



An Explanation of "Lingering" Opiate Deaths? Relative Concentration of Opiates in Medulla and Femoral Blood Following Lethal Intoxications.



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Abstract

Introduction: Toxicologists and pathologists are sometimes confronted with difficult cases where the case history surrounding the deaths indicates an opiate overdose, but the postmortem blood levels measured are only in the therapeutic range. These deaths are generally referred to as "Lingering Deaths" and the decedent is thought to have reached a lethal level of intoxication but remains alive sufficiently long enough to metabolize and eliminate the high level of opiates from blood down to therapeutic concentrations. Death from opiate intoxication is most often a result of respiratory and cardiac depression with resultant pulmonary pathology producing increased lung weights. Neurological control of respiration and cardiac rhythm resides in the medulla oblongata. Cases selected for this study were chosen based on the suspicion of overdose indicated in the case history.

Objective: To uncover a possible explanation of lingering deaths, this study examined the relative concentration of opiates in femoral blood compared to opiate concentrations in the medulla oblongata. **Methods:** Specimens were collected during autopsy and kept refrigerated until processed for analysis. Extraction of drugs was accomplished using solid phase extraction (UCT Clean Screen ZSDAU020) followed by derivatization with MSTFA (UCT). Analytes were separated, detected and quantitated by an Agilent GC/MS in the SIM mode using a Restek Rxi-5ms, 30 m X 0.25 mm i.d., 0.25 µm film thickness, analytical column.

Results: As is shown in Table 1, the average opiate concentrations for morphine, codeine and 6-acetylmorphine were higher in medulla than in blood.

Table 1: Distribution of Opiates in Blood and Brain (ng/mL):

Sample	Blood Morphine	Brain Morphine	Blood Codeine	Brain Codeine	Blood 6-AM	Brain 6-AM	Brn:Bld Morphine	Brn:Bld Codeine	Brn:Bld 6-AM
Average	136	189	16	50	15	51.2	1.39	3.07	3.31

Five of the twenty cases examined had morphine concentrations higher in blood than brain. However, examination of the case histories revealed that these cases were acute exposures with drug paraphernalia still present at the death scene in three of the five cases. It is likely that the heroin did not have sufficient time to distribute to brain before death occurred. In all cases, the codeine and 6-acetylmorphine levels in medulla were higher than that determined for blood. Examination of the brain:blood ratio for the three analytes demonstrated an increasing ratio from morphine, to codeine, to 6-AM; which directly corresponds to the relative lipophilicity of these analytes. Other opioids investigated (oxycodone and hydrocodone) demonstrated the same preferential distribution to medulla relative to femoral blood.

Conclusion: The preferential distribution of opiates to medulla (site of respiratory control) suggest that lingering opiate deaths may be explained, at least in part, because of higher relative concentrations of drug in brain, compared to femoral blood.

Keywords: opiates, medulla, lingering deaths

Objectives

- The objective of this study was to uncover a possible explanation for "lingering" opiate deaths.
- To compare the relative concentration of opiates found in femoral blood with the concentration detected in brain samples from the same case.

