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Fatal versus non-fatal heroin "overdose": blood morphine concentrations with fatal outcome in comparison to those of intoxicated drivers

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Abstract

The study was performed to distinguish fatal from non-fatal blood concentrations of morphine. For this purpose, blood levels of free morphine and total morphine (free morphine plus morphine conjugates) in 207 cases of heroin-related deaths were compared to those in 27 drivers surviving opiate intoxication. The majority of both survivors and non-survivors were found to show a concomitant use of depressants including alcohol or stimulants. Blood morphine levels in both groups varied widely, with a large area of overlap between survivors (free morphine: 0–128 ng/ml, total morphine: 10–2110 ng/ml) and non-survivors (free morphine: 0–2800 ng/ml, total morphine: 33–5000 ng/ml). Five (18.5%) survivors and 87 (42.0%) non-survivors exhibit intoxication only by morphine. In these cases, too, both groups overlapped (survivors-free morphine: 28–93 ng/ml, total morphine: 230–1451 ng/ml; non-survivors-free morphine: 0–2800 ng/ml, total morphine: 119–4660 ng/ml). Although the blood levels of free or total morphine do not allow a reliable prediction of survival versus non-survival, the ratio of free/total morphine may be a criterion to distinguish lethal versus survived intoxication. The mean of the ratio of free to total morphine for all lethal cases ($N = 207$) was 0.293, for those that survived ($N = 27$) 0.135, in cases of intoxication only by morphine 0.250 ($N = 87$) and 0.080 ($N = 5$), respectively. Applying a cut-off of 0.12 for free/total morphine and performing ROC analyses, fatal outcome can be predicted in 80% of the cases correctly, whereas 16% of the survivors were classified as dead. Nevertheless, in this study, all cases with a blood concentration of 200 ng/ml and more of free morphine displayed a fatal outcome.

Keywords: Heroin; Morphine concentrations; Free morphine; Total morphine; Lethal intoxication

1. Introduction

Like other drugs, heroin should show a correlation between dosage or blood levels and its psychotropic effect [1]. Heroin itself is an ester compound, rapidly hydrolyzed to 6-acetylmorphine and morphine [2]. So, a relation of the drug concentration and the psychotropic or toxic effect of heroin can only be detected in terms of blood concentration of metabolites, especially morphine, the main metabolite of heroin [3]. Whereas fatal doses can be easily determined in animal studies, long-term heroin addiction by humans can lead to tolerance of extremely high doses [4–6]. Recently, it has been shown that heroin overdose is not restricted to intravenous injection only, but is observed after nasal administration and swallowing, too [7]. Consequently, morphine levels in victims of lethal heroin overdose can vary widely [8–12], reported levels ranging from <25 [13]to 4.700 ng/ml [14]. Unfortunately, there is an overlap of blood morphine levels between victims of heroin overdose and users surviving heroin intake [15,16]. On the other hand, 49% of drug users reported suicidal ideas before overdosing in a study in the UK [17].

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Forensic pathologists and toxicologists are often confronted with cases requiring the determination of a "certainly fatal" concentration of morphine in blood. The ability to clearly discriminate the "certainly fatal" concentration of morphine in blood from other causes of death has been elusive, because of the variation of free and conjugated morphine in blood and co-administration of other drugs. Until now no toxicological data are available to address a cut-off concentration of morphine to distinguish between a lethal and non-lethal heroin overdose [18].

In the present study, we compared the free and total morphine levels and their ratio in blood of victims of "confirmed lethal" heroin intoxication with those in surviving heroin users whose blood was tested on suspicion they were driving while intoxicated. The aim of our study was to obtain information about fatal morphine concentrations in blood, because of the high importance of distinguishing a death by acute intoxication from other natural causes (e.g. pneumonia, myocarditis).

2. Materials and methods

2.1. Case material

The cases were divided into two groups based on evaluation of police or public prosecutor records, autopsy findings, results of microscopic examination and toxicological analyses.

