

ORIGINAL ARTICLE

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Drugs in blood samples from unconscious drug addicts after the intake of an overdose

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Abstract This investigation includes whole blood samples from 53 drug addicts found unconscious in the Copenhagen area with evidence of a heroin overdose. Heroin/morphine was detected in 85% of the patients and other opioids in 11%. One or more benzodiazepines, most often diazepam, were detected in 75% of the patients. A blood alcohol concentration higher than 1.00 mg/g was detected in 57% of the patients. Methadone was detected in seven patients, ketobemidone in four, amphetamine in five and cocaine in one. This investigation showed widespread multi-drug abuse and heroin/morphine alone was detected in only one patient. As indicators of heroin intake, 6-monoacetylmorphine (MAM) and morphine were detected in this investigation.

Key words Drug addicts · Drug-related emergencies · Morphine · 6-Monoacetylmorphine · Addiction patterns

Introduction

When a drug addict is found unconscious in the Copenhagen area, a mobile intensive care unit is sent to perform first aid including injection of an antidote for opioids. Most of these drug addicts leave shortly after the first aid treatment and do not want hospitalization. The purpose of this study was to gather information on the misuse pattern and to investigate the morphine blood concentrations in the unconscious stage.

Material and methods

This investigation includes whole blood samples from 53 drug addicts found unconscious in the Copenhagen area during a 1.5-

month period in 1991 with evidence of an overdose of heroin. The blood samples were taken from the patients while the antidote was being prepared. After awakening the patients were informed that the blood samples had been taken and thereby given the opportunity to refuse further investigation. The investigation was approved by the local ethics committee.

The blood samples were investigated for the presence of heroin/morphine and other strong analgesics such as methadone, ketobemidone and buprenorphine as well as amphetamine, cocaine, benzodiazepines and alcohol. Other drugs found by the toxicological investigation were noted. Heroin is metabolized to 6-monoacetylmorphine (MAM) very rapidly after intake and more slowly to morphine. In this study both morphine and MAM were detected.

The analytical methods used were radioimmunoassay [Roche Abuscreen morphine, DPC buprenorphine (double antibody) and DPC cocaine metabolite (Coat-A-Count)], a radioreceptor method [1], and gas, thin-layer and high-performance liquid chromatography methods [2, 3]. The determination of morphine and MAM was performed by high-performance liquid chromatography with ultraviolet light and electrochemical detectors after solid-phase extraction using Bondelut Certify columns.

Results

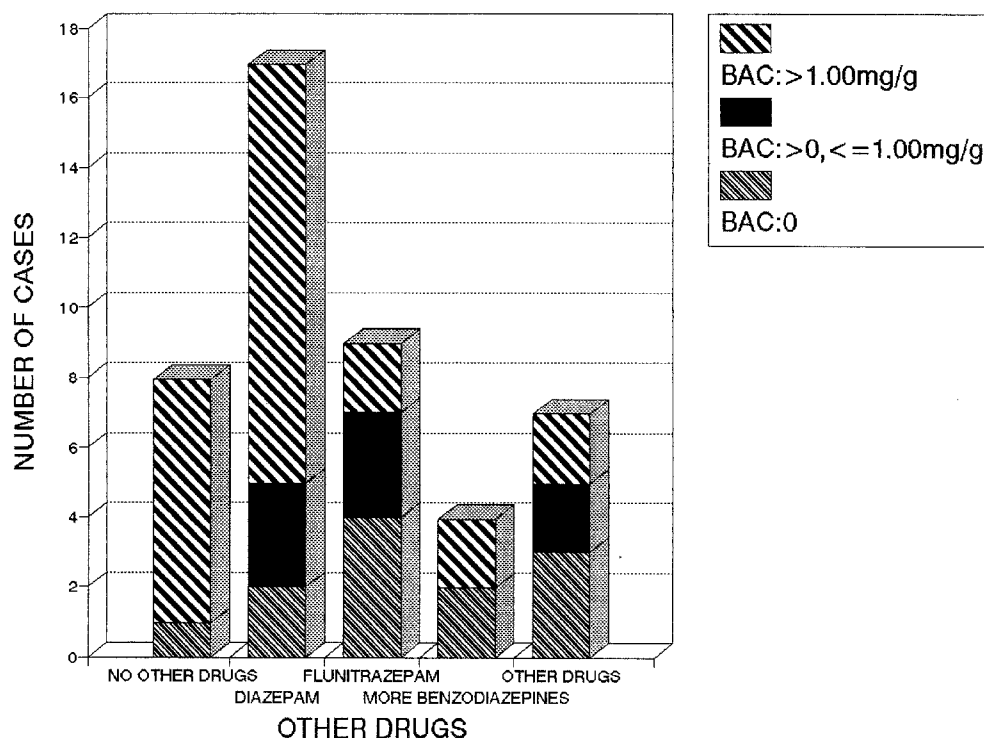
The mean age of the 53 drug addicts was 24 years (range 19–46 years); 19% were females. Of the 53 blood samples, 45 (85%) were found positive for morphine, and MAM was detected in 26 (58%). The concentrations of morphine and MAM are shown in Table 1. Alcohol was detected in 33 of the 45 patients positive for morphine, and in 25 the blood alcohol concentration (BAC) was higher than 1.00 mg/g (Fig. 1). In 34 (76%) of the heroin/morphine-positive patients one or more drugs of the benzodiazepine type were detected (Fig. 1), in 17 patients diazepam and in 9 patients flunitrazepam. Different combinations of drugs were detected in the group “other drugs”, including benzodiazepines, methadone, ketobemidone and amphetamine. Cocaine was detected in one patient only. In eight patients no heroin/morphine was detected (Table 2) and in six of these methadone and/or ketobemidone were detected. Diazepam and/or flunitrazepam were detected in six of the heroin/morphine-negative patients. In only two patients were no strong analgesics detected. A

