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ORIGINAL ARTICLE

An epidemic of fatal 3-methylfentanyl poisoning in Estonia

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Abstract An exceptional epidemic of poisonings due to the highly potent opioid designer drug 3-methylfentanyl (TMF) was revealed among Estonian drug users in 2005–2006 by post-mortem forensic toxicology. Quantitative analysis of *cis*-TMF, *trans*-TMF, and fentanyl was performed by liquid chromatography–tandem mass spectrometry. Comprehensive toxicological analysis was performed using a multi-technique approach. The number of TMF-related fatal accidental poisonings identified was 46 and 71 for 2005 and 2006, respectively. The proportion of male victims was 91.5% and the mean age of all victims was 26 years at death. TMF was used predominantly by intravenous injection. There was no significant difference in the blood concentrations of *cis*-TMF and *trans*-TMF between pure TMF poisonings and mixed TMF poisonings. The mean combined concentration of TMF stereoisomers among pure TMF cases (1.9 μg/l) was more than ten times lower than the mean fentanyl concentration in fentanyl-related fatalities. Concomitant use of other drugs involved alcohol, amphetamines, benzodiazepines, and cannabis, but very rarely other opioids.

Keywords 3-methylfentanyl · Fatal poisoning · Post-mortem · Blood concentration · Designer drug

Introduction

Alpha-methylfentanyl, the first designer drug, appeared on the illicit drug market in California in 1979. In 1984, another fentanyl derivative, 3-methylfentanyl (TMF), was identified and the drug was involved in an epidemic of overdoses in California in 1984–1985 [1]. The first TMF seizures in Russia took place in 1990 in St. Petersburg [2]. The slang terms for alpha-methylfentanyl and TMF include "china white", "china girl", "Persian white", "egg white", "crocodile", "dragon", "999", and "synthetic heroin". TMF has so far been involved only in relatively short-lived epidemics [3, 4]. This is obviously due to the high potency of this opioid drug and the associated dosing problems: the *cis*-(+)-isomer of TMF is approximately 7,000 times as potent as morphine while the *trans*-(±)-isomer is approximately 1,000 times as potent [5]. Figure 1 shows the chemical structures of fentanyl, alpha-methylfentanyl, and *cis*- and *trans*-TMF. The compounds metabolize by *N*-dealkylation with loss of a phenethyl group, TMF yielding nor-TMF whereas alpha-methylfentanyl and fentanyl yielding norfentanyl [6].

According to Europol [7], fentanyl and its derivatives are becoming available in Estonia, Finland, Latvia, Lithuania, Sweden, and countries on the eastern border of the European Union. Fentanyl may earlier have originated mainly from the Russian Federation and Ukraine, but since 2003, experimental fentanyl production has also been reported elsewhere [7]. The Russian Federal Drug Control Service (FSKN) has reported a sharp increase in seizures of TMF by Russian law enforcement. In the first 6 months of

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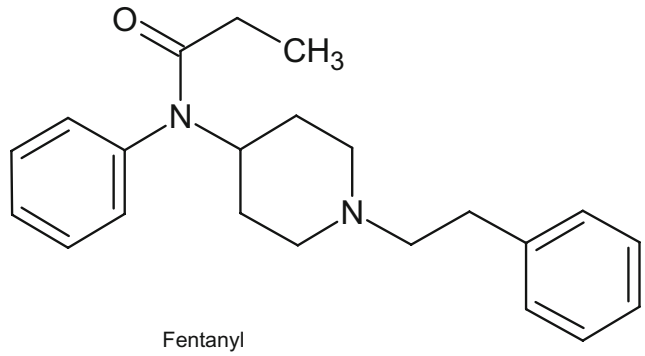

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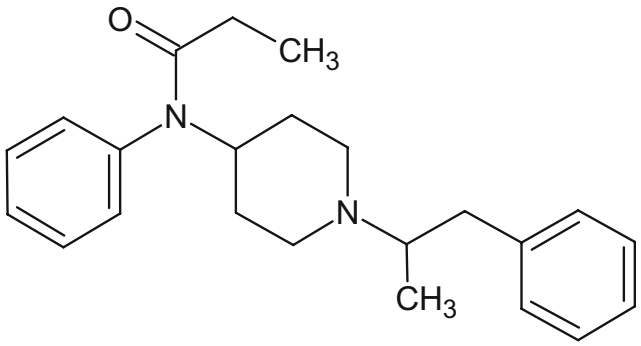