2.1.1. Group 1

Two hundred and seven cases of heroin-related deaths from the Departments of Legal Medicine in Luebeck and Bremen occurred from 1991 to 1996. The determination of the cause of death was based on gross autopsy findings, microscopic study and toxicological analyses. When fatal disease or traumatic injury were excluded, the detection of the heroin metabolite morphine in blood lead to the assumption of heroin-related death. Victims of intoxication by morphine alone (group 1a, $N = 87$) as well as cases with concomitant use of other substances (group 1b, $N = 120$)

Table 1
Median and range of morphine levels in the blood in cases of multiple drug intoxication and intoxication only by morphine in the non-survivors and survivors

Group	N	Total morphine (ng/ml)		Free morphine (ng/ml)		Mean of ratio free/total morphine
		Median	Range	Median	Range	
All cases						
Lethal intoxication	207	980	33–5000	208	0–2800	0.293 ± 0.203
Survived intoxication	27	396	10–2110	30	0–128	0.135 ± 0.200
Total	234	891.5	10–5000	184	0–2800	0.274 ± 0.209
Multiple drug intoxication						
Lethal intoxication	120	888	33–5000	232	5–2542	0.323 ± 0.209
Survived intoxication	22	283.5	10–2110	20.5	0–128	0.148 ± 0.221
Total	142	737.5	10–5000	199	0–2542	0.296 ± 0.219
Intoxication only by morphine						
Lethal intoxication	87	1032	34–4660	170	0–2800	0.250 ± 0.189
Survived intoxication	5	918	230–1451	65	28–93	0.080 ± 0.026
Total	92	1026	34–4660	165.5	0–2800	0.241 ± 0.188

Table 2
Number (N) and percentage (%) of non-survivors and survivors according to the drug(s) detected in the blood

Drug	Lethal intoxication ($N = 207$)		Survived intoxication ($N = 27$)	
	N	%	N	%
Morphine	87	42.0	5	18.5
Morphine + alcohol	58	28.0	0	0
Morphine + central nervous system depressants	40	19.3	17	62.9
Morphine + central nervous system depressants and stimulants	4	1.9	1	3.7
Morphine + alcohol + central nervous system stimulants	3	1.4	0	0
Morphine + central nervous system stimulants	15	7.7	4	14.8

