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Antemortem Conversion of Codeine to Morphine in Man

In the routine screening of postmortem specimens in this laboratory, whenever codeine is detected, morphine is almost always found concurrently. Adler [*1*] and Mannering et al [*2*] demonstrated that, in man, codeine is demethylated to morphine, and that as much as 17.2% of codeine appears as bound and unbound morphine in urine.

From the data collected in acute drug deaths involving codeine, our objectives were to establish and compare the relative amounts of codeine and morphine found in various tissues and relate this to the problem of determining whether codeine alone was taken by the deceased or if morphine was also taken.

Method

We reviewed 45 fatalities involving the use of codeine during a 12-month period in which more than 1050 cases were screened for possible narcotic use.

The gas chromatography (GC) detection and determination procedures for codeine and morphine in blood and other postmortem specimens were essentially those of Nakamura and Way [*3*]. Codeine and morphine were determined in the same tissue or body fluid sample. A pH of 9.0 was used for the extraction of both codeine and morphine. All tissue samples, except blood, were acid hydrolyzed prior to extraction. Adler et al [*4*] and Axelrod and Inscoe [*5*] demonstrated that codeine and morphine were conjugated and excreted as a glucuronide in the urine.

Results

Codeine and morphine determinations were conducted on available blood, liver, kidney, bile, and urine specimens from 45 death cases involving codeine use. The concentrations of codeine and morphine in the various tissues are shown in Table 1. Also shown are blood concentrations of drugs other than codeine and morphine. In 6 of the 45 cases, autopsy examination revealed "track" marks on the antecubital fossae of the decedents, and their history indicated past addiction to or use of narcotcs. These six cases were grouped at the bottom of Table 1 as Cases 40 through 45. They were not included in the data evaluation for codeine-implicated deaths since the compiled data supported either heroin or morphine use.

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Table 2 lists the number of specimens containing codeine at various concentrations. Most of the blood, liver, and kidney values were between 0.01 to 0.49 mg/100 ml for codeine. From the analyses, 30 of 38 blood specimens, 27 of 30 liver specimens, and 11 of 19 kidney specimens were in this range.

The concentration of codeine in bile and urine was predominantly in the higher concentration range. Twenty-three of 36 specimens of bile and 9 of 18 urine specimens analyzed were in the range of 0.5 to 4.99 mg/100 ml; other urine specimens had higher concentrations of codeine, and all but one bile specimen were also higher. The results emphasize the buildup of this drug in bile and urine, which are both excretory reservoirs.

Autopsy findings in cases involving codeine overdoses were similar to those generally observed in deaths due to central nervous system depressants; at autopsy, visual signs of visceral congestion, especially pulmonary edema, were noted. As to modes of death, 9 cases were determined to be suicide, 28 accidental, and the remaining 8 "undetermined." All of the 9 cases of suicide were committed by persons 30 years of age or more; 7 were female and 2 were male. These codeine-implicated deaths involved 24 females and 21 males; 2 of the females were 17 years old and 1 male was 15 years old.

Discussion

Table 2 shows that 79% of the 39 acute overdose death cases had blood concentrations of codeine between 0.01 and 0.49 mg/100 ml. The assignment of a lethal level of codeine was tenuous because of the presence of drugs in blood other than codeine and its conversion product, morphine (see Table 1). Also, the unavailability of information concerning survival time and dosage made it difficult to determine what blood concentration should be associated with lethality. All specimens in the 45 cases involving codeine use were examined for morphine. The morphine values were presumed to be those from codeine metabolism unless analytical data and history indicated that a part of the morphine value could have heroin as a source. As mentioned previously, 6 of the 45 cases were in this category.

In these cases involving codeine we noted that codeine concentrations were higher in some tissues and morphine concentrations were higher in others. This led to a comparison of the ratio of codeine to morphine concentrations in all tissues studied.

