



Methadone Related Deaths: Identifying the Vulnerable Patients

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Abstract

Methadone has been used in opioid dependence treatment since the 1960s and is now prescribed also as a chronic pain treatment. Even though its effectiveness has been worldwide assessed, literature reports several cases of death associated with the administration of this drug. Risk factors are still uncertain and the frequent combination with other substances of abuse makes it even more difficult to determine the exact role of methadone in the pathogenesis of fatalities. In this paper the authors present the autopsy findings in a subset of deaths characterized by blood being positive for the methadone only at a therapeutic dose in order to point out those pre-existent pathologic conditions that seem to increase the risk of death in methadone treatment.

A routine screening test for a broad spectrum of drugs in urine samples (including methadone, benzodiazepines, cocaine, amphetamines/methamphetamine, opioids, barbiturates, tetrahydrocannabinol, tricyclic antidepressants) using the ASCENDTM Multi-immunoassay kit (TriageTM8 - Merck®) was performed in all cases of suspected drug-related death, which occurred in the East side of Rome during 2011 (a total of 104 subjects; 73 % male; 27 %female; mean age 32 years old). Among all the subjects examined, 51 were positive for methadone but only 8 belonging to this subset were negative for any other tested drug. A complete autopsy and histological examination was performed in cases where methadone was detected alone and the results were analysed. The histological findings and our observations demonstrated pre-existing conditions affecting the heart and lungs and/or the liver suggesting the importance of an accurate screening/follow up focused on these organs prior to and during treatment in order to promptly identify the presence/onset of clinical conditions increasing the patient's vulnerability to methadone treatment.

Introduction

Methadone is a full μ -opioid agonist that inhibits monoamine reuptake and N-methyl-D-aspartate receptors. It is metabolized in the liver by the P450, CYP3A4. It is a weak inhibitor of the C3A4 system and a minor weak substrate of 2C89, 2C19 and 2D6 [1,2]. Since the 1960s it has been used to treat heroin addiction [3]. Several studies have shown Methadone Maintenance Treatment (MMT) to reduce crime, HIV seroconversion and risk of death when compared to illegal heroin abuse, though in recent years its increased use not

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only in MMT but also in chronic pain management has evidenced methadone's negative aspects, such as adverse effects and related deaths. The worldwide diffusion of the substance justifies testing for its presence during the routine toxicological analysis performed on urine and blood samples collected during forensic autopsies, but establishing whether its administration is involved in the pathogenesis of death or not, is far more complicated [4-12]. Where multiple substances are detected, it may not be possible to identify which substance was the principal cause of poisoning, and hence, mentions of methadone on the death certificate may be incidental [13].

Unlike other drugs, the lethal concentration in blood is uncertain as the range varies from 0.4 to 4.07 $\mu\text{g/ml}$, with a median concentration of 1.0 $\mu\text{g/ml}$ (Table 1); it appears to be influenced by several individual factors such as age, P450 polymorphisms (perhaps related to the genetic polymorphisms of the C3A4 system), liver and kidney function, while the way of administration (oral or i.v) doesn't seem to make any difference. More over most of the times methadone is detected together with multiple substances (e.g. alcohol, benzodiazepines, amphetamines, other opioids.).

In order to overcome the lack of knowledge about the lethal effect of methadone alone and with the aim of highlighting the influence of individual risk factors, such as preexistent conditions, in increasing the risk of death during methadone administration, we decided to concentrate on the cases in which the post mortem toxicological analysis detected methadone alone.

Even though such findings aren't common among all the cases in which methadone can be found, its study may provide a valuable contribution to understanding the role of methadone in the causation of death. The importance of such knowledge is easier to understand considering that now, more than ever, the widespread use of methadone on medical prescriptions implies a growing responsibility of the doctor when adverse events occur (Table 1).

Materials and Methods

A routine screening test for blood alcohol using headspace

Table 1: Lethal blood concentrations of methadone reported in literature.

Author	Blood Methadone Concentration ($\mu\text{g/ml}$)
Robinson AE et al 1971	0,2-3,0
Irey NS et al 1974	0,2-4,05
Segal RY et al 1974	0,1-2,6
Drummer OH et al 1992	0,3-2,9
Barrett DH et al 1995	1,0-2,0
Clarck JC et al 1995	0,2-1,8
Milroy CM et al 2000	0,58
Winec CL et al 2001	0,4-1,8
Musshoff E et al 2003	0,03-4,07
Drummer OH 2004	1,0
Couper FJ et al 2005	0,67

gas chromatography and the search of a broad spectrum of drugs on urine samples (including methadone, benzodiazepines, cocaine, amphetamines/methamphetamines, opioids, barbiturates, tetrahydrocannabinol, tricyclic antidepressants) using the ASCENDTM Multi-immuno-assay kit (TriageTM8 - Merk®) was performed in all cases of suspected drug-related death, which occurred in the East side of Rome during 2011 (a total of 104 subjects; 73% male; 27 %female; mean age 32 years old). Among the cases tested positive for methadone, only the ones in which the drug was detected alone were considered for the purposes of this study.