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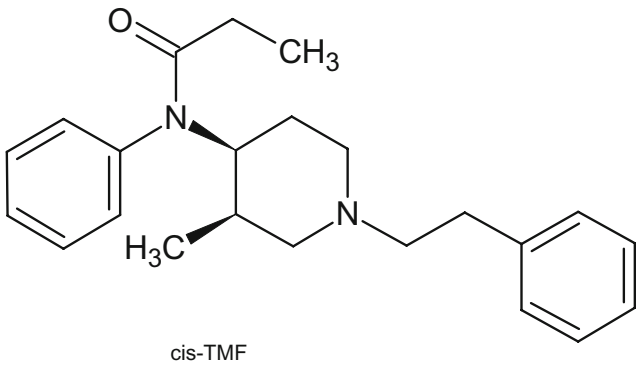
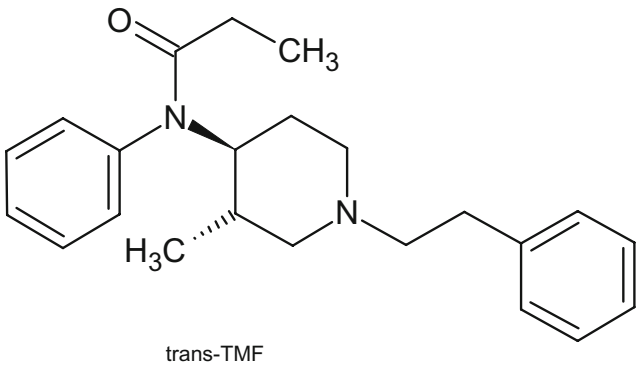


cis-TMF



trans-TMF

Fig. 1 Structures of fentanyl, alpha-methylfentanyl, and *cis*- and *trans*-TMF

2006, FSKN recorded five times more seizures of TMF than during the same period in 2005. The majority of these seizures were made in the northwest and western parts of Russia [8]. The Russian authorities reported the seizure of a large-scale TMF laboratory in Leningrad Oblast in 2007 [7].

In 2002, TMF first appeared on the Estonian drug market and by 2005, TMF and TMF-fentanyl mixtures accounted for the majority of the seizures of opiates [9]. Preliminary records from Estonia indicated 85 TMF-related deaths in 2004 and since then, the epidemic has shown no signs of subsiding. Revealing fatal TMF poisonings and quantifying the fentanyl derivatives in human samples require sophisticated analytical technology not in use until recently [10–12]. Based on TMF analysis by liquid chromatography–tandem mass spectrometry (LC–MS/MS) and comprehensive drug screening by other techniques, the main analytical toxicology findings of 117 fatal TMF cases in Estonia during 2005–2006 are reported in this study.

Methods

Standards and samples

Reference standards for *cis*- and *trans*-TMF were obtained from the United Nations International Drug Control Programme, Vienna International Centre, Austria. Fentanyl and the isotope-labeled internal standard fentanyl-d5 were purchased from Cerillant (Round Rock, TX, USA).

Post-mortem samples were collected at autopsy at the northern and eastern Departments of the Bureau of Forensic Medicine of Estonia. Blood and urine samples and the evidentiary material from the scene, when applicable, were initially analyzed for TMF by gas chromatography–mass spectrometry (GC–MS) to detect TMF positive cases.

Analysis of TMF and fentanyl by LC–MS/MS

Quantitative analysis of *cis*-TMF, *trans*-TMF, and fentanyl was performed using a dedicated LC–MS/MS method in multiple reaction monitoring mode. Preparation of blood and urine samples involved liquid–liquid extraction with butyl acetate at pH 7 as follows. Urine samples (1 ml) were hydrolyzed with 20 μl of β-glucuronidase enzyme by incubating 16 h in a water bath at 46°C. Internal standard fentanyl-d5 (20 μl of the solution 1 μg/ml) was added to 1 ml of whole blood or hydrolyzed urine samples. A 400-μl volume of Na_2HPO_4 buffer (pH 9) was added and the sample was extracted with 600 μl of butyl acetate in a vortex mixer (2 min). The organic layer was separated by centrifuging, transferred into a conical tube, and evaporated to dryness in a water bath (40°C) under air flow. The

residue was reconstituted with 150 µl of ammonium acetate buffer (10 mmol/l, 0.1% formic acid, pH 3.2) and the sample was vortexed and sonicated for 5 min. After centrifugation (5,000 rpm, 5 min), the extract was transferred to an autosampler vial and 10 µl was injected into LC–MS/MS.