Introduction

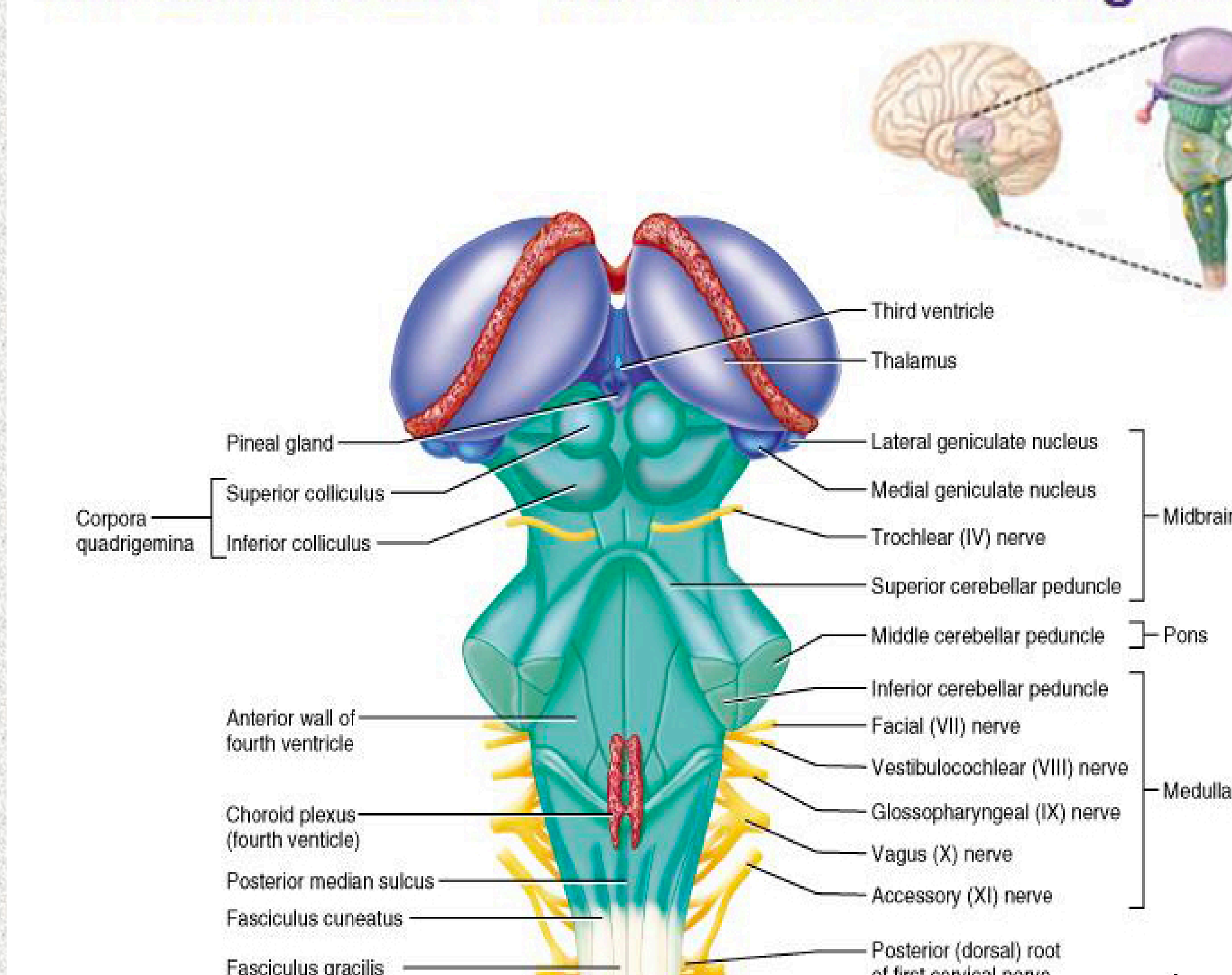
- Often times the circumstances of a death indicate opiate overdose, but the toxicological findings do not clearly support that ruling.
- Common findings at autopsy when an opiate overdose is suspected are heavy lungs, as a result of congestion and possible pulmonary edema or pneumonia⁽¹⁾.
- Death from opiate overdose is most frequently due to respiratory depression⁽²⁾.
- The medulla oblongata, located in the brainstem, controls many involuntary activities. The "respiratory center" for humans is located in both the medulla and the pons portions of the brain⁽³⁾.

- Within the medulla there are two anatomical sections which deal with respiration⁽³⁾:

- Dorsal Respiratory Group- Causes inspiration and the basic rhythm of respiration (12-16 breaths/min.).
- Ventral Respiratory Group- Causes both inspiration and expiration. It is this region of the medulla which appears to be a primary location for respiratory depression caused by opiates⁽⁴⁾.

- High concentrations of opioid receptors⁽²⁾, specifically μ and δ receptors⁽⁵⁾ are present in the medulla. Both μ and δ agonists cause respiratory depression⁽⁵⁾.
- As would be expected, maximal respiratory depressant effects occur more quickly with more lipophilic opiates, since these drugs cross the blood-brain barrier with greater ease⁽²⁾.
- Heroin, 6-acetylmorphine (6-AM) and codeine cross the blood brain barrier more readily than morphine⁽⁶⁾.

The Brain Stem—The Medulla Oblongata



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Methods

Cases:

- Specific cases for this study were selected based on the case history indicating an overdose.
- The medulla was excised by scalpel at autopsy (unfixed state), and was placed into a sterile conical tube and labeled.
- Cases which produced negative or non-heroin related results were excluded from this data set.
- 41 total cases were evaluated in this study (at the time of abstract submission, 20 cases had been evaluated).