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Table 1 Whole blood concentrations of morphine and 6-monoacetylmorphine (MAM). BAC Blood alcohol concentration

	Morphine $\mu\text{mol/kg}$ ($\mu\text{g/g}$)		MAM $\mu\text{mol/kg}$ ($\mu\text{g/g}$)	
	Range	Median value	Range	Median value
<i>MAM: 0</i>				
BAC = 0 ($n = 4$)	0.07–0.31 (0.02–0.09)	0.24 (0.07)		
BAC > 0 \leq 1.00 mg/g ($n = 2$)	0.14–0.21 (0.04–0.06)	0.18 (0.05)		
BAC > 1.00 mg/g ($n = 13$)	0.03–0.52 (0.01–0.15)	0.13 (0.04)		
<i>MAM: positive</i>				
BAC = 0 ($n = 8$)	0.18–1.54 (0.05–0.44)	0.75 (0.21)	0.07–0.51 (0.02–0.15)	0.14 (0.04)
BAC > 0 \leq 1.00 mg/g ($n = 5$)	0.19–0.99 (0.05–0.28)	0.33 (0.09)	0.09–0.30 (0.03–0.09)	0.16 (0.05)
BAC > 1.00 mg/g ($n = 13$)	0.14–0.58 (0.04–0.17)	0.25 (0.07)	0.05–0.28 (0.01–0.08)	0.12 (0.03)

Fig. 1 Other drugs and alcohol in the heroin/morphine-positive cases. BAC blood alcohol concentration

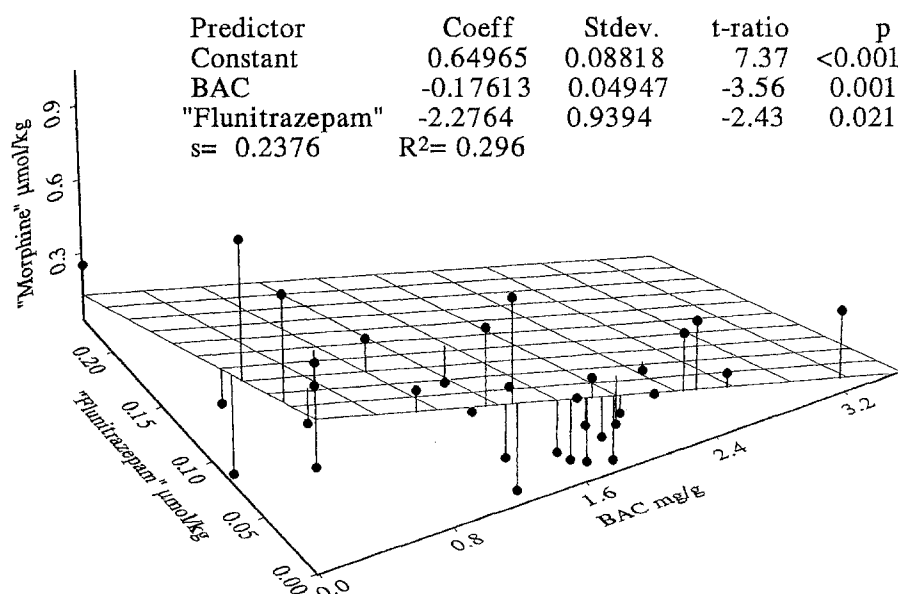
BAC of 2.71 mg/g was found in one of these patients and a BAC of 2.79 mg/g in combination with a high concentration of flunitrazepam in the other. In only one patient were neither alcohol nor other drugs detected. A BAC higher than 1.00 mg/g was detected in 57% of the 53 drug addicts. Buprenorphine was not found.

