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Original article

THE ROLE OF DEXTROMETHORPHAN IN EIGHT FATAL OVERDOSES: IS IT SOLELY A CUTTING SUBSTANCE FOR HEROIN OR COULD IT BE SOMETHING MORE?

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Summary

The Authors evaluate the role of dextromethorphan as heroin adulterant. From December 2010 through April 2013, in our Laboratory of Forensic Toxicology of University of Catania, eight fatal overdose of heroin cut with dextromethorphan were observed. Our first case (December 2010) was the earliest report in Italy. For these reasons we focused our interest on this cutting substance, studying its pharmacological interaction with the depressive morphine action on central nervous system.

Introduction

Widespread public perception is that illicit drugs represent a serious risk to health; however, adulterants are often not considered in clinical or forensic toxicology as contributing to the pharmacological effects.

As is well known, adulterants and diluents are deliberately and fraudulently added to illicit drugs to enhance the total weight of the drug by the pusher. However, while the diluents are inerter substances, such as sugars, the adulterants have pharmacological effects. An adulterant is defined as a foreign or inferior substance that is added to mask the smaller quantity of active substance, imitating its pharmacological effects. They predominantly represent substances which are readily available, such as: caffeine, procaine, paracetamol, etc. These are likely to have minimal impact on users' health at low dosages. Other adulterants, particularly in injectable drugs, have the potential to cause serious health problems [1].

Many adulterants have been identified in heroin samples over the years. One such drug identified recently in heroin is dextromethorphan (DXM).

Most drug-related deaths are attributable to various factors, which sometimes have a reciprocal influence [2]. Indeed, in acute drug intoxication, a particularly low personal degree of tolerance, the presence of particular pathological issues, and the previous or concomitant consumption of other substances may assume significant importance [3].

From December 2010 to April 2013, we recorded 25 heroin-related deaths, eight of

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which showed DXM as heroin adulterant at our Laboratory of Forensic Toxicology of University of Catania. Our first case (December 2010) was the earliest report in Italy [2].
In the same period, the Italian National Early Warning System (NEWS, Department of Antidrug Policy, Presidency of the Council of Ministers) collected numerous warnings from national collaborating centres (forensic laboratories, law enforcement, health services, research centres) related to heroin containing DXM [4].
The Authors here describe eight fatal overdoses from heroin cut with DXM and examine the role of this adulterant in causing death.

Materials and methods

In all cases a complete autopsy and histopathological analysis were performed, which allowed us to exclude traumatic injuries as well as other pathologies or other causes of death. The histological examination established nonspecific findings in the heart and lungs.
Toxicological analysis on the tissue and body fluids collected during autopsy was performed by GC/MS according to the method suggested by Goldberger et al [5]. For the detection and measurement of DXM and methadone a liquid/liquid extraction (LLE) was performed according to the procedure for the extraction pathway for strong bases by Moffat et al [6]. In seven to eight cases plastic cylindrical boxes were seized (Fig.1 A, B).

Results

The results of the toxicological analysis performed on biological samples are shown in Tables 2-3.The analysis of the seized paraphernalia revealed the presence of opiates (acetylcodeine, 6-MAM and morphine), as well as caffeine and dextromethorphan.
The GC-MS analysis of the powder showed the presence of heroin (7.2-9.3% w/w), morphine (0.1-0.2% w/w), 6-MAM (1% w/w). The adulterants identified by GC-MS were paracetamol, dextromethorphan (11.2% - 18.8%) and caffeine.

Discussion

From December 2010 to April 2013, our Laboratory of Forensic Toxicology saw eight fatal overdoses of heroin cut with dextromethorphan as detailed above. For these reasons, we focused our interest on this cutting substance, which is quite unusual compared to the other substances commonly used on the illicit market.
Dextromethorphan is the *d*-isomer of 3-methoxy-N-methylmorphinan (methorphan), a synthetic opiate, analogue of codeine. It acts on the central nervous system (CNS), raising the

