

Case Series

Injection of fentanyl patches – a deadly route

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Abstract

Transdermal fentanyl therapeutic system was developed to provide continuous, controlled, systemic release of fentanyl. Modifying the route of administration of the drug by violating the appropriate, proposed medical method for the treatment regimen can be fatal. We present four (4) fatal cases of intravenous abuse of fentanyl transdermal patches, which took place in the wider region of Northern Greece in a short time period. We review the reported cases worldwide and emphasize the importance of public awareness for the prevention of fatalities.

Key words: fentanyl-related death, intravenous drug abuse, transdermal fentanyl patches

Introduction

Fentanyl is an extremely potent analgesic and anesthetic synthetic opioid, whose chemical properties enable different routes of administration. This novel drug was synthesized in the 60's and is widely used since. The development of multiple pharmaceutical dosage forms increased its market dissemination and availability. One of these formulations was the transdermal therapeutic system (TTS) which provides continuous, controlled, systemic release of fentanyl [1].

Opioids constitute a significant part of the drug abuse problem, including fentanyl abuse, which rapidly increased with the introduction of transdermal patches [2].

The increase in fentanyl-related mortality, both through prescription medication and through illicit use, was attributed to the toxicity of fentanyl, either as a single administration or in combination with other drugs, to the extent that it was characterized in developed countries, such as the United States of America and Canada, as "fentanyl epidemic" [3], [4].

The drug's potency and the lack of awareness for the great importance of its proper use intensified the problem in the years following the introduction of fentanyl into the pharmaceutical market [5].

The high toxicity of fentanyl, combined with its addictiveness, as it produces 50 to 2000 times greater than heroin euphoric symptoms, if IV applied, has signaled an alert for the ease with which it can be spread to drug addicts' circles [6]. To quickly achieve the euphoric level, drug users modify the delivery route of the transdermal patch, in violation of the drug's instructions [2]. It should be noted that high toxicity is not the only factor contributing to the increased risk of fentanyl abuse with respect to other opioids; fentanyl transdermal patch (the 72h regimen) contains a fatal amount of opioid when it is intravenously administered [7]. The first case of intravenous abuse of a transdermal fentanyl patch was reported by DeSio and his colleagues [7] in 1993.

We present four (4) fatal cases of intravenous abuse of fentanyl TTS originating from the wider region of Central and Eastern Macedonia and

Thrace. Three of these were processed at the Laboratory of Forensic Medicine and Toxicology of Democritus University of Thrace and the fourth at the corresponding Laboratory of Aristotle University of Thessaloniki. All cases occurred within three years' time.

In the light that the reported number of deaths from intravenous fentanyl patches abuse is only 12 worldwide; our report reflects the rare phenomenon of the accumulation of four fatalities in a short period in a small Greek territory.

Case Presentations

In all cases, the death scene was examined to exclude the possibility of a criminal act, including the position of the deceased. Medical history and clinical records of the victims and additional information from the deceased's relatives or friendly environment and police investigating authorities was obtained. Later, autopsy was performed to clarify the cause of death and collect biological samples for toxicological analysis. External examination of the body included recording body weight and height and identifying and photographing skin features, such as tattoos, venipunctures, recent or old scars, etc. Thorough internal examination of the deceased was performed, during which biological material (blood, urine, bile) and visceral tissue biopsies were obtained and forwarded, for laboratory documentation of the use of addictive substances. All biological samples were screened for ethanol and drugs of abuse. For presumptive positive screening tests, confirmatory analysis was performed by Gas Chromatography/Mass Spectrometry (GC-MS).

Case 1

A 46-year-old female of 57 kg weight and 1.66 m height, with a known long history of heroin

and ethanol abuse, was found dead at home. Externally, the decedent had a recent venipuncture on her left arm. An empty Durogesic 12 µg/h package was found in the trash, but no sign of a patch was spotted on her skin and no syringe or other drug IV equipment was discovered. Presumably, paraphernalia were removed from the scene by co-users, friends, or relatives. During forensic autopsy, the brain was markedly edematous and in the thoracic region there was pulmonary congestion and edema. From the presumptive screening tests of biological fluids (blood and urine), performed at the Laboratory of Pharmacology of the General University Hospital of Alexandroupolis, resulted negativity for ethanol, cannabinoids and opiates and positivity for benzodiazepines. After these results, additional confirmatory toxicological analysis was carried out at the Laboratory of Forensic Medicine and Toxicology of the National and Kapodistrian University of Athens and concluded positivity for fentanyl at a concentration of 8 ng/mL in blood sample.

