DIAGNOSIS OF ILLICIT DRUG OVERDOSES: DIFFICULTIES FOUND

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ABSTRACT: This paper describes a retrospective study on drugs found in samples taken from dead individuals known to be drug addicts. Cases of heroin overdoses are only considered when the concentration of free morphine in the blood is 0.2 μg/ml or higher and when there is no other cause of death. The remaining positive cases, with lower readings than the above cut-off, are considered as drug-related deaths. Opiates were detected in 97.7% of the cases, 17.3% of that were associated to cocaine.

KEY WORDS: Illicit drugs; Interpretation of analytical results; Drugs of abuse.

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INTRODUCTION

In the context of the tendencies of drug addicts in Portugal, heroin [6] (and cocaine in some cases) remains the most commonly used drug and presents an important health problem. The consumer's behaviour, particularly where heroin is involved, causes suicides, crimes, traffic accidents and other social problems, contributes to the increase in divorces and hospital admissions connected with psychiatric complications (depression, anxiety, personality changes, sexual dysfunction, hallucinations, anti-social behaviour and affectivity problems).

The main purpose of this study is to show the difficulties in the interpretation of the findings of analytical results in order to diagnose the cause of death in fatal cases involving drug addicts.

This study determined the above-mentioned hard drugs in 177 cases of overdose and drug-related cases referred to the Laboratory of Forensic Toxicology of the Institute of Legal Medicine of Coimbra (IMLC).

Morphine (MOR) and codeine (COD) concentrations, both free and total, are presented in the blood samples of abuse addicts. In some urine samples, 6-monoacetylmorphine (6-MAM) is detected. Cocaine (COC), benzoylecgonine (BE) and ecgonine methyl ester (EME) concentrations were determined in 34 cases. Four cases were exclusively attributed to this drug. Total MOR and COD concentrations were analysed in liver and kidney samples in some of the victims.

Cocaine has become a widespread drug of abuse in recent times, first in the USA and later in Europe (but not yet in Portugal); its use as a doping agent has also been reported, although in some countries (such as the USA) heroin remains a common drug of abuse among addicts.

The ethanol levels and other medical products which sometimes are associated as well are mentioned.

The identification and measurement of the drugs is performed by GC/MS, SIM mode.

MATERIAL AND METHODS

Biological material

The various samples were taken from cadavers. Their autopsy was performed in Coimbra's Regional Forensic Jurisdiction, and the specimens were analysed at the IMLC. The samples were frozen at –18°C until assayed.

Procedure

The free opiates and cocaine and its metabolites in blood samples were determined through the method of Aderjan et al. and in urine samples through our previously described method [7]. Total MOR and COD concentrations in blood, liver and kidney samples were obtained according to Pare et al. [10], with modifications in the amounts of the samples (2 ml or 2 g) and addition of 0.4 g of sodium sulphate in the blood sample after hydrolysis.

When urine samples were available, fluorescence polarization immunoassay technique was used, with Abbott TDx-FLx. All positive results were confirmed by GC/MS.

Ethanol in blood samples was analysed by GC/HS with flame ionization detector according to our previously described method [5]. The medical substances were determined by a wide range of methods: GC/MS, gas chromatography with nitrogen-phosphate detector, and high-performance liquid chromatography with ultraviolet detection at specific wavelength, and more recently with a photodiode array detector.

RESULTS AND DISCUSSION

Figure 1 presents the frequency of the fatalities from 1990 to 1998. The fatalities were due to accidental or suicidal intoxication. The available information indicates intravenous use. Most of the drug addicts were male (92%) (Figure 2). The majority of the cases fell within the 25 to 34 age group, irrespective of gender (Figure 3). No information was available for 15.8% of the cases. The victims were found dead in bed, in

toilets, in public places, in the street or in prison, or died in hospital while under treatment. Syringes were found stuck to various parts of the body, and spoons, cotton wool, lemons, powder and other items related to heroin abuse were found nearby. The subjects lived in Portugal's Central Region, which represents approximately one-third of the country and is predominantly rural. A much larger number of deaths by overdose and drug-related deaths were noted in other regions of Portugal. Opiates were determined in 173 cases, and were associated to cocaine in 30 of them.

