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The Role of Ethanol in Heroin Deaths

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ABSTRACT: The purpose of this study was to evaluate the role of ethanol in deaths due to heroin intoxication. Over a 12 month period, all cases investigated by the Office of the Chief Medical Examiner, State of Maryland where a blood screen by Roche Abuscreen radioimmunoassay (RIA) was positive at a cutoff of 100 ng/mL were included in the study. Free morphine was quantitated using the Coat-A-Count RIA and ethanol was quantitated by head space gas chromatography. All presumptive morphine positive cases were confirmed by gas chromatography/mass spectrometry. Seventy of the 119 cases where death was attributed to narcotic or alcohol and narcotic intoxication had blood ethanol concentrations (BAC) greater than or equal to 0.02 g/dL; 48 had BAC $\geq$ 0.10 g/dL. Only 3 of 45 cases where morphine was identified but was unrelated to death had BAC $\geq$ 0.02 g/dL. At all ranges of free morphine concentrations, there was a greater percentage of narcotic deaths when ethanol was present. From the data, we conclude that 1) the use of even small amounts of ethanol with heroin is clearly a risk factor in deaths due to heroin, 2) there are some heroin deaths where no free morphine is identified in the blood. In these deaths, ethanol is unlikely to be present, 3) at blood ethanol concentrations between 0.20 and 0.29 g/dL, the morphine concentrations in heroin deaths increased significantly, 4) at blood ethanol concentrations greater than 0.30 g/dL, morphine became less of a factor than the ethanol in causing death.

KEYWORDS: pathology and biology, heroin, ethanol, death

Despite the increased use of cocaine in the past ten years, heroin remains the most common cause of drug death in the State of Maryland. The involvement of ethanol in heroin deaths has been studied previously. Ruttenber et al. [*1*] analyzed differences between heroin related deaths with blood alcohol concentrations above and below 0.10 g/dL. They found that high ethanol decedents had significantly lower blood morphine concentrations than low ethanol decedents and identified a significant inverse correlation between concentration of ethanol and morphine in blood. Monforte [*2*] reported that in the presence of ethanol, three-quarters of the narcotic deaths occurred at morphine concentrations less than 200 ng/mL.

The assignment of heroin or morphine as the cause of death is complicated by many factors. There are wide variations reported in the literature for blood morphine concentrations in narcotic deaths, presumably due in part to the development of tolerance to narcotics. Blood morphine concentrations in deaths due to other causes often overlap blood morphine concentrations seen in drug deaths. Abusers of heroin often use other drugs such as ethanol and cocaine, so deaths may be due to the combined effects of these drugs. Morphine is rapidly inactivated by phase II metabolism to the inactive morphine-3-glucuronide, such that the measurement of free morphine in the blood yields negative results, but the narcotic could still be responsible for death.

This report is a compilation of data accumulated over a twelve month period in cases investigated by the Office of the Chief Medical Examiner, State of Maryland. The purpose of this report was to determine the role of ethanol in narcotic deaths.

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Experimental

Specimen Acquisition

Specimens were obtained from cases investigated by the Office of the Chief Medical Examiner, State of Maryland. All determinations of the cause and manner of death were made by medical examiners following investigation, autopsy and toxicological analysis.

Ethanol Analysis

Ethanol was quantitated by head-space gas chromatography. The procedure and instrument conditions have been published previously [*3*].

Morphine Analysis

Roche Abuscreen Radioimmunoassay (RIA)—Abuscreen RIA kits were purchased from Roche Diagnostics, Nutley, N.J. The procedure was modified as follows to give quantitative results. A calibration curve consisting of a blank, 100, 250, 500, 750 and 1000 ng/mL was prepared with each batch. Each blood specimen was diluted 1:24 with saline. To 100 mcL standard, control and case specimen were added 200 μL ^{125}I-labeled morphine and 200 μL antibody. After a 30 minute incubation, 500 μL of a second antibody and 200 μL saturated ammonium sulfate were added to each tube. Precipitation occurred by permitting the tubes to stand for 10 minutes and by centrifuging at 2000 rpm for 30 minutes. Five hundred microliters of the supernatant were counted for 1 minute. "Morphine equivalent" concentrations for each case specimen were read from the standard curve.

Free Morphine Analysis—The Coat-A-Count RIA for free morphine was obtained from Diagnostic Products Corporation, Los Angeles, CA. The quantitative procedure as recommended by the manufacturer was followed. All case blood specimens were diluted 1:9 with saline prior to analysis. This established a quantitative cut-off of 25 ng/mL.

Morphine Confirmation—The method of Saady et al. [*4*] was used to confirm all presumptive positives.