Table 3 shows that blood, liver, kidney, and urine had a higher ratio of codeine to morphine. In each of the specimens analyzed, 80 to 100% of the cases showed a codeine to morphine ratio which exceeded 1.00. However, bile analysis revealed a marked reversal in this ratio; only 30% of the cases were more than 1.00. In 70% of the bile specimens analyzed, the morphine value exceeded that of codeine. This can be attributed to the active demethylation of codeine in the liver. This phenomenon was observed in rats by Yeh and Woods [6].

If bile alone is sampled in a coroner's laboratory and the result shows a higher concentration of morphine than codeine, this finding may lead to an interpretation that heroin or morphine was taken. Another specimen, such as blood, urine, liver, or kidney, should be tested for its codeine to morphine ratio.

Table 3 shows that in 5 of 29 liver samples, the morphine values exceeded those of codeine. These cases are represented by Cases 6, 7, 9, 12, and 23 in Table 1 and are not to be construed as a combined use of heroin/morphine and codeine; the histories did not indicate past narcotic addiction. A plausible explanation in these instances is that death did not occur suddenly and that there was time available for a prolonged enzymatic demethylation in the liver.

In four cases in which the blood-morphine concentrations exceeded concentrations of codeine the case history suggests heroin addiction or findings, at autopsy, of needle

TABLE 1—*Codeine and morphine distribution in fatal cases involving codeine.*[a]

Case	Blood		Bile		Liver		Kidney		Urine		Other Drugs in Blood	
	Morphine	Codeine	Morphine	Codeine	Morphine	Codeine	Morphine	Codeine	Morphine	Codeine		
1	ND	ND	0.26	0.06	...[b]	...	0.04	0.01	ND	0.32	ethchlorvynol	0.8
2	...[b]	0.01	ND	0.18	...	...	...	...	...	...	phenobarbital	0.7
											diazepam	0.6
											propoxyphene	2.2
3	...[b]	0.02	4.80	0.73	0.03	0.08	...	...	0.70	1.48	pentobarbital	2.0
4	0.02	0.03	ND	ND	...	...	...	...	...	...	ethanol	150
5	ND	0.04	0.02	0.08	0.06	0.32	...	...	ND	ND	ethanol	160
6	...[b]	0.04	24.10	1.80	0.30	0.19	...	...	3.40	10.30	pentobarbital	0.1
7	0.01	0.04	3.89	0.70	0.64	0.52	0.18	0.31	0.76	1.92	...	
8	...[b]	0.04	0.90	0.18	0.03	0.06	0.03	0.15	...	...	...	
9	0.01	0.05	0.31	0.29	0.25	0.20	...	...	...	...	salicylate	5.0
											phenobarbital	1.7
											secobarbital	0.4
											ethanol	70
10	0.01	0.04	1.68	0.37	0.05	0.07	0.13	0.24	6.98	13.60	glutethimide	0.5
11	...[b]	0.06	0.20	0.50	0.06	0.22	...	...	...	...	salicylate	4.6
											secobarbital	1.5
12	0.03	0.07	11.90	1.07	0.21	0.18	0.43	0.46	5.01	5.70	salicylate	2.8
											trichlorethanol	0.5
13	0.02	0.08	2.36	0.60	0.03	0.12	...	...	0.92	5.70	ethchlorvynol	0.2
											pentobarbital	0.4
											phenobarbital	1.1
14	0.02	0.12	0.76	1.36	...	...	...	...	...	...	phenobarbital	1.1
15	0.01	0.12	1.10	0.51	...	...	...	...	...	...	ethanol	110
											salicylate	7.0
											meprobamate	5.8
16	0.01	0.12	3.83	1.11	0.09	0.30	0.15	0.62	5.79	22.90	pentobarbital	0.9
17	ND	0.12	ND	0.14	...	...	...	...	...	...	ethanol	110
											salicylate	7.0
											meprobamate	5.8
18	0.09	0.13	1.70	0.68	...	...	...	...	...	...	...	

