

Trends in methadone-related deaths in Zurich

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Abstract Methadone has a long and successful history in the treatment of opioid addiction. In recent years, it has become popular again—as potent and inexpensive analgesic in patients with chronic pain. Since methadone has been used fatalities have been reported. In our study all methadone-associated deaths in Zurich from 1998 to 2007 were analysed. Most of the 146 detected deaths of the past 10 years occurred during substitution programmes or illicit intake of methadone while only three of them could be attributed to methadone used as an analgesic. Noticeable in our study was the high percentage of cases of combined drug intoxication (76%). The most frequent co-intoxicants were alcohol and cocaine. Mortalities attributed to methadone intoxication alone were a rare finding and could only be detected in five cases of deceased who had received methadone maintenance treatment. The aim of our study is to assess the trends in the number and nature of methadone-related fatalities in Zurich during the last 19 years. For this purpose a previous study from Zurich (1989–1997) was included, whereby a very long observation period and large number of cases resulted.

Keywords Methadone · Maintenance treatment · Drug addiction · Toxicological analysis · Methadone-related death · Parallel consumption

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Introduction

The opioid methadone was initially synthesised by the chemists Max Bockemühl and Gustav Erhart in 1939 and first used as a highly potent analgesic [1]. Because of its long half-life, good enteral resorption and low costs it became an important substance in the treatment of opiate addiction [1–4]. This measure successfully helped to reduce mortality, criminal behaviour and the spreading of disease transmitted through intravenous drug use [1, 5]. Other studies showed a significant lower rate of additional consumption of drugs—especially of opioids—and an increase in quality of life [5, 6].

Methadone maintenance treatment (MMT) for heroin-addicted persons started in the United States in 1964 and in Europe (Uppsala, Sweden) in 1966. Maintenance programmes in Switzerland were made legal in 1975 and have always been using only the racemic mixture (dl-methadone). Easy access to substitution programmes was implemented in the canton of Zurich in 1991 [1, 7, 8].

Since initiation of the official statistics Swiss Health Authorities have recorded approximately 18,000 methadone-treated addicts each year. Through the whole period from 1999 to 2007 the number of persons enrolled in a methadone programme in Zurich also remained stable with about 3,900 individuals per year [9].

In recent years the usage of methadone as an analgesic has become more important again and a correlation between increased methadone distribution and a rise of methadone-associated mortality is seen [10].

Since the substance has first been used, methadone-related deaths have been reported. Several studies focussed on forensic autopsies in which methadone was detected in postmortem toxicology and tried to point out its role in drug-associated deaths [1–23].

In the catchment area of the Institute of Legal Medicine of Zurich a large drug scene is located and one third of all drug deaths of Switzerland are undergoing forensic examination here. With our research we wanted to evaluate the changes in Zurich during the past 19 years, and also the proportion of death due to methadone as an analgesic. Is there still a progressive increase in death cases related to methadone?

Methods

All autopsies during a 10-year-period ($n=4,121$), from 1998 to 2007, were retrospectively evaluated. Searching the keyword methadone in our archive revealed 159 cases.

In all of the 146 included methadone-related fatalities without severe decomposition a complete autopsy had been carried out and detailed documentation was available from which demographic data and the cause and manner of death could be extracted.

Results of chemical-toxicological testings were mainly based on blood and urine samples. Only in a few cases toxicologic analysis were performed in organs and tissues (kidney and muscle). As part of routine toxicologic analysis urine drug screens were performed by immunoassay testing for EDDP (2-ethylidene-1.5-dimethyl-3.3-diphenylpyrrolidine; CEDIA[®]-test), opioids, benzoylcegonine, cannabinoids, amphetamines, benzodiazepines and barbiturates. Whenever possible blood from the femoral vein was preferred and tested after extraction with solid phase extraction by gas chromatography–mass spectrometry (GC-MS), quantifying methadone and illicit drugs. Alcohol analyses had been carried out with GC-FID (headspace). In cases with appropriate history, psychotropic agents—such as antidepressants—were also included in the screening. Analysis of hair samples had not been performed by default.

Unfortunately only few of our records contained full information pertaining history of drug consumption, especially of methadone intake, duration of a current maintenance programme, daily methadone dosage and circumstances of death. For this reason it was not possible to appraise the phenomenon of drug tolerance. The manner of death therefore could not often be clearly classified as a suicidal or accidental drug overdose.

In a further step we compared our data with the data of a previous study (1989–1997) raised by colleagues of our Institute.