LC separations were carried out with an Agilent LC 1100 binary pump, autosampler, vacuum degasser, and column oven (Agilent Technologies, Waldbronn, Germany). Separation was performed with a Phenomenex Gemini C_{18} column (100×2.0 mm, particle size 3 µm, Phenomenex, Torrance, CA, USA) and a 4.0×2.0-mm guard column. The mass spectrometric analysis was performed using an AB/MDS Sciex 3200 QTrap LC–MS/MS (Applied Biosystems, Concord, Canada) instrument in triple quadrupole mode, equipped with an AB/MDS Sciex Turbo Ion Spray interface. Analyst 1.4.1 software was used. The analytical column was stabilized at 35°C. The mobile phase gradient consisted of acetonitrile (containing 0.1% formic acid) and the ammonium acetate buffer as follows: the acetonitrile proportion was 15% for 9 min to equilibrate the column, then increased to 30% in 13 min and further increased to 80% in 10 min, and finally to 95% in 1 min to clean the column. Total flow rate through the column was 150 µl/min and run time was 38 min.

Total eluent flow from the LC was directed without splitting to the turbo ion spray source that was operated in positive mode. Needle voltage was 5.5 kV, turbo ion spray heater temperature 375°C, nebulizer gas (nitrogen) 55 psi, and turbo heater gas (nitrogen) 60 psi. Curtain gas (nitrogen) was set at 10 and collision gas (CAD, nitrogen) at 2 on the Sciex control software. The optimum values for collision energy, declustering potential, and cell entrance potential were optimized individually for each compound. Two intense fragments for the analytes and one for the internal standard were monitored. Dwell time of 50 ms was used for the transitions.

Figure 1 of the Electronic Supplementary Material presents LC–MS/MS analysis of a case positive for *cis*- and *trans*-TMF, showing the extracted ion chromatograms for both of the findings. Table 1 of the Electronic Supplementary Material shows the LC–MS/MS operational parameters and validation data for *cis*- and *trans*-TMF and fentanyl. Matrix effects were studied by comparing the relative standard deviation of drug concentrations between replicate measurements of individual spiked autopsy blood samples and different spiked autopsy blood samples. The results for the two groups showed no significant difference, suggesting that the matrix effects for the analysis of fentanyl and derivatives in blood were not significant.

Comprehensive toxicological analysis

Comprehensive toxicological analysis of blood and urine samples was performed using a multi-technique approach. Urine samples were screened for approximately 700 drugs by immunoassay, LC–MS/MS, and LC coupled with time-of-flight mass spectrometry [13]. Simultaneously, blood samples were quantitatively monitored for 200 drugs by three techniques: GC–MS for acidic/neutral drugs, GC with electron capture detection for benzodiazepines, and GC with nitrogen phosphorus detection for basic drugs [14]. Confirmation and additional determinations were carried out using GC–MS and LC–MS/MS in both urine and blood. The screening approach covered the majority of psychotropic drugs available on the licit and illicit markets, with a special emphasis on abused substances. Ethanol was analyzed in blood and urine samples by headspace GC.

Results

As shown in Table 2 of the Electronic Supplementary Material, the number of TMF-related fatal poisonings

Table 1 Concentrations of 3-methylfentanyl (TMF), fentanyl, and ethanol in blood

Year		Pure TMF cases				Mixed TMF cases			
		cis-TMF (µg/l)	*trans*-TMF (µg/l)	Fentanyl (µg/l)	Ethanol (g/kg)	*cis*-TMF (µg/l)	*trans*-TMF (µg/l)	Fentanyl (µg/l)	Ethanol (g/kg)
2005		*n*=18	*n*=17	*N*=10	*n*=5	*n*=28	*n*=28	*n*=16	*n*=17
	Mean	1.22	0.96	1.57	0.72	0.96	0.72	1.35	1.72
	Median	1.15	0.72	0.94	0.94	0.82	0.58	0.82	1.51
	Min	0.06	0.19	0.26	0.19	0.25	0.18	0.17	0.48
	Max	2.59	1.88	6.93	1.09	2.88	1.53	4.16	3.60
2006		*n*=32	*n*=32	*N*=28	*n*=12	*n*=38	*n*=39	*n*=31	*n*=17
	Mean	0.93	0.77	0.49	0.75	0.87	0.77	0.50	2.15
	Median	0.78	0.68	0.37	0.77	0.82	0.57	0.37	1.92
	Min	0.21	0.19	0.12	0.41	0.13	0.10	0.13	1.20
	Max	2.17	1.91	1.60	1.00	3.03	3.24	1.44	4.38