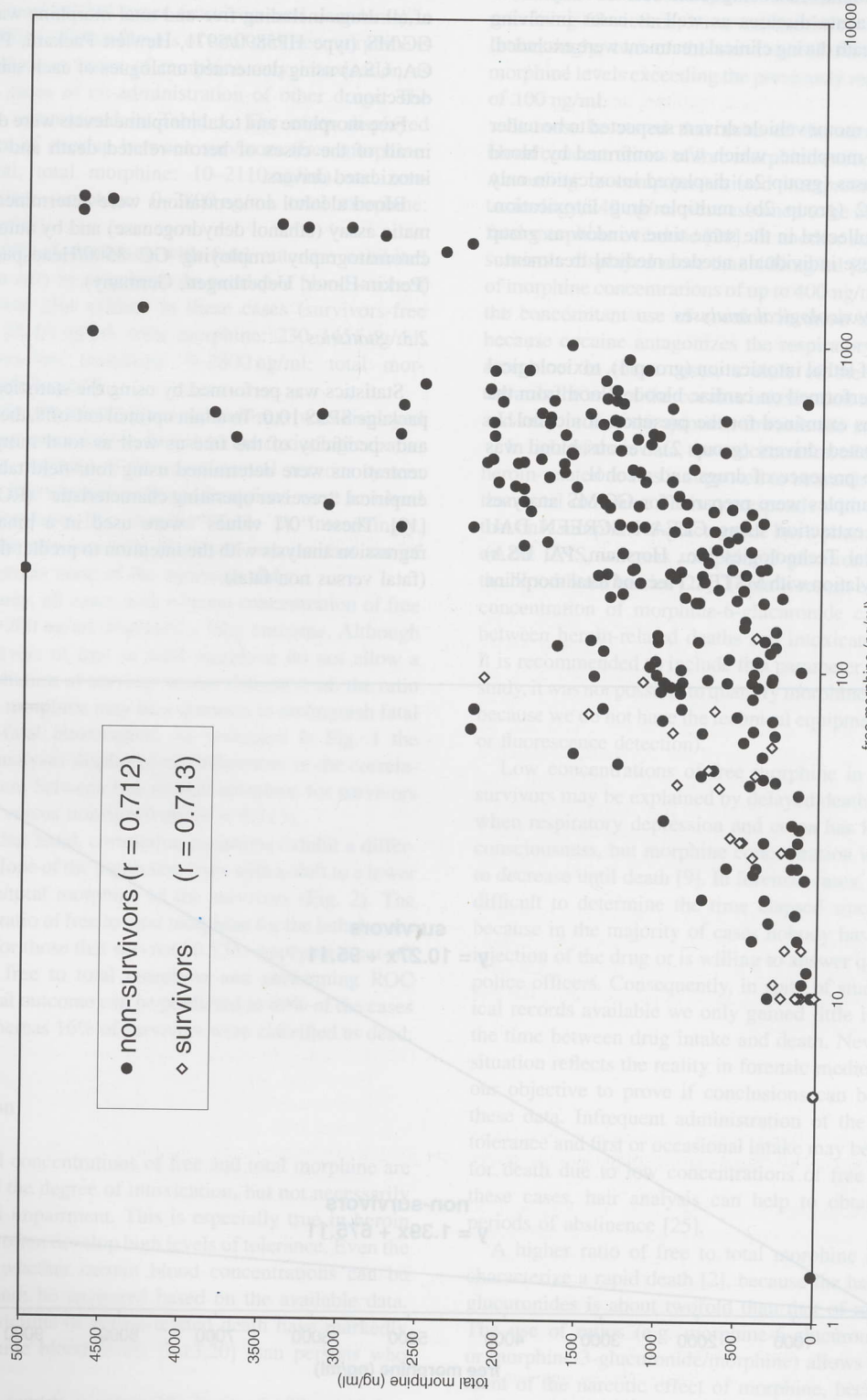

Fig. 1. Data for concentrations of free morphine and total morphine in non-survivors ($N = 207$; ●) and survivors ($N = 27$; ◇). An overlap is observed for concentrations of free morphine and total morphine in the two groups.

