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ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

The importance of 6-MAM levels and morphine/codeine ratio in diagnosis of death among drug addicts

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SUMMARY

Introduction/Objective Heroin is metabolized to 6-monoacetylmorphine (6-MAM) and morphine. The objective of this study is to examine 6-MAM, morphine, and codeine relationships in order to distinguish deaths related to heroin consumption from deaths related to morphine and/or codeine consumption.

Methods The autopsy blood and urine samples from 45 opioid drug addicts were examined. Gas chromatography/mass spectrometry was applied to evaluate morphine, 6-MAM, and codeine. Two groups were formed: 6-MAM-positive (n = 35) and 6-MAM-negative (n = 10).

Results Compared to the 6-MAM-negative group, blood morphine levels were higher in the 6-MAM-positive group ($p = 0.022$), while blood codeine levels were similar ($p = 0.575$). In the 6-MAM-negative group, the blood morphine/codeine ratio was 8.3, and it was 4.3 in the 6-MAM-positive group. There was no difference between the groups regarding urine morphine levels ($p = 0.859$). The urine morphine/codeine ratio was 6.2 in the 6-MAM-negative group, whilst it was 32.2 in the 6-MAM-positive group. In the blood samples, morphine and codeine concentrations were significantly correlated ($r = 0.607$; $p = 0.006$). In urine samples, correlations between morphine and codeine ($r = 0.766$; $p < 0.001$), morphine and 6-MAM ($r = 0.650$; $p < 0.001$), as well as codeine and 6-MAM ($r = 0.620$; $p < 0.001$), were also significant.

Conclusion Analyses of 6-MAM and morphine/codeine ratio in blood and urine autopsy samples may be used as diagnostic tools to distinguish deaths related to the consumption of different opioid drugs.

Keywords: autopsy; heroin; 6-MAM; morphine; codeine

INTRODUCTION

Heroin (3,6-diacetylmorphine) is an opioid drug synthesized by acetylation of morphine derived from crude opium. Beside morphine, the crude opium contains several other alkaloids, including codeine (3-methoxymorphine). During morphine synthesis, codeine also undergoes acetylation reaction yielding 6-acetylcodeine. As the result, heroin often contains a certain quantity of codeine as an impurity.

Heroin and codeine are actually prodrugs, which are both metabolized into the common active form – morphine. Heroin is metabolized into morphine via several intermediary products. After an intravenous injection, heroin is within three minutes converted into 6-monoacetylmorphine (6-MAM) by hydrolysis of one acetyl group. Thereafter, 6-MAM is metabolized into morphine during a time frame between 20 minutes and three hours [1, 2]. Codeine is converted into morphine by o-demethylation via hepatic cytochrome P450-containing enzyme – CYP2D6 [3]. Compared to heroin metabolism to morphine, the conversion of codeine into morphine is a relatively slow process, and in codeine intoxication it may take 24 hours before measurable morphine levels appear in the blood [4].

Positive detection and measurement of heroin metabolites in autopsy body fluids, without previous knowledge of death circumstances, can be ascribed to heroin consumption, but also to morphine intoxication which may occur during medical treatment of acute and chronic severe pain. According to the literature data, there are two indicators of heroin exposure in living individuals: the presence of 6-MAM in body fluids and tissues, and morphine/codeine ratio > 1. The latter is considered to be

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especially important in cases where 6-MAM was not detected, as well as in cases suspected for codeine intoxication [5, 6, 7]. However, these relationships seem to be by far the most complex in forensic autopsy samples, and, with few exceptions, poorly investigated in Serbian drug addicts.

This study evaluated blood and urine toxicological indicators of heroin use, 6-MAM and morphine/codeine ratio, obtained during medicolegal death investigation of cases suspected of heroin or morphine intoxication, in order to distinguish deaths related to heroin consumption from those related to the consumption of morphine and/or codeine.