Gas Chromatography - Mass Spectrometry (GC-MS) was used for quantifying the substance in whole blood.

Autopsy was performed and completed by collecting specimens of the organs for histological analysis. Where there was no macroscopic evidence of organ lesion requiring special observation, the specimens were collected according to the following scheme: 1 from the brain, 4 from the heart (right anterior ventricular wall, free ventricular wall, left ventricular wall, septum) 1 from each pulmonary lobe, 1 from the liver, 1 from the pancreas, 1 from each kidney, 1 from the spleen. A routine microscopic histopathological study was performed on specimens fixed by using buffered formalin 10%, embedded in paraffin and stained with haematoxylin/eosin. All specimens were examined with a light microscope (DMLB 100T Leica, Wetzlar).

Autopsy was performed in every case and was completed by collecting specimens of the organs for histological analysis. Where there was no macroscopic evidence of organ lesion requiring special observation, the specimens were collected according to the following scheme: 1 from the brain, 4 from the heart (right anterior ventricular wall, free ventricular wall, left ventricular wall, septum) 1 from each pulmonary lobe, 1 from the liver, 1 from the pancreas, 1 from each kidney, 1 from the spleen. A routine microscopic histopathological study was performed on specimens fixed by using buffered formalin 10%, embedded in paraffin and stained with hematoxylin/eosin. All specimens were examined with a light microscope (DMLB 100T Leica, Wetzlar).

In each case, information about the circumstances of death and the clinical history, with particular referral to the drug abuse habits, was collected.

Results

During a 1 year period, the authors examined 104 apparent or suspected drug-related deaths. Among all the subjects examined, 51 (49%) tested positive for methadone. Within this subset, 8 (7,7% of total; 15,7% of subjects tested positive for methadone; 6 male; 2 female; mean age 34,8 – range between 21 and 45 years old-) tested negative for any other substance.

Only the eight that tested positive for methadone only were included in our study. The analysis of circumstantial data revealed that all 8 subjects tested positive for methadone alone, had a long history of opiate addiction and were following an Opioid Maintenance Treatment Program. None of the patients was a naïve user; they were all receiving a stable daily dose in a range between 100-150 mg.

3 died out in the street, 2 died in a private home, 1 died in a car and 2 died in prison.

In the cases in which methadone was detected alone, Gas Chromatography - Mass Spectrometry (GC-MS) was used for quantification in whole blood (Table 2).

Among the 8 cases examined, 7 showed a blood concentration of methadone in a range between 0.5 and 0.9 µg/dL consistent with treatment for therapeutic purposes of 100-150 mg/die of methadone, during MMT. In one case (Case 1 - Table 2 the blood concentration of methadone (17 µg/mL) highly exceeded this range and was consistent with an acute intoxication. Further analysis of the circumstantial data indicated that the deceased had received the methadone for a complete month of treatment a few days earlier and had suicidal intent.

In each case that met our inclusion criteria, both the autoptical and histological findings demonstrated pre-existent conditions affecting the heart and lungs and/or the liver.

Table 2: Table showing blood concentration and pathological findings in cases in which methadone was detected alone.

Case Number	Provenance	Age	Gender	Methadone Hematic Concentration	Use	Pathological findings
1	Street	41	F	17 µg/ml	Therapy	Heart: Hypertrophic Cardiomyopathy Lungs: massive Bilateral Bronchopneumonia Liver: micro and macro nodular hepatic cirrhosis.
2	Jail	26	M	0.7 µg/ml	Therapy	Patient in treatment for a congenital hydrocephalus, secondary to a subtentorial cerebral malformation. Lungs: bilateral bronchopneumonia with evidence of inhalation of food material.
3	Car	45	M	0.9 µg/ml	Therapy	Heart: dilative cardiomyopathy with histological evidence of cardiac cellular necrosis. Lungs: bilateral bronchopneumonia. Liver: active chronic hepatitis.
4	Home	21	M	0.5 µg/ml	Therapy	Heart: rheumatic Heart Disease. Lungs: bilateral bronchopneumonia. Liver: Active Chronic Hepatitis.
5	Street	33	M	0.8 µg/ml	Therapy	Heart: hypertrophic cardiomyopathy with evidence of sclerotic areas. Mitral heart valve replacement surgery.
6	Jail	28	M	0.6 µg/ml	Therapy	Heart: hypertrophic cardiomyopathy. Lungs: bilateral bronchopneumonia.
7	Street	44	M	0.7 µg/ml	Therapy	Heart: hypertrophic cardiomyopathy Lungs: evidence of pulmonary inflammation. Liver: micronodular hepatic cirrhosis.
8	home	41	F	0.8 µg/ml	Therapy	Heart: acute Myocardial ischemia. Evidence of contraction band necrosis in the right ventricle. Lungs: Evidence of pulmonary inflammation. Liver: inflammation of the porto-biliary spaces.

Evidence of hypertrophic or dilatative cardiomyopathy and early signs of myocardial ischaemia such as contraction bands and undulation of the fibres could be seen while observing the heart specimens.

