

Original Research

Toxicology and pathology of deaths related to methadone: retrospective review

ABSTRACT ● **Objectives** To clarify the mechanisms and risk factors of methadone toxicity and to describe the findings of deaths related to methadone use Design Retrospective review of case notes in the records of the San Francisco Medical Examiner comparing the findings in cases where methadone was deemed the cause of death with findings in decedents where methadone was an incidental finding, and with 50 age-matched, disease and drug free, trauma victims. ● **Results** 38 cases out of the 3317 processed by our office during 1997-1998 were identified in which methadone had been detected. Cases were mostly male 28/38 (74%) and white, 28/38 (74%). In 17 of 38 cases death was deemed to have been caused by methadone toxicity. For the group the mean blood methadone concentration for all 38 patients, was 957 ng/ml SD = .681, SE = .14). The mean blood concentration of the main methadone metabolite (EDDP) was 253 ng/ml, SD = 529 ng/ml, SE = .089. The mean ratio of methadone in the blood to EDDP in the blood was 13.6:1 Values were not significantly different between cases in which methadone toxicity was the cause of death and in those in which it was an incidental finding. Cocaine, or the cocaine metabolite benzoylecgonine, was detected in the blood or urine of 16/38 cases (42%); morphine in one-third (13/38) and methamphetamine in only one. Pulmonary edema was evident in all cases, coronary artery disease in 9/38 (24%) and cirrhosis in 7/38 (18%) of the methadone users. Necrotizing fasciitis was the cause of death in 4 of the 38 methadone users (11%). Nationally, a sizeable percent of methadone deaths are from drugs diverted from treatment programs. ● **Conclusions** The presence of methadone is often an incidental finding during postmortem examination which is unrelated to the cause of death. Postmortem measurements of methadone or its metabolite, or both, cannot be used in isolation to identify which deaths are associated with methadone toxicity.

The Office on National Drug Control Policy is committed to making methadone treatment programs more widely available; deaths related to heroin use fall when where methadone replacement programs are available.¹⁻³ Unfortunately, methadone is toxic. A total of 552 methadone-related deaths were reported to the government in 1996, making methadone the seventh most frequent cause of drug-related death in the United States (nearly 4000 deaths related to heroin were reported during that same period).⁴

Most deaths that are related to methadone occur during the first few weeks of maintenance treatment; they are often the result of the dosage having been increased so quickly that fatal respiratory depression occurs.⁵⁻⁶ The relative risk of fatal respiratory depression occurring during the first 2 weeks of methadone maintenance treatment is nearly seven times higher than that in untreated heroin addicts and 97.8 times higher than for patients who have been on methadone maintenance for more than 2 weeks.^{3,7}

New opiate users who are using illicitly obtained methadone are also at risk. The amount of methadone diverted from treatment programs, and by inference the number of deaths occurring as a result, is limited because the number of heroin users actually enrolled in methadone programs is comparatively small. There are an estimated 810,000 heroin addicts in the United States but only 115,000 participate in maintenance programs.⁴ If metha-

done becomes more widely available opportunities for diversion from treatment programs will increase and so will the number of deaths.¹ Some of these deaths might be prevented, especially if the underlying cause of death was better understood. Little is known about the pharmacokinetics of methadone in opiate users. The data that have been published are largely derived from studies of single doses given to healthy volunteers or intravenous doses given to patients with cancer. Whether such studies are relevant to the pharmacokinetics in chronic heroin users is not known. Furthermore, nearly all of these studies were undertaken before differences in the tissue distribution of

Steven B Karch
Boyd G Stephens
Office of the Medical Examiner
City and County of San Francisco
Hall of Justice
850 Bryant Street
San Francisco, CA 94103

Correspondence to:
Steven B Karch
fdaa@batnet.com

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Summary points

- Isolated postmortem measurements of blood concentrations of methadone or its metabolite cannot reliably be used to discriminate between cases who have died from methadone toxicity and cases in which the presence of the drug is an incidental finding
- In nearly half of the cases in which death was related to methadone, cocaine was also found to have been used
- New opiate users take longer to clear methadone from their bodies, placing them at greater risk of overdose
- Necrotizing fasciitis occurring in methadone users seems to be more common than had previously been recognized; methadone may not be able to normalize the functioning of the immune system

methadone isomers were understood,⁸ before methadone metabolites could be routinely measured, before chiral (special chemical techniques used to separate dextro- from levo- isomers of the same molecule) separation of methadone isomers was possible⁹ and before the problem of determining the redistribution of drugs after death was appreciated.¹⁰

MATERIALS AND METHODS

Records of the San Francisco Medical Examiner were reviewed to identify all cases in which methadone had been detected from the beginning of 1997 through the end of 1998. Positive screening tests were confirmed using gas chromatography with mass spectrometry. Blood samples were screened in cases for which no urine was available. Concentrations of methadone in the blood and concentrations of the methadone metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) were both measured using gas chromatography with nitrogen-phosphorous detector detection. Chiral separation was not performed.