METHODS

This study was performed at the Milovan Milovanović Institute for Forensic Medicine, Faculty of Medicine, University of Belgrade, Serbia, after ethical institutional clearance was obtained. From January 2006 to December 2015, a total of 12,817 autopsies were done, of which 351 autopsy cases of adult drug addicts, of both sexes. The inclusion criteria in the study were as follows: (1) death due to suspected accidental heroin intoxication, and (2) in addition to morphine, the presence of codeine and/or 6-MAM in autopsy blood and urine samples. Forensic autopsy files, heteroanamnestic data from the closest relatives, police records, and medical history files for all the studied cases were also collected. Of all autopsies performed in that period, 219 were associated with psychoactive substances abuse, but only 134 cases satisfied the inclusion criteria.

The postmortem blood and urine samples were taken with sterile syringe into chemically clean glass tubes. Approximately 50–100 mL of blood was taken from the femoral vein, and about 50–100 mL of urine was taken through the intact urine bladder wall. The samples were thereafter aliquoted and kept in closed tubes at -20°C for no longer than four weeks before analyzing.

Morphine, codeine, and 6-MAM were screened and quantitatively analyzed by gas chromatography (GC) with mass spectrometry (MS) detection, using a headspace technique, adopted for opiates [8]. We used Agilent 7000 GC/MS triple quadrupole gas chromatograph (Agilent Technologies, Inc., Santa Clara, CA, USA), connected to the flame ionization MS detector. Opiates were extracted from specimens according to instructions, using a capillary extraction column Oasis MCX-3cc (Waters Oasis®, Waters Corporation, Milford, MA, USA) [8]. Free morphine and codeine were screened in the 40–500 range, and a specific m/z ratio was used for the detection of a target ion. All positive specimens were further analyzed according to the manufacturer's instructions, using the selective ion monitoring mode [9]. Morphine was determined at m/z 429 (retention time: 11.6 min.), codeine at m/z 371 (retention time: 11.19 min.), and 6-MAM at m/z 399 (retention time: 12.47 min.). Concentrations of morphine, codeine, and 6-MAM were calculated from correspondent standard curves.

The data were processed using the statistical program package SPSS, version 22 (IBM Corp., Armonk, NY, USA). The data was presented according to standard descriptive statistics. Discontinual variables were expressed as frequencies and continual variables as median values (and range). Differences between the groups were tested by the Mann–Whitney U-test. Correlation analysis was accomplished by calculating Spearman's coefficient. Findings were considered statistically significant at $p < 0.05$.

RESULTS

By screening of autopsy samples from 219 death cases associated with the use of psychoactive substances, the detection of morphine alone occurred in 134 cases (63%), and in 63 other cases (28.8%) morphine was combined with another psychoactive substance, most frequently with codeine (56 cases; 25.6%). The results are presented in Table 1.

Samples where morphine alone was detected (n = 134) were further quantitatively analyzed. Beside morphine, detectable quantities of codeine and/or 6-MAM were found in 49 cases. The morphine/codeine concentration ratio (M/C) was calculated. In 45 cases, the M/C ratio in the blood and/or urine was > 1, and four urine samples had M/C ratio < 1. Of 45 cases with M/C ratio > 1, measurable levels of 6-MAM in body fluids were found in 35 cases (77.8%), and those comprised the 6-MAM-positive group. In other cases (n = 10), no measurable 6-MAM was detected, and these comprised the 6-MAM-negative group. The results are presented in Tables 2 and 3.

Median values of blood morphine and codeine, and urine morphine and codeine concentrations in 6-MAM-positive and 6-MAM-negative groups are presented in Table 4. As presented, blood morphine levels significantly differed between the groups and were approximately two times higher in the 6-MAM-negative than in the 6-MAM-positive group ($U = 3.5$; $p = 0.022$). Concentrations of blood codeine were similar in both groups ($U = 19.0$; $p = 0.575$). However, in the 6-MAM-negative group, the median blood M/C ratio was 8.25 and in the 6-MAM-positive group the median blood M/C ratio was 4.25.