Case 2

A 24-year-old man of 81 kg weight and 1.73 m height, with a history of alcoholism and continuous intravenous heroin use over the last four years, was found dead after a day's search, at a building under construction. During examination of the scene, we found equipment for intravenous drug use and a used Durogesic 12 µg/h package. An insulin syringe full of yellowish liquid was observed on his left arm and a tourniquet above it. Additionally, there was evidence of contusions on his left facial, frontal and nasal area, which were not responsible for his death and attributed to falling on the building materials, where he was found. During autopsy, we observed marked brain edema and severe congestion of the lungs.

	Author	Year	Cases	Gender		Drug Inter-actions	Deaths
				Male	Female		
1	DeSio et al. [7]	1993	1	-	1	-	-
2	Reeves & Ginifer [8]	2002	2	1	1	-	1
3	Kuhlman et al. [9]	2003	5*	3	2	2	5
4	Tharp et al. [10]	2004	4	4	-	3	4
5	Lilleng et al. [11]	2004	2	2	-	2	2
6	Jost et al. [22]	2004	1	1	-	-	-
7	Martin et. al. [23]	2006	10*	10	-	1	10
8	Magdalan [24]	2009	1	1	-	-	-
9	Schauer et al. [25]	2015	1	-	1	-	-
10	Sinicina et al. [15]	2017	72*	Not reported	Not reported	Not reported	72
	Total		99	22	5	8	94

Table 1. Review of reported cases of abuse of fentanyl transdermal system with intravenous administration (* 5 out of 23 / 10 out of 112 and 72 out of 242 fatal cases.)

Blood and urine samples were sent for toxicological analysis to the Laboratory of Pharmacology of the General University Hospital of Alexandroupolis, as well as to the Laboratory of Forensic Medicine and Toxicology of the National and Kapodistrian University of Athens. The presumptive screening tests were positive for benzodiazepines and cannabinoids and negative for opiates. Biological materials processed by the Laboratory of Forensic Medicine and Toxicology of the National and Kapodistrian University of Athens, were negative for ethanol and positive for bromazepam, cannabinoids and fentanyl, that was detected and quantified in the blood sample at the concentration of 98 ng/mL. Fentanyl was also identified in the remnants from the syringe.

Case 3

A 37-year-old man, of 86 kg weight and 1.81 m height, was found dead in his home by his father two days after he had last been known to be alive. The deceased had a history of hepatic cirrhosis, due to chronic alcoholism and use of addictive substances (opioids, cannabis and benzodiazepines). Tools for intravenous drug use were found at the death scene, as well as a coffee pot containing a molten plastic residue from a Durogesic transdermal patch. At external examination, we observed a tourniquet in his right upper limb and a recent venipuncture under it, while old needle marks were seen to both his

upper limbs. During forensic autopsy, severe cerebral edema was found, while the lungs were edematous. The toxicological analysis by the Laboratory of Toxicology of Aristotle University of Thessaloniki was positive for benzodiazepines and positive for fentanyl in blood sample. Although the fentanyl concentration in the blood was “very high”, quantification was not possible.

Case 4

A 34-year-old man, of 83 kg weight and 1.77 m height, chronic user of addictive substances (heroin, benzodiazepines, cannabis) for at least five years, was found dead in a building under construction. External examination revealed old needle puncture sites in his upper and lower extremities and a recent venipuncture on his left arm. During forensic autopsy, acute pulmonary and cerebral edema was found. The results of the toxicological analysis by the Laboratory of Toxicology of Aristotle University of Thessaloniki were positive for diazepam, nordiazepam, oxazepam, bromazepam, temazepam, 7-amino flunitrazepam and fentanyl in blood sample. In this case fentanyl was primarily detected, but again quantification was not possible.

Discussion

Fentanyl abuse and related deaths has a young to middle aged male predilection [26].

Accordingly, our cases comprised 3 males and 1 female with ages ranging from 24 to 46 years.



Figure 1. Isolation by heating of the active substance from fentanyl transdermal patch (Case 3).



Figure 2. Intravenous injection of fentanyl (Case 2).