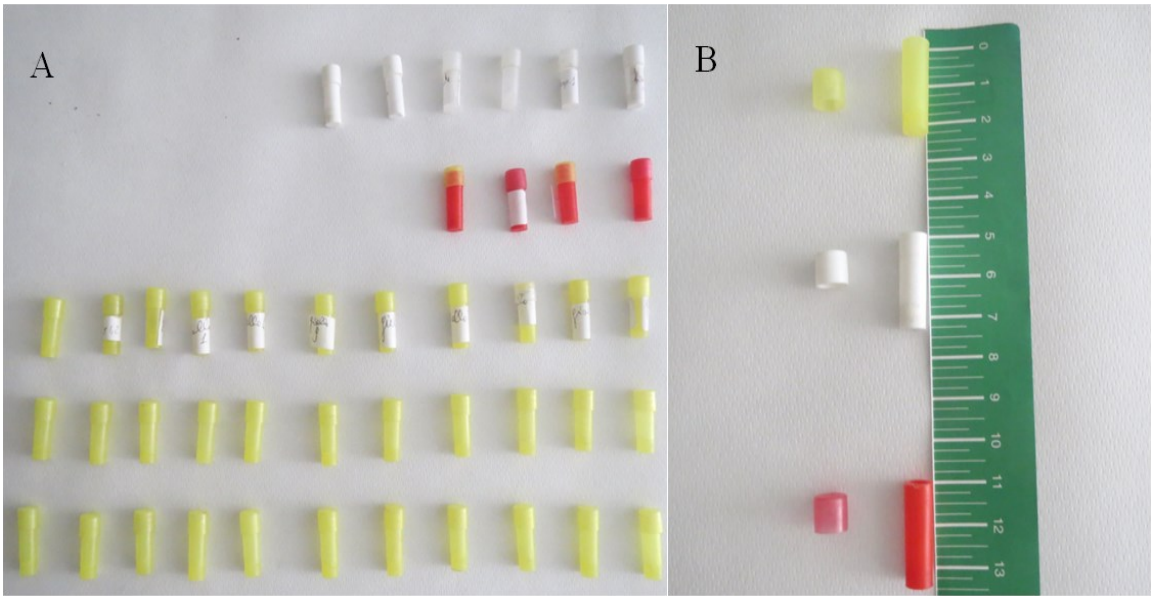

Figure 1 A, B The seized plastic cylindrical boxes.

Cases	Timeline	Sex (Age)	Findings	Significant Pathology Findings	Paraphernalia
Case 1	December 2010	M (33)	Drug addict; Found dead at home by his roommate	Myocardial examination: no atherosclerotic coronary artery disease; hypertensive changes with enlargement of the cardiac nuclei.	2 syringes; 1 bottle of methadone; 3 plastic containers with residues of grey powder
Case 2	March 2011	M (37)	Found dead at home	Liver: portal inflammation (predominantly lymphocytic infiltrate with some plasma cells and occasional neutrophils).	2 bottles of methadone; 2,5 mL syringe with traces of blood; 4 plastic boxes with 35 mg of grey powder
Case 3	July 2011	F (23)	Found dead in her bedroom	Myocardial examination: no atherosclerotic coronary artery disease.	1 spoon with burn marks; 2 syringes; 1 plastic box with 14.5 mg of grey powder
Case 4	February 2012	F (32)	Found dead in her bed	Pulmonary oedema; Myocardial examination: interstitial fibrosis; no atherosclerotic coronary artery disease.	3 syringes; 1 spoon
Case 5	March 2012	M (36)	Found dead by his wife at home	Myocardial examination: localized fibrosis extending to the anterior wall; minor atherosclerotic coronary artery disease.	1 syringe; 1 opened vial; 1 plastic box with residues of grey powder
Case 6	June 2012	M (40)	Found dead in his bedroom	Pulmonary oedema with low protein content. Focal segmental glomerulosclerosis.	43 plastic boxes with traces of grey powder
Case 7	March 2013	M (51)	Found dead in his car	Myocardial examination: minor atherosclerotic coronary artery disease.	1 metal spoon; 1 syringe with traces of blood
Case 8	April 2013	M (38)	Found dead in a country road	Renal pathology: focal segmental glomerulosclerosis; interstitial nephritis with fibrosis.	1 metal spoon; 1 syringe with traces of blood; 1 plastic containers with residues of grey powder

Table 1 Cases description.

