J Forensic Sci, Jan. 1974, Vol. 19, No. 1

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Methadone—A Cause of Death

The past few years have seen a dramatic increase in the use of methadone in the United States, predominantly as a method of treating narcotic addiction. Concomitant with this has been a proportionate rise in the number of deaths in which methadone is either the cause of death or an incidental toxicologic finding. This indicates an increasingly widespread abuse of methadone. In Philadelphia, for example, there were only 4 deaths related to methadone between 1967 and 1969. The number rose dramatically in 1970 to 22, in 1971 to 27, and in the first 10 months of 1972 to 37. Of those deaths in 1972, 17 were directly attributable to methadone, 15 were attributable to a combination of methadone and one or more other narcotic and dangerous drugs, and 5 were due to causes other than drugs but methadone was found by postmortem toxicology.

Early in 1970 methadone deaths were viewed in essentially the same way as heroin deaths and, for want of a better understanding of the mechanism involved, were considered to be an "adverse reaction to narcotic drugs" (that is, not necessarily an overdose). As the number of methadone cases increased it became apparent that significant differences existed between heroin and methadone deaths. It is the purpose of this presentation to comment as forensic pathologists on some observations made in correlating the circumstances surrounding the death, autopsy, and toxicologic findings in deaths due to methadone. First, the majority of deaths due to methadone followed ingestion rather than injection. Also, the temporal sequence of events preceding death was frequently dramatically different depending on the route of administration. Thirdly, as quantitative toxicologic data accumulated, it was possible to identify some definite and meaningful patterns in the methadone deaths.

Three well documented cases that clearly and dramatically show the differences between deaths following ingestion and injection of methadone are presented. Of particular note is the 2- to 3-h interval between ingestion of methadone and the onset of symptoms. The third case demonstrates the rapid onset of symptoms and death following intravenous injection of methadone, a pattern seen repeatedly following intravenous administration of heroin.

Case A

This 18-year-old caucasian merchant seaman was known to use pills and had a history of hepatitis. On the evening prior to his death he went to a movie with a friend. On the

The opinions expressed in this paper are those of the authors and do not necessarily represent official positions of the Medical Examiner's Office, the Health Department, or the City of Philadelphia.

Received for publication 19 March 1973; revised manuscript received 11 June 1973; accepted for publication 12 June 1973.

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way home from the movie they stopped at a friend's home where, at about 11:00 p.m., the decedent drank a bottle of methadone. Both returned to the decedent's home at about 2:00 a.m. The decedent discovered the door bell was not functioning, obtained a screwdriver, and repaired it. At this time his mother saw him and stated that he appeared to be normal. Shortly afterward everyone went to bed. At about 6:00 a.m., the mother observed that her son was in severe respiratory distress. He was rushed to the hospital and was dead on arrival.

Postmortem examination revealed only early focal acute bronchopneumonia. No old or recent needle tracts were noted and no trauma or other natural disease was found to account for his death.

Toxicologic studies revealed a 0.03 mg percent blood methadone level with 0.63 mg percent in the urine and 0.28 mg percent in the stomach. No other drugs were found.

Case B

This 17-year-old negro man was not a drug addict. On the evening preceding his death he was visiting with two friends who were addicts on methadone maintenance. At approximately 11:00 p.m., he obtained a bottle of methadone from one of them and drank approximately 3½ oz, a total of 280 mg of methadone. He suffered no ill effects and at 1:00 a.m., he went to bed stating that he felt "nice." At 6:45 a.m., he was discovered by his friends to be unconscious and in respiratory distress. He was rushed to the hospital, arriving there at 8:00 a.m., and was pronounced dead on arrival.

Postmortem examination revealed only pulmonary edema and acute bronchopneumonia. No old or recent needle marks could be found. No trauma or other natural disease was found to account for his death.

Toxicologic studies demonstrated 0.05 mg percent methadone in the blood, 0.20 mg percent in the urine, and 0.82 mg percent in the stomach. No other drugs were found.