Toxicological Analyses:

- Medulla samples were homogenized at a 1/3 dilution using deionized water.
- Cases were screened for Opiates using an ELISA Opiate Kit (Immunoanalysis® Cat. #207-0480).
- Positive Opiate screens were confirmed by GC/MS in SIM mode using a Restek Rxi-5ms capillary column and a previously published UCT method for Opiates.

Results

Figure 1. Demographics: Age

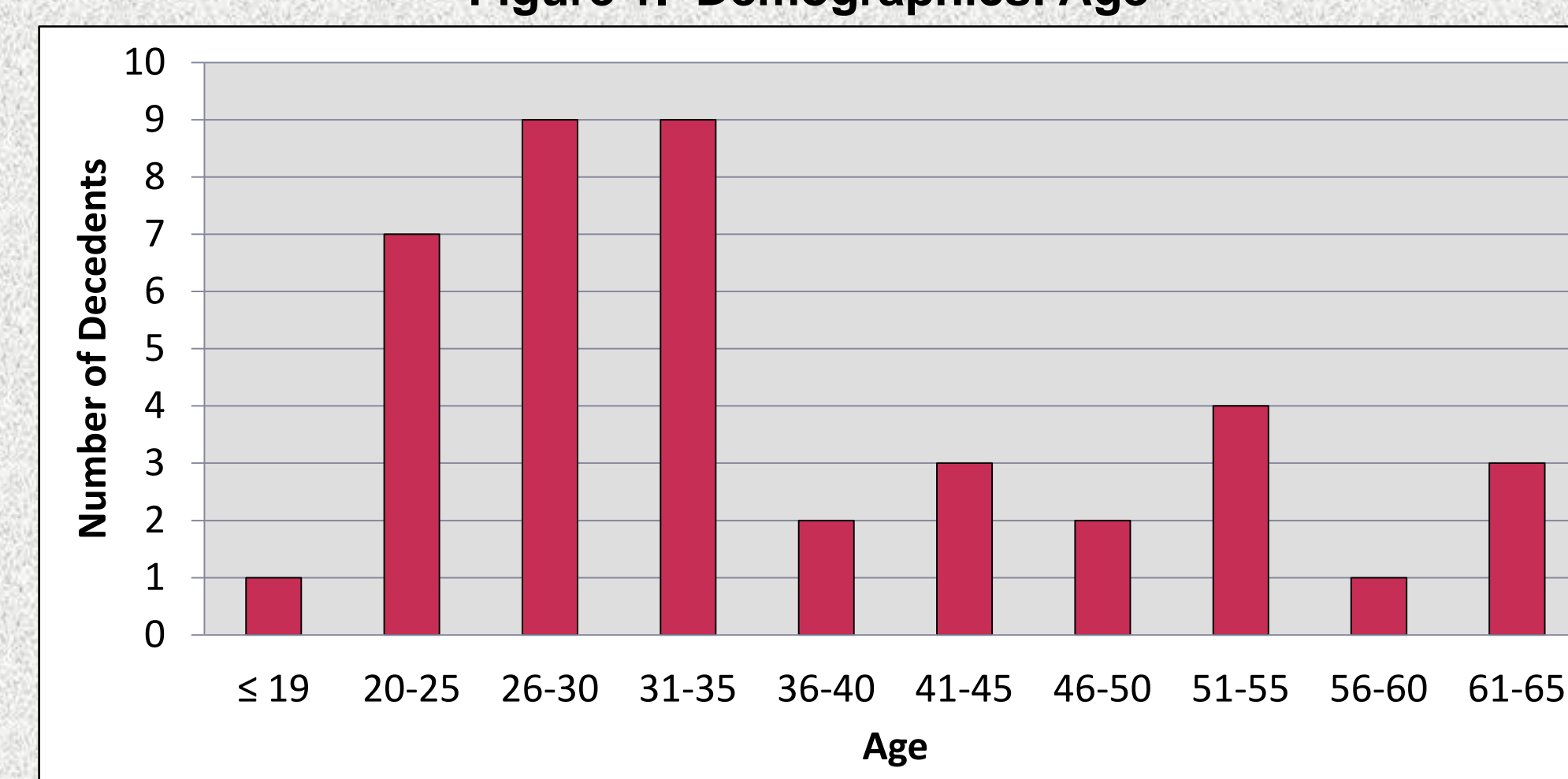


Figure 2. Demographics: Body Mass Index

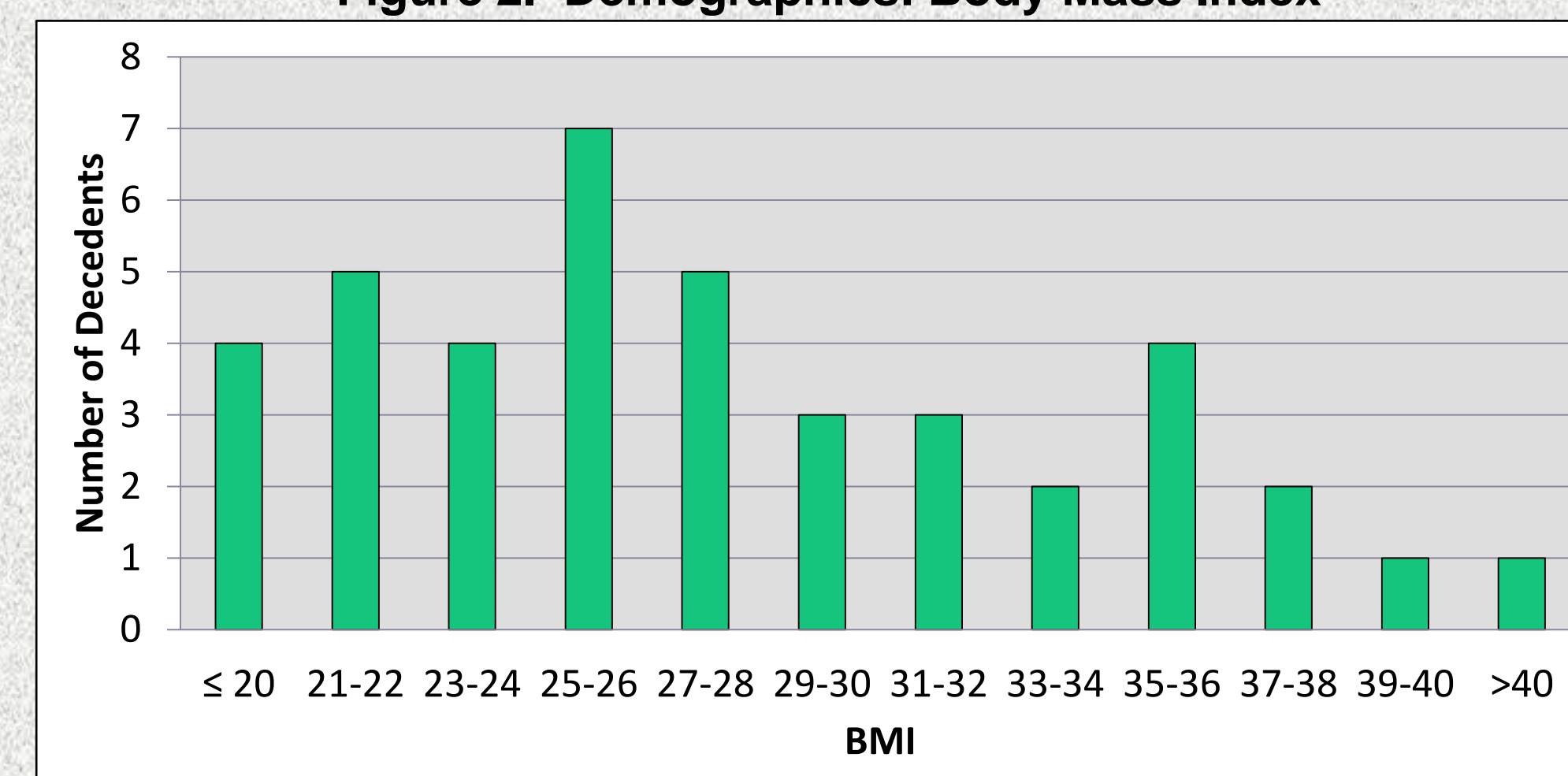
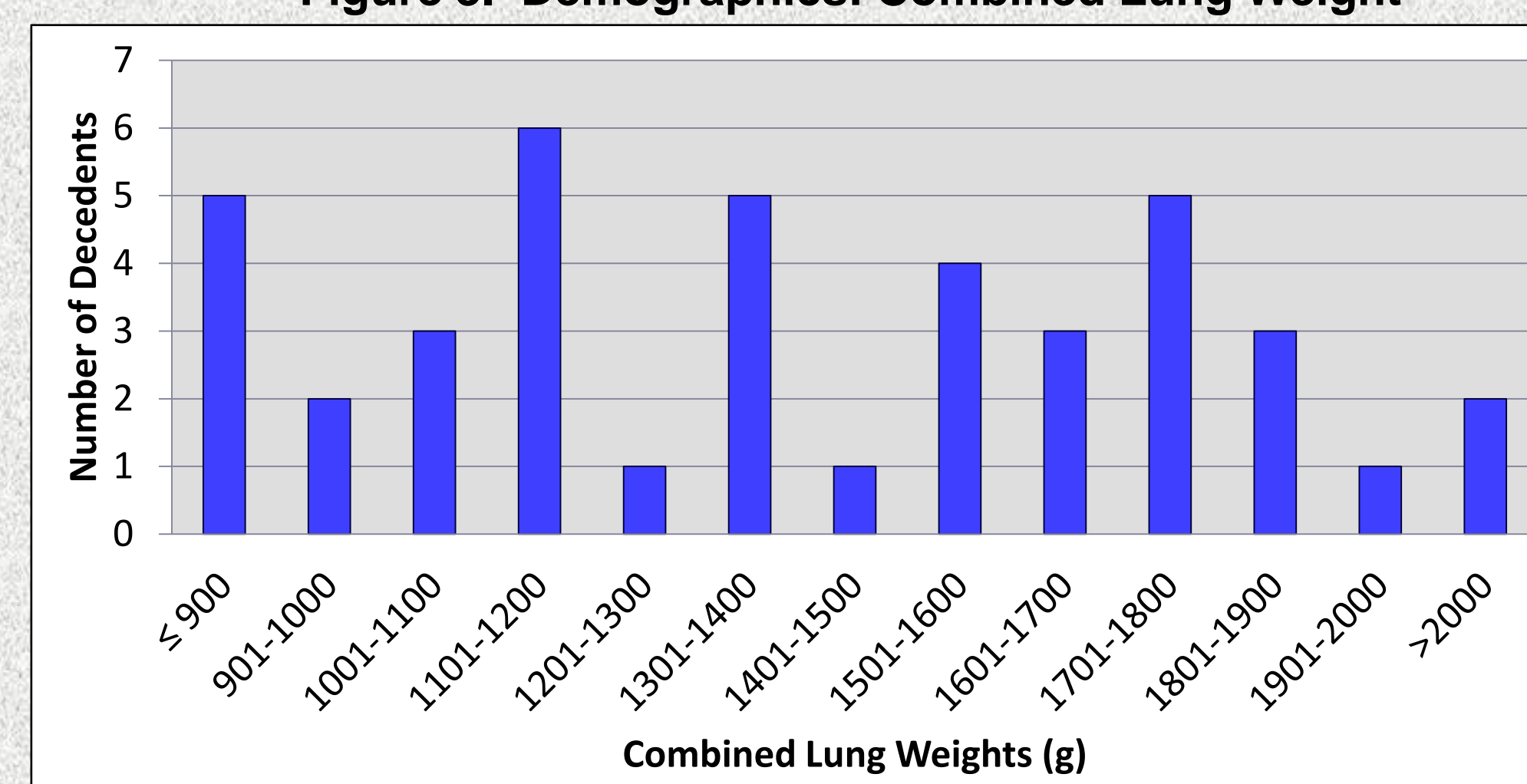


