CASE REPORT

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Distribution of Morphine in Body Fluids and Tissues in Fatal Overdose

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ABSTRACT: Two cases of fatal overdose with morphine are presented. Large amounts of the drug were involved in both cases, one by oral ingestion, the other by intravenous injection. Morphine concentrations in various body fluids and tissues are compared to those in the literature.

KEYWORDS: pathology and biology, toxicology, morphine, death

Two cases of morphine overdose were investigated by this laboratory recently. And in both cases, pharmaceutical preparations of morphine were involved. The amount of morphine administered was large, and the outcome of both was fatal.

One case that involved oral intake of morphine solution was witnessed, and the time course of events was documented. In the other case, a syringe containing morphine was recovered nearby. Results from autopsy indicated the deceased might have lived for several hours. The distribution of morphine in body fluids and tissues in these two cases will be discussed.

Case 1

The subject, W. W., was a 30-year-old male. He was markedly obese and known to be a heavy drinker and a drug user. On the day he died, he was drinking beer at a friend's house. For no apparent reason, he drank about 50 mL of liquid from a bottle labelled "morphine HCl." The medication was prescribed to his friend's wife who was suffering from terminal cancer. Shortly after consuming the liquid, the deceased reportedly lapsed into a state of unconsciousness, and died about an hour later. All this happened in the presence of his friend whom he was visiting, and this friend was drinking with him.

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Autopsy results did not show any anatomical cause of death, and it was concluded death was a result of the toxic effect of a combination of alcohol and morphine. On analysis, the blood and urine ethanol levels were 0.32 and 0.39 g/dL, respectively, while total morphine concentrations in blood and bile were 1.53 and 312 mg/L. No other drugs were present in the body fluids. The liquid in the bottle contained 3.8 mg/mL of morphine base.

Case 2

The deceased, D. J., was a male physician, age 31. He was found dead lying on the living room floor of his residence. A 12-mL syringe was recovered from the trash can in the kitchen. A burnt cigarette was found beside the body. It would appear that the deceased did not lapse into unconsciousness immediately, but had time, at least, to smoke a cigarette. On autopsy, acute inflammation was found in the superficial mucosa of the respiratory tract and extending in a peribronchial distribution. This would be consistent with Mendelson's syndrome. The inflammation was the result of chemical irritation caused by the aspiration of gastric fluid while the deceased's cough reflex was depressed by an overdose of morphine. Assuming that the inflammation was of this etiology, it was then concluded that several hours lapsed between the administration of the morphine and death. The mode of administration was assumed to be intravenous, and the site was thought to be in the webbed space between the thumb and the index finger. The only significant toxicological findings were total morphine level in the blood of 0.42 mg/L and that in the bile of 248 mg/L. The contents of the syringe contained 10.0 mg/mL of morphine base.

Experimental Procedure

Materials

Pure drug substances used in the analysis were generous gifts of Parke-Davis Canada Inc. (codeine phosphate), Hoffman-LaRoche Limited (flurazepam hydrochloride), Bureau of Dangerous Drugs, Health and Welfare Canada (morphine sulfate), and Merck Frosst Laboratories (nalorphine hydrochloride). Other chemicals and solvents used were best grades available.

Measurements of morphine and codeine concentrations in biological fluids and tissues were performed with gas chromatography; in the case of morphine, by electron capture detection after derivatization; while in the case of codeine, by nitrogen-specific detection. The procedures are well established, and are described briefly in the following.

Free Morphine—Unconjugated morphine in the blood was extracted at pH 8.9, buffered with borate buffer (0.05*M* boric acid and 0.043*M* sodium borate), into a nine-to-one mixture of chloroform/isobutanol. For further cleanup, the analytes were back extracted into 0.5*N* hydrochloric acid. The acid layer was again buffered to pH 8.5 with sodium bicarbonate. Finally the drugs were extracted into a nine-to-one mixture of ethyl acetate/isopropanol. The organic layer was dried, and derivatization of the drugs with pentafluoropropionic anhydride was carried out at room temperature. Nalorphine, which was added initially to the blood specimen, was used as an internal standard. The reaction mixture was dried and reconstituted with ethyl acetate for analysis by gas chromatography.

Total Morphine—Conjugated morphine in the biological matrix: blood, bile, and urine or liver homogenate was hydrolyzed using concentrated hydrochloric acid at 100°C. The mixture was then neutralized with 6*N* sodium hydroxide and buffered to pH 8.9 using borate buffer. Nalorphine was also added initially to the specimen as an internal standard. The extraction and derivatization procedures for free morphine determination were then followed.