The cause and manner of death were reviewed to determine whether death was related to methadone toxicity (drug related) or whether methadone was merely an incidental finding. Death certificates cannot be used to make this distinction because in California and most other states, drug-related deaths are considered to be accidents. Drug-related deaths were defined as those in which a direct toxic effect of methadone caused or contributed to death. Findings in cases classed as being drug related were compared with findings from cases in which methadone was incidental and also with findings from a group of 50 controls in which toxicology screening was negative and who had died as a result of trauma.

RESULTS

Demographic findings

A total of 38 cases in which methadone had been detected were identified out of 3317 cases processed by our jurisdiction during that period. The decedents were predominantly male (28/38, SD = 9, SE = 2 or 74%). The mean

age of the 21 cases whose deaths were deemed to have been drug related was 46.2 (7.9) years. The mean age of the 17 cases whose deaths were deemed not to have been drug related was 46.3 years (SD = 7.9, SE = 1.9). Decedents dying from methadone toxicity were almost all white (1/17, 95%); decedents where methadone toxicity was an incidental finding were racially mixed, with 57% white (12/21), 38% black (8/21), and one Asian.

Anatomical and medical findings

Table 1 shows the mean weight of the heart, lungs, liver, spleen, and brain of the 38 cases in which methadone was detected and in 50 controls. The weight of each organ was significantly increased in all cases. Table 2 shows the nine most commonly encountered physical findings in the 38 cases. Terminal aspiration and pneumonia occurred in 6/38 (16%) cases. Necrotizing fasciitis, a much less common complication of drug abuse, was the cause of death in four (11%) cases. Necrotizing fasciitis occurred in middle aged people (40, 44, 46, and 54 years old); two were white, one was black, and the race of one was impossible to determine.

Toxicological findings

The mean interval before the postmortem examination occurred was 17.1 hours. The interval did not differ significantly between those cases in which death was deemed to have been drug related and in those in which it was not (17.7 vs 17.6 hours). Blood was available for measurement for all cases and urine in 16/38 (42%) cases. The mean blood methadone concentration for all 38 patients, was 957 ng/ml (SD = .681, SE = .14). The mean blood concentration of the main methadone metabolite (EDDP) was 253 ng/ml (SD = 529 ng/ml, SE = .089). The mean ratio of the concentration ratio of methadone in the blood to EDDP in the blood was 13.6:1. Urine concentrations of methadone were similar between the group in which death was deemed to have been drug related and in that in which it was not (mean concentration of 5.2 mg/L, SD = 3.6 mg/L, in drug related deaths and 5.86 mg/L, SD = 6.4 mg/L in cases where methadone was an incidental finding

Table 1 Weight of organs at postmortem examination in 38 cases in which methadone was detected and in 50 controls in which toxicology screening was negative

Group	Mean age (years)	Mean weight (g)				
		Heart	Lungs	Liver	Spleen	Brain
Control (n = 50)	37.0	345	1175	1516	141	1336
Cases in which death was methadone related (n = 21)	48.3***	408*	1482*	2059*	278***	1305
Cases in which methadone was incidental (n = 17)	46.3***	437*	1308	1935*	304***	1389

*P < 0.05, **P < 0.01, ***P < 0.001 for comparison with controls.

Table 2 Nine most common physical findings on postmortem examination in 38 cases in which methadone was detected

Finding	Number (%) of cases
Track marks	13 (34)
Coronary artery disease	9 (24)
Cirrhosis	7 (18)
Pneumonia	6 (16)
Hepatic fibrosis	5 (13)
Fatty liver	4 (11)
Necrotizing fasciitis	4 (11)
Birefringent crystals	4 (11)
HIV infection	3 (8)

($p=0.797$). Concentrations of EDDP were not significantly different between the two groups either. The EDDP concentration for drug related deaths was 6.55 mg/L (SD = 5.6 mg/L) vs 11.8 mg/L (SD = 16.7 mg/L, $p = .3480$).

The methadone/ EDDP ratio for the 38 cases was 13.58 (SD = 17.4, SE = 3.35; range 0.572 to 60). Cocaine or the cocaine metabolite benzoylecgonine, or both, was detected in 16/38 (42%) cases. Six of the 16 (38%) who had used cocaine also had detectable concentrations of morphine. Morphine was detected in nearly one-third (12/38) of the cases; concentrations ranged from 40 to 1728 ng/ml. Fentanyl was also detected in the case that also had the highest concentration of morphine. If the case with the highest concentration was excluded, the mean concentration of morphine in all 38 methadone users who were also taking morphine (presumably as heroin) was 345 ng/ml (SD = 325, SE = .09 ng/ml). Ethanol was present in 10 of 38 cases (26%) in a mean concentration 0.113 mg/dl (range 0.020-0.340, SD = .073, SE = .012). Other prescription drugs identified, which were generally present in subtherapeutic or therapeutic concentrations, are listed in table 3.

