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Postmortem Redistribution of Morphine and Its Metabolites

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ABSTRACT: The postmortem redistribution of morphine, morphine-3-glucuronide, morphine-6-glucuronide and total morphine was assessed in 40 heroin-related deaths. In blood taken from subclavian, heart, and femoral regions, concentrations of morphine and its metabolites were similar. While there was a trend for higher concentrations in heart blood, when compared with femoral or subclavian blood, this was not significant. There was also no significant difference in concentrations between admission and autopsy blood in which the postmortem interval was on average 59 h. From our observations, significant postmortem redistribution of morphine and its metabolites seems unlikely.

KEYWORDS: forensic science, postmortem redistribution, morphine, morphine-glucuroindes, forensic toxicology

While the phenomenon of postmortem redistribution has been reported for many drugs (1–4), few studies have assessed the redistribution of morphine and metabolites in postmortem tissues (3,5).

Suggestions of postmortem redistribution for morphine have come from rat studies (5) in which elevated cardiac blood morphine (free) concentrations were detected over a 24 h postmortem interval. Significant increases in free morphine were also detected in liver, heart, and forebrain, while urine morphine levels decreased. The authors suggested that a possible explanation for the increased levels of free morphine in some tissues might be the hydrolysis of morphine glucuronides to morphine.

Prouty and Anderson (4) found a higher morphine concentration in heart blood compared with femoral blood in one case. In contrast, Logan and Smirnow (8) found no difference in concentration of free morphine in blood taken from different anatomical sites in 32 cases.

Since there is conflicting data on the subject of postmortem redistribution, a number of studies were conducted to investigate this phenomenon. These included a comparison of drug concentrations in admission blood to autopsy blood, and a comparison of postmortem blood drug concentrations from different collection sites at autopsy (subclavian and heart and femoral).

Subjects and Methods

Postmortem admission and autopsy blood were collected from the femoral region in 10 mL plastic tubes containing preservative (1% sodium fluoride and potassium oxalate) and were stored at −20°C until assay. Other blood specimens were collected from various sites (femoral, subclavian, and heart blood) and were also stored in plastic tubes containing preservative at −20°C until assay.

Analysis of specimens for morphine-3-glucuronide (M3G), morphine-6-glucuronide (M6G), normorphine (NM), free morphine (FM), total morphine (TM), was performed by high-performance liquid chromatography with dual ultraviolet and electrochemical detection as described previously (6). Total morphine was determined by the addition of molar amounts of M3G, M6G, and FM. The pH of blood from femoral, subclavian, and heart specimens was also measured using a benchtop pH meter (Hanna Instruments, Biolab, Australia). Cases were selected on the basis of police reports of death of individuals suspected of dying from heroin use. Heroin use was confirmed in the laboratory by either the recent mention of heroin use in the circumstances and/or the presence of 6-monoacetylmorphine (6-MAM) in urine (7). In some cases heroin or 6-MAM was detected in physical exhibits located near the body. The mortuary staff were notified when a suspected heroin user was admitted to the mortuary of the Victorian Institute of Forensic Medicine (VIFM). Each case was subjected to a routine autopsy performed by full-time forensic pathologists. Autopsy included macroscopic and microscopic examination of all the major organs. Statistical evaluation of the data was performed using the In-Stat V2.01 program run on an Apple Macintosh computer. The type of test performed is indicated alongside the respective data.

Results

Postmortem Intervals

A total of 40 cases were investigated. The time of death until the time of admission to the mortuary and the time to autopsy are shown in Table 1. In 34 cases (85% of all cases) investigated, the time of death was able to be determined. The average time to autopsy in these cases was 59 h.

There were six cases in which the time of death was not able to be determined from the case circumstances and, hence, the time of the postmortem interval for these cases could not be established. These were all cases in which the deceased had died alone.

Admission Versus Autopsy Blood

Concentrations of morphine and its metabolites were compared for blood taken at admission and at autopsy from the femoral region in 21 cases (Table 2, admission blood was not collected for all 40 cases). The median concentrations of M3G, M6G, NM, FM, and TM at admission were similar at autopsy compared to admission blood (Mann Whitney, paired test $p > 0.05$).

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TABLE 1—*Elapsed times of death until admission and autopsy in 40 fatalities attributable to heroin.*

Interval	Death Until Admission $n = 34$	Admission Until Autopsy $n = 40$	Death Until Autopsy—PMI* $n = 34$
Time, h†	15 ± 14	44 ± 21	59 ± 25
Range, h	2.5–66	8.5–83	11–122

† PMI = postmortem interval.
* Mean ± standard deviation.

