

## Methadone overdose in patients following methadone maintenance treatment: A three years overview in the district of Bari (South-Italy)

M. Favia<sup>1</sup>, I. Santoiemma<sup>1</sup>, Q. Mita<sup>1</sup>, G. Strisciullo<sup>1</sup>, F. Introna<sup>1</sup>, A. De Donno<sup>1</sup>

<sup>1</sup>Department of Legal Medicine, University of Bari, Bari, Italy

### Abstract

**Background.** Methadone maintenance treatment (MMT) is recognized as a reference treatment for opioid dependence. According to Italian Law, at the beginning of the treatment patients must receive medication under the supervision of a physician, to avoid overdose. After a period of stability, patients could be allowed to take methadone at home in pre-arranged and personalized concentrations, in order to empower their self-responsibility. The aim of the present investigation is to underline the presence of a “glitch in the system” of the MMT.

**Methods.** In the last three years, 7 forensic autopsies and toxicological analysis on corpses of regular opioid users were performed into the Institute of Legal Medicine of Bari.

**Results.** In all these cases very high methadone concentration in blood were found. All the 7 subjects were following a MMT in a Public Health Institute and the cause of death was respiratory depression by overdose of methadone in 6 cases.

**Conclusion.** Therefor an improvement of the MMT's guideline is needed to reduce methadone overdose deaths in future. *Clin Ter* 2021; 172 (3):247-249. doi: 10.7417/CT.2021.2323

**Key words:** Methadone overdose, Methadone maintenance treatment, Guidelines

### Introduction

Methadone is an opioid, like heroin or opium. Opioid maintenance treatment with methadone or buprenorphine decreases illicit opioid use and reduces morbidity and mortality among opioid dependent individuals. These substances can give people with a heroin dependence an opportunity to cut back on their heroin consumption and improve their life situation. Like morphine, methadone is an agonist at the  $\mu$ -opiate receptor, but its longer elimination half-life and improved oral bioavailability make it an attractive alternative for pain medication as well as Methadone maintenance treatment (MMT) programs. MMT is established in many countries as the treatment of choice in opiate addiction,

but methadone related overdose deaths can occur among individuals receiving legally prescribed methadone or among persons using illegal diverted methadone. However, methadone is now well recognized as a significant poison in both opiate addicts and in other subjects who are exposed to diverted methadone. Cases of methadone overdose in patients following MMT are already described in the existing scientific literature (1,2,3,4,5,6). Since the start of methadone programmes and the increase in prescriptions for methadone, reports have appeared detailing methadone deaths. In early studies, the problems of inappropriate prescribing and uncontrolled dispensation were identified. The later studies have identified the problems of naive users, highlighting the deaths of those entering methadone programmes and those who have obtained diverted methadone. (7)

According to Italian Law, at the beginning of the treatment patients must receive medication under the supervision of a physician, to avoid overdose. After a period of stability, patients could be allowed to take methadone at home in pre-arranged and personalized concentrations, in order to empower their self-responsibility.

It has been estimated that plasma methadone levels should be at least 0.05-0.10 mg/L (50-100 ng/ml) to prevent withdrawal symptoms in narcotic maintenance patients. In methadone maintenance subjects, the mean blood level of methadone is around 110 ng/ml. Detected average concentration of methadone was 280 ng/ml in 59 victims of fatal methadone overdose (range 0.06-3.1). (8)

Methadone is largely metabolized by mono and di-N-demethylation, with spontaneous cyclization of the resulting unstable metabolites to form 2-ethylidene-1,2-dimethyl-3,3-diphenylpyrrolidine (EDDP) and 2-ethyl-5-methyl-3,3-diphenylpyrroline (EMDP).

In some cases, it may be useful to quantitate EDDP concentrations, as the presence of the metabolite in substantial amounts may indicate prior usage of the drug and therefore tolerance to its effects, although the organs relative amounts of methadone and EDDP would of course also depend on survival times after administration.

## Material and methods

In the last three years, 7 forensic autopsies, histological and toxicological analysis on corpses of regular opioid users were performed into the Institute of Legal Medicine of Bari.

Six of them were found dead in their home, in four cases with empty and loaded syringes next to their body and multiple track marks over the body. In case number 3 the subject died from a stabbing, but she also was following MMT. Both Methadone (MTD) and its metabolite (2-Ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine EDDP) were identified and quantified by gas chromatography-mass spectrometry (GC/MS) analysis on an Agilent 6890 GC coupled 5973 inert mass spectrometer, previous liquid-liquid extraction (LLE) from cadaveric blood by organic mixture solvents at pH 9.0. The amount of sample for analysis was 1 ml.

## Results

Autopsies revealed the presence of hepatic steatosis and bronchopneumonia in the case 2 and cirrhotic liver in the case 7. They are not specific signs but, according to literature, liver damage can decrease methadone metabolism. (9)

Histological examinations didn't show any specific alterations.

No other noteworthy signs were found in order to establish the cause of death.

In all these cases very high methadone concentration in blood were found:

- Case 1: 785 ng/ml
- Case 2: 1356 ng/ml
- Case 3: 1188 ng/ml
- Case 4: 626 ng/ml
- Case 5: 983 ng/ml
- Case 6: 378 ng/ml
- Case 7: 4643 ng/ml).