Case C

This 24-year-old caucasian man had a history of drug abuse dating back a number of years. He had been seen by a number of physicians for this problem without success. During the course of his life he had abused almost every possible drug but he usually preferred "downs," claiming at one time to have taken as many as fifty 100-mg seconal capsules per day. Complicating his drug abuse was a severe overriding complex psychiatric problem which was also unsuccessfully treated by a number of physicians.

On the day of his death, he and a friend purchased a 20-ml vial of injectable methadone. The friend first injected 9 ml in his own arm vein, then 2 ml in his girlfriend's jugular vein, 7 ml in the decedent's jugular vein, and the last 2 ml beneath the decedent's skin. Within minutes the decedent lost consciousness and approximately 15 min later was dead on arrival at a hospital one block away. The two companions survived without any ill effects.

Postmortem examination revealed only the needle mark in the neck and pulmonary edema without pneumonia. No trauma or other natural disease was found to account for his death.

Toxicologic studies demonstrated a 0.09 mg percent methadone level in the blood. No methadone was found in the urine or stomach. Nonlethal amounts of methaqualone were found in the body tissues. The possibility of drug interaction is not excluded, but in the opinion of the authors the methaqualone played only a minor role.

Methods

A review of all 90 cases from the Philadelphia Medical Examiner's Office involving methadone between 1967 and October 1972 was undertaken. The circumstances surrounding the deaths were noted. An attempt was made to determine the route of administration from history, interviews, and physical evidence at the scene of death. In those cases where no such determination could be made, the autopsy findings[2] were reviewed with particular attention to the presence or absence of old and/or recent needle marks. The absence of recent needle marks was considered fairly reliable evidence of ingestion while their presence was considered presumptive evidence of injection. The authors are aware of at least one case of methadone ingestion which was followed by multiple intravenous injections of salt in an attempt to revive the individual. In those cases where the route was determined solely by the presence or absence of needle marks, a question mark has been placed before the indicated route in Tables 1, 2, and 3 to show a degree of uncertainty. The cause of death was obtained from the autopsy report. All toxicologic reports were reviewed and tabulated. The concentration of methadone was determined by preparing a chloroform extract of the sample followed by gas chromatographic analysis of the extract. The reported value represents the concentration of methadone not including metabolites. Three microscopic sections of the lungs were examined for each case in which methadone was the cause of death. A case was considered positive for bronchopneumonia if there were areas of polymorphonuclear leukocytes within the alveolae. If only pulmonary congestion and edema were present, with or without hemorrhage, the case was considered negative. In addition, when certain points needed clarification, the case was discussed with the pathologist or toxicologist involved. After compiling this data, 47 cases have been excluded from this study because of either the presence of drugs such as morphine, quinine, or high levels of other depressants or stimulants, or failure to determine the route of administration.

Results

The 43 cases included in this study have been divided into three groups. The first two groups include 33 cases where death was due to an adverse effect of methadone. The third group, a control group, includes 10 cases where death was due to causes other than drugs and where methadone was only an interesting incidental finding.

In 8 of the 11 cases in Group A (Table 1), death followed the intravenous injection of methadone. In all but one case the level of methadone in the blood was found to be 0.05 mg percent or greater. In Case 3 no methadone was found in any of the body tissues despite an unquestionable history of injection. The absence of methadone could be accounted for by the 13-h delay. In 6 of the 8 cases no methadone was detectable in the gastric content and in the other 2 cases only low levels of methadone were detected in the stomach. In all cases, the ratio of the concentration of methadone in the stomach to that in the blood was 4:1 or less. In 2 of the 8 cases, microscopic examination of the lungs demonstrated the presence of bronchopneumonia; one of these was in the case with the 13-h delay.

In 2 of the 11 cases in Group A, Cases 4 and 7, the route of administration was determined solely by the presence of fresh needle marks. Each had a low blood methadone level and a relatively high gastric methadone level with a stomach to blood ratio well above 4:1. Each had bronchopneumonia. These cases better fit the pattern of ingestion

[2] In Philadelphia, all cases where the death is suspected of being due to narcotics or dangerous drugs receive a complete autopsy and toxicological examination.