Results

A total of 146 cases (3.5% of all performed autopsies) showed positive results for methadone in the postmortem toxicologic analysis. Figure 1 shows the development of

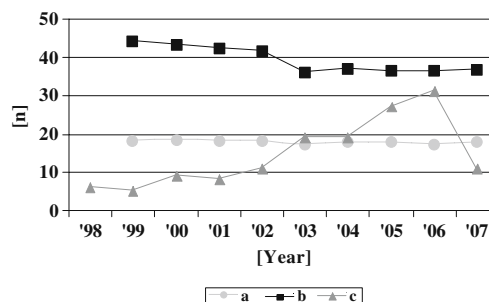


Fig. 1 Methadone maintenance treatment (MMT) and methadone-related deaths in Switzerland and Zurich. **a** Persons in MMT in Switzerland ($\times 1,000$). **b** Persons in MMT in Zurich ($\times 100$). **c** Methadone-related deaths in Zurich

drug-related deaths during the investigated time period. A progressive increase until 2006 and a sudden drop in 2007 are obvious. Table 1 provides an overview of the whole data. The individuals were predominantly male ($n=102$, 70%) and ranged from 17 to 59 years (mean age 36 years). The females ranged between 17 and 61 years (mean age 37 years). Methadone blood levels (MBL) ranged from 70 to 14,000 $\mu\text{g/L}$ (mean 1,324 $\mu\text{g/L}$, median 700 $\mu\text{g/L}$).

Fifty-seven deceased (39%, mean age 37 years) had been enrolled in MMT (42 men and 15 women) and had received a methadone dosage between 20 and 300 mg day^{-1} . MBL ranged from 100 to 12,000 $\mu\text{g/L}$ (mean 1,574 $\mu\text{g/L}$, median 900 $\mu\text{g/L}$).

The group of 86 individuals without MMT (59%, mean age 35 years) included 60 males and 26 females with a daily consumption of methadone of 15–300 mg. MBL ranged from 70 to 9,000 $\mu\text{g/L}$ (mean 1,022 $\mu\text{g/L}$, median 615 $\mu\text{g/L}$).

Three women (2%, 37, 43 and 53 years) had received methadone as an analgesic. MBL of 430, 1,200 and 14,000 $\mu\text{g/L}$ were found.

Mortalities (7.5%; $n=11$, mean age 39 years) were attributed to methadone intoxication alone (MBL, 500 to 2,500 $\mu\text{g/L}$, mean 1,073 $\mu\text{g/L}$, median 850 $\mu\text{g/L}$). Five of these 11 patients (45%)—all females—died while receiving MMT (MBL, 650–1,700 $\mu\text{g/L}$; mean 1,040 $\mu\text{g/L}$, median 850 $\mu\text{g/L}$). The group of the six remaining individuals who were not participating in MMT (MBL, 500 to 2,500 $\mu\text{g/L}$; mean 1,100 $\mu\text{g/L}$, median 780 $\mu\text{g/L}$) was predominated by males.

Combined drug intoxication was identified in 111 of 146 individuals (76%, mean age 35) and included 81 men (mean age 35 years) and 30 women (mean age 36 years). MBL ranged from 70 to 14,000 $\mu\text{g/L}$ (mean 1,492 $\mu\text{g/L}$, median 700 $\mu\text{g/L}$). The combination of methadone and one other substance ($n=49$) was dominated by alcohol. The group with the combination of methadone and only benzodiazepines was dominated by females—all other groups of combined drug toxicity were predominated by

Table 1 Changes in methadone-related deaths in Zurich from 1989 to 2007

	Zurich [1989–1997]	Zurich [1998–2007]
Cases [<i>n</i>]	114	146
Males [%]	61	70
Females [%]	39	30
Mean age [years]	29	36
MBL-range [$\mu\text{g/L}$]	30–4,500	70–14,000
Mean MBL [$\mu\text{g/L}$]	730	1,324
Median MBL [$\mu\text{g/L}$]	500	700
MMT [%]	39	39
Methadone as analgesic [%]	0	2
Methadone mono-intoxication [%]	10.5	7.5
Combined intoxication [%]	64	76
Natural death [%]	9.7	7.5
Non-natural death (except intoxication) [%]	15.8	3.4
Unclear death [%]	0	5.5

MBL methadone blood level,
MMT methadone maintenance
treatment

males. The combination of three to six substances was found in 62 cases.

Just four of these 111 cases of combined drug intoxication could definitely be classified as a suicidal incident. In all of the remaining 107 individuals no further assessment could be made whether a suicidal or accidental intoxication was present.

Alcohol—at the top of the list of all detected co-intoxicants—was present in 58 of all 146 cases (40%). Blood alcohol concentration levels ranged between 0.02 and 4.07 g/L (mean 0.76 g/L, median 0.32 g/L).