Table 2 Concentrations of 3-methylfentanyl (TMF) and fentanyl in urine

Year		Pure TMF cases			Mixed TMF cases		
		cis-TMF (μg/l)	*trans*-TMF (μg/l)	Fentanyl (μg/l)	*cis*-TMF (μg/l)	*trans*-TMF (μg/l)	Fentanyl (μg/l)
2005		*n*=15	*n*=15	*n*=9	*n*=21	*n*=21	*n*=14
	Mean	3.07	3.75	9.56	1.87	1.98	5.76
	Median	1.41	2.23	3.97	1.23	1.24	1.90
	Min	0.22	0.20	0.64	0.07	0.07	0.13
	Max	17.80	19.60	37.40	9.04	9.44	38.80
2006		*n*=19	*n*=20	*n*=17	*n*=34	*n*=34	*n*=26
	Mean	2.58	3.64	2.69	1.62	2.09	3.19
	Median	1.89	2.13	1.44	0.54	0.66	1.31
	Min	0.05	0.12	0.17	0.02	0.05	0.11
	Max	11.40	15.80	8.58	17.60	27.50	46.50

identified in the northern and eastern provinces of Estonia for 2005 and 2006 was 46 and 71, respectively. In all cases, the underlying cause of death was poisoning by TMF alone or together with other drugs and the manner of death was accidental. The proportion of male victims was 91.5% and the mean age of all victims was 26 years. The body was found outdoors in 19.6% and 19.7% of cases in 2005 and 2006, respectively. In 2006, the scene of death was a jail in three cases. A needle mark was detected in 97.8% and 88.7% of victims and a syringe was recovered by the police in the vicinity of the victim in 37.0% and 21.1% of cases in 2005 and 2006, respectively.

The distribution of *cis*-TMF, *trans*-TMF, and fentanyl concentrations of the individual cases in 2005 and 2006 is shown in Figs. 2 and 3 of the Electronic Supplementary Material, respectively. The low concentrations found in case 22/2005 (Fig. 2 of the Electronic Supplementary Material) are due to the fact that the victim survived for a few hours in hospital after being found unconscious at home. In cases 13/2005 and 29/2005 (Fig. 2 of the Electronic Supplementary Material), the immediate cause of death was drowning.

Basic statistical parameters for the concentrations of *cis*-TMF, *trans*-TMF, fentanyl, and alcohol in blood are shown in Table 1. A division was made into two groups: pure TMF cases, in which blood alcohol concentration was lower than 1.2 g/kg and there were no findings in the blood indicating current intoxication by other drugs, and mixed TMF cases, in which higher concentrations of alcohol and other drugs were accepted. Although the blood concentrations of both *cis*-TMF and *trans*-TMF in pure cases were generally slightly higher than in mixed cases, the groups were not found to be significantly different regarding TMF concentrations by statistical analysis (*t*-test, $p>0.05$) even when combining the 2-year data. The average combined blood concentration of the two TMF stereoisomers in the pure and mixed TMF cases was 1.9 μg/l and 1.7 μg/l, respectively. Table 2 shows the corresponding comparison of concentrations in urine.

The prevalence of drug findings other than TMF and fentanyl is shown in Table 3 of the Electronic Supplementary Material. In the following 11 cases, high toxic concentrations of other drugs or alcohol were found in blood (see Figs. 2 and 3 of the Electronic Supplementary Material): 6/2005 tramadol 2.8 mg/l, 12/2005 ethanol 3.6 g/kg, 31/2005 amphetamine 2.5 mg/l, 7/2006 ethanol 2.8 g/kg, 18/2006 amphetamine 9.1 mg/l and MDMA 2.8 mg/l, 29/2006 ethanol 2.7 g/kg, 33/2006 MDMA 1.9 mg/l, 39/2006 ethanol 2.6 g/kg, 40/2006 amphetamine 1.2 mg/l, 49/2006 ethanol 2.6 g/kg, and 54/2006 ethanol 4.4 g/kg. The other drug findings represented moderate or low concentrations in blood or past usage detected in urine analysis. No opioids other than the low number of heroin/morphine, methadone, and tramadol listed in Table 3 of the Electronic Supplementary Material were revealed by the dedicated LC–MS/MS method.

In addition to the accidental TMF poisonings described, TMF was found in the following two other fatal cases in each of the study years, but these cases were excluded from the study. In 2005, a 24-year-old female was found dead in a lavatory. A needle mark was detected and a syringe was found on the floor. She was found to be HIV positive and blood concentrations of 379, 287, and 1,290 μg/l of *cis*-TMF, *trans*-TMF, and fentanyl, respectively, were detected. These levels, which were hundreds of times higher than those generally found in the study cases, suggest grossly erroneous administration of TMF or a suicidal intention. In the other case from 2005, the cause of death was explosive trauma. In the two cases from 2006, the cause of death was hanging.