19	. . .[b]	0.15	0.73	0.50	0.03	0.08	0.05	0.23	0.55	4.98	ethanol	210
20	0.01	0.15	9.60	2.54	0.32	0.51	0.03	0.32	2.00	4.46	butalbital	2.1
											salicylate	5.2
21	0.02	0.15	1.32	0.86	0.07	0.19	0.08	0.30	1.39	13.80	pentobarbital	1.6
22	0.03	0.18	. . .	. . .	. . .[b]	0.67	0.09	3.63	. . .	. . .	pentobarbital	1.1
23	0.05	0.30	6.30	0.68	0.63	0.38	0.45	0.65	3.50	13.18	salicylate	8.8
24	0.02	0.77	2.31	2.84	0.03	0.06	0.24	0.71	. . .	. . .	secobarbital	2.1
25	0.04	0.88	0.31	3.29	0.27	4.49	0.23	2.67	0.48	2.91	ethanol	220
											phenylbutazone	2.7
26	ND	0.01	ND	0.05	ND	0.40	ND	2.49	ND	2.99	salicylate	7.4
											secobarbital	0.4
27	0.03	0.12	1.04	0.54	0.09	0.13	. . .	. . .	. . .	. . .	. . .	
28	ND	ND	0.33	0.10	0.01	0.01	0.01	0.01	. . .	. . .	secobarbital	1.1
29	ND	ND	1.11	0.13	0.01	0.02	. . .	. . .	0.10	0.24	. . .	
30	0.01	0.01	. . .	. . .	. . .	. . .	. . .	. . .	. . .	. . .	salicylate	3.0
											methyprylon	1.5
31	ND	ND	2.65	0.63	. . .	. . .	. . .	. . .	. . .	. . .	. . .	
32	ND	ND	0.10	0.09	ND	ND	ND	ND	. . .	. . .	phenobarbital	12.9
33	ND	0.02	0.09	0.05	ND	0.03	ND	0.03	. . .	. . .	salicylate	2.0
											pentobarbital	1.8
34	ND	0.02	. . .	0.50	. . .[b]	0.32	. . .[b]	0.09	ND	2.99	salicylate	7.4
35	ND	0.10	0.46	0.93	ND	0.28	. . .	. . .	ND	10.42	pentobarbital	0.2
36	0.04	0.06	. . .	. . .	0.14	0.51	. . .	. . .	. . .	. . .	pentobarbital	4.3
37	ND	0.04	2.03	1.27	0.04	0.41	0.04	0.10	0.72	5.85	. . .	
38	ND	ND	6.43	2.17	0.01	0.02	. . .	. . .	0.18	0.98	diazepam	0.08
39	0.01	0.17	11.72	4.30	0.12	0.36	0.52	1.44	. . .	. . .	amobarbital	1.8
											salicylate	4.0
40	0.02	0.01	9.45	0.38	0.21	0.08	1.24	0.41	0.21	0.91	. . .	
41	0.07	. . .[b]	1.70	ND	0.27	0.02	0.25	0.03	1.75	2.00	diazepam	0.06
42	0.02	0.31	4.11	0.69	0.21	0.29	0.23	0.31	2.30	1.83	phenobarbital	1.5
43	0.05	0.03	0.17	0.09	0.36	0.11	0.14	0.07	. . .[b]	1.02	. . .	
44	0.04	0.01	1.01	0.71	. . .	. . .	. . .	. . .	. . .	. . .	. . .	
45	0.02	0.12	35.30	2.13	0.25	0.13	. . .	. . .	1.91	1.85	pentobarbital	0.5

ND = not detected.

[a] Measured in mg/100 ml or mg/100 g.

[b] Less than 0.01 mg/100 ml or 0.01 mg/100 g detected.

TABLE 2—*Range of codeine concentration in specimens analyzed in 39 acute deaths involving codeine.*[a]

Concentration Group, mg/100 ml or 100 g	Blood	Liver	Kidney	Bile	Urine
0 to trace	6	1	1	1	0
0.01 to 0.09	17	9	4	5	0
0.10 to 0.49	13	15	7	7	1
0.50 to 0.99	2	4	3	13	1
1.00 to 4.99	...	1	4	10	8
5.00 to 9.99	...	...	...	...	2
10.00 to 44.9	...	...	...	...	6
Specimens analyzed, no.	38	30	19	36	18

[a] Excluded were cases in which concomitant heroin use was suspected.

