

Unpredictable and Unusual Cause of Death Due to Methadone Intoxication: A New Disaster in Healthy Human Being, the Problems of Toxicology Investigation and Pathology Diagnosis: A Case Report

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Objective: To demonstrate the medical morbidity risk factors of methadone intoxication in normal persons and non-opioid-user, and to show that methadone is a new disaster in Thailand.

Case Report: A 35-year-old man was found dead with an unknown cause. No evidence of violence was found at the scene of death. Autopsy confirmed that death was not related to any injuries or diseases. Gross and microscopic pathologies of pulmonary and brain edema were obvious, which were caused by anoxia. No other abnormal evidence of definite pathology was found. In the present case, toxicological analyses of toxic substances and drugs were performed by liquid chromatography-mass spectrophotometry-mass spectrophotometry (LC-MS-MS) and found that the blood methadone concentration was at the lethal concentration. Therefore, the cause of death in this case was methadone toxicity. The blood concentrations of methadone and 2-ethylidene-1, 5-dimethyl-3,3-diphenylpyrrolidine (EDDP) were 1.9 µg/ml and 0.058 µg/ml, respectively. The concentration ratio of methadone and EDDP was 32.7:1, which was more than the previous death cases of methadone toxicity. The other addictive substances, such as heroin, morphine, cocaine, or ethanol, were not detected in the present case by LC-MS-MS.

Conclusion: Methadone was the cause of death in this case. There was no evidence of other causes of death, especially other opiates or opioids substances. This is a big problem, because methadone is used as the substitute for heroin addiction in Thailand. The authors claim that it will be the new disaster substance and become an important cause of death in Thailand and other parts of the world, because it has been prescribed worldwide for patients undergoing a program of opioid maintenance treatment (OMT). Methadone is not controlled well. The authors demonstrated that the deceased was not in the OMT program, and the cause of death was methadone intoxication, which was a very rare case.

Keywords: Methadone, Opioids, EDDP, Morphine, Ethanol, Drug substitution

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Gustav Ehrhart and Max Bockmühl synthesized methadone in Germany from 1937 to 1939^(1,2) and was approved in the United States in 1947⁽³⁾. Methadone

is the most effective and safest drug used in opioid maintenance treatment (OMT) programs⁽⁴⁾, and was on the World Health Organization's List of Essential Medicines.

The World Health Organization (WHO) recommendation and many studies showed that methadone was the most effective for OMT^(2,3,5-7). According to many studies of Methadone treatment programs, the recommendation dosage is 80 mg per day and an average of 0.4 mg per L blood concentration, which ensure that the outcome of the treatment is very good^(1,2,8).

The metabolite methadone is effective for up to six hours⁽³⁾. In long term use, the effects lasted between 8 and 36 hours in normal people^(3,5). Two-ethylidene-1, 5-dimethyl-3,3-diphenylpyrrolidine (EDDP) is the principle metabolite of methadone and

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it is an important evidence to diagnose the cause of death⁽⁹⁾. The mean ratio of methadone, the metabolite of methadone, to EDDP in the blood has been 13.6:1. Values were not significantly different between cases in which methadone toxicity was the cause of death, and in those where it was an incidental finding⁽¹⁰⁾.

Fatal toxicities are respiratory failure, prolonged QT interval, and cardiac arrhythmia⁽⁵⁾. Most cases of methadone poisoning occurred in persons who were not participating in OMT programs^(11,12). Approximately 82 percent of deaths have occurred from methadone and the most common manner of death was accidental. However, benzodiazepines were the most common combined drugs in the cases of methadone intoxication and death^(13,14). Methadone intoxication was the most common opioid found as a single drug⁽¹⁵⁾. The most common drug of use and related death was heroin 42.4% and methadone related death was 3.8%⁽¹⁶⁾. There were heroin and methadone deaths in Sweden, England, and Wales between 2000 and 2011⁽¹⁷⁻¹⁹⁾. The middle-aged men had the highest rates⁽²⁰⁾. Several studies showed that the prescription-related deaths and prescribing patterns were the most common problems in the OMT programs⁽²¹⁻²⁸⁾.

The data of methadone related deaths were previously studied and defined by a Substance Abuse and Mental Health Services (SAMHSA) consensus panel⁽²⁹⁾. Methadone intoxication alone with death is very rarely reported⁽³⁰⁾. The reference of lethal concentration of methadone did not differ significantly between methadone intoxication only and concomitant with other non-drug related causes of death^(31,32).

However, the median lethal concentration of methadone (MLCM) intoxication reported in many journals were that the MLCM of decedents in OMT and not in OMT were 0.06 to 2.0 mg/L and 0.07 to 0.62 mg/L^(30,33-37), respectively.

Case Report

A 35-year-old male was found dead by the police at the rental home. The death was classified as unnatural and unexpected causes. The autopsy was performed at the Department of Forensic Medicine, Faculty of Medicine, Chiang Mai University, Thailand.