Comparison of Site of Sampling: Femoral Blood Versus Subclavian Blood Versus Heart Blood

The concentration of morphine and its metabolites in 40-matched autopsy femoral and subclavian blood specimens were compared (Table 3). There were no obvious trends in the concentrations of morphine and morphine glucuronides between these two sites of sampling (Wilcoxon non-parametric paired test [WNPPT], $p > 0.05$).

TABLE 2—*Concentrations of morphine and its metabolites in matched admission and autopsy blood from 21 cases.*

Blood $n = 21$	Drug Concentration, mg/L				
	M3G	M6G	NM	FM	TM
1	0.55 (0.63)	0.09 (0.1)	nd (nd)	0.18 (0.23)	0.58 (0.68)
2	0.22 (0.07)	0.05 (0.09)	nd (nd)	0.21 (0.17)	0.38 (0.28)
3	0.69 (0.58)	0.21 (0.08)	nd (nd)	0.14 (0.13)	0.69 (1.3)
4	1.6 (1.2)	0.3 (0.12)	0.22 (0.26)	0.80 (0.80)	2.2 (2.6)
5	0.75 (0.39)	0.16 (0.99)	0.26 (0.26)	0.40 (0.15)	1.2 (1.0)
6	2.2 (2.5)	0.5 (0.45)	nd (nd)	0.27 (0.27)	1.9 (2.1)
7	1.7 (2.1)	0.32 (0.39)	0.12 (0.08)	0.26 (0.45)	1.6 (2.0)
8	0.36 (0.66)	0.08 (0.22)	nd (nd)	0.08 (0.07)	0.35 (0.61)
9	0.16 (1.4)	0.02 (0.11)	nd (nd)	0.71 (0.36)	0.82 (1.3)
10	0.3 (0.17)	0.06 (0.12)	0.06 (0.09)	0.70 (1.2)	0.98 (1.5)
11	0.27 (0.15)	0.07 (0.05)	nd (nd)	0.20 (0.08)	0.41 (0.23)
12	0.55 (0.90)	0.16 (0.15)	nd (nd)	0.21 (0.19)	0.65 (0.84)
13	1.2 (0.78)	0.38 (0.17)	nd (nd)	0.69 (0.9)	1.7 (1.48)
14	0.57 (0.31)	0.17 (0.27)	nd (nd)	0.08 (0.19)	0.54 (0.55)
15	0.20 (0.27)	nd (0.10)	nd (nd)	0.06 (0.57)	0.18 (0.95)
16	0.78 (1.1)	0.23 (0.58)	nd (nd)	0.36 (1.92)	0.98 (2.95)
17	0.20 (0.27)	0.02 (0.02)	nd (nd)	0.50 (0.41)	0.63 (0.58)
18	0.32 (0.26)	0.18 (0.06)	nd (nd)	0.08 (0.05)	0.38 (0.24)
19	0.15 (0.15)	0.1 (0.05)	nd (nd)	0.36 (0.16)	0.51 (0.28)
20	0.63 (0.45)	0.08 (0.09)	nd (nd)	0.21 (0.5)	0.65 (0.83)
21	0.5 (0.56)	0.09 (0.10)	nd (nd)	0.17 (0.12)	0.53 (0.53)
Admission	0.66 ± 0.56 [0.55]	0.16 ± 0.13 [0.16]	0.03 ± 0.07 [0.0]	0.32 ± 0.23 [0.21]	0.85 ± 0.56 [0.65]
Autopsy	0.72 ± 0.65* [0.55]	0.21 ± 0.23* [0.11]	0.03 ± 0.08* [0.0]	0.49 ± 0.55* [0.23]	1.07 ± 0.80*[0.84]

[Median concentration mg/L], * $p > 0.05$, means ± standard deviation, morphine-3-glucuronide [M3G], morphine-6-glucuronide [M6G], normorphine [NM], free morphine [FM], total morphine [TM], admission blood was not collected for all 40 cases, nd = not detected.