TABLE 3—*Ratio of codeine to morphine in postmortem specimens analyzed in 39 acute deaths involving codeine.*[a]

Measurement	Blood	Bile	Liver	Kidney	Urine
Codeine/morphine ratio <0.99, no.	0	25	5	1	0
Codeine/morphine ratio >1.00, no.	32	11	24	17	19
Specimens analyzed, no.	32	36	29	18	19
Cases of codeine level higher than morphine, %	100	30	82	94	100

[a] Excluded were cases in which concomitant heroin use was suspected.

track marks on the decedent's antecubital fossae. These four cases are shown as Cases 40, 41, 43, and 44 in Table 1 but were not included in Table 3.

Many of the early findings on the conversion of codeine to morphine in man were disclosed from urinalysis, such as from the investigations of Adler [*1*], Mannering et al [*2*], and Redmond and Parker [*7*]. The codeine/morphine ratio values obtained from the GC analysis of postmortem urine included in this report compared favorably with the data of these investigators. Adler's average codeine/morphine ratio was 4.2, and Redmond and Parker's figure was 4.1. The 14 cases in Table 1 yielded an average ratio of 4.5.

In Cases 42 and 45, shown in Table 1, urine codeine/morphine ratio values were lower than 1.0; autopsy revealed track marks from needle punctures on the arms of the decedents. In acute drug deaths, a high morphine to codeine ratio in urine suggests a prior or concomitant use of heroin or morphine.

In considering cases involving heroin use, the presence of codeine in postmortem tissues may be attributed to the ingestion of codeine or to the use of illicit heroin containing acetylcodeine [*8*]. Yeh [*9*] has presented evidence that production of codeine by methylation of morphine does not occur in vivo. The ratio of codeine to morphine found in urine specimens of Cases 40 to 45 is too high to attribute its source to acetylcodeine. In illicit heroin preparations, acetylcodeine is generally found in amounts of approximately one part to every ten parts of heroin [*8*]. While a higher proportion of morphine to codeine amounts in blood, liver, kidney, and urine may indicate heroin use, such data needs to be correlated with history and autopsy findings.

In the course of this work, it was necessary to verify that the concentrations of codeine and morphine were not changed during storage. There are no data in the literature that show what happens to these drugs under the conditions in which we store the tissues.

Darby et al [*10*] showed that human liver microsomes from postmortem specimens obtained soon after death were capable of demethylating codeine in vitro. The authors

used microsomal preparations to which enzyme-activating agents such as reduced diphosphopyridine nucleotide, nicotinamide, and magnesium sulfate were added. These authors also reported that extensive liver damage (for example, from long-term anoxia), resulted in the destruction of the drug-metabolizing capability of microsomes. Gram and Fouts [*11*], studying hepatic microsomal enzymes of rats, rabbits, and mice, found that codeine *o*-demethylase was among the least stable of the enzymes studied.

The fragility and special requirements of enzyme activators and protection against anoxia suggest that tissues containing codeine and morphine stored under routine conditions would not show altered concentrations of these drugs by demethylation of codeine to morphine. We found that the concentrations of codeine and morphine in postmortem tissues containing these drugs were not altered during conditions of storage at 2°C (36°F) for 30 days. Six blood and six liver samples were tested. The blood samples contained sodium fluoride, and no preservatives were added to the liver samples.

Summary

Forty-five drug overdose cases involving codeine were investigated. Concentrations of codeine and morphine were determined in blood, bile, liver, kidney, and urine. Ratios of codeine to morphine values for each of these specimens were compared and evidence was developed that codeine was metabolized partially into morphine in the antemortem stage. Morphine concentration was less than that of codeine in blood, liver, kidney, and urine. However, bile analyses showed that the amount of morphine exceeded that of codeine, suggesting a more active demethylation activity in the hepatic system than in the blood and other tissues studied.

Controlled in-vitro studies showed that no codeine demethylation occurred in postmortem tissues during cold storage for a period as long as 30 days.

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