The relationship between morphine, alcohol, diazepam and flunitrazepam was investigated in the 35 cases with morphine and one or more of the three other substances present and no other drugs detected. In the calculations, "morphine" is the sum of the concentrations of morphine and MAM, "diazepam" the sum of diazepam and desmethyldiazepam and "flunitrazepam" the sum of flunitrazepam and desmethyflunitrazepam. By a linear multiple regression with "morphine" as the response variable and BAC, "diazepam" and "flunitrazepam" as explanatory

Table 2 Other drugs found in the heroin/morphine-negative patients

BAC	Number	Other drugs detected
0	1	Methadone + amphetamine + diazepam + flunitrazepam
> 0 \leq 1.00 mg/g	2	Methadone + ketobemidone + diazepam Methadone + diazepam
> 1.00 mg/g	5	Methadone Ketobemidone + flunitrazepam Ketobemidone + diazepam + flunitrazepam Flunitrazepam None

Fig. 2 The relationship between "morphine" (morphine + 6-monoacetylmorphine), BAC and "flunitrazepam" (flunitrazepam + desmethyl-flunitrazepam) and the summary of the regression



variables, only BAC and "flunitrazepam" showed significant results. The summary of the regression analysis and the regression plane are shown in Fig. 2. The model was checked by residual plots and a normal probability plot and found to be satisfactory. By introducing the product of BAC and "flunitrazepam" in the model as a new explanatory variable, no interaction was seen between BAC and "flunitrazepam" ($P = 0.322$). From the summary of the regression it can be seen that the variance in this study is considerable ($s = 0.2376$, $R^2 = 0.296$). It can be seen that if the mean increase in BAC is 1 mg/g then the "morphine" level decreases by 0.18 $\mu\text{mol/kg}$ (0.05 $\mu\text{g/g}$), and if the mean increase in "flunitrazepam" is 0.10 $\mu\text{mol/kg}$ (0.03 $\mu\text{g/g}$), then the "morphine" level decreases by 0.23 $\mu\text{mol/kg}$ (0.07 $\mu\text{g/g}$).

Discussion

The average age of the drug addicts in this investigation was 24 years, in contrast to the average age of drug addicts found dead in Denmark in 1991, which was 32 years [4]. The lower average age in this investigation may be explained by better health of younger drug addicts, giving them a greater chance of surviving until the arrival of the ambulance. Multi-drug abuse was very pronounced in this investigation, and heroin/morphine alone was detected in one patient only. One or more benzodiazepines were detected in 75% of the patients, and diazepam was detected in about half of the drug addicts found dead in 1991 [4] and about half of the drug addicts in this study. The frequent use of benzodiazepines among drug addicts is also in accordance with the statistics from the police for the same period, when diazepam and flunitrazepam dominated among prescription drugs on the illicit market. In this study flunitrazepam was detected in 26% of the patients compared with only 5% of the drug addicts found dead [4]. An explanation for this difference could be the

degradation of flunitrazepam to 7-aminoflunitrazepam in autopsy blood samples [5]; analyses for this degradation product were not routinely performed in 1991.

An investigation of emergency cases in Hamburg in 1991–1992 [6] showed a BAC higher than 1 mg/g in 20% of the patients, compared to 57% in this investigation. The difference was not so pronounced for drug addicts found dead during the same period. A BAC higher than 1 mg/g was seen in 17.5% of the drug addicts found dead in Hamburg compared to 25% in Denmark [4].

No information was available about methadone treatment in the seven patients positive for methadone. In this study, methadone was detected in 13% of the cases, compared to 36% in drug addicts found dead [4]. Methadone is frequently used in the treatment of drug addicts in Denmark [7]. Control measures for the dispensing of methadone are, however, often insufficient, and according to the annual report from the Danish police methadone is traded illicitly [8].

Despite the increasing abuse of amphetamine in Denmark since the late 1980s [9], amphetamine was detected in only five cases, in four of these in combination with heroin/morphine, possibly from "speedball", an illicit preparation of these two drugs. Also in the drug addicts found dead, amphetamine was detected in only a few cases [4].

During the period from 1991 until 1995 the drug abuse pattern in drug addicts found dead in the Copenhagen area did not change. Only few cocaine-positive cases were found, and no increase was seen in the number of cases positive for cocaine and amphetamine during this period.

In this investigation it was shown that the blood level of morphine resulting in unconsciousness is significantly influenced by the presence of alcohol and/or flunitrazepam. An average increase in BAC of approximately 1 mg/g or in the flunitrazepam concentration of 0.1 $\mu\text{mol/kg}$ corresponds to a decrease of 0.2 $\mu\text{mol/kg}$ in the morphine concentration resulting in unconsciousness. In other

words, the more alcohol or flunitrazepam taken, the less heroin/morphine is needed for intoxication.

The morphine concentrations in the blood samples in this investigation were within the range seen in fatal intoxications with heroin and/or morphine in drug addicts [10, 11]. Low blood concentrations are often seen in fatal intoxications with heroin and other strong analgesics like methadone and ketobemidone in drug addicts [7, 12], and from all information available about a case it will be possible to determine whether the cause of death could be intoxication, possibly in combination with poor health. This investigation furthermore confirms that it is almost impossible to make a toxicological evaluation of a case from blood concentrations alone.

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