The postmortem timing was two to four hours after death and there was a mild contusion at the right eye. The internal organs showed no evidence of cerebrovascular accident, acute myocardial infarction, malignancy, exsanguination, or other natural diseases. The right and left lung weighted

446 and 360 grams, the heart weighted 287 grams, and no abnormal pathologic lesions were seen. Pulmonary and brain edema were obviously found in this case. Blood, vitreous humors, urine, and gastric content were analyzed, using liquid chromatography-mass spectrophotometry-mass spectrophotometry (LC-MS-MS) to assess the presence of heroin, 6-monoacetylmorphine (6-MAM), morphine, and other metabolites. The system used was an Agilent Technologies 6,460 Triple gaud LC/MS with Column of Eclipse Plus C18 1.8 μ m 2.1 \times 100 mm. The specimens (100 ml of femoral blood, 100 ml of urine, and 2ml of vitreous humor) were collected from the corpse and preserved in the refrigerator at below four degrees Celsius and analyzed by LC-MS-MS. The etiology of death of this man was unknown at the time of the investigation. The results are shown in Table 1.

The limit of quantification (LOQ) for the methods was approximately five times lower than the administrative cut-off limit of 0.060 mg/L. All results under 0.060 mg/L were rejected. Proficiency testing was performed twice annually and an acceptable quality for methadone was documented. Toxicological data were obtained from the Departments of Forensic Medicine. Since heroin, 6-MAM cannot be directly detected in body fluids, the presence of methadone was confirmed during postmortem examination.

Results

The presence of methadone was demonstrated in the blood and urine. The present study found that methadone and its metabolite (EDDP) could be detected in blood by LC-MS-MS (Table 1). The results can be important and provide decisive evidence in the justice system⁽¹⁾.

Analysis strategy

The samples of methadone overdose and related death were investigated in the corpse. Variables potentially associated with detection of non-prescribed methadone were estimated by logistic regression⁽³⁸⁾. Methadone concentration in the blood was 1.9 mg per L and EDDP was 0.058 mg per L. The ratio between methadone and EDDP was 1.9:0.058=32.8, which was much more than the cases caused by methadone only.

Discussion

Methadone related deaths are increasing because of high incoming doses, increased dosages, and interaction with other drugs. In the United States, patient education and increased clinical vigilance are essential during the process of methadone induction to

Table 1. LC-MS/MS: Agilent Technology 6460 Triple Quad LC/MS Column: Eclipse Plus C 18 1.8 um 2.1×100 mm

Substance	Precursor ion	Product ion	Polarity
Morphine	286.2	165.1	Positive
	286.2	152	
6-MAM	328.2	165.1	Positive
	328.2	43.1	
Codeine	300.2	165.1	Positive
	300.2	128	
Methadone	310.2	265.1	Positive
	310.2	105	
EDDP	278.2	234.1	Positive
	278.2	219.1	

Sample	Analysis			
	Substance	Result	Method	Sensitivity
Femoral blood	Ethanol	Negative	GC-HS	LOQ 10 mg% LOD 5 mg%
Heart blood	Methadone	1.9 mg/L	LC-MS-MS	>LOQ (0.06 mg/L)
	EDDP	0.058 µg/ml	LC-MS-MS	
	EDDP	0.058 mg/L		
	Morphine	Negative	LC-MS-MS	
	Methamphetamine	Negative	LC-MS-MS	
	Benzodiazepines	Negative	LC-MS-MS	
	Cholinesterase enzyme	9,087 U/L	Spectrophotometry	
Vitreous humor	Ethanol	Negative	GC-HS	LOQ 10 mg% LOD 5 mg%
Gastric content	Phenothiazines	Negative	FPN reagent	25 mg/L
	Cyanide	Negative	Prussian blue test	10 mg/L
	Paraquat	Negative	Dithionite test	2 to 5 mg%
	Arsenic/zinc phosphide	Negative	Gutzeit's test	2 to 5 mg/L
	Urine	Morphine	Negative	Immunoassay
Methamphetamine		Negative	Immunoassay	1.0 mg/L
Tricyclic antidepressant		Negative	Immunoassay	1.0 mg/L
Benzodiazepines		Negative	Immunoassay	0.30 mg/L
Cocaine		Negative	Immunoassay	0.30 mg/L
Phenothiazines		Negative	Immunoassay	0.30 mg/L
Methadone		Positive	LC-MS-MS	1.0 mg/L
EDDP		Positive	LC-MS-MS	25 mg/mL

6-MAM=6-monoacetylmorphine; EDDP=2-ethylidene-1, 5-dimethyl-3,3-diphenylpyrrolidine; GC-HS=gas chromatographic-headspace; LC-MS-MS=liquid chromatography-mass spectrophotometry-mass spectrophotometry; LOQ=limit of quantification; LOD=limit of detection

reduce the risk of overdose or death related to OMT⁽³⁹⁾. According to an American study, the proportion of methadone-related deaths increased by 300% between 2001 and 2006. The subjects that took methadone for heroin dependence accounted for an insignificant number of methadone related deaths⁽⁴⁰⁾. If methadone became more widely available, opportunities for

diversion from treatment programs will increase and so will the number of deaths. However, awareness of increased opioid-related deaths with increased opioid prescription has been related to the maintenance programs⁽²⁵⁾. Kenan et al reported that the number of opioid prescriptions increased by 35.2% and higher opioid dosage was associated with a higher risk of

overdose^(26,28).