Cocaine or its metabolites were detected in 55 of the 146 cases (38%) ranging from 5 to 190 $\mu\text{g/L}$ for cocaine (mean 45 $\mu\text{g/L}$, median 25 $\mu\text{g/L}$), from 6 to 1,500 $\mu\text{g/L}$ for benzoylecgonine (mean 50 $\mu\text{g/L}$, median 110 $\mu\text{g/L}$) and from 10 to 6,000 $\mu\text{g/L}$ for methylecgonine (median 1,068 $\mu\text{g/L}$, median 535 $\mu\text{g/L}$). In four cases, ethylecgonine was found as a marker for combined use of alcohol and cocaine. Eighteen of these 55 deceased (32%) had been in a current MMT.

Benzodiazepines were found in 41 of 146 samples (28%), among them the most frequent were nordazepam, oxazepam and diazepam. In 37% ($n=15$) the intake was related to participation to MMT.

Other opioids were seen in 37 of the 146 cases (25%)—morphine 5 to 5,000 $\mu\text{g/L}$ (mean 517 $\mu\text{g/L}$, median 50 $\mu\text{g/L}$), codiene 3 to 700 $\mu\text{g/L}$ (mean 62 $\mu\text{g/L}$, median 15 $\mu\text{g/L}$) and monoacetylmorphine (six cases) 5 to 40 $\mu\text{g/L}$ (mean 17 $\mu\text{g/L}$, median 25 $\mu\text{g/L}$). Fourteen of these 37 persons (38%) were enrolled in MMT. Psychotropic agents—mainly antidepressants—were detected in 24 of 146 samples (16%).

Amphetamines (1%) and cannabinoids (1%) could not be detected as single intoxicants in combination with methadone and played a minor role in patients with a combination of three or more substances.

In 11 of the 146 cases (7.5%) methadone could be detected but death was attributed to natural causes including cardiovascular disease ($n=4$), hypovolemic shock ($n=3$), pneumonia ($n=2$), insufficiency of the liver ($n=1$) and acute pancreatitis ($n=1$). In these cases MBL ranged from 120 to 1,200 $\mu\text{g/L}$ (mean 529 $\mu\text{g/L}$, median 430 $\mu\text{g/L}$).

In the five cases (3.4%) of non-natural death that could not be attributed to the consumption of substances, we found two cases of failure of central regulation after blunt trauma and one case each of drowning, hypothermia and polytrauma (MBL, 170–2,500 $\mu\text{g/L}$; mean 1744 $\mu\text{g/L}$, median 250 $\mu\text{g/L}$).

In eight of the 146 cases (5.5%) the cause of death remained unexplained despite extensive forensic examination. MBL ranged from 330 to 900 $\mu\text{g/L}$ (mean 653 $\mu\text{g/L}$, median 620 $\mu\text{g/L}$).

Discussion

Several studies have discussed the role of drug-related deaths involving methadone. We observed an increase in the number of methadone-related deaths in recent years which is consistent with the findings of many other investigators [1, 4, 6, 13, 16]. One author however found a decrease [3]—but this finding may result from only a small collective.

The total number of cases found during the investigated time periods varies a lot. These differences may be explained by the study's design, regional, social and cultural factors or simply the availability of drugs or maintenance programmes.

Among the long-term studies [13–15, 17] with an observation period of 10 years or more with 146 deceased, we investigated a relatively large number of cases. However, some shorter studies of 5 years in length or less

presented data with an even larger number of victims [1, 12]. The study by Hauri et al. [15] (Table 1) reviewed 114 methadone-associated deaths between 1989 and 1997.

Compared to his data our study revealed an increase of 28% of methadone-associated deaths in Zurich in the last 10 years, while the number of drug addicts in MMT in Zurich and Switzerland remained stable [9]. We could not find a conclusion for the sudden drop in the number of fatalities in Zurich in 2007. An increase in the proportion of men and mean age was also seen in our collective. Other significant differences to Hauri were a tripling of the highest MBL and a doubling of the mean MBL in our study while the median MBL did not differ that much (500 µg/L vs. 700 µg/L). By substantial changes in methodology from gas chromatography–nitrogen phosphorus detector to GC-MS in Zurich between 1989 and 2007 the sensitivity of detection increased, but the quantitative results for the therapeutical levels remained comparable. The number of persons in MMT did not change over the years. New findings were fatalities associated with methadone used as an analgesic—an observation which had also been discussed by health authorities in the last time [10]. According to our evaluation the total number of cases which could be assigned to methadone intoxication alone, natural death and non-natural death (except lethal intoxication) decreased. In Hauri's collective, 64% of deaths could be attributed to combined drug intoxication. We found a distinct increase up to 76%. Between 1989 and 1997 in Zurich the most frequent additional substances used with methadone were benzodiazepines, alcohol and other opioids. The main co-intoxicants in our blood samples were alcohol and cocaine while the influence of benzodiazepines and other opioids appeared to regress.