Discussion

The epidemic of TMF abuse with hundreds of fatal poisonings that has now been revealed in Estonia is rare

in three respects. Firstly, for the first time the epidemic takes place in Europe instead of the USA, where street fentanyls have been available since 1979 [15]. Secondly, the epidemic is exceptionally long-lived and pernicious, having now been underway for 5 years and having claimed hundreds of victims. Thirdly, very little is known on the phenomenon at the international level, judging by the absence of information on TMF poisonings in the annual drug situation reports of the United Nations and the European Union. Consequently, the present study is the first that reports the magnitude of the problem along with key analytical findings based on full post-mortem forensic toxicology investigation.

The results strongly suggest that within the present epidemic, TMF is used predominantly by intravenous injection. Hence, its abuse patterns are more similar to heroin than to the conventional abuse of fentanyl, which commonly occurs by transdermal application of commercial fentanyl patches [16–19]. Fentanyl abuse patterns have, however, approached heroin abuse recently through the practice of injecting the contents of fentanyl patches [20, 21] and, very recently, due to the production of illicit fentanyl for intravenous use by clandestine laboratories [22]. Another new feature at the drug scene is the appearance of fentanyl-laced heroin and cocaine in the US [23].

Ages of the TMF victims, averaging 26 years, are comparable to the average ages found previously in fatal heroin poisonings. However, ages in the latter group have grown steadily [24]: a large Italian study of heroin-related deaths revealed an increase in average ages from 26 to 34 during 1985–1998 [25]. In an earlier TMF epidemic (1987–1988), TMF overdose fatalities had an average age of 35 years [3, 4]. Four recent North American studies on fentanyl-related deaths reported the victims' average ages in years as 37 [16], 39 [21], 45 [17], and 46 [19]. The Estonian victims of fatal TMF overdose are thus exceptionally young compared to drug addicts in general, which may reflect the extremely high potency and problematic dosing of this fentanyl analogue causing death at a young age.

It has been stated that the poor quality of the heroin available on the local market in Estonia has been compensated for since 2002 by the introduction of synthetic opiates [26]. This is the opposite of neighboring Finland where heroin has been absent since the Afghanistan crisis but where intravenous buprenorphine is abused instead [27]. Only three TMF deaths have been reported in Finland, all of them taking place in 2002 [11]. One reason for the popularity of TMF in Estonia may be the country's large Russian-speaking population, which makes it easier to interconnect with drug traffickers on the Russian side. It is not known if fatal TMF poisonings occur in other countries of the Baltic area as post-mortem cases are not being screened for TMF regularly in all countries.

TMF exhibits very low concentrations in biological samples and requires dedicated qualitative and quantitative methods of analysis. Previously, analysis of fentanyl and its analogues in human samples has mainly been performed by urine and blood radioimmunoassay [28], but at present, enzyme immunoassays with sufficient sensitivity are also available [29]. Immunoassays cannot, however, differentiate between various fentanyl analogues, much less their stereoisomers. Based on initial GC–MS screening for TMF in diverse specimens and subsequent LC–MS/MS quantification, we are now able to reliably detect the victims of TMF and determine the *cis*- and *trans*-TMF concentrations in blood and urine. The average combined concentration of these two stereoisomers in blood among the pure TMF cases, being 1.9 μg/l, is more than ten times lower than the mean fentanyl concentration (25 μg/l) found in fatal poisonings attributed solely to fentanyl [17].

There was no statistically significant difference in blood TMF concentrations between the pure TMF cases and the mixed TMF cases (Table 1). This is consistent with the previous knowledge that, with opioid drugs, there is no obvious relationship between blood concentration of the drug and outcome [24, 30]. The finding also strengthens the assumption that immediate overdose of TMF was the underlying cause of death irrespective of other drugs present. Eleven cases were identified in which high concentrations of other drugs or alcohol were measured in blood, but these levels were not necessarily fatal for addicts with high tolerance. Several examples exist in the literature of motorists with >5 mg/l of amphetamine [31] or 0.4% *w/v* of alcohol in their blood [32]. In any event, the concomitant use of alcohol and other CNS depressants, as shown in Table 3 of the Electronic Supplementary Material, obviously plays a role in the present TMF-related fatalities.

The Estonian epidemic of fatal TMF poisonings warrants international public awareness, as this new drug problem may proliferate and affect the whole of Europe. More research on the abuse patterns of TMF is needed to assess suitable preventive measures and to reduce mortality among drug users. Post-mortem epidemiology has proved to be a powerful approach to reveal trends in illicit drug use and to improve drug safety in general [33–35].

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