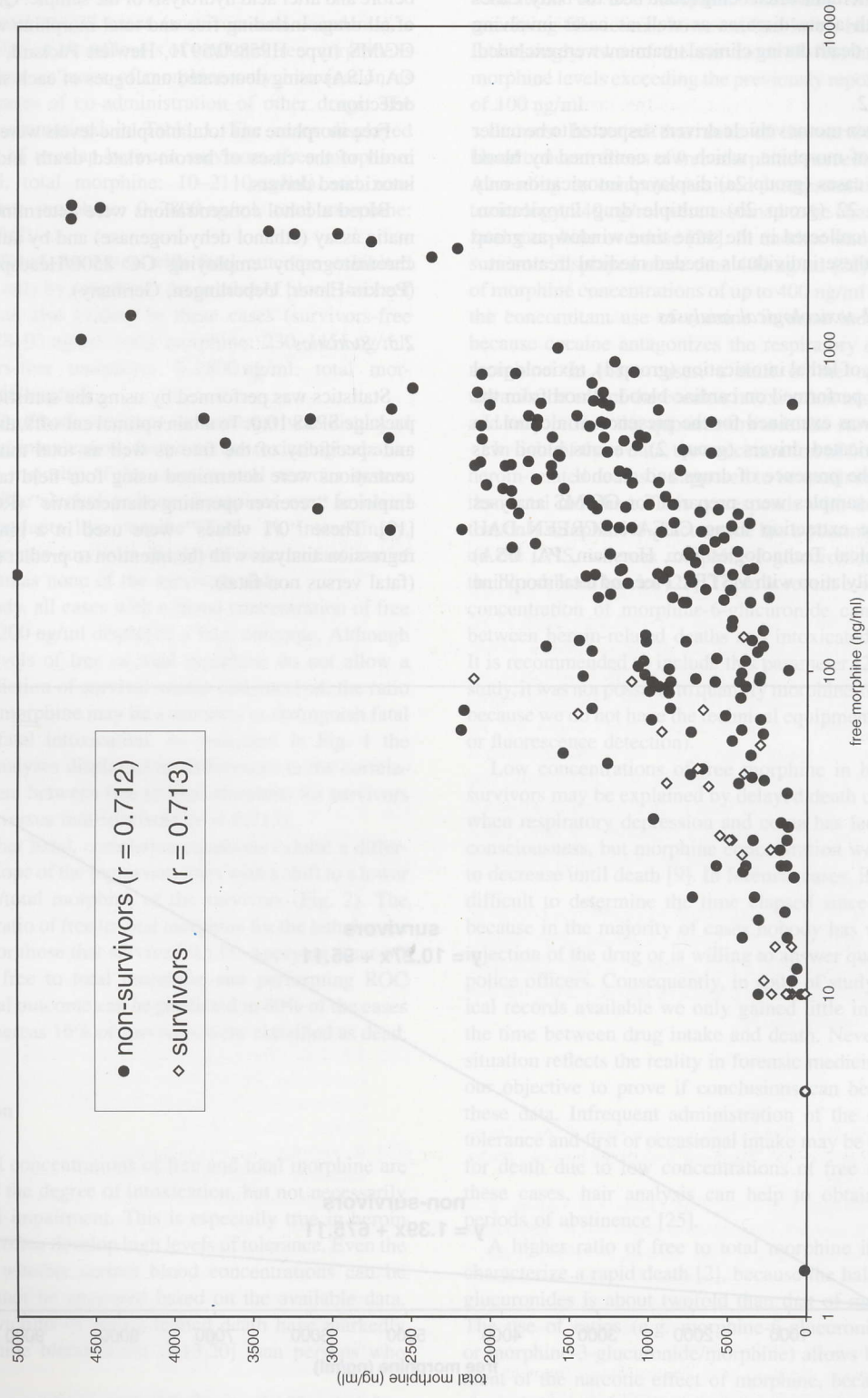

Fig. 1. Data for concentrations of free morphine and total morphine in non-survivors ($N = 207$; ●) and survivors ($N = 27$; ◇). An overlap is observed for concentrations of free morphine and total morphine in the two groups.

were included. The majority of the victims died suddenly, the drug paraphernalia often being found near the body. Cases associated with acute diseases as well as cases involving putrefaction or death during clinical treatment were excluded.

2.1.2. Group 2

Twenty-seven motor vehicle drivers suspected to be under the influence of morphine, which was confirmed by blood analysis. Five cases (group 2a) displayed intoxication only by morphine, 22 (group 2b) multiple drug intoxication. Samples were collected in the same time window as group 1. No one of these individuals needed medical treatment.

2.2. Chemical–toxicological analyses

In all cases, of lethal intoxication (group 1), toxicological analyses were performed on cardiac blood. Blood from the femoral vein was examined for the presence of alcohol. In cases of intoxicated drivers (group 2), venous blood was analyzed for the presence of drugs and alcohol.

The serum samples were prepared for GC/MS analyses by solid-phase extraction using CLEAN SCREEN DAU (United Chemical Technologies Inc., Horsham, PA, USA) and trimethylsilylation with MSTFA. Free and total morphine were quantified by determination of morphine concentration before and after acid hydrolysis of the sample. Quantification of all drugs including free and total morphine was done by GC/MS (type HP5890/5971, Hewlett Packard, Paolo Alto, CA, USA) using deuterated analogues of each substance for detection.

Free morphine and total morphine levels were determined in all of the cases of heroin-related death and of heroin-intoxicated drivers.

Blood alcohol concentrations were determined by enzymatic assay (ethanol dehydrogenase) and by automated gas chromatography employing GC 8500/Headspace HS 40 (Perkin-Elmer, Ueberlingen, Germany).

