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Characteristics of methadone-related fatalities in Norway

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ABSTRACT

There are currently over 7000 patients enrolled in opioid maintenance treatment (OMT) programs in Norway. A rise in methadone-related deaths proportional to increasing methadone sales over the period 2000–2006 has been observed, but the causative factors for these fatalities have been elusive. In the present study, individual characteristics, methadone concentrations and additional toxicological findings were analyzed. Methadone intoxication deaths (n = 264) were divided into 3 groups according to toxicological findings in whole blood: group 1 – methadone detected alone, or together with one additional drug at low or therapeutic levels, or a low concentration of ethanol (<1 g/L) (n = 21); group 2 – multiple additional drugs/substances detected below lethal levels (n = 175); group 3 – one or more additional drugs/substances detected at lethal levels, or ethanol >3 g/L (n = 55). Methadone blood concentrations in decedents who had been enrolled in OMT were higher than for decedents not in treatment, in all groups. Blood methadone concentrations around 1 mg/L were present in fatal multi-drug intoxications in OMT patients. Results suggest that some patients may be at risk of dying when combining therapeutic concentrations of methadone with other psychoactive substances. Somatic disease was a common finding among deceased OMT patients. Concentrations in methadone users not enrolled in OMT were predominantly between 0.3 and 0.4 mg/L and were not related to the presence of other drugs. However, methadone concentrations below 0.1 mg/L may be associated with intoxication following methadone use, both alone and in combination with other drugs. Younger male users (mean age 34 years) seemed to have a higher susceptibility to methadone intoxication.

1. Introduction

Opioid maintenance treatment (OMT) is a key factor in the treatment of heroin addiction and in reducing the morbidity and mortality related to heroin use. By reducing intravenous drug use, OMT additionally helps reduce the spread of HIV and hepatitis C, as well as the medical morbidity associated with these diseases.[1–3]

The World Health Organization (WHO) recommends either methadone or buprenorphine for opioid agonist maintenance treatment, and refers to studies showing more effective retention in treatment and reduction in heroin use by methadone when compared to buprenorphine in standard doses.[4] A recently published study on the evidence-based treatment of opioid addiction[5] highlighted the importance of using a daily methadone dose exceeding 80 mg and achieving an average plasma concentration of about 0.4 mg/L (corresponding to a concentration in whole blood of approximately 0.3 mg/L, based on a plasma-blood ratio of 1.3:1[6,7]), to reduce illicit drug use and achieve better treatment outcomes. However, as this concentration[5] and several other reported therapeutic levels[7–9]

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overlap with concentrations reported in the literature for methadone-related deaths (Table 1), this could give rise to concern regarding the safety of such recommendations. As summarized below, previous studies of methadone fatalities have not always defined whether decedents were enrolled in OMT or not, whether additional potentially toxic blood drug concentrations were present in addition to methadone or whether decedents had a history of somatic illness. These are all factors that may be relevant in determining causality in methadone-related deaths.

Findings in methadone fatalities in Norway over the period 2000–2006 are previously published.[10] The deaths were in most cases characterized by the presence of multiple additional psychoactive substances. Less than a quarter of the deceased died while in OMT. Methadone concentrations in post-mortem blood from decedents who had died of methadone intoxication did not differ significantly from concentrations in decedents who had died due to other, non-drug related causes of death. This raised the question as to what extent methadone was a critical factor in the deaths attributed to intoxication and, accordingly, whether a specific methadone concentration level could be regarded as potentially life threatening.

Additional information about the causal role of methadone might be garnered through a detailed study of the drug concentrations measured in the previous study.[10] We hypothesized that a causal role for methadone in fatal intoxications would be revealed by lower concentrations in cases where other substances were present at potentially lethal blood concentrations. Methadone concentrations in the absence of lethal levels of other drugs would therefore represent potentially risky concentrations for methadone users. In decedents who had been enrolled in OMT, the effect of a history of somatic disease and/or somatic findings at post-mortem on blood methadone concentrations was studied.

Ultimately, the aim of the present study was to identify potentially life threatening blood methadone concentrations for different groups of methadone users in the studied deceased population.