Results and Discussion

All cases included in this study were comprehensively tested for ethanol, therapeutic and abused drugs by a combination of color tests, gas chromatography and immunoassay. Urine was initially tested if sufficient volume was submitted. Otherwise, bile or blood, in that order were alternate initial screening specimens.

Specimens initially testing positive for opiates by Roche Abuscreen were confirmed for morphine as the trifluoroacetyl derivative by gas chromatography/mass spectrometry. The blood was then quantitated by a modified procedure with Roche Abuscreen. A cut-off of 100 ng/mL was used, all blood specimens quantitating greater than 100 ng/mL of "morphine equivalent" were quantitated by Coat-A-Count for free morphine. All blood specimens were diluted ten-fold, thus establishing a cut-off of 25 ng/mL.

The Roche Abuscreen immunoassay for morphine shows significant cross-reactivity to free morphine, morphine-3-glucuronide, codeine, hydromorphone and hydrocodone [5]. This broad-based cross-reactivity is more useful when performing comprehensive testing for opiates which is necessary in postmortem forensic toxicology laboratories. On the other hand, the Coat-A-Count free morphine assay shows virtually no cross reactivity to the other opiates or conjugated morphine [6]. Although the assay was designed for serum, previous work in this laboratory had demonstrated its utility on postmortem blood specimens (unpublished data).

This office undertakes a standard procedure prior to assigning a cause of death to narcotic intoxication. A full autopsy is performed to rule out trauma or natural disease processes. The toxicology findings must include a blood concentration greater than 100 ng/mL of "morphine equivalents" by Abuscreen, a confirmed positive for morphine by gas chromatography/mass spectrometry and the absence of cocaine or significant amounts of other drugs or ethanol in the blood. If the heart blood ethanol concentration exceeds 0.10 g/dL, then the ethanol is included in the cause of death. For the purpose of this study, only those cases positive for morphine with or without ethanol were included.

Over the approximately one year period of this study, 119 deaths were attributed to narcotic or narcotic and alcohol intoxication. Of these, 70 or 59% of the total had a blood ethanol concentration greater than or equal to 0.02 g/dL. This ethanol concentration was chosen as a cutoff since ethanol concentrations less than 0.02 g/dL can be associated with postmortem ethanol formation as well as antemortem ethanol consumption. Of these 70 cases, 48, or 69% had blood ethanol concentrations at or above 0.10 g/dL. Over a similar period, 45 cases were identified with either morphine or morphine and ethanol as incidental findings in deaths due to other causes. Only three of these cases, or 6.7% were associated with blood ethanol concentrations greater than 0.02 g/dL. This suggests that ethanol plays a role in narcotic deaths. If ethanol was an incidental finding in narcotic deaths, then one would expect a similar incidence of ethanol in narcotic and non-narcotic deaths.

Ranges of ethanol and free morphine concentrations in narcotic and non-narcotic deaths are given in Tables 1 and 2. From these data, several points are apparent. Thirteen percent of the narcotic deaths (16 of 119) and 62% of non-narcotic deaths (28 of 45) had free morphine concentrations less than 25 ng/mL. Since the free morphine assay was initiated by an Abuscreen test greater than 100 ng/mL, this indicates that 63% (28 of 44) of the cases where the Abuscreen assay exceeded 100 ng/mL and the free morphine was less than 25 ng/mL were not drug deaths. This is not surprising since higher free or active morphine concentrations would be more likely to produce respiratory depression and death.

TABLE 1—*Ethanol and free morphine concentrations in narcotic deaths.*[a]

Ethanol Conc. (g/dL)	Free morphine conc. (ng/mL)				
	<25	25–99	100–299	300–499	>500
<0.02	13	12	14	7	3
0.02–0.09	2	6	12	2	0
≥0.10	1	14	25	5	3

[a]Numbers in columns refer to the number of reported cases with the associated concentrations.

TABLE 2—*Ethanol and free morphine concentrations in non-narcotic deaths.*[a]

Ethanol Conc. (g/dL)	Free morphine conc. (ng/mL)				
	<25	25–99	100–299	300–499	>500
<0.02	27	10	4	1	0
0.02–0.09	1	1	1	0	0
≥0.10	0	0	0	0	0

[a]Numbers in columns refer to the number of reported cases with the associated concentrations.