2.3. Statistics

Statistics was performed by using the statistical software package SPSS 10.0. To attain optimal cut-offs, the sensitivity and specificity of the free as well as total morphine concentrations were determined using four-field tables and an empirical "receiver operating characteristic" (ROC) method [19]. These "0/1 values" were used in a binary logistic regression analysis with the intention to predict the outcome (fatal versus non-fatal).

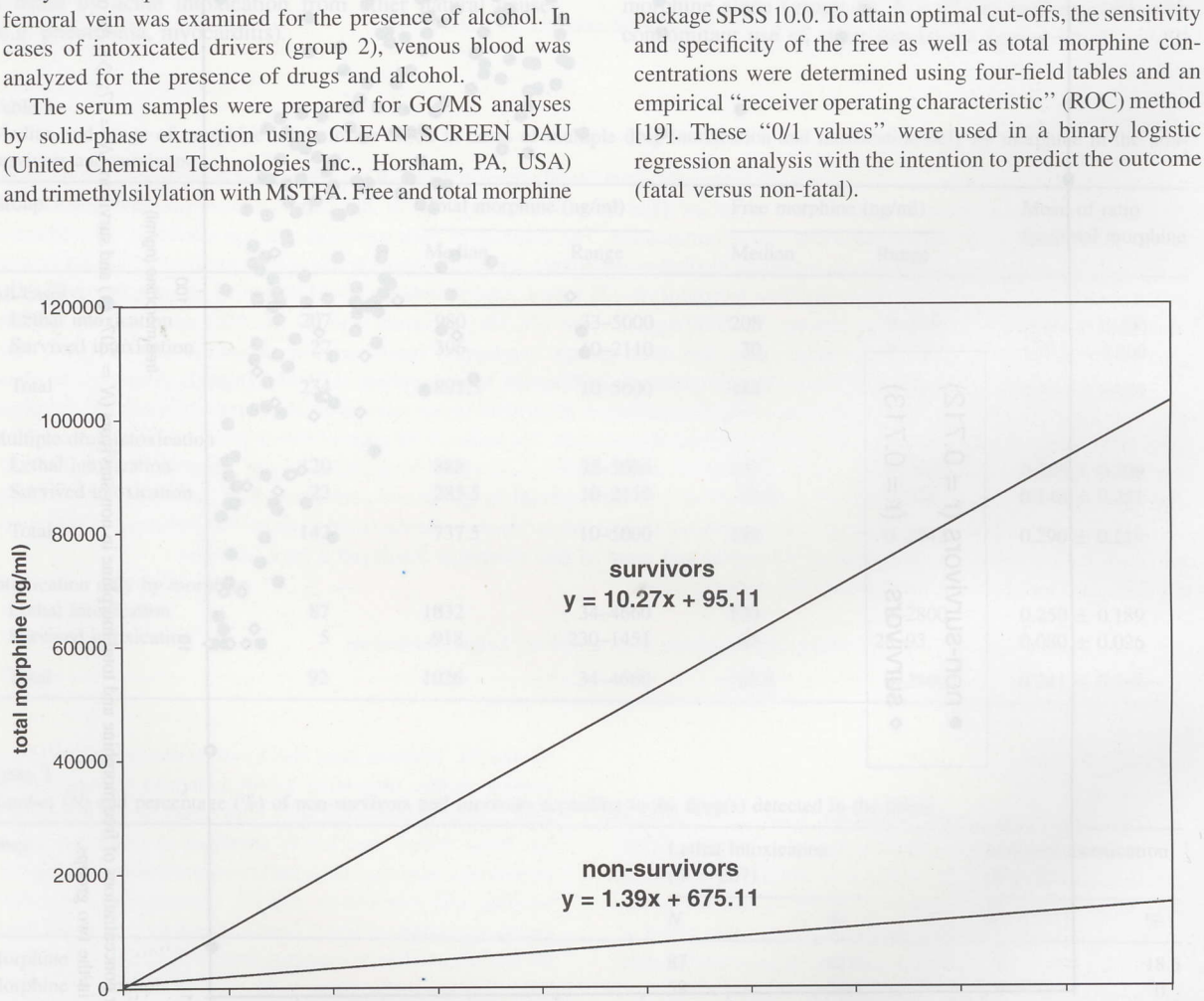

Fig. 2. Correlation equations of survivors in comparison with non-survivors. Note the different slope of the regression lines with a shift to a lower ratio of free/total morphine in survivors.