Codeine—Codeine in the biological matrix was extracted into *n*-butyl chloride at pH 10, buffered with a saturated sodium carbonate solution. Flurazepam was added initially as the internal standard. The organic solvent was then dried and reconstituted with methanol.

A Hewlett-Packard 5880A gas chromatograph fitted with capillary columns was used in these analyses, with either an OV-1, or an OV-17 column, both 12-m by 0.2-mm inside diameter (i.d.)

Results and Discussion

The distribution of morphine in various body fluids and tissues is listed in Table 1. Some typical chromatograms are shown in Fig. 1.

In Case 1, the liquid consumed by the deceased was found to contain 3.8 mg/mL of morphine base. Since the volume involved was about 50 mL, the amount of drug ingested was

TABLE 1—*Distribution of morphine in body fluids and tissues.*

	Morphine Levels, mg/L or mg/kg				
	Blood		Bile	Urine	Liver
	Free	Total		Total	
Case 1	0.35	1.53	312	22	7.0
Case 2	0.07	0.42	248	323	2.9

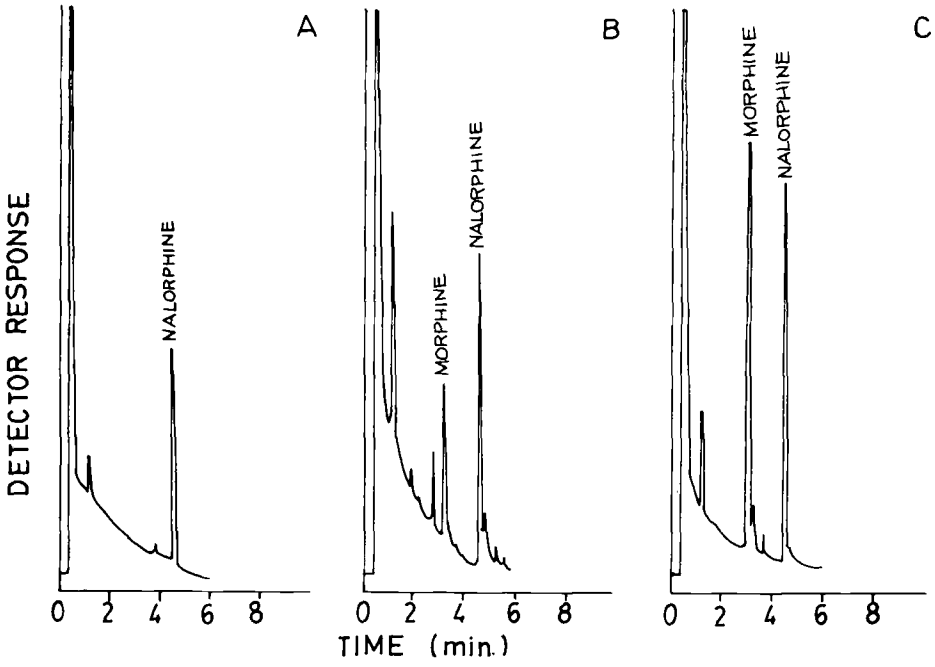

FIG. 1—*Gas chromatograms in morphine analysis:* (a) *drug-free blood spiked with nalorphine:* (b) *total morphine level in the blood of Case 1; and* (c) *total morphine level in the diluted bile (× 100) of Case 1.*

190 mg. The high levels of morphine in different fluids and tissues reflect this. In particular, morphine was accumulated significantly in the bile. The bile concentration of 312 mg/L was higher than all but one case in a very extensive listing of morphine overdose cases compiled by Gottschalk and Cravey [*1*]: mean = 33.7, median = 14.4, range = 0 to 922 mg/L, and $N = 119$. Similarly, the total blood morphine level of 1.53 mg/L is very high when compared to the cases from the same source: mean = 0.47, median = 0.24, range = 0 to 12 mg/L, and $N = 126$.

In Case 2, while there was no witness to the tragic incident, an estimate of the amount of morphine injected could still be made. The syringe used had a capacity of 12 mL. Assuming only one syringeful of drug used, the amount of morphine solution injected could not be more than 10 mL, as about 2 mL were left. The concentration of morphine base in the solution was found to be 10 mg/mL; therefore, the amount of drug injected was 100 mg. Again, morphine accumulated to a very high level in the bile: 248 mg/L.