Compared to the 6-MAM-negative group, median values of urine morphine levels were somewhat higher in the 6-MAM-positive group (Table 4), but the difference between the groups was not significant ($U = 134.0$; $p = 0.859$). Compared to the 6-MAM-negative group, the medium urine codeine concentrations were about three times lower in the 6-MAM-positive group. The differences between the groups regarding urine codeine levels were also not significant ($U = 129.0$; $p = 0.734$). However, in the 6-MAM-negative group, the median urine M/C ratio was 6.2, whilst in the 6-MAM-positive group, the median urine M/C ratio was 32.2, and this difference was statistically significant ($p < 0.001$).

We further analyzed relationships between morphine, codeine, and 6-MAM within each body fluid compartment. The results are presented in Table 5. In the current study there were significant correlations between blood morphine and blood codeine levels ($r = 0.607$; $p = 0.006$), urine morphine and urine codeine levels ($r = 0.766$;

Table 1. Opiates and their combinations in drug addicts who died from abuse of psychoactive substances from January 2006 to December 2015

Psychoactive substance(s)	Number of cases (n)	%
Morphine	134	63
Codeine	2	0.9
Methadone	4	1.8
Others	1	0.4
Morphine + codeine	56	25.6
Morphine + methadone	2	0.9
Morphine + tramadol	2	0.9
Morphine + methadone + tramadol	1	0.5
Morphine + codeine + tramadol	1	0.5
Morphine + codeine + methadone	1	0.5
Unknown	11	5
Total	219	100

Table 2. Distribution of opioid addict cases according to the presence of 6-MAM

Presence of 6-MAM	Number of cases (n)	%
6-MAM-negative	10	22.2
6-MAM-positive	35	77.8
Total	45	100

Table 3. Distribution of opioid addict cases with M/C ratio > 1, according to the presence of 6-MAM in the blood and urine

Presence of 6-MAM	Body fluid			
	Blood		Urine	
	n	%	n	%
6-MAM-negative	3	15.8	9	22.5
6-MAM-positive	16	84.2	31	77.5
Total	19	100	40	100

Table 4. Morphine and codeine concentrations in postmortem body fluids according to the presence of 6-MAM

Opioids in body fluids (μg/ml)	6-MAM n body fluids			
	6-MAM-negative		6-MAM-positive	
	n	Median (range)	n	Median (range)
Morphine (blood)	3	0.33 (0.23–0.39)	16	0.17 (0.03–0.41)
Morphine (urine)	9	2.37 (0.03–17.20)	31	3.33 (0.10–44.28)
Codeine (blood)	3	0.04 (0.02–0.11)	16	0.04 (0.004–0.090)
Codeine (urine)	9	0.38 (0.01–4.93)	32	0.11 (0.01–8.65)

Table 5. Correlation analysis for relationships between morphine, codeine, and 6-MAM within each body fluid compartment

Drug	Body fluid		Codeine (μg/mL)		6-MAM (μg/mL)	
			Blood	Urine	Blood	Urine
Morphine (μg/mL)	Blood	r	0.607		-0.162	
		p	0.006*		0.580	
		n	19		14	
	Urine	r		0.766		0.650
		p		< 0.001*		< 0.001*
		n		40		29
Codeine (μg/mL)	Blood	r			0.114	
		p			0.699	
		n			14	
	Urine	r				0.620
		p				< 0.001*
		n				28

Spearman's correlation coefficient (r) was calculated, and significant relationships were marked (*).

p < 0.001), urine morphine and urine 6-MAM levels (r = 0.650; p < 0.001), and between urine codeine and urine 6-MAM levels (r = 0.620; p < 0.001).