Benzodiazepines drugs have been added in the OMT program and it is very dangerous because its synergistic effect with methadone toxicity and deaths^(22,41). The Drug Abuse Warning Network reported that admissions to hospital for benzodiazepine and opioids toxicity were higher than with benzodiazepines alone⁽⁴¹⁻⁴³⁾. The American Society of Interventional Pain Physicians has recommended that benzodiazepines with opioids were contraindicated and caused increased deaths^(15,41,44,45). Alprazolam was the most common in the case of benzodiazepines death and clonazepam was the most common prescription⁽⁴⁶⁾.

However, the younger users of methadone (mean age 34 years) who were not participated in an OMT program had a greater risk of dying in methadone-related causes. Many diseases may also play a significant role. The MLCM in corpses with deaths ascribed to methadone alone and multiple additional drugs were 0.09 mg per L and 0.06 mg per L, respectively⁽³⁰⁾.

Post-mortem redistribution of methadone concentration is a principle problem^(10,47-49) that is varied and complicated in forensic toxicological assessment. The postmortem concentration of methadone increases approximately 20% in blood after death because it is lipid soluble^(48,50).

The authors still cannot find any solution to prevent prescription-related deaths. However, using data, providing good communication, methadone prescribing precautions, established standards for chronic prescriptions, and decreasing opioid and benzodiazepine combinations are highly recommended. The programs of paying for prescription may be very dangerous and the patients may end up death⁽¹⁸⁾. There is an overlap between therapeutic and lethal methadone concentrations. Caution must be taken in documenting lethal concentrations because postmortem redistribution is very important. Pathologists and toxicologists should carefully examine all postmortem evidences in identifying causes of death.

Methadone can be distributed from other tissues to the blood and from the blood to other tissues. This contribute to the problems of determining an accurate concentration of methadone relating to cause of death. The site dependence and postmortem redistribution are problems of concern. However, complete autopsy, pathological examination, and toxicological findings are very advantageous for diagnosis. The pathologists are satisfied that methadone related cause of death are

not over estimated^(34,51).

The diagnosis of methadone poisoning as a cause of death should be of significant concern because the concentration recommended for the OMT program was more than the group of deaths that were described as methadone intoxication⁽⁵²⁻⁵⁴⁾. Postmortem with methadone related deaths only reported blood concentrations below 0.4 mg per L. However, the MLCM only-related deaths were 0.435 mg per L. The MLCM only group was more than the combination in the additional drugs death group⁽³⁴⁾.

Hair analysis is an effective and important method helping to diagnose fatal methadone intoxication or drug use before death in the case of decomposed corpses to support the evidence of a lack of tolerance to opioids implicated. If both methadone and morphine test negative in analysis, it means that tolerance to opiates can be excluded. Methadone may be the cause of death in the cases when ethanol or other psychoactive drugs are not found⁽¹⁹⁾.

Conclusion

Methadone only related deaths are very rare, especially in non-OMT. The MCLM with additional drugs and substances was below lethal levels of methadone intoxication only. However, the MCLM that were below 0.1 mg per L, may be associated with fatal intoxication in both groups. A combination of methadone and alcohol or psychoactive drugs may have an increased risk of death. The underlying diseases were common and significantly concomitant with increasing severity and intoxication. Studies showed that therapeutic concentrations of methadone may be the cause of death when the drug is abused in normal persons and naïve users⁽⁴⁹⁾.

The patients who received excessive starting doses or methadone with take-home doses during the induction phase of OMT died in many cases. The abuse of methadone was usually found in persons who took methadone by themselves. More care must be taken during induction of methadone treatment because tolerance to opiates is unknown⁽¹⁹⁾.

Take-home doses of methadone could be dangerous, if there were children living in the house and the drug was not safely stored⁽⁵⁰⁾.

In the present case study, the authors concluded that methadone intoxication was the only cause of death in non-opioid-maintenance therapy. This was a very rare case in the general population. However, the authors believe that methadone intoxication will be a very common cause of death, because it is prescribed easily and freely to addicted patients and it is not well

controlled. Methadone may be the new disaster drug.

What is already known on this topic?

Methadone will be the new addict substance and it will be a big problem, if the management of OMT is not efficient.

What this study adds?

The collaboration of institutes that manage the OMT program must be concerned about the efficacy of methadone for heroin substitution.

Conflicts of interest

The authors declare no conflict of interest.

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