TABLE 3—*Concentrations (mean, range, and median) in postmortem subclavian, heart, and femoral blood specimens from 40 heroin-related deaths.*

Blood ($n = 40$)	Drug Concentration mg/L			
	M3G	M6G	M	TM
		Subclavian*		
Mean	0.60 ± 0.62	0.14 ± 0.14	0.27 ± 0.32	0.70 ± 0.68
Range	0.11–2.04	0.02–0.55	0.05–1.37	0.16–2.59
Median	0.42	0.11	0.16	0.58
		Heart†		
Mean	0.67 ± 0.66	0.17 ± 0.19	0.34 ± 0.45	0.87 ± 0.76
Range	0.07–2.56	0.02–0.99	0.05–1.95	0.18–2.95
Median	0.57	0.11	0.19	0.76
		Femoral‡		
Mean	0.61 ± 0.57	0.13 ± 0.11	0.31 ± 0.22	0.78 ± 0.57
Range	0.13–2.22	0.02–0.50	0.06–0.08	0.08–2.30
Median	0.43	0.09	0.25	0.64

* Three of the 40 cases contained NM.
† No cases were detected with normorphine.
‡ Six of the 40 cases contained NM; mean ± standard deviation.

TABLE 4—*Comparison of blood pH in 40 cases in three different specimens.*

Blood Specimen	Blood pH Mean ± Standard Deviation (Range)
Femoral	6.7 ± 0.4 (6.3–7.2)
Subclavian	6.8 ± 0.4 (6.3–7.2)
Heart	6.9 ± 0.3 (6.3–7.2)

The concentration of morphine and its metabolites were also compared in 40-matched autopsy femoral and heart blood specimens. Again, as with subclavian blood there was no statistical difference between any of the species detected in either femoral or heart blood (WNPPT, $p > 0.05$), although heart blood concentrations were ~10 to 12% higher than femoral blood.

The concentration of morphine and its metabolites was also compared in 40-matched autopsy subclavian and heart blood specimens. Again, as with femoral blood, there was no statistical difference between any of the species detected in either subclavian or heart blood (WNPPT, $p > 0.05$), although the subclavian and heart blood was greater than femoral blood by ~20%.

Comparison of Blood pH

There was no statistical difference in the pH of femoral (pH 6.7), subclavian (pH 6.8), and heart blood (pH 6.9) in 40 cases (WNPPT, $p > 0.05$, Table 4).

Discussion

Studies assessing the redistribution of morphine postmortem have been limited. These studies have shown that redistribution occurs in rat studies (5) but not in human cadavers (3).

In a recent study, Logan and Smirnow (8) found no difference in the concentration of free morphine with postmortem interval at either central or peripheral sites in 32 cases. However, they did notice a trend, because cardiac blood gave consistently higher morphine concentrations than blood taken from peripheral sites; this finding is also supported by our work.

Our results show that morphine and its glucuronide metabolites do not exhibit any significant postmortem redistribution. Morphine and morphine-glucuronide concentrations were similar in blood taken from subclavian, heart, and femoral regions (Table 3). While there was a trend for higher concentrations in heart blood when compared with femoral or subclavian blood, this was not significant. There was also no significant difference in concentrations between admission and autopsy blood in which the postmortem interval was on average 59 h.

It has been suggested that increased levels of free morphine in heart tissue, and consequently heart blood, may be due to the hydrolysis of morphine glucuronides to morphine (5). Our recent work has shown that both glucuronide metabolites (M3G and M6G) do not hydrolyze readily to free morphine in blood (submitted for publication). Moreover, glucuronide concentrations did not rise significantly between admission and autopsy blood (Table 2).

Sawyer and Forney (5) established that as the postmortem interval increased, an apparent increase in concentration of metabolites occurred (290% for blood). The phenomenon of redistribution of morphine in rats (5) has been explained as being caused by an accelerated release of fluids from tissues after death in small animals, and once an initial blood specimen has been removed antemortem, the drug concentration in fluids taken postmortem may give rise to elevated concentrations of morphine (8).

Blood pH has also been mentioned as another possible explanation for differences in drug concentration (5). Sawyer and Forney showed that tissues with low postmortem pH gave the greatest increase in morphine concentrations. We were able to establish that blood pH was very similar for femoral, subclavian, and heart blood, with the average pH of blood changing little for all three specimens.

While concentrations of free morphine were found not to alter significantly with postmortem interval at either central or peripheral sites, Logan and Smirnow (8) suggested caution when interpreting blood heart concentrations of morphine in the absence of femoral data, particularly in acute overdose cases.

The use of peripheral blood has been previously recommended (9). Paterson recommended that femoral vein blood be used for toxicological analysis since femoral blood provides a more representative concentration at the time of death. Similar recommendations have also been made by others (1–4,10). Our data would support this view, in that femoral blood gives the lowest concentration of morphine. However, if blood is taken from other sites, then one would expect only small increases in the concentration for morphine and its glucuronide metabolites.

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