DISCUSSION

The M/C ratio is now considered to be a useful parameter to distinguish heroin-associated death from death associated with codeine abuse, since in the latter cases the M/C ratio is often ≤ 1 [7, 10]. Beside morphine, the presence of codeine and/or 6-MAM was detected in 49 of 134 cases (36.5%) in the current study. In 45 cases, the M/C ratio in the blood and/or urine was > 1, and in four cases the urine M/C ratio was < 1. Of these 45 morphine- and codeine-positive cases, in 35 cases (77.8%) we also detected measurable amounts of 6-MAM in the blood and/or urine samples. The M/C ratio in morphine- and codeine-positive cases varied 2.5–13. Previously, the M/C ratio was determined exclusively in the blood samples [5, 11, 12], and more recently the M/C ratio was calculated from both blood and urine samples [4].

For identification and measurement of 6-MAM, as currently most accurate molecular fingerprint of heroin exposure, it is often recommended to employ urine samples. The main reason is that, in contrast to the blood, 6-MAM once excreted into the urine is not further metabolized in organism [13, 14]. In Norway, Konstantinova et al. [4] investigated the M/C ratio in a large number of cases (n = 2,438), positive for 6-MAM and/or morphine and codeine in the blood and urine samples. In that study, in 98% of blood samples and in 96% of urine samples, the M/C ratio was > 1, and varied 5–10, which is largely in accordance with our findings. Moreover, one Swedish study of 747 cases related to heroin abuse also reported that in 98.9% of 6-MAM-positive cases the M/C ratio was > 1, although the M/C ratio was actually very high, with median value found to be 11 [6]. Estimating the survival times in acute heroin intoxication, Darke and Duflou [1] reported 6-MAM in 43% of the cases. This study also reported that 6-MAM-positive cases have two times higher morphine levels than 6-MAM-negative cases, which was also found in the current report (Table 4). Ceder and Jones [5] evaluated 6-MAM, morphine, codeine, and M/C ratio in living persons imprisoned for driving under the influence of drugs. Of 675 blood samples in that study, 6-MAM was present in 16 (2.3%), and of 339 urine samples, 6-MAM was recorded in 212 samples (62%). When 6-MAM was detected in urine, the blood M/C ratio was always > 1, and varied 1–66, with a median value of 6 [5].

However, the M/C ratio should be analyzed through the prism of free morphine and codeine levels. In the current study, we observed high median levels of blood morphine in both 6-MAM-positive (0.17 mg/L) and 6-MAM-negative cases (0.33 mg/L), and even higher median levels of urine morphine in 6-MAM-positive (3.33 mg/L) and 6-MAM-negative cases (2.37 mg/L). In contrast to that, median values of either blood or urine codeine levels were much lower and were not related to the 6-MAM status (0.04 mg/L, and 0.11 mg/L, respectively). These results are in accordance with several other studies who reported

that blood free morphine levels vary 0.22–0.60 mg/L and blood free codeine levels vary 0.01–0.07 mg/L after heroin exposure [4, 6, 7, 8].

We observed that, compared to the 6-MAM-negative group, concentration of the blood free morphine was lower in the 6-MAM-positive group (0.33 mg/L *vs*. 0.17 mg/L). Although this is opposite to several other studies which reported higher blood morphine levels in the6-MAM-positive group [4], our findings are in accordance with Ceder and Jones [5], who also found higher median values of blood morphine in the 6-MAM-negative group.

Also, morphine levels were higher than codeine levels in all 6-MAM-positive cases and all 6-MAM-negative cases with M/C ratio > 1, either in the blood or urine samples (Table 4). Moreover, blood morphine and blood codeine levels, as well as urine morphine and urine codeine levels, were significantly correlated (Table 5). These findings are somewhat expected, and may be partly explained by the fact that illegal production of heroin from crude opium is necessarily accompanied by the increased presence of codeine, as an impurity, thus heroin drug addicts consume some codeine as well. In the 6-MAM-positive group, there were statistically significant correlations between 6-MAM and morphine, as well as between 6-MAM and codeine in urine samples. Similar results were reported on cadaveric samples, as well as on samples from living drug addicts, thereby confirming that morphine and codeine levels in the body fluids are tightly related to the quantity of heroin taken with the dose [4, 5, 7].