TABLE 1—*Group A—Intravenous.*

Number	Route	Stomach[1]	Blood[1]	Urine[1]	Stomach : Blood[2]	Delay[3]	Pathology	Comments
1	I.V.	0	0.07	0.62	0	?	−	
2	I.V.	0	0.07	0.65	0	?	−	
3	I.V.	0	0	0	0	13 h	+	No question of I.V. methadone
4	?I.V.	0.39	0.02	0.93	20	?	±	Fresh needle marks
5	I.V.	0	0.23	0.81	0	6 h	−	
6	I.V.	0	0.19	0.30	0	?	−	Dolophine in bottle and syringe
7	?I.V.	2.10	0.01	0.61	210	?	+	Fresh needle marks
8	I.V.	0	0.09	0	0	20 min	−	Methaqualone also present
9	I.V.	0.20	0.05	0.36	4	?	+	Syringe, Dolophine found
10	?I.V.	0.15	0.12	0.7	1.2	3 h	−	Recent needle marks on neck and arms
11	I.V.	0.20	0.25	0.70	0.8	?	−	Recent needle marks, 4 vials Dolophine

I.V. = Intravenous.

[1] The values for blood, urine, and stomach are given in mg percent.

[2] The stomach to blood ratio is obtained by dividing the concentration of methadone in the stomach by the concentration in the blood.

[3] The delay is determined by history and is the time elapsed between administration of the drug and death.

than injection. Case 10 was also placed in this group solely because of the presence of fresh needle marks. This case fits the pattern of injection.

Group B (Table 2) contains 14 cases where death followed the ingestion of methadone and an additional 8 cases where death was presumed to follow the ingestion of methadone because no fresh needle marks could be identified. In all but 2 cases (Cases 15 and 21[3]) the levels of methadone in the blood were 0.05 mg percent or less. In all but one case (Case 6) methadone was present in the gastric content and that case involved a 36-h delay in the hospital. In all but 4 cases the stomach to blood ratio was 10:1 or greater. One of these was Case 6 with the 36-h delay and another was Case 21.[3] In 16 of the 22 cases microscopic bronchopneumonia was present.

Group C (Table 3), the control group, contains 8 cases in which the cause of death was unrelated to drugs. The levels found in these individuals reflect levels that are compatible with life and presumably could be found in anyone receiving therapeutic doses of methadone. For the most part, the blood methadone levels range from 0.03 to 0.06 mg percent.

The last two cases in this group are examples of deaths due to the combined effect of drugs. They are of interest because the methadone was administered intramuscularly. The blood levels were 0.04 mg percent and 0.06 mg percent and Case 9 had a low level of methadone in the stomach.

It is clear from these data that individuals dying from an adverse effect of methadone frequently have levels no higher than individuals dying of totally unrelated causes. This finding is further substantiated by the following two clinical experiments.

Experimental Data

Two clinical experiments were undertaken to further document some of the conclusions suggested by the above material. Neither was intended to be a definitive research project.

[3] Case 21 is a death which occurred in 1967 and is not strictly comparable to the other cases since the method of analysis changed between 1967 and 1969.