3. Results

For the total of 234 cases (survivors and decedents), a wide variability of blood levels of total and free morphine is readily evident in cases of morphine-only intoxication as well as in cases of co-administration of other drugs. The results are summarized in Table 1. The cases displayed a large area of overlap between survivors (free morphine: 0–128 ng/ml, total morphine: 10–2110 ng/ml) and non-survivors (free morphine: 0–2800 ng/ml, total morphine: 33–5000 ng/ml).

The 42.0% of the cases with fatal outcome exhibited intoxication only by morphine. An overlap of blood levels of morphine was also evident in these cases (survivors-free morphine: 28–93 ng/ml, total morphine: 230–1451 ng/ml; non-survivors-free morphine: 0–2800 ng/ml; total morphine: 34–4660 ng/ml).

The 60.6% of both survivors and non-survivors displayed multiple drug intoxication. Based on the toxicological analyses, in the majority of the cases central nervous system depressants like alcohol or benzodiazepines were involved as were stimulants like cocaine (Table 2). Interestingly, 28.0% of the non-survivors displayed concomitant use of alcohol, whereas none of the survivors did.

In this study, all cases with a blood concentration of free morphine $\geq$200 ng/ml displayed a fatal outcome. Although the blood levels of free or total morphine do not allow a reliable prediction of survival versus non-survival, the ratio of total/free morphine may be a criterion to distinguish fatal versus non-fatal intoxication. As indicated in Fig. 1 the regression analyses displayed no differences in the correlation coefficient between free to total morphine for survivors ($r = 0.712$) versus non-survivors ($r = 0.713$).

On the other hand, correlation equations exhibit a difference of the slope of the regression lines with a shift to a lower ratio of free/total morphine of the survivors (Fig. 2). The mean of the ratio of free to total morphine for the lethal cases was 0.293, for those that survived 0.135. Applying a cut-off of 0.12 for free to total morphine and performing ROC analyses, fatal outcome can be predicted in 80% of the cases correctly, whereas 16% of survivors were classified as dead.

4. Discussion

The blood concentrations of free and total morphine are indicators of the degree of intoxication, but not necessarily of functional impairment. This is especially true in heroin addicts, who often develop high levels of tolerance. Even the question of whether certain blood concentrations can be survived cannot be answered based on the available data. Sometimes victims of heroin-related death have markedly lower morphine blood levels [7,13,20] than persons who survive.

Literature reports a survivable limit of 100 ng/ml free morphine in the blood [21]. In the present study, 144 cases of heroin-related death (69.5%) did in fact have blood concentrations of free morphine exceeding 100 ng/ml. The remaining 63 victims, however, had levels below this limit. Interestingly, two of the survivors (7.4%) had free blood morphine levels exceeding the previously reported fatal limit of 100 ng/ml.

It must be stated that none of the survivors exhibited blood concentrations of free morphine exceeding 200 ng/ml. According to computer-assisted interpretation of forensic toxicology, 240 ng/ml were assumed to be characteristic of a fatal morphine overdose [21]. In another study, none of the survivors displayed more than 400 ng/ml [22]. The survival of morphine concentrations of up to 400 ng/ml may be due to the concomitant use of cocaine in these individual cases, because cocaine antagonizes the respiratory depression by morphine. In these cases, a shift of the opiate toxicity towards the end of the cocaine intoxication may be observed and may reduce the quotient towards the survivors.