Toxicological analysis also showed very high concentration of EDDP in blood:

- Case 1: 1494 ng/ml
- Case 2: 2790 ng/ml
- Case 3: 1565 ng/ml
- Case 4: 1233 ng/ml
- Case 5: 490 ng/ml
- Case 6: 1012 ng/ml
- Case 7: 5880 ng/ml.

The average blood level of methadone in these cases was 1422 ng/ml, against 2066 ng/ml of EDDP. In the third case, also cocaine was found. No other substance of abuse were found in the other cases. (Fig. 1)

## Discussion

Overdose with methadone is characterized by stupor, muscle flaccidity, respiratory depression, cold and clammy skin, miosis, hypotension, coma, and circulatory collapse. The primary mechanism contributing to fatal opioid overdose is respiratory depression and concurrent use of other central nervous system (CNS) depressants such as benzodiazepines elevates the risk of overdose. In severe overdose, apnea, cardiac arrest and death may occur. The onset of a coma represents the effect of the opioid blocking the brain acetylcholine receptors in the ascending reticular activating system. Even at low doses, methadone may cause somnolence and coma in elderly or debilitated patients because of the exaggerated plasma level seen in these patients.(10) The main cause of overdose is respiratory depression with pulmonary edema, developing 12 to 14 hours after ingestion especially in naive or weakly tolerant individuals. The edematous reaction is very commonly severe leading to aspiration pneumonia and death from respiratory failure. (11)

According to literature, the most frequent finding at the autopsies was nonspecific asphyxia death signs. (5) No

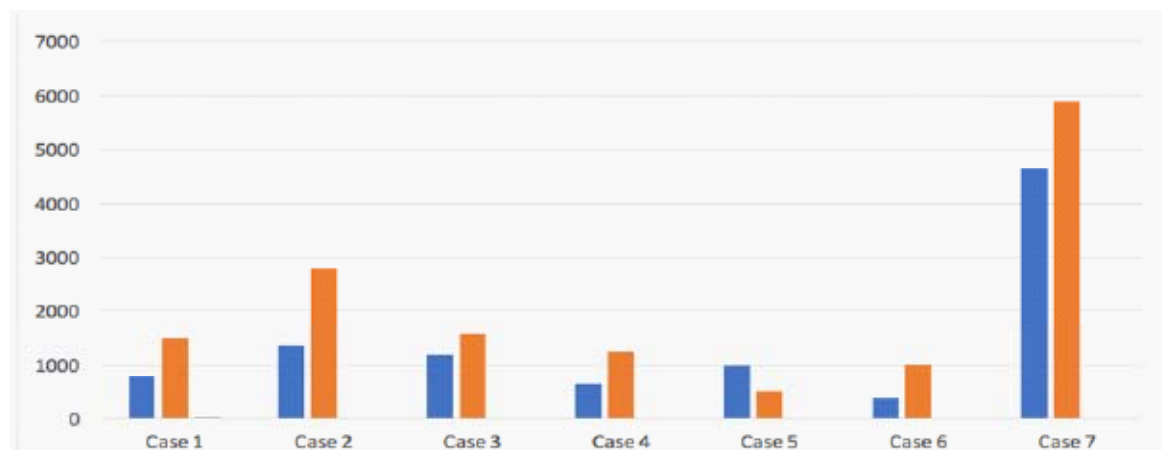


Fig. 1. Methadone and EDDP concentrations in all the cases.

histological features specific for methadone overdose deaths are described in literature.

After performing autopsy and ancillary analysis, it was possible to conclude that the cause of death was respiratory depression by overdose of methadone in 6 cases. In the cases described in this study no other substance of abuse were found, apart from the third case that showed both methadone and cocaine abuse. All the 7 subjects were following a MMT in a Public Health Institute. Even though the methadone related death in patient following MMT was already known in Italy, we have registered in our district 7 cases just in the last three years. The risks associated with methadone intake are often underestimated by clinicians prescribing the drug: sometimes methadone is prescribed without taking into account patient's tolerance to opiates, and a large number of subjects enrolled in methadone maintenance programs in Italy, have also been given take-home doses, thus increasing the risk of abuse and diversion. (4)

Fatalities in adults from methadone overdose have increased significantly in many urban areas as a result of the widespread availability of the drug, both from licit and illicit sources. Sometimes patients do not take the drug regularly or sell their doses, taking methadone only when heroin is not available.

In Italy, take-home doses are largely prescribed and include up to 75% of patients following the maintenance treatment. (12)

The causes of methadone diversion in Italy is still not clear. The most probable source of methadone is the black market. In fact, a study carried out by Rees Davis and Bruce Johnson (13), revealed that 60% of subjects on methadone maintenance in New York City used to sell their doses, and other persons in treatment could then imply more methadone diverted from the programs. This work has demonstrated the need for further research among patients following MMT in order to clarify understanding of their methadone use and misuse.

The data also suggest the importance of learning more about how the patients can sell methadone evading the control measures of MMT.

## Conclusions

An improvement of the Italian MMT's guideline is needed to reduce methadone overdose deaths in future. We observed that abuse of illegally obtained methadone, often by patients who were allowed to take it home, is rather common. The authors suggest delivering methadone under strict medical control, not only to avoid cases of overdose but also the possibility that opioid users following the MMT sell methadone on the black market. A strict monitoring of the drug concentration in the blood of the addict attending MMT in order to assess adherence to the medical plan is also recommended.

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