



K28 Methadone Overdose in Patients Following Methadone Maintenance Treatment: An Italian Issue

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Learning Overview: The goal of this presentation is to increase awareness of the problem of overdose deaths in patients following Methadone Maintenance Treatment (MMT) in Italy.

Impact on the Forensic Science Community: This presentation will impact the forensic science community by underlining the importance of developing new guidelines in methadone maintenance treatment for opioid-addicted patients in order to avoid overdose deaths.

Methadone is an opioid like heroin or opium. MMT is recognized as a reference treatment for opioid dependence. Cases of methadone overdose in patients following MMT are already described in the existing scientific literature.

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

It has been estimated that plasma methadone levels should be at least 0.05mg/L–0.10mg/L (50ng/ml–100ng/ml) to prevent withdrawal symptoms in narcotic maintenance patients.

In methadone maintenance subjects, the mean blood level of methadone is around 110ng/ml. Detected average concentration of methadone was 280ng/ml in 59 victims of fatal methadone overdose. 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-diphenylpyrrolidine (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.

In the past year, five forensic autopsies on corpses of regular opioid users were performed at the Institute of Legal Medicine of Bari, Italy. Four were found dead in their homes. In two of those cases, there were empty and loaded syringes next to their bodies and multiple track marks over the bodies. In one case, the subject died from a stabbing, but she was following MMT.

In all these cases, very high methadone concentrations in blood were found (785ng/ml, 1,356ng/ml, 1,188ng/ml, 626ng/ml, 983ng/ml). Toxicological analysis also showed very high concentrations of EDDP in blood (respectively 1,494ng/ml, 2,790ng/ml, 1,565ng/ml, 1,23 ng/ml, 490ng/ml). The average blood level of methadone in these cases was 987.6ng/ml, against 1,514.4ng/ml of EDDP. 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, following Liquid-Liquid Extraction (LLE) from cadaveric blood by organic mixture solvents at pH 9.0. The amount of sample for analysis was 1ml.

Overdose with methadone is characterized by stupor, muscle flaccidity, respiratory depression, cold and clammy skin, miosis, hypotension, coma, and circulatory collapse. After performing an autopsy and ancillary analysis, it was possible to conclude that the cause of death was respiratory depression by overdose of methadone in four cases. In the cases described in this study, no other substance of abuse was found, apart from the fifth case that showed both methadone and cocaine abuse. All five subjects were following an MMT in a public health institute.

Fatalities in adults from methadone overdose have increased significantly in many urban areas because of the widespread availability of the drug, both from licit and illicit sources. An improvement of the MMT's guideline is needed to reduce future methadone overdose deaths. This study suggests delivering methadone under strict medical control, not only to avoid cases of overdose, but also the possibility that opioid users following MMT are selling methadone on the black market. A strict monitoring of the drug concentration in the blood of the addict attending MMT to assess adherence to the medical plan is also recommended.

Methadone, Overdose, Methadone Maintenance Treatment