Figure 3. Demographics: Combined Lung Weight



Results

Table 2. Toxicology Findings

Case #	Morphine Blood	Morphine Brain	Codeine Blood	Codeine Brain	6-AM Blood	6-AM Brain	Morphine Brn:Bld Ratio	Codeine Brn:Bld Ratio	6-AM Brn:Bld Ratio
1	398	379	26	42	11	29	0.95	1.62	2.64
2	150	178	27	35	ND	ND	1.19	1.30	--
3	62	129	10	35	4	43	2.08	3.50	10.75
4	42	71	12	25	ND	ND	1.69	2.08	--
5	116	135	19	35	ND	ND	1.16	1.84	--
6	90	171	19	62	4	26	1.90	3.26	6.50
7	23	56	11	31	ND	ND	2.43	2.82	--
8	157	93	ND	ND	8	20	0.59	--	2.50
9	112	148	ND	ND	23	62	1.32	--	2.70
10	159	249	22	41	28	43	1.57	1.86	1.54
11	73	105	14	30	ND	ND	1.44	2.14	--
12	89	86	17	29	ND	ND	0.97	1.71	--
13	211	126	16	36	11	78	0.60	2.25	7.09
14	409	615	39	85	49	64	1.50	2.18	1.31
15	58	24	ND	ND	3	8	0.41	--	2.67
16	91	148	16	32	3	15	1.63	2.00	5.00
17	384	633	42	154	26	245	1.65	3.67	9.42
18	129	243	19	35	10	34	1.88	1.84	3.40
19	54	138	18	28	ND	ND	2.56	1.56	--
20	81	92	22	42	ND	ND	1.14	1.91	--
21	148	371	13	89	12	20	2.51	6.85	1.67
22	235	464	34	78	23	41	1.97	2.29	1.78
23	116	160	24	67	4	33	1.38	2.79	8.25
24	169	352	23	101	56	100	2.08	4.39	1.79
25	138	170	26	66	4	14	1.23	2.54	3.50
26	66	77	16	38	3	12	1.17	2.38	4.00
27	117	131	20	51	ND	ND	1.12	2.55	--
28	110	83	16	41	8	30	0.75	2.56	3.75
29	172	126	28	48	36	41	0.73	1.71	1.14
30	131	142	25	36	14	74	1.08	1.44	5.29
31	29	125	19	51	ND	ND	4.31	2.68	--
32	116	69	16	51	ND	ND	0.59	3.19	--
33	329	186	27	62	57	179	0.57	2.30	3.14
34	23	56	ND	ND	ND	ND	2.43	--	--
35	211	260	22	38	22	171	1.23	1.73	7.77
36	167	368	21	54	17	269	2.20	2.57	15.82
37	78	92	ND	ND	ND	ND	1.18	--	--
38	39	17	ND	ND	ND	ND	0.44	--	--
39	41	52	ND	ND	ND	ND	1.27	--	--
40	348	196	ND	ND	16	131	0.56	--	8.19
41	55	37	ND	ND	ND	ND	0.67	--	--
Avg.	140	179	21	52	18	71	1.42	2.48	4.86

*Concentration of morphine in blood is higher than that observed for brain.

Additional Demographics:

- In this study there were 10 FEMALES and 31 MALES.
- The MANNER of death was ruled ACCIDENTAL in 35/41 cases. The remaining six cases are still PENDING.
- The CAUSE OF DEATH (COD) was ruled ACUTE OVERDOSE for 34/41 of the cases. One case was ruled SEPSIS, with a contributing factor of an OPIATE OVERDOSE. The remaining six cases are still PENDING.
- Of the 35 cases that have been ruled on: 66% of COD rulings included Heroin + Other Drugs; 29% Heroin only; 5.7% Opiate intoxication.

Conclusions

- A person may die of an opiate overdose with non-lethal levels of drug being detected in postmortem samples.
- One explanation for these "Lingering Deaths" may be that the relative concentration of the drug in the brain is sufficiently high to cause death.
- Morphine concentrations were more concentrated in the medulla in 70% (29/41) of the cases examined (Table 2). The source of morphine in these cases was heroin. White and Irvine, 1999, suggested that heroin acts as a pro-drug and facilitates the entry of morphine into the brain⁽⁵⁾.
- A possible explanation for the lower morphine levels in the medulla may be that death occurred before heroin was completely distributed to the brain. Out of the 12 cases where morphine levels were higher in the blood, seven of the scenes contained drug paraphernalia, suggesting acute exposure.
- Codeine and 6-AM were more concentrated in the medulla, compared to blood. Examination of the brain:blood ratio for the three analytes demonstrated an increasing ratio from morphine, to codeine, to 6-AM; which directly corresponds to the relative lipophilicity of these analytes (Table 2).
- These results suggest that elevated opiate levels in the medulla oblongata, compared to levels measured in blood, may at least in part, explain the "Lingering Death" phenomenon.
- Another possible contributor to this phenomenon is sleep. Opiates as CNS depressants produce sleep. Sleep naturally decreases sensitivity of the medullary centers to CO₂. The effects of opiates and sleep are additive⁽²⁾.
- It was noted in this study that the average lung weights of the decedents were in fact elevated: Right: 757g; Left: 671g (Combined : 1428g). A healthy, average lung weight for an adult is: Right: 450g; Left: 375g⁽⁷⁾ (Combined: 825g).
- No correlation was detected between lung weight and BMI. As height increased there was a slight increase in lung weight. Males tended to have higher lung weights.
- No correlation was found between BMI and morphine, codeine or 6-AM concentrations and no correlation was found between combined lung weight and drug concentrations.

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