TABLE 2—*Group B—Oral.*

Number	Route	Stomach[1]	Blood[1]	Urine[1]	Stomach: Blood[2]	Delay[3]	Pathology	Comments
1	P.O.	0.28	0.01	0.47	28	?	+	In hospital; methadone, 40 mg the day before death
2	P.O.	0.82	0.05	0.20	16	3 h	+	Drank 3 ½ oz Tang
3	P.O.	0.28	0.03	0.63	10	±3 h	+	
4	?P.O.	3.50	0.05	0.23	70	±8 h	sl+	No needle marks
5	?P.O.	0.22	0.02	0.11	11	6 h	±	No needle marks
6	P.O.	0	0	0.33	0	±36 h	−	Received dose in hospital
7	P.O.	0.67	0.01	0.29	67	?	+	Methadone in hospital, 10 mg QID
8	P.O.	0.29	0.04	0.15	7	?	+	Sick 2 days, methadone in bottle
9	P.O.	0.41	0.01	0.25	41	?	−	Drank methadone
10	?P.O.	+QNS	0.02	0.1	−	?	−	
11	?P.O.	0.05	0	0.3	∞	? few h	+	No needle marks
12	P.O.	1.5	0	0.3	∞	?	±	Methadone presciption 14 tablets, 10-mg container empty at death
13	P.O.	0.07	0.02	0.40	3.5	?	+	No needle marks
14	P.O.	0.1	0.007	0.3	17	12 h	+	
15	P.O.	1.5	<0.1	0.8	15	5 ½ h	+	Resolving myocarditis
16	?P.O.	QNS	0.03	QNS	−	?	+	Body decomposed
17	?P.O.	1.20	0.03	0.04	40	?	−	Pill abuser, suicidal
18	?P.O.	2.4	0.04	0.4	60	?	+	No fresh marks
19	P.O.	0.7	0.006	0.4	117	2+ h	+	No old or recent marks
20	?P.O.	ND	0.04	0.2	−	?36 h	+	Cell death
21	P.O.	17	2.6	−	6.5	?	ND	3-year-old child
22	P.O.	2.40	0.045	QNS	53	?	−	18-month-old child, accident

P.O. = oral.
QNS = quantity not sufficient.
ND = not determined.
sl = slightly.

[1] The values for blood, urine, and stomach are given in mg percent.

[2] The stomach to blood ratio is obtained by dividing the concentration of methadone in the stomach by the concentration in the blood.

[3] The delay is determined by history and is the time elapsed between administration of the drug and death.

Nonetheless, we think that they are useful in helping to explain some of our findings.

a. Blood samples were obtained from eight heroin addicts on a methadone maintenance program just prior to receiving their daily dose and 24 h after receiving their last known dose. Each had a blood methadone level of 0.02 to 0.04 mg percent. This indicates that apparently healthy addicts have levels of 0.02 to 0.04 mg percent methadone in blood and that these levels can be maintained for periods of up to 24 h after ingestion.

b. Four addicts, admitted to a local hospital for methadone detoxification, were chosen for the second study. Each was administered 20 mg of methadone by mouth and samples of blood were drawn at approximately 0, 1, 3, 5, and 9 h after ingestion. The results are indicated in Fig. 1. Patients A, B, and C showed no rise in their blood methadone level for 1 to 3 h. Following this period, a rising level peaked at 3 to 5 h and then gradually dropped to a lower level. Patient C then shot up sharply at 9 h, a result which is totally unexplainable. Patient D shows a different curve with an initial rapid rise, peaking at 3 h and dropping by 5 h.

Based on these results and the findings of Inturrisi and Verebely [*1*, *2*] it seems fair to say that following an oral dose of methadone a delay period is followed by a rising blood

TABLE 3—*Group C—Control Group.*

Number	Route	Stomach[1]	Blood[1]	Urine[1]	Stomach : Blood[2]	Delay[3]	Cause of Death	Comments
1	?P.O.	0	0.06	0.24	0	?	Gunshot wound	
2	?I.V.	0	0.03	0.08	0	?	Gunshot wound	Needle tracts
3	P.O.	9	0.05	0.08	180	?	Arteriosclerotic heart disease	Bottle of methadone on person, coronary collapse in bar
4	?P.O.	neg.	neg.	<0.006	–	27 h	Alcoholism, pancreatitis	"Off heroin"
5	?	0	0.04	0.3	0	?	Gunshot wound	Morphine, quinine, and methamphetamine also found
6	P.O.	ND	0.05	ND	–	3–6 h	Arteriosclerotic heart disease	On methadone program
7	P.O.	ND	0.03	0.20	–	?	Cancer-stomach	Methadone tablets, 10 mg for pain
8	?P.O.	0.8	0.12	0.15	0.7	?	Pneumonia	Diabetes, cirrhosis, alcoholism, no fresh needle marks
9	I.M.	0.1	0.06	ND	1.7	?	ARND	Morphine, quinine, chlorpromazine; methadone in hospital I.M. 10 mg QID
10	I.M.	ND	0.04	0.54	–	?	ARND	Not autopsied, quinine in blood

P.O. = oral.
I.V. = intravenous.
I.M. = intramuscular.
ND = not determined.
ARND = adverse reaction to narcotic drugs.
QID = four times a day.