All cases had a known prior history of drug abuse. Information gathered from co-consumers and / or relatives revealed that the supply of fentanyl transdermal patches was through legal prescription to patients, who were relatives of the deceased. The latter, after illegally obtaining the pharmaceutical preparations, isolated fentanyl by heating the patch and injected it in their body (Fig. 1, Fig. 2).

In most fentanyl abuse cases reported in the international literature, death comes due to interaction with other toxic substances, mainly ethanol, amphetamine, cocaine, codeine, benzodiazepines and others [9], [10], [12], [13], [14], [15].

The toxicological analysis of all four cases detected the presence of other addictive substances in addition to fentanyl including cannabinoids and benzodiazepines and so the intoxication could not be attributed to fentanyl alone. In view of the low concentrations of the accompanying drugs compared to the fentanyl concentration, fentanyl was considered as the leading substance.

Despite extensive international research efforts, as in Andresen et al. [16] review, it is not

possible to determine a marginal level between toxic and non-toxic concentrations of fentanyl. The determination of the precise antemortem dose of fentanyl with the use of its postmortem concentrations is impossible in cases of abuse [17], and even in cases of prescriptive therapeutic use [18].

In fact, many factors may play a role in each case: the degree of opioid tolerance is the most important, as it can explain why new users show extremely high concentrations of the substance and run the risk of a single application of the transdermal patch being fatal [13].

The diversity of postmortem fentanyl concentration levels involves the time elapsed from fentanyl use to the time of death and the possibility of multiple, simultaneous routes of administration [14] [15] [26]. Postmortem redistribution of fentanyl should also be considered, since completely different pharmacokinetics of the substance is observed in new users [17]. Other idiosyncratic factors may also play a role, such as obesity [16]. As observed from body mass indexes (BMI) none of the decedents in our cases were obese; they were in weight normal range.

The reported levels of fentanyl (8 and 98 ng/mL for cases 1 and 2 respectively) were consistent with the Anderson and Muto [19] suggestion that "Postmortem blood fentanyl levels following therapeutic administration can range to 7 µg/L." Furthermore, the post-mortem fentanyl redistribution phenomenon seems to be enhanced as the drug levels increase [19]. Fentanyl related death occurs from acute respiratory failure, accompanied by severe cerebral and pulmonary edema, as has been observed in all our cases, in accordance with international literature.

It is also noteworthy that in the death reports associated with fentanyl's abuse, there is a period of accumulation of fatal incidents, ranging from 2 to 55 months [10], [12], [20]. The same plateau was also observed in our cases, considering that three out of four (in the Thrace district) took place in just a three-month period. This observation demonstrates that probably the information about fentanyl isolation and abuse methods is rapidly spread among drug addicts' circles.

Another important factor is that transdermal fentanyl patches are relatively easy to obtain. Users can secretly or violently detach them from their chronically ill relatives [13] or they can obtain them by misleading doctors to multiple prescribing [7], or even remove them from the dead body of cancer patients [21].

In several reported cases of transdermal fentanyl-related deaths, it is not entirely possible to document the precise way of use of the patch. Its intravenous abuse is deduced from the presence of needle puncture sites on the cadaver, either from testimonies of relatives or friends and "co-users" of the deceased, or when it is the most likely cause of death, with the method of exclusion [15].

In our literature search, we unearthed 10 reports, with 99 cases of intravenous abuse of fentanyl patches, 94 of which fatal (Table 1). The large study of fentanyl-related deaths in Germany by Sinicina et al (2017) considerably raises the number of the reported abuse cases, but no further information is available regarding gender and mixed intoxication of the cases.

There is a remarkable proposal, introduced by Reeves & Ginifer [8], highlighting the importance of

proper use of transdermal patches after legal prescribing and safe storage, to avoid the possibility of them being stolen. They also suggested that accounting of the transdermal patches should be legislated, accompanied by the obligation to return the used patches to make it possible for new ones to be prescribed. The latter method does not find us in agreement, as there is no way to ensure that the transdermal patches have been appropriately used.

Conclusion

Public warning about the danger of fentanyl, targeted on both health care professionals and drug addicts, is crucial to fatalities prevention. In our point of view, more than monitoring its prescription, bringing the lethal potential of fentanyl abuse to public attention is the most important factor for eliminating its further illegal and uncontrolled use.

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