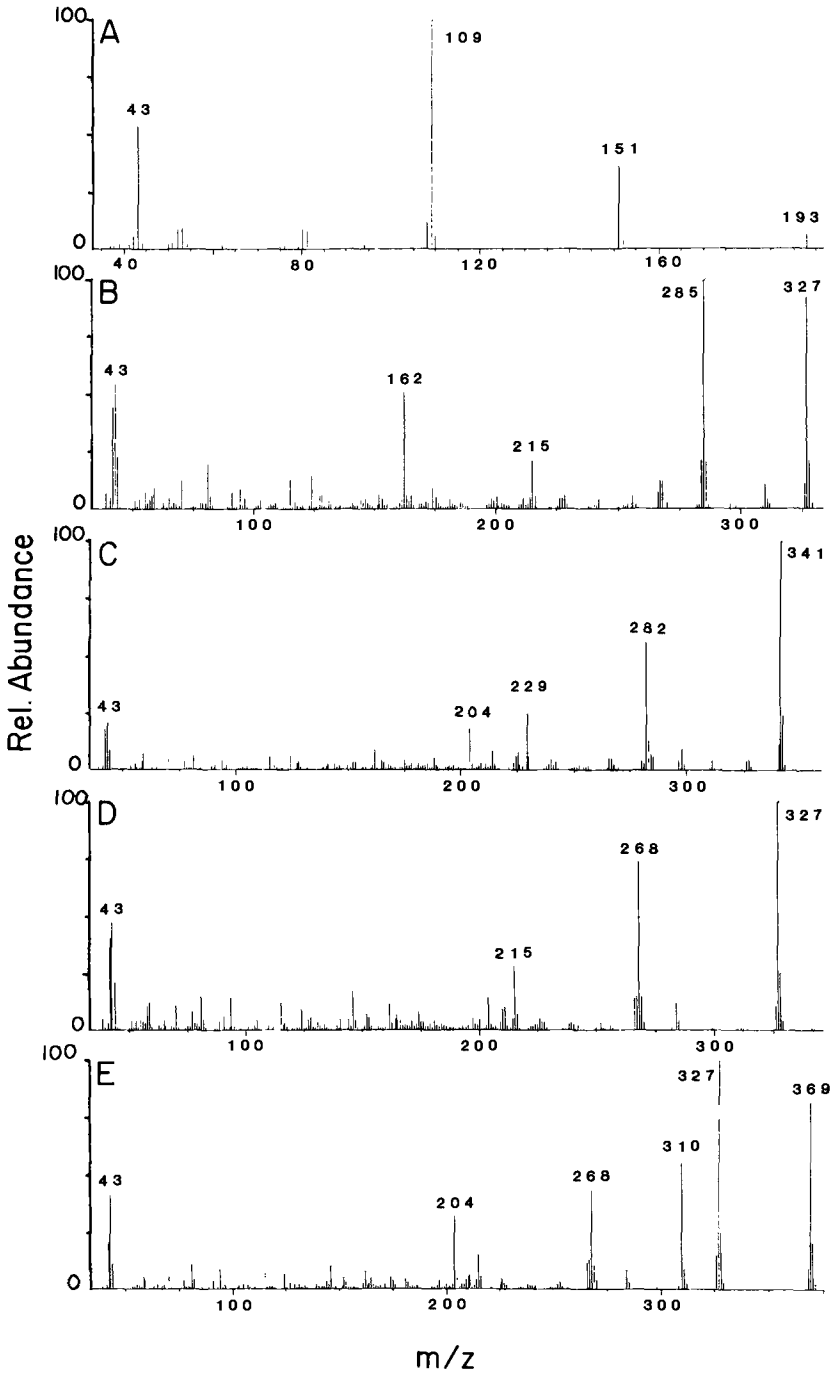


FIG. 3—*Mass spectra of the acetylation products:* (A) *acetylacetaminophen,* (B) *3-O-acetylmorphine,* (C) *6-O-acetylcodeine,* (D) *6-O-acetylmorphine, and* (E) *heroin.*

TABLE 1—*Opium acetylation products.*

Run No.	Sample	3-MAM[a]	6-AC[b]	6-MAM[a]	Heroin[a]	ACAPAP[c]
	unknown No. 1	35	35	25	17	43
	unknown No. 2	41	(20)[d]	22	13	27
1	opium/APAP, 130°C	0	0	0	0	0
2	opium/APAP, 170°C	2	21	22	1	0
3	opium/ASA, 130°C	26	74	26	37	...
4	opium/ASA/APAP, 170°C	3	60	67	4	0
5	opium/ASA/APAP, 130°C	24	33	27	10	41
6	opium/2 ASA/APAP, 130°C	22	80	30	42	56
7	opium/4 ASA/APAP, 130°C	32	87	5	62	91
8	opium/0.3 ASA/APAP, 130°C	45	37	19	11	21
9	opium/ASA/0.3 APAP, 130°C	29	49	30	24	54

[a]Percent of total morphine-derived opiates.
[b]Percent of total codeine-derived opiates.
[c]Percent of acetaminophen-derived products.
[d]Approximate.

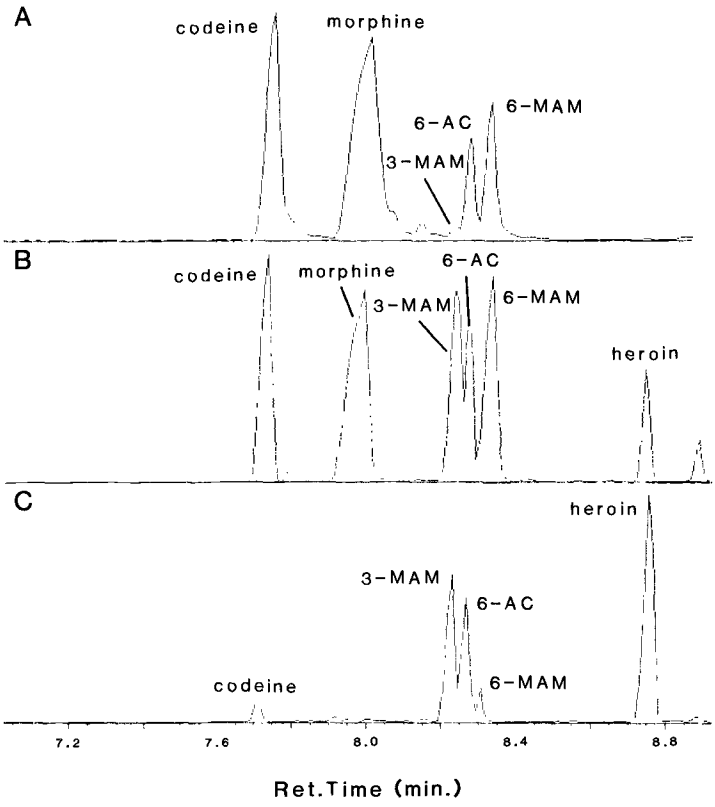


FIG. 4—*Enlarged portion of chromatograms from acetylation reactions showing acetylated opiates:* (A) *opium/APAP at 170°C,* (B) *opium/ASA/APAP (1:1:1) at 130°C, and* (C) *opium/ASA/APAP (1:4:1) at 130°C.*

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