Liver morphine levels were reported in eight cases of fatal overdose [*1*], and the mean was 1.8, the median 2.0, and the range 0 to 3.6 mg/kg, respectively. In another report of ten fatalities [*2*], the mean was 3.0 mg/kg, and the range was 0.4 to 18 mg/kg. Our results confirm these previous findings. Furthermore, they indicate there is no accumulation of morphine in the liver even though the bile levels are extremely high. As a comparison, the mean bile level in the cases cited earlier [*1*] was 19.4 mg/L ($N = 7$).

The major metabolite of morphine is morphine-3-glucuronide, produced by the enzymatic conjugation with glucuronic acid in the liver. While the metabolite accounts for a major portion of total morphine in blood, our results indicate a significant amount of free (unconjugated) morphine persists. In Case 2 where death occurred several hours after injection of the drug, the ratio of free morphine remained 17%, while in Case 1 the ratio was 23%.

The lower level of urine morphine in Case 1 (22 mg/L) reflected that death occurred a short time after the drug use. In Case 2, there was a longer time lapse; the urine level was much higher (323 mg/L).

We have also observed the presence of codeine in some of the body fluids in these cases. The concentrations are listed in Table 2. Some of the chromatograms are shown in Fig. 2. It has been suggested that codeine could be a metabolite of morphine through 0-methylation [*3*]. In tolerant subjects, codeine concentrations in the urine were found to be between 6 to 10% relative to those of morphine. In nontolerant subjects, the ratios were between 0.7 to 0.9%. These observations were disputed by Yeh [*4*], who was unable to confirm the presence of large amounts of codeine in the urine of morphine users, and instead suggested that the origin of codeine was as an impurity in morphine. While codeine was found in the urine in both cases under study, 0.4 and 0.04% relative to morphine, respectively, the ratios were much less than the 6 to 10% observed previously [*3*]. Furthermore, codeine was present in both the morphine preparations as an impurity. In Case 1, the liquid in the bottle contained 42 μg/mL of codeine, therefore it is estimated that 2.1 mg of codeine was consumed by the deceased. In Case 2, the liquid in the syringe contained 28 μg/mL; that is to say 0.28 mg was injected. However, the amount of codeine involved in both cases was low, and may not be enough to explain the codeine concentrations of the various fluids that were observed. For

TABLE 2—*Distribution of codeine in body fluids.*

	Codeine Levels, mg/L		
	Blood	Bile	Urine
Case 1	0.03	0.44	0.09
Case 2	0.08	0.22	0.13

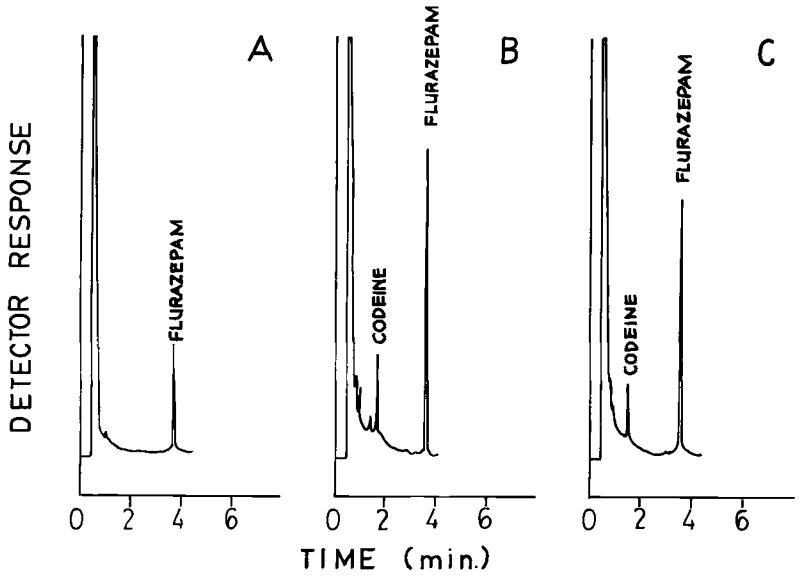

FIG. 2—*Gas chromatograms in codeine analysis:* (a) *drug-free blood spiked with flurazepam;* (b) *codeine level in the bile of Case 2; and* (c) *codeine level in the urine of Case 2.*

example, in a study involving oral dosing of 65 mg of codeine phosphate (49 mg of codeine base) by volunteers [*5*], the peak plasma level, which appeared within 0.75 to 1 h, ranged from 0.194 to 0.340 mg/L. Compared to Case 1, the amount of codeine used was 23 times more, but the blood level was only increased between 6.5 to 10 times. In Case 2, the codeine levels observed were even more significant, since the amount injected was only 0.28 mg. However, as the original solutions used were contaminated with codeine, no conclusive inference could be made.

References

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