Tables 1 and 2 reveal some interesting relationships between ethanol, free morphine and cause of death. For instance, 27% (13 of 49) of the narcotic death cases where the blood ethanol concentration is negative had free morphine concentration less than 25 ng/mL. On the other hand, 64% (27 of 42) of the non-narcotic deaths where the blood ethanol concentration is negative had free morphine concentrations less than 25 ng/mL. When no ethanol was present and the free morphine was between 25 and 99 ng/mL, 55% of the cases were drug caused deaths; when the ethanol was positive 95% of these cases were drug caused deaths. This trend continued as the free morphine concentration increased. All cases with free morphine concentration exceeding 25 ng/mL and ethanol concentration exceeding 0.10 g/dL were drug caused deaths, that is, there were no trauma or natural disease to account for death. One would expect that significant concentrations of ethanol would contribute to the mortality produced by morphine. Both can cause central nervous system depression [7]. Table 3 indicates that even concentrations of ethanol less than 0.10 g/dL seem to contribute to morphine deaths. If these relatively small amounts of ethanol were incidental findings in these cases, then at a given morphine concentration, the percentage of total deaths being narcotic deaths would be the same. Instead, what was observed was that for all ranges of free morphine, there was a greater percentage of narcotic deaths when the blood ethanol concentration was between 0.02 and 0.09 g/dL. Surprisingly, there were three narcotic deaths which had a morphine concentration

TABLE 3—*Percent of total deaths that were narcotic deaths at blood ethanol concentrations less than 0.10 g/dL.*

Ethanol Conc (g/dL)	Free morphine conc. (ng/mL)			
	<25	25–99	100–299	>300
<0.02	33%	55%	78%	95%
0.02–0.09	67%	86%	92%	100%

less than 25 ng/mL and a positive blood ethanol. One would expect that these cases would have been associated with high ethanol concentrations such that these deaths were most likely caused by ethanol. However, the blood ethanol concentration in these three cases were 0.06, 0.08 and 0.10 g/dL, respectively.

Table 4 gives a further breakdown of the ethanol and free morphine data in narcotic deaths. The mean free morphine concentration remain essentially unchanged as long as the ethanol concentration remained below 0.20 g/dL. The median free morphine concentration increased slightly when ethanol was present, but was less than 0.20 g/dL. When the ethanol concentration reached or exceeded 0.20 g/dL changes in this pattern were observed. The mean and median free morphine concentration increased to 260 and 230 ng/mL, respectively, when the blood ethanol concentration was between 0.20 and 0.29 g/dL. Upon initial consideration, this is surprising; since both drugs are depressants, an additive effect could be hypothesized. Thus, one would expect a lower morphine concentration in combination with the ethanol would account for death. However, the opposite was observed. There are several possible explanations for this. It is possible that these concentrations of ethanol are inhibiting the phase 2 metabolism of morphine, thus permitting an increased amount of circulating free morphine to reach the brain. This proposed effect of ethanol has not been reported previously and is therefore unlikely. It is also possible that these deaths were more acute than the other deaths because of the additional depressant effects of the two drugs. When the blood ethanol concentration was at or exceeded 0.30 g/dL, this pattern reversed itself. At these ethanol concentrations, it is likely that the effects of the ethanol far surpass the effects of morphine to the point that the morphine, although not an incidental finding, is still a minor factor when compared to the ethanol.

It is difficult to compare the results of this study to previously published data. For instance, the data compiled by Ruttenber et al. used total morphine as measured by radioimmunoassay [*1*]. The study presented here attempted to separate free morphine from the inactive conjugated morphine. Spiehler [*8*] used data from 200 morphine involved deaths and an artificial intelligence computer program to develop rules for identifying morphine overdoses. One of these rules identified blood unconjugated morphine concentrations greater than 240 ng/mL as being characteristic of a morphine overdose. In the presented study, only 1 of 21 cases with a free morphine concentration greater than 300 ng/mL was not a narcotic death.

TABLE 4—*Statistical distribution of free morphine concentrations in narcotic deaths.*

Ethanol Conc. (g/dL)	Free morphine concentrations (ng/mL)				
	Number <25 ng/mL	Number >25 ng/mL	Mean	Median	Range
<0.02	13	36	210 (160)	96	<25–640
0.02–0.09	2	20	170 (150)	110	<25–400
0.10–0.19	1	28	170 (160)	110	<25–630
0.20–0.29	0	14	260	230	72–850
≥0.30	0	5	95	86	40–170

NOTE: The numbers in parentheses under the mean column represent the mean by counting the cases less than 25 ng/mL as 0.

Based on this study, the following conclusions can be drawn:

1. The use of even small amounts of ethanol with heroin is clearly a risk factor in deaths due to heroin.
2. There are some heroin deaths where no free morphine is identified in the blood. In these deaths, ethanol is unlikely to be present.
3. At blood ethanol concentrations between 0.20 and 0.29 g/dL, the morphine concentrations in heroin deaths increased significantly.
4. At blood ethanol concentrations greater than 0.30 g/dL, morphine became less of a factor than the ethanol in causing death.

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