[1] The values for blood, urine, and stomach are given in mg percent.

[2] The stomach to blood ratio is obtained by dividing the concentration of methadone in the stomach by the concentration in the blood.

[3] The delay is determined by history and is the time elapsed between administration of the drug and death.

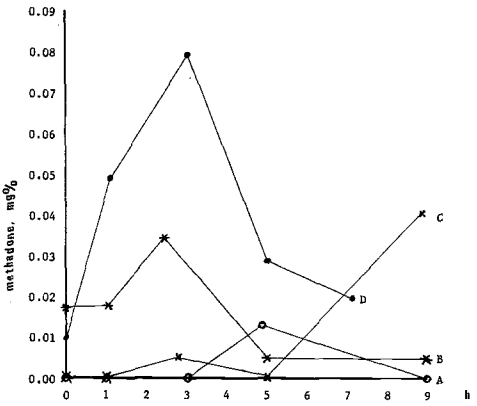

FIG. 1—*Concentration of blood methadone following the oral administration of 20 mg of methadone at 0 time to 4 addicts admitted for detoxification.*

level, peaking in 1 to 3 h, and then by a fall which plateaus. This explains the clinical picture in the first two case histories presented at the beginning of the paper.

Discussion

Ninety cases of deaths involving methadone have been reviewed. Of these, 33 were directly attributable to an adverse effect of methadone. Eleven deaths followed the intravenous administration of methadone and 22 followed the ingestion of methadone.

There are overlapping but distinct differences in the mode of death, the toxicologic findings, and the pulmonary findings depending upon the route of administration. In general, deaths following the intravenous use of methadone occurred rapidly, just as they do with intravenous heroin. In our laboratory the blood levels were usually greater than 0.05 mg percent and the stomach contained either low levels of methadone, presumably secreted, or none at all. Evidence for gastric secretion of methadone-like drugs was found in experiments with mice [*3*]. Robinson and Williams [*4*] also demonstrated the presence of methadone in the stomach in two cases where the drug was apparently injected. Further indication of gastric secretion was found in Case 9, Group C, where the drug was administered intramuscularly. In most cases, the ratio of stomach methadone to blood methadone was below 4:1. In addition, pulmonary edema without pneumonia was the usual finding. On the other hand, individuals who died following the ingestion of methadone may have had a period of up to a few hours where they manifested no ill effects of the drug. This was followed by a period of increasing cerebral and respiratory depression and death. Postmortem chemistry usually showed a blood level of 0.05 mg percent or less with a relatively high amount in the gastric content and a stomach to blood ratio greater than 10:1. Frequently the lungs showed pulmonary edema with early focal acute bronchopneumonia.

Clinical experimental data are presented which indicate that blood methadone levels of 0.02 to 0.04 mg percent can be found in addicts on methadone who are alive and apparently well. The data presented in Group C also indicate that levels in this range or even higher are not necessarily lethal. From these data, it must be concluded that those individuals in Group B who died from ingestion of methadone did not die from an overdose in the usual sense, and that these deaths are best classified as an "adverse reaction to narcotic drugs." Those individuals in Group A who died following the intravenous injection of methadone, usually had levels higher than those in the non-drug death sample and might justifiably be considered true overdoses. There are, however, documented cases where one individual survived the intravenous administration of methadone in quantities equal to or greater than that which killed another. For this reason, and until such time as a clearer understanding of the precise pathophysiologic mechanism(s) is(are) defined, the authors choose to consider all deaths due to methadone, regardless of the route of administration, as "adverse reactions to narcotic drugs."

Addendum

An additional 15 deaths related to methadone occurred in the last 2 months of 1972 bringing the total for the year to 52 cases. Among the additional deaths, 10 were directly attributable to methadone and 4 to a combination of methadone and one or more other narcotic and dangerous drugs. One was most likely a suicide following ingestion of methadone and other sedative medications.

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