Table I show the average, standard deviation and range MOR concentrations in the blood of 92 cases which were considered of death by overdose. It was assumed that, for a cut-off of 0.2 μg/ml of free MOR, and in the absence of any other cause of death, there was an overdose. The values of 81 drug-related cases (MOR concentration < 0.2 μg/ml) with no specific cause of death are also presented in Table I.

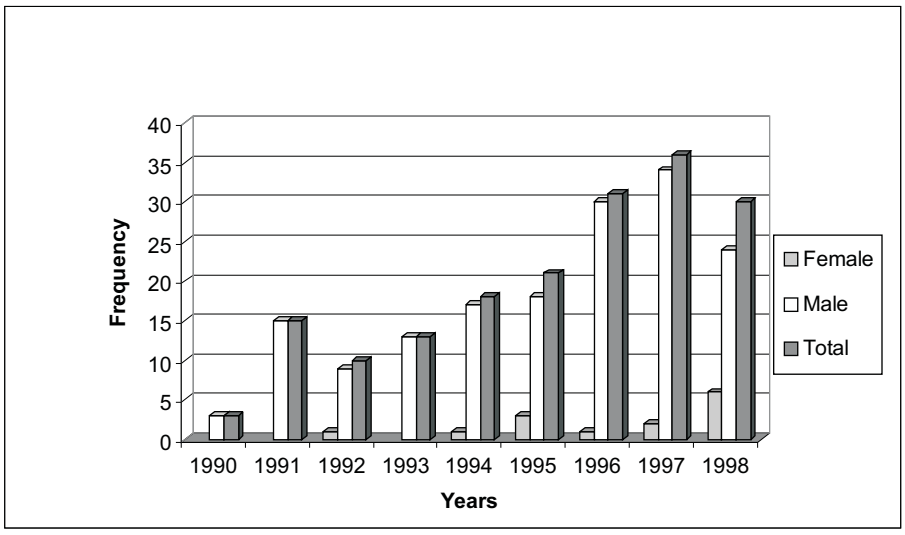

Fig. 1. Frequency of lethal cases from 1990 to 1998.

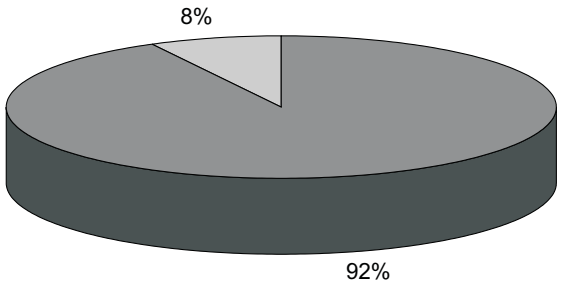

Fig. 2. Percentage of lethal cases by gender.

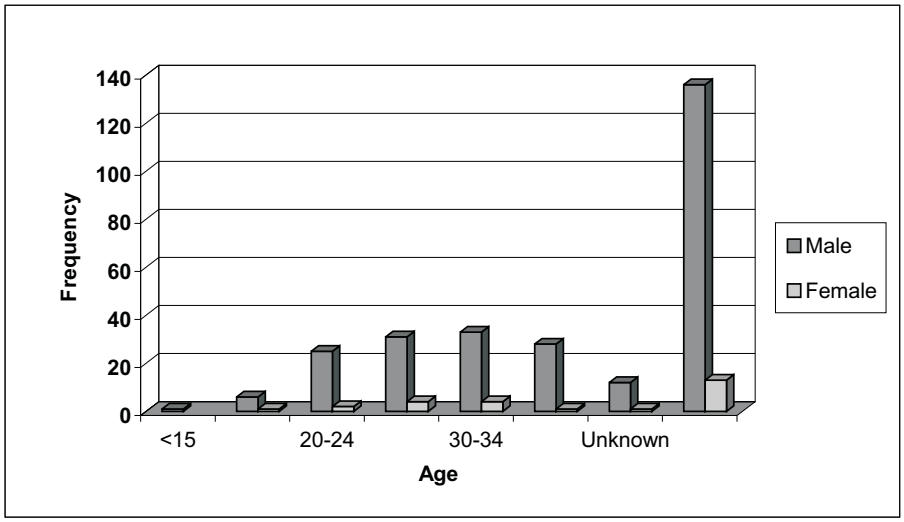

Fig. 3. Age distribution in overdose deaths and drug-related deaths from 1990 to 1998.