In four 6-MAM-negative cases the blood M/C ratio was > 1, whilst the urine M/C ratio was < 1, with a median of 0.55. Konstantinova et al. [4] also reported low values of M/C ratio in 2% of blood and 4% of urine samples but among 6-MAM-positive cases, while Ceder and Jones [5] reported M/C ratio < 1 in 15% cases of 6-MAM-positive living, imprisoned drug addicts. One probable explanation of such divergent M/C ratio findings observed among 6-MAM negative cases could be related to longer survival time, during which the blood 6-MAM could undergo further metabolic reactions yielding products that were not targeted in our study.

Codeine is an opioid analgesic drug. However, median concentration of free codeine in four cases with urine M/C ratio < 1 in our study was 0.67 mg/M (0.31–1.10 mg/L). This was 2.4 times higher than free morphine levels in the same group (median 0.28 mg/L; range: 0.024–0.94 mg/L), and several times higher than therapeutic codeine dose. Pharmacokinetic studies have well documented that the blood concentration of free codeine is several times higher than free morphine after one or more codeine doses [9, 15, 16]. Kronstrand et al. [17] reported, for example, that ingestion of 100 mg codeine phosphate gave rise to the free blood codeine to 0.183 mg/L, while in the study by Quiding et al. [13], ingestion of 60 mg codeine phosphate gave rise to blood codeine of 0.115 mg/L. Ceder and Jones [5] reported blood free codeine levels of 0.180 mg/L in living drug addicts with M/C ratio < 1. These and our results suggest that a low M/C ratio probably indicates that codeine was deliberately used some time before death, or, more likely, that codeine as an impurity was highly present in the heroin dose.

CONCLUSION

The current study of death related to chronic heroin exposure indicates that the presence of 6-MAM and M/C ratio in body fluids may be used as reliable tools to differentiate cases in which it is unclear whether death resulted from (chronic) heroin and morphine consumption for non-medical (recreational) purposes, or from accidental therapeutic use of morphine.

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Значај концентрације 6-MAM и односа морфин/кодеин у дијагностици смрти наркомана

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САЖЕТАК

Увод/Циљ Хероин се у организму метаболише у 6-моноацетилморфин (6-MAM) и морфин. Циљ рада је да испитујући концентрације 6-MAM, морфина, кодеина и њихових односа диференцијално дијагностички дефинишемо разлику између смрти које су наступиле уношењем хероина у организам од оних које су наступиле коришћењем морфина и или/кодеина.

Методе Код 45 обдукованих наркомана код којих је у узорцима крви и урина однос вредности концентрација морфин/кодеин > 1, гасном хроматографијом / масеном спектрометријом одређиване су концентрације морфина, 6-MAM-а и кодеина. Формиране су две групе испитаника: 6-MAM позитивна ($n = 35$) и 6-MAM негативна група ($n = 10$).

Резултати У поређењу са 6-MAM негативном групом, концентрација морфина у крви је била значајно већа у 6-MAM позитивној групи ($p = 0,022$), док се вредности кодеина у крви нису разликовале ($p = 0,575$). У 6-MAM негативној групи однос морфин/кодеин у крви је био 8,3, док је у 6-MAM позитивној био 4,3. Није било значајне разлике у концентрацији морфина у урину међу групама ($p = 0,859$). Однос морфин/кодеин у урину у 6-MAM негативној групи је био 6,2, док је у 6-MAM позитивној групи био 32,2. Концентрације морфина и кодеина у крви су значајно корелирале ($r = 0,607$; $p = 0,006$), као и концентрације морфина и кодеина у урину ($r = 0,766$; $p < 0,001$), морфина и 6-MAM у урину ($r = 0,650$; $p < 0,001$) и кодеина и 6-MAM у урину ($r = 0,620$; $p < 0,001$).

Закључак Присуство 6-MAM у узорцима телесних течности и однос морфин/кодеин могу бити корисни индикатори и послужити у дијагностици смрти повезаној са узимањем опијата.

Кључне речи: обдукција; хероин; 6-MAM; морфин; кодеин