In light of these data, the concentration of free morphine in heroin-related deaths is supposed to be much more important than total morphine. This corresponds with the observation that only morphine-6-glucuronide has a pharmacologic effect on the CNS, whereas morphine-3-glucoronide cannot pass the blood-brain barrier [23]. There is recent evidence that the concentration of morphine-6-glucuronide can discriminate between heroin-related deaths and intoxicated drivers [24]. It is recommended to include this parameter [23], but in our study, it was not possible to quantify morphine-6-glucuronide, because we do not have the technical equipment (e.g. LC/MS or fluorescence detection).

Low concentrations of free morphine in blood of non-survivors may be explained by delayed death of the addicts, when respiratory depression and coma has led to a loss of consciousness, but morphine concentration would continue to decrease until death [9]. In forensic cases, it is often very difficult to determine the time elapsed since drug intake, because in the majority of cases nobody has witnessed the injection of the drug or is willing to answer questions of the police officers. Consequently, in spite of studying all medical records available we only gained little information on the time between drug intake and death. Nevertheless, this situation reflects the reality in forensic medicine and it was our objective to prove if conclusions can be drawn from these data. Infrequent administration of the drug, loss of tolerance and first or occasional intake may be other reasons for death due to low concentrations of free morphine. In these cases, hair analysis can help to obtain data about periods of abstinence [25].

A higher ratio of free to total morphine in blood may characterize a rapid death [2], because the half-life of both glucuronides is about twofold than that of morphine [23]. The use of ratios (e.g. morphine-6-glucuronide/morphine or morphine-3-glucuronide/morphine) allows better assessment of the narcotic effect of morphine, because the time elapsed since the last administration is considered [24]. In our study the mean of the ratio of free to total morphine for the

lethal cases was 0.293, for those that survived 0.135. In another study, this ratio has been calculated as 0.53 in rapid deaths and 0.34 in delayed deaths [2]. Moreover, applying a cut-off of 0.12 for free to total morphine and performing ROC analyses allows to classify the majority of the cases correctly.

As discussed a few years ago, fatalities involving heroin only constitute a minority among overdose occasions and the issue of multiple drug intoxication is a very important one [13]. A significant negative correlation among fatal cases between blood alcohol concentration and morphine concentration has already been established [16]. These observations are in accordance with our study, because no individual of the living group had consumed alcohol, but 24% of the fatalities did. On the other hand, in our study 19.3% of the non-survivors, in contrast to 62.9% of the survivors had concomitant use of other CNS depressants (e.g. benzodiazepines or barbiturates). Therefore, combined CNS depression may not explain the effect completely, so that the role of these CNS depressants in combination with morphine has to be elucidated in further studies.

5. Conclusion

In the present study, we examined levels of total and free morphine in the blood as well as survival and death in an attempt to determine whether survivors of heroin abuse could be distinguished from non-survivors based only on levels of free or total morphine in the blood. Our results show that a fatal morphine concentration cut-off could not be established. In our study none of the survivors revealed a blood concentration of free morphine of $\geq$200 ng/ml. The ROC analyses of the ratio of total to free morphine allows a prediction of fatal outcome with a sensitivity of 80% and a specificity of 84%. This means that the majority of cases can be classified correctly.

Additionally, it is recommended to perform a complete toxicological analysis of the blood including other stimulants or depressants, and a hair analysis to get additional information about the abuse pattern of heroin during the last weeks before sample-taking.

References

[1] R.D. Baselt, R.H. Cravey (Eds.), Disposition of Toxic Drugs and Chemicals in Men, Chemical Toxicology Institute, Foster City, CA, 1985.

[2] B.A. Goldberger, E.J. Cone, T.M. Grant, Y.H. Caplan, B.S. Levine, J.E. Smialek, Disposition of heroin and its metabolites in heroin-related deaths, J. Anal. Toxicol. 18 (1994) 22–28.

[3] P.P. Rop, M. Fornaris, T. Salmon, J. Burle, M. Bresson, Concentrations of heroin, 6-monoacetylmorphine, and morphine in a lethal case following an oral heroin overdose, J. Anal. Toxicol. 21 (1997) 232–235.