TABLE I. FREE MORPHINE CONCENTRATIONS [μg/ml] IN BLOOD SAMPLES

Parameter	n	Overdose cases (> 0.2)	n	Drug-related cases (< 0.2)
$\bar{X} \pm SD$ (range)	92	0.668 ± 0.986 (0.20–0.74)	81	0.100 ± 0.052 (0.01–0.19)

We noted in the first and second types, respectively, the average concentrations and ranges from 0.688 μg/ml (0.20 μg/ml to 0.74 μg/ml) to 0.1 μg/ml (0.01 μg/ml to 0.19 μg/ml). The minimum lethal concentration of MOR has been reported as 0.2 μg/ml of blood [3]. Monfort [9] mentions that none of the homicide victims had a greater blood concentration than 0.25 μg/ml, and in over 75% of the deaths attributed to narcotic overdoses the MOR concentration in the blood was also less than 0.25 μg/ml. Low blood heroin concentrations are often found in fatal intoxication. Ethanol and other medical substances were determined. In 132 cases we ethanol concentrations were determined and the results were positive in 44% of the cases, with an average of 1.18 g/l in the blood, and ranged from 0.11 g/l to 3.82 g/l. The results were negative in 56% of the cases.

This analytical test was not applied to the remaining cases. There were associations with medical products in 25 cases (Table II). Other researchers [12, 17] reported that there are influences of other strong analgesics like methadone and ketobemidone in drug addicts.

TABLE II. MEDICAL PRODUCTS INCLUDED IN ROUTINE DRUG SCREENING

Benzodiazepines	**Antidepressants**	**CSN Stimulants**
Diazepam Nordiazepam Oxazepam Bromazepam Flurazepam	Amitriptyline Desipramine Doxepin Imipramine Nortriptyline	Amphetamine Methamphetamine
Phenotiazines	**Narcotic analgesics**	**Non-narcotic analgesics**
Chlorpromazine Thioridazine	Methadone Propoxyphene	Acetaminophen Salicylate

Table III shows that, in cases considered to be overdose, the average conjugated MOR is 2.5 times greater than that of free MOR, whereas in drug-related cases (Table IV) it is 1.2. However, conjugated MOR was lower than free MOR in 65% of the overdose cases, and in 20% of the drug-related cases, which indicates a recent heroin injection; in the remaining cases the conjugated MOR in blood is compatible with different survival times. The MOR in the human body is primarily (60–75%) excreted as the inactive conjugated and free MOR (2–18%). Free MOR has an elimination half-life of 2–4 h, while the conjugated MOR formed in the liver from free MOR has an entero-hepatic recirculation, which accounts for nanogram levels of MOR in blood greater than 24 h [13]. Heroin is very quickly metabolised to 6-MAM. We detected 6-MAM in 9 overdose cases with available urine, but in 8 drug-related cases with available urine 6-MAM was detected in 75% of them. It follows that heroin absorption must have been recent in these cases, which indicates than an overdose was the likely cause of death. Since 6-MAM is considered as a heroin absorption biomarker, its presence has been utilised as an indicator of heroin use.

As regards COD (Tables II and III), concentrations in blood are higher in the first type of cases (average 0.044 μg/ml), but are always lower than MOR concentrations, which appear to indicate the use of heroin rather than the use of codeine.