	Sample	Mor-phine	Co-deine	6-MAM	DXM	Metha-done	EDDP
Case 1	blood	307.8	49.2	21.15	45.1	n.d.	n.d.
	brain	394.9	96.9	207.1	270.3	48.4	n.d.
	lung	1858.6	231.9	n.d.	1525.2	327.6	41.5
	liver	449.9	38.8	n.d.	235.6	164.5	105.1
	kidney	1916.9	132.4	n.d.	363.6	45.6	n.d.
	gastric content	13106.5	701.9	n.d	181.7	n.d.	n.d.
	vitreous humor	218.3	32.5	131.9	n.d.	n.d.	n.d.
	hair (ng/mg)	0.8	0.1	0.2	n.d.	0.9	n.d.
Case 3	Sample	Mor-phine	Co-deine	6-MAM	DXM	Metha-done	EDDP
	blood	250.7	18.6	n.d.	41.5	n.d.	n.d.
	brain	380.9	36.4	15.3	229.8	n.d.	n.d.
	lung	2102.8	28.1	n.d.	1754.2	n.d.	n.d.
	liver	386.3	15.5	n.d.	193.3	n.d.	n.d.
	kidney	270.2	69.1	n.d.	732.6	n.d.	n.d.
	urine	72.8	n.d.	5.6	n.d.	n.d.	n.d.
	vitreous humor	151.1	15.3	n.d.	12.1	n.d.	n.d.
	hair (ng/mg)	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
Case 7	Sample	Mor-phine	Co-deine	6-MAM	DXM	Cocaine	BZE
	blood	227.4	65.1	11.6	155.7	29.0	1.3
	brain	632.0	102.6	101.9	308.5	10.7	227.3
	lung	1618.3	405.2	35.4	3435.5	n.d.	n.d.
	liver	291.1	40.7	n.d.	77.1	n.d.	n.d.
	kidney	1391.5	107.7	27.1	340.2	n.d.	n.d.
	urine	2830.4	1.3	n.d.	7.2	13.7	2148.5
	gastric content	3861.8	200.1	280.5	n.d.	n.d.	n.d.
	vitreous humor	235.8	155.6	126.5	n.d.	71.4	92.1
	hair (ng/mg)	0.2	0.1	0.1	n.d.	3.4	0.2
Case 8	Sample	Mor-phine	Co-deine	6-MAM	DXM	Metha-done	Cocaine
	blood	271.8	26.5	n.d.	14.9	25.6	n.d.
	brain	848.7	107.5	238.6	30.5	16.7	n.d.
	lung	2254	144.6	n.d.	447.6	306.3	n.d.
	liver	863.8	27.8	n.d.	20.1	200.7	n.d.
	kidney	2651.8	61.7	n.d.	92.3	68.4	n.d.
	urine	2830.4	43.6	n.d.	7.2	115.3	n.d.
	gastric content	1796.9	112.2	5.3	19.2	n.d.	n.d.
	vitreous humor	1048.9	26.6	15.0	n.d.	n.d.	n.d.
	hair (ng/mg)	0.2	0.1	0.3	n.d.	0.6	1.7

Table 2 Cases with short perimortem interval after drug injection: Concentrations of morphine, codeine, 6-MAM, dextromethorphan (DXM), methadone, EDDP, cocaine and benzoylecgonine (BZE) found in organs, fluids (ng/g) and hair (ng/mg) of Cases 1, 3, 7 and 8.