2. Material & methods

Methadone-related deaths in Norway over the period 2000–2006 were studied. A total of 264 fatal methadone intoxications were reported in Norway over the studied period. Identification, collection and classification (according to registered ICD-10 diagnoses) of the data for these deaths is previously described.[10] These deaths are equivalent to methadone-caused deaths as defined by a Substance Abuse and Mental Health Services (SAMHSA) consensus panel.[11] In an attempt to estimate the effect of concomitant drug findings, the material was divided into three groups, as follows:

- Group 1: Methadone detected alone, or together with 1 additional drug at therapeutic/low levels, or blood alcohol concentrations less than 1 g/L.

Table 1
Summary of previously published methadone findings arranged in ascending order of median concentration, compared to the concentrations detected in this study (values for individual groups, presented in italics). In the event that multiple populations were studied in these references, for example OMT patients and decedents not in OMT, values are given for each population. MRD – methadone-related deaths.

Reference	Population studied (where relevant)	Number of cases, N	Blood methadone concentration (mg/L)		
			Median	Lowest	Highest
Worm et al.[41]	Deceased addicts	59	**0.28**	0.06	3.09
Musshoff et al.[42]		38	**0.30**	0.03	4.07
Seymour et al.[37]	MRD	135	**0.3**	0.01	3.84
Danielson et al.[43]		46	**0.32**	0.07	0.89
Group 1[b]	*Decedents not in OMT*	*18*	***0.33***	*0.09*	*1.24*
Group 2[b]	*Decedents not in OMT*	*147*	***0.37***	*0.06*	*5.88*
Drummer et al.[28]		10	**0.39**	0.27	2.5
Capelhorn and Drummer[19]	MRD	56	**0.40**	0	5.5
Jones et al.[39]	Drug-related deaths	346	**0.4**	–	6.7
Albion et al.[36]	Methadone detected alone	11	**0.41**	0.2	3.0
Worm et al.[41]	OMT patients	11	**0.43**	0.03	1.24
Group 3[b]	*Decedents not in OMT*	*51*	***0.43***	*0.09*	*6.50*
Clark et al.[44]		18	**0.44**	0.20	1.90
Milroy and Forrest[7]		50	**0.44**	0.08	2.70
Madden and Shapiro[45]		76	**0.46**[a]	0.05	3.79
Chugh et al.[46]		22	**0.50**	0.1	0.9
Laberke and Bartsch[35]	MRD in Zurich 1989–1997	114	**0.5**	0.03	4.5
Shields et al.[47]		176	**0.54**[a]	0.02	4.0
Van den Broecke SML et al.[29]		37	**0.54**	0.10	4.13
Levine et al.[48]	- Heart blood	15	**0.55**	0.10	2.7
	- Alt. blood	15	**0.56**	0.09	1.5
Albion et al.[36]	Methadone detected with other drugs	25	**0.59**	Trace	6.0
Capelhorn and Drummer[49]		33	**0.60**	–	–
Pilgrim et al.[38]		206	**0.6**	0.1	3.0
Buchard et al.[50]		90	**0.62**	0.01	8.0
Laberke and Bartsch[35]	- Total MRD in Zurich 1998–2007	146	**0.7**	0.07	14.0
	- OMT patients	57	**0.9**	0.10	12.0
Seymour et al.[37]	Methadone detected alone	52	**0.7**	0.08	2.63
Group 3[b]	*OMT patients*	*17*	***0.71***	*0.09*	*6.19*
Aromatario et al.[30]	Methadone detected alone	8	**0.75**	0.5	17
Group 2[b]	*OMT patients*	*28*	***1.02***	*0.37*	*4.64*
Group 1[b]	*OMT patients*	*3*	***1.55***	*1.55*	*3.10*

[a] Mean concentrations reported.
[b] Concentrations reported in this study, where group 1 represents cases where only methadone or low concentrations of other drugs/substances were detected, group 2 where multiple drugs/substances were detected below lethal levels and group 3 where lethal levels of other drugs/substances were detected.