DISCUSSION

A redistribution of drugs through the body occurs after death making it impossible to estimate the true concentration of methadone or any other basic drug, such as a mild alkali in the period just before death until autopsy.¹⁴ Therapeutic monitoring of people on methadone maintenance is problematic. Dosages are estimated based on pharmacokinetic measurements made in healthy volunteers not addicts. These estimates have proven to be extremely inaccurate suggest a falsely short terminal half-life and a falsely low volume of distribution in addicts.^{12,13}

The S- form (S, Latin for sinister) of methadone exerts little narcotic effect but pure R- isomer is expensive to manufacture, so a racemic mixture of the D and S forms (or right and left) mirror images of the methadone is widely used. The isomers have different volumes of distribution (defined as the amount of drug in the body divided by the blood concentration at equilibrium) is much greater for the S form than for the R form, while the R form is cleared from the system (has a shorter half-life, much more quickly than the S form. At at equilibrium, more of the inactive S- form than the active R-form can be found in the bloodstream.¹⁴⁻¹⁷ Chiral interaction can probably be used to explain why postmortem concentrations of methadone overlap among patients whose death is drug related and those whose death is not. The active R-isomer has a smaller volume of distribution than the inactive S- isomer, which means that more of the active drug, R-methadone, is found in the bloodstream than in the tissue. If only a small percentage of the S- isomer is released from tissue back into the bloodstream, measured concentrations will be falsely raised.

The conversion of methadone to the metabolite EDDP is mediated by liver microsomes, mainly CYP3A4 and possibly CYP2C9 and CYP2C19.¹⁸ Methadone induces hepatic production of these microsomal enzymes, accelerating the metabolism of methadone in chronic users. These enzyme systems will not have been induced in new opiate users who will thus take longer to clear metha-

Table 3 Other drugs detected at therapeutic or subtherapeutic concentrations in postmortem blood samples in 38 cases in which methadone was also present

Drug	Number of cases (%)
Alprazolam	1 (3)
Amitriptyline	2 (6)
Carbamazepine	N/A
Diazepam	9 (24)
Chlorpheniramine	1 (3)
Clonazepam	1 (3)
Diphenhydramine	4 (11)
Doxepin	1 (3)
Ephedrine	2 (5)
Fluoxetine	1 (3)
Haloperidol	1 (3)
Imipramine	1 (3)
Promethazine	1 (3)

done from their bodies, placing them at greater risk of overdose. If other drugs are misused, or if prescription drugs are taken, the picture is further complicated since these drugs can induce, inhibit or compete for the same microsomal enzymes. The interactions between methadone and certain antiviral drugs are a recognized complication of treatment for HIV infection.¹⁹

In a recent study, antibodies to methadone were detected in more than half of the 46 heroin addicts who were tested.²⁰ Antibodies were detected in nearly all of the cases with HIV, and concentrations of methadone in the blood were higher in patients who were infected with HIV than in those who were not (398 ng/ml vs 265 ng/ml). Thus, it is impossible to draw conclusions about the toxicity of a given dose of methadone or of a particular concentration of methadone in the blood without the use of chiral separation and without additional clinical information and information about the patient's history.

Medical consequences

Most of the findings made during the postmortem examination, such as the terminal aspiration and pneumonia that occurred in 16% of cases, are recognized complications of intravenous opiate use. However, necrotizing fasciitis is a much less common complication, and it is not clear why four members of this cohort died from it. Necrotizing fasciitis is characterized by a rapid and progressive course, and unrecognized infection spreads along fascial planes. It is usually caused by group A β hemolytic streptococci but other Gram negative bacilli, alone or in combination with hemolytic streptococci, may also be responsible.²¹ Usually there is also a history of alcoholism, diabetes mellitus, intravenous drug use, or some other disorder that impairs resistance.²²

There was evidence of prior intravenous drug use in only one of the four cases of necrotizing fasciitis described here. In two of the cases complete toxicology testing identified the presence of methadone only. In the other two cases, cocaine and cocaine metabolite were found in both blood and urine samples. A link between cocaine use and necrotizing skin infection has previously been reported.²³

The incidence of necrotizing fasciitis among intravenous drug users is clearly increasing in San Francisco, and these four cases may reflect the increased prevalence of this disorder in our jurisdiction.²⁴ But the occurrence of this disorder in those who may have been in methadone maintenance programs is particularly worrisome because methadone is supposed to help normalize immune responses, even in those drug users not infected with HIV.²⁵

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