[4] R.G. Richards, D. Reed, R.H. Cravey, Death from intravenously administered narcotics: a study of 114 cases, J. Forensic Sci. 21 (1976) 467–482.

[5] J. Wessel, Zu den Umständen des Todes bei Drogentodesfällen, Z. Rechtsmed. 96 (1986) 215–228.

[6] K. Pueschel, F. Teschke, U. Castrup, Etiology of accidental/unexpected overdose in drug-induced deaths, Forensic Sci. Int. 62 (1993) 129–134.

[7] S. Darke, J. Ross, Fatal heroin overdoses resulting from non-injecting routes of administration, NSW, Australia, 1992–1996, Addiction 95 (2000) 569–573.

[8] S. Felby, H. Christensen, A. Lund, Morphine concentrations in blood and organs in case of fatal poisoning, J. Forensic Sci. 3 (1974) 77–81.

[9] J.R. Monforte, Some observations concerning blood morphine concentrations in narcotic addicts, J. Forensic Sci. 22 (1977) 718–724.

[10] C. Lora-Tamayo, T. Tena, G. Tena, Concentrations of free and conjugated morphine in blood in twenty cases of heroin-related deaths, J. Chromatogr. 422 (1987) 267–273.

[11] C. Staub, R. Jeanmonod, O. Fryc, Morphine in postmortem blood: its importance for the diagnosis of deaths associated with opiate addiction, Int. J. Legal Med. 104 (1990) 39–42.

[12] K. Pueschel, Drug-related death—an update, Forensic Sci. Int. 62 (1993) 121–128.

[13] B. Levine, D. Green, J.E. Smialek, The role of ethanol in heroin death, J. Forensic Sci. 40 (1995) 808–810.

[14] B.K. Logan, J.S. Oliver, H. Smith, The measurement and interpretation of morphine in blood, Forensic Sci. Int. 35 (1987) 180–194.

[15] S. Darke, D. Zador, Fatal heroin overdose: a review, Addiction 91 (1996) 1765–1772.

[16] S. Darke, S. Sunjic, D. Zador, T. Prolov, A comparison of blood toxicology of heroin-related deaths and current heroin users in Sydney, Australia, Drug Alcohol Depend. 47 (1997) 45–53.

[17] J. Neale, Suicidal intent in non-fatal illicit drug overdose, Addiction 95 (2000) 85–93.

[18] K.A. Sporer, Acute heroin overdose, Ann. Intern. Med. 130 (1999) 584–590.

[19] C.E. Metz, Basic principles of ROC analysis, Sem. Nucl. Med. 8 (1978) 283–298.

[20] M. Schulz, A. Schmoldt, Therapeutic and toxic blood concentrations of more than 500 drugs, Pharmazie 52 (1997) 895–911.

[21] V.R. Spiehler, Computer-assisted interpretation in forensic toxicology: morphine-involved deaths, J. Forensic Sci. 34 (1989) 1101–1104.

[22] P.X. Iten, Fahren unter Drogen- oder Medikamenteneinfluss, Forensische Interpretation und Begutachtung, Institut für Rechtsmedizin, Forensische Toxikologie, Universität Zürich, Zürich, 1994, pp. 36–39.

[23] R. Osborne, S. Joel, D. Trew, M. Slevin, Morphine and metabolite behavior after different routes of morphine administration: demonstration of the importance of the active metabolite morphine-6-glucuronide, Clin. Pharmacol. Ther. 47 (1990) 12–19.

[24] R. Aderjan, S. Hofmann, G. Schmitt, G. Skopp, Morphine and morphine glucuronides in serum of heroin consumers and in heroin-related deaths determined by HPLC with native fluorescence detection, J. Anal. Toxicol. 19 (1995) 163–168.

[25] R. Kronstrand, R. Grundin, J. Jonsson, Incidence of opiates, amphetamines, and cocaine in hair and blood in fatal cases of heroin overdose, Forensic Sci. Int. 92 (1998) 29–38.