We showed a distinct and even increasing predominance of males among methadone-related deaths which is also a common finding in other studies [3–6, 9]. The only exception is the study by Worm [23]. However she presented just a small number of cases where the data cannot be accepted as representative of all cases.

The mean age in other investigations, including the studies from Zurich, ranged from the late 1920s to the late 1930s [1, 3, 4, 6, 8, 23]. Our recent study, however, showed the mean age increase by 7 years. This supports findings that mortality is reduced as a consequence of MMT [1].

Of note in our study were blood concentrations of methadone with values up to 14,000 µg/L. Compared to the results of other authors this is more than a tripling [1, 6, 8, 15]. The existence of such high MBL implies a methadone-induced tolerance and enough survival time for resorption in case of oral application or an intravenous application of a large dosage of methadone [21]. With regard to the increasing age of the deceased in our study, an induction of tolerance is quite comprehensible and would also lead to

an intake of a higher daily methadone dosage. The comparability of the data from Zurich is ensured by the use of the racemic mixture from the start of MMT in Switzerland—a fact that was not traceable in other studies and which may have a severe influence in the direct comparison of detected MBL. In our study, only eight of 146 cases showed a MBL over 4,500 µg/L. This explains the high mean MBL of 1,324 µg/L and the “usual” median MBL of 700 µg/L. However, many previous investigators have also commented on the difficulty in performing postmortem toxicologic analyses, interpreting the results and establishing a lethal MBL [1, 4, 6, 11, 14, 19, 21]. Therefore a large degree of error is possible.

The ratio of persons in Zurich with and without MMT has not changed in the last 20 years. Compared to other studies our detected rate of deceased receiving treatment (39%) is in the lower range. Accordingly 61% of the victims in our collective must have received their methadone illegally and without medical support. The apparently low acceptance of MMT in the canton of Zurich cannot be understood by the authors because to the easy access to substitution programmes in that area.

Many previous studies have emphasised the frequent presence of other drugs in methadone-related deaths. In our study, 76% of the deceased died as a result of combined drug intoxication. A similar or even higher percentage of combined toxicity was seen in other studies [1, 3, 4, 6, 14, 15, 22]; however not all of them are representative—some sampled only a very small number of cases. The development in Zurich from 1989 to 2007 documents the rising problem of parallel consumption of several substances and an increased importance of alcohol, while the consumption of benzodiazepines and other opioids decreased—a finding consistent only in the study by Graß [14]. In contrast most of the previous studies, revealed benzodiazepines as the most frequent additional substances [3, 4, 15, 22, 23]. According to the development in Zurich's and Switzerland's drug scene in recent years [20], we detected cocaine in second place which seemed to be of no particular relevance in other studies.

In Dobler-Mikola's study [7], a more frequent use of illicit drugs during MMT in Switzerland was seen and explained by a presumably higher activity of the drug scene. On the other hand, it is possible that due to a higher sensitivity of the toxicological analyses more additional substances were detected.

As aforementioned in many cases it was not possible to classify the manner of death as a suicidal or accidental drug overdose due to a lack of information. Only four of our 111 deceased (3.6%) had verifiably committed suicide with the intake of several substances while other studies showed a ratio of suicides close to 50% [16]. Hauri et al. [15] identified 12 cases (10.5%) of suicide in Zurich between 1989 and 1997.

In the last few years several case reports and studies have described the occurrence of cardiac arrhythmia with the use of methadone particularly with regard to prolongation of the QT-interval [2, 18]. To determine the cause of death clearly as fatal arrhythmia it would be necessary to have very detailed information about the deceased—general medical anamnesis and extensive data of the current MMT.

Finally, MMT, if carried out correctly, is a very useful and save tool in the treatment of heroin addiction. Only five deaths in our 10-year-study were attributed to methadone intoxication alone while receiving MMT. Compared to an average of 3,900 substituted persons in the canton of Zurich each year this is a very rare finding (0.1%). Furthermore the mean age in the deceased in our collective increased by an average of 7 years (in the group of MMT by 8 years), which is presumably another positive effect of methadone, especially in MMT. In most of our cases combined drug intoxication was present in terms of parallel consumption of other substances which should not occur according to the guidelines of MMT. Thus, a stricter control of the participants in maintenance treatment and additional support in cases of concomitant drug use should be considered in the future.

Our study pointed out the general problem of interpretation of postmortem MBL and the retrospective collection of reliable data. Therefore a prospective study in close collaboration with an institution for substitution treatment is pursued, with special regard to pain treatment and cardiac side effects of methadone.

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