Evidence of acute inflammation was often observed in the lungs as the expression of pathological patterns going from isolated inflammatory foci to bronchopneumonia.

Chronic active inflammation of the porto-biliary spaces was almost always present variously associated with aspects of steatosis or of severe macro nodular cirrhosis (Table 2).

Discussion

Aside from the great enthusiasm for the effectiveness of MMT in the treatment of opioid dependence – as in several Cochrane reviews – and the World Health Organization's proposal to include methadone as an essential medicine, lethal events related to blood tests positive for methadone are always more often cited in literature [6,14,15]. In the majority of the reported cases, methadone is detected together with other substances which are known to have a depressant effect on the respiratory system (e.g. benzodiazepines, opioids and alcohol); therefore its role in the pathogenesis of death cannot be clearly determined [12]. An extensive bibliographic research was carried out on PUBMED using the keywords (Methadone) AND (Death); (Methadone Maintenance Treatment) AND (Death); (Methadone Blood Concentration) AND (Treatment).

Among all the cases cited in literature there are only few referrals to the mortality rate in cases in which methadone is detected alone and, also extending the observation period to more than one year, the reported percentages appear to be way below the 15.7% we found our experience [12,16-18].

However, due to its variable pharmacokinetics and its known association with electrocardiographic QT complex (QTc) prolongation and the subsequent increased risk of the onset of a fatal arrhythmia, known as Torsade de Pointes (TdP), methadone can be considered a possible cause of death by itself or, at least, a potential risk factor for vulnerable patients [19,20].

In order to identify useful signs to promptly recognize the vulnerable patients we decided to focus on macro and microscopic aspects in patients who died after the sole assumption of methadone at therapeutic doses.

In this discussion we are going to exclude the one case of acute intoxication (Case 1: Table 2) in which the pre-existent conditions, though present, were not significant in the pathogenesis of death, given the high blood concentration of methadone.

The 7 remaining cases we analysed were characterized by evidence of pre-existent conditions affecting the lungs, the heart and the liver which may be considered to be in causal relationship with the lethal effects of methadone.

The frequent evidence of pulmonary inflammation, especially when it is massive, is by itself a possible risk factor for respiratory depression. Drug abusers, because of their irregular lifestyle, frequent poor nutrition and immune-depression, are more susceptible to respiratory infections. Moreover opioids in general and methadone in particular increase the risk of *ab ingestis* pneumonia as, not only they have a pro-emetic effect, but they also inhibit the cough reflex [21].

The pathological alterations that were observed in the heart tissue recall the aspect of sudden cardiac death with signs of acute myocardial ischaemia. According to the latest studies, methadone would be responsible for a QTc prolongation, which, in some patients, evolves in a lethal arrhythmia known as TdP. No dose relation has yet been found between methadone and QTc prolongation, nor have the risk factors for TdP been ascertained. At the present moment, high daily doses of methadone, medications that cause QTc prolongation, or inhibit CYP3A4, hypomagnesaemia, hypokalaemia, and/or a history of unexplained syncope or seizures should be considered risk factors for TdP and evaluated in risk benefit analysis before starting MMT [22,23].

As far as the liver abnormalities we described in "Results" are concerned, it is important to consider that they deeply influence the rate of metabolism of the methadone by slowing it down. Pre-existent conditions affecting the liver therefore represent another important risk factor in patients in MMT, especially during the induction period which is already by itself characterized by slower elimination, longer half-life, and a tendency to accumulate methadone.

Defining the role of methadone in the pathogenesis of death of patients in MMT or in chronic pain treatment is often a difficult challenge for the forensic pathologists, as the underlying causes that lead to an increased susceptibility may be superimposed by the toxicity of the methadone itself. In the lack of guidelines for the therapeutic use of methadone it is our strong believe that our study can be a starting point in identifying potential vulnerable patients prior to treatment in order to achieve a better risk-benefit ratio and, in the end, reduce the mortality rate in patients in MMT, which appears to be significantly higher in comparison with the same age groups in the general population [24].

There is no doubt that further studies will be needed to ascertain the actual role of methadone in the pathogenesis of death in a larger population of patients, especially given the great variability in pharmacokinetics and the difficult interpretation of opioid blood concentrations because of the overlap between therapeutic and toxic concentrations. By choosing a strict inclusion criterion, such as the detection of methadone alone in post mortem toxicological analysis, we were aware that the results would be limited to a small population and, therefore not easily generalizable. Nevertheless, the fact that the number of cases identified in our study, in a delimited urban area during one year, exceeds the cases reported in literature in longer observation periods is clear evidence of an increasing problem that deserves immediate attention. According to our results, the frequent evidence of heart, lung and liver conditions in MMT-related deaths, suggests that an accurate screening focused on these organs should be performed on the patients prior to the beginning of treatment. A strict and targeted follow up should also be scheduled in order to promptly identify signs and symptoms associated with the onset of those clinical conditions that may increase the patient's vulnerability to methadone administration.

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