TABLE III. REE AND TOTAL MORPHINE AND CODEINE CONCENTRATIONS [μg/ml] IN BLOOD IN OVERDOSE CASES (n = 40)

MOR		COD	
Free	Total	Free	Total
$\bar{X} \pm SD$ (range)	$\bar{X} \pm SD$ (range)	$\bar{X} \pm SD$ (range)	$\bar{X} \pm SD$ (range)
0.373 ± 0.210 (0.21–1.10)	1.597 ± 1.057 (0.28–7.44)	0.044 ± 0.032 (0.01–0.13)	0.070 ± 0.050 (0.02–0.34)

TABLE IV. FREE AND TOTAL MORPHINE AND CODEINE CONCENTRATIONS [μg/ml] IN BLOOD IN DRUG-RELATED CASES (n= 35)

MOR		COD	
Free	Total	Free	Total
$\bar{X}$ ± SD (range)	$\bar{X}$ ± SD (range)	$\bar{X}$ ± SD (range)	$\bar{X}$ ± SD (range)
0.123 ± 0.064 (0.010–1.180)	0.275 ± 0.185 (0.025–0.440)	0.011 ± 0.005 (0.005–0.130)	0.019 ± 0.005 (0.010–0.118)

TABLE V. TOTAL MORPHINE CONCENTRATIONS [μg/g] IN LIVER AND KIDNEY SAMPLES IN OVERDOSE CASES AND DRUG-RELATED CASES

Kind of case	Total morphine concentration $\bar{X}$ ± SD (range)	
	Liver	Kidney
Overdose cases (1.6 μg/ml in blood)	6.551 ± 6.230 (0.030–15.550)	6.901 ± 5.200 (0.130–76.660)
Drug-related cases (0.095 μg/ml in blood)	0.954 ± 1.865 (0.015–7.450)	0.520 ± 0.575 (0.030–2.000)

The average MOR concentrations in the liver and kidneys (Table V) are also greater in both types than those found in the blood, which agrees with Goldberger et al. [4], but there are a great dispersion between the determined values which may help ascertain the elapsed time between ingestion and death.

In 17.3% of the cases, COC and its metabolites were determined (Table VI) in addition to opiates. In all cases, the free concentrations of MOR in blood were greater than 0.2 μg/ml. The average concentrations were higher for COC than for BE. EME was found in all studied cases and presents lower concentrations. In the 4 lethal cases of COC ingestion alone, the averages of COC and BE are shown in Table VII. COC levels were higher than those found when associated to opiates, and these values were greater than BE. Cut-off values of 0.1 μg/ml were considered for both COC and BE. The concentrations that we found are not necessarily the same as those presented by other researchers [2, 11, 16], although they are still within the results mentioned by various authors [6, 8, 15].

TABLE VI. CONCENTRATION [μg/ml] OF DRUGS IN BLOOD IN CASES OF ASSOCIATION OF HEROIN AND COCAINE (n = 30)

Drug	$\bar{X}$	SD	Range

MOR	0.688	0.986	0.200–0.740
COC	0.501	0.723	0.030–35.00
BE	1.050	0.783	0.070–2.350
EME	0.386	0.484	0.001–1.830

TABLE VII. COC AND BE CONCENTRATIONS [μg/ml] IN BLOOD IN CASES IN WHICH ONLY COCAINE ABUSE WAS DETECTED

COC	BE	EME*
$\bar{X} \pm SD$ (range) 22.650 ± 21.991 (7.10–38.20)	$\bar{X} \pm SD$ (range) 3.500 ± 2.121 (2.00–5.00)	

*EME metabolite was detected in all samples.

One body packer was examined, and was found to have a plastic bag in the gastric tube with a large amount of COC. The COC, BE and EME concentrations in the blood were 16.5 μg/ml, 1.6 μg/ml and 1.8 μg/ml, respectively. These COC levels are higher than those reported by Wetli et al. [14] with "Body Packing Syndrome".

CONCLUSIONS

As explained above, it is extremely difficult to evaluate the significance of a concentration of free morphine found in the blood sample of a victim.

Although we considered a cut-off of 0.2 μg/ml of free morphine to determine an overdose, we noted that this parameter does not necessarily apply to all case. Each case must be interpreted with the largest possible amount of data – both analytical data and general information (circumstantial evidence and the presence of complementary products).

We conclude that our assumed criterions is not correct and that it can be used only to diagnose that heroin was the cause of death through the combination of free and conjugated morphine concentrations in blood, its distribution in the liver and kidneys, and the presence of 6-monoacetylmorphine, as well as its association with ethanol and medical substances, and the research on complementary products, even if morphine values in the blood are less than the considered cut-off.

As regards cocaine and its metabolites, the concentrations found in blood are compatible with the values mentioned in deaths by cocaine.

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