Case 2	Sample	Mor-phine	Co-deine	6-MAM	DXM	Metha-done	EDDP
	blood	60.5	7.9	n.d.	115.9	148.9	33.4
	brain	222.9	7.3	n.d.	127.4	353.5	20.2
	lung	443.3	41.3	n.d.	634.3	2672.2	2282.1
	liver	201.4	11.3	n.d.	35.4	654.6	234.3
	kidney	2180.5	40.8	n.d.	143.1	617.7	27.3
	urine	33297.8	392.1	n.d.	84.1	562.7	22233.5
	hair (ng/mg)	0.6	0.1	0.5	0.2	21.8	n.d.
Case 4	Sample	Mor-phine	Co-deine	6-MAM	DXM	Metha-done	EDDP
	blood	90.8	6.7	0.3	100.2	744.7	n.d.
	brain	239.6	15.2	0.3	459.0	205.3	n.d.
	lung	459.5	34.5	n.d.	980.3	736.2	n.d.
	liver	186.2	16.7	n.d.	841.7	819.4	n.d.
	kidney	128.7	40.00	n.d.	332.0	251.4	n.d.
	urine	5212.6	403.9	3172.7	1303.8	211.35	n.d.
	hair (ng/mg)	n.d.	n.d.	n.d.	n.d.	0.7	n.d.
Case 5	Sample	Mor-phine	Co-deine	6-MAM	DXM	CPZ	Cocaine
	blood	144.1	4.3	1.5	45.1	86.3	n.d.
	brain	212.3	20.2	11.7	120.3	1291.2	n.d.
	lung	233.5	15.9	2.7	232.4	1350.1	n.d.
	liver	241.1	7.3	n.d.	65.6	1590.4	n.d.
	kidney	144.1	5.9	n.d.	201.3	596.3	n.d.
	gastric con-tent	160.2	4.9	2.7	71.0	512.5	n.d.
	urine	97.1	3.1	106.6	45.1	n.d.	n.d.
	vitreous hu-mor	112.4	0.9	26.1	n.d.	n.d.	n.d.
	hair (ng/mg)	n.d.	n.d.	n.d.	n.d.	n.d.	2.8
Case 6	Sample	Mor-phine	Co-deine	6-MAM	DXM	Cocaine	BZE
	blood	52.7	18.6	n.d.	12.4	n.d.	n.d.
	brain	484.4	32.7	n.d.	104.1	n.d.	n.d.
	lung	171.7	56.9	n.d.	168.4	n.d.	n.d.
	liver	537.9	15.8	n.d.	192.8	n.d.	n.d.
	kidney	263.0	14.4	n.d.	85.2	n.d.	n.d.
	hair (ng/mg)	0.3	0.1	0.2	n.d.	0.2	0.1

Table 3 Cases with long perimortem interval after drug injection: Concentrations of morphine, codeine, 6-MAM, dextromethorphan (DXM), methadone, EDDP, cocaine, benzoylecgonine (BZE) and chlorpromazine (CPZ) found in organs, fluids (ng/g) and hair (ng/mg) of Cases 2, 4-6.

threshold of stimulation of the cough reflex effectively to at least equal that of codeine [7]. It interacts with the σ-opioid receptors with resulting antitussive activity, while it does not show any significant affinity for the μ and δ opioid receptors. Dextromethorphan exhibits antitussive activity; as such, it is used in many over the counter products. Following oral administration, it is quickly absorbed from the gastrointestinal tract and rapidly metabolized by N- and O-demethylation with subsequent conjugation with glucuronic acid [8].

The half- life of the parent compound is approximately 2 to 4 hours in people with normal metabolism [9]. Approximately 8% of a dose is excreted as unchanged drug in the urine in 6 hours [6]. DXM is rapidly converted into the active metabolite dextrorphan (DP) in the liver by the cytochrome P450 enzyme CYP2D6 [8]. Moreover, both DXM and its metabolite dextrorphan are reported to inhibit reuptake of serotonin, and to have competitive 5HT1 agonist activity. On this basis, DXM abuse could lead also to serotonin syndrome [10].

This drug is also a potent N-methyl-D-aspartate (NMDA)-receptor antagonist, as are phencyclidine and ketamine.

DXM abuse is well documented in literature [5]. In particular, it is classified among the so-called *recreational drugs* [11] and is known under various street names: *Robo, Skittles, Velvet* [12].

The effects vary with the dose taken and consumers describe a series of dose-related "levels", ranging from a mild stimulant effect with distorted visual perceptions, to a sense of complete dissociation from the body similar to that induced by phencyclidine and ketamine [13].

Typically, these symptoms occur at doses greater than 2 mg/kg; higher doses (> 7 mg/kg) produce dissociative effects of greater intensity. Massive ingestions of the drug may be associated with untoward effects, including tachycardia, hypertension, and respiratory depression [13-14].

Generally, the effects last for 6 hours and are often accompanied by euphoria, ataxia, restlessness and loss of concentration [15].

Despite its widespread abuse, cases of lethal poisoning by DXM are rare and all these cases follow oral intake [16-17]. To the best of our knowledge, in only one other case has DXM been hypothesized to have direct toxic effects playing an important role in causing death, and the authors showed that the methorphan in the seized heroin was pure d-methorphan [18].

Analyzing our eight fatal cases, we evaluated the hypothesis that this cutting substance could have acted through a synergistic or additive effect with the depressive morphine action on CNS. In fact, although the qualitative and quantitative determination of heroin metabolites allowed us to reach a diagnosis of death by overdose, this was not sufficient to clarify the exact pathogenetic mechanism underlying death. For this reason, our attention was focused on two main aspects: the mechanism of action and the route of administration.

It is our opinion that, DXM played a fundamental role in causing death, by increasing central respiratory depression through its action on NMDA-receptors. This hypothesis draws support from numerous published findings. Indeed, experimental studies carried out by Foutz et al. demonstrated that NMDA-receptor antagonists might induce alteration of respiratory rhythm by a decrease in the duration of the expiratory phase, which is dissociated by the duration of the inspiratory phase [19]. It was also observed that the combined blockade of NMDA receptors and non-NMDA receptors can lead inspiratory pause until respiratory arrest in inspiratory phase (apnea) [20]. It is important to highlight that all types of neurons within the medullary respiratory neuronal network are subject to endogenous excitatory activation of glutamate, which is the first mover of the train of action potentials of the respiratory tract that takes place through the sequential activation of NMDA receptors and non-NMDA receptor subtypes [21]. Other studies showed that NMDA-receptor antagonists can dramatically increase the lethality and catalepsy induced by morphine, as well as increase

respiratory depression induced by opiates [22], emphasizing their dangerous interaction with opiates [23].

Therefore, in the eight cases reported herein, the respiratory depression induced by morphine through mu-receptors may have been further enhanced by intravenous co-administration of a NMDA-receptor antagonist as DXM [19].

As far as the route of administration, it is relevant to stress that the available DXM pharmacokinetic data referred only to the oral route of administration, being sold exclusively in products for oral use. Instead, the literature data on the effects of DXM administered intravenously is lacking. The pharmacokinetic parameters of DXM after intravenous (2.2 mg/kg) and oral administration (5 mg/kg) were evaluated in an experimental study on dogs [24]. Kukanich et al. reported that after intravenous administration the concentrations were approximately 1000 ng/mL, while after oral administration peak plasma concentrations did not exceed 100 ng/mL [24]. These results are congruent with preclinical safety data on the acute toxicity of DXM, which showed that the LD_{50} in mice, rats and rabbits require doses ranging between 150 and 350 mg/kg when administered orally; whereas, doses 10 times lower are sufficient (between 15 and 40 mg/kg) when administered intravenously.

On this basis, it is clear that DXM toxicity is approximately 10 times higher when administered intravenously than orally. Hence, immediately after intravenous administration, DXM concentrations were significantly higher than those detected at the time of death, and therefore these concentrations were able to carry the toxic effects of interaction with the heroin.

This is supported by the toxicokinetic evaluation of analytical data. In fact, in most of our cases, DXM blood concentrations are lower than those detected in lung. These findings have to be correlated both with the existence of an agonizing period between assumption and death, and the route of administration.

In cases 1, 3, 7 and 8 the high morphine and DXM concentration found in the lung, led us to establish these deaths occurred a relatively short period of time (less than 90 minutes) after taking heroin. This fact was also confirmed by detection of 6-MAM in the brain and in the vitreous humor.

Cases 2, 4, 5 and 6 were characterized by low morphine blood concentrations compared with those detected in other organs and by no presence of 6-MAM in all samples examined. In these cases, death occurred a relatively long period of time (more than 90 minutes) after heroin injection; this would explain the low DXM concentrations observed.

In conclusion, it should be highlighted that the occurrence of these eight fatal cases coincided with the appearance in the illegal urban market of a particular type of heroin. In fact, in the same period, the police seized several small white plastic boxes containing heroin (7-9% w/w) cut with a variable percentage of DXM and caffeine.

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