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CASE REPORT

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Oral Abuse of Fentanyl Patches (Duragesic®): Seven Case Reports

ABSTRACT: In order to increase the understanding regarding the oral abuse and potential toxicity of fentanyl patches seven cases were identified over a 3-year period where fentanyl, either alone or in combination with other factors, contributed to death following the oral abuse of Duragesic® patches. The decedents comprised three females and four males with ages ranging from 20 to 51 years. Postmortem blood fentanyl concentrations were determined in all cases and ranged from 7 to 97 ng/mL. Two deaths were classified as a fentanyl overdose, three deaths were classified as a fentanyl and ethanol overdose, one death was considered a mixed drug intoxication and the remaining death was determined to be a combination of fentanyl and medical causes. These cases represent the largest reported series of deaths following the oral administration of transdermal fentanyl patches and provide detailed information on the potential for the abuse of transdermal Duragesic® patches via this route. The postmortem blood fentanyl concentrations detected for each of the decedents demonstrate the potentially fatal blood concentrations that can arise after this relatively rare route of administration.

KEYWORDS: forensic science, forensic toxicology, fentanyl, death, blood concentration, postmortem, oral, Duragesic®, transmucosal

Fentanyl is a synthetic narcotic analgesic that is available for the management of chronic pain. In Canada, one of the available formulations of fentanyl is a transdermal patch (i.e., Duragesic®, Janssen-Ortho, Toronto, Ontario, Canada). Transdermal patches contain 2.5, 5, 7.5 or 10 mg of fentanyl and provide a dose of 25–100 μg/h for up to 72 h. The patch is constructed as a rectangular, transparent unit composed of four functional layers and a protective peel strip. The drug reservoir layer is housed behind a rate-control membrane and contains fentanyl in an alcohol based gel. In addition, fentanyl is also present in the silicone adhesive layer.

Aside from the drug's therapeutic applications, fentanyl is a potent drug of abuse. In particular, the abuse of transdermal fentanyl patches has received increasing attention in recent years (1,2). The abuse of fentanyl patches by the nontreatment population is not restricted to transdermal application and reports of intravenous injection of patch contents (3,4) as well as oral/transmucosal administration (5–8); rectal insertion (9); and volatilization and inhalation of fentanyl patches (10) have been identified.

This report describes the oral abuse of transdermal fentanyl patches in seven cases and provides detailed histories to increase the information on this potential route of administration of fentanyl. The resulting postmortem blood concentrations achieved following this route of administration are also provided.

Methods

Fentanyl-related deaths following the oral/transmucosal administration of transdermal patches were identified via a retrospective analysis of fentanyl-related deaths occurring in the province of Ontario for the 3-year time period between January 1, 2002, and December 31, 2004. The route of fentanyl administration was classified as oral/transmucosal based on witness reports of the individuals chewing fentanyl patches prior to death or the finding of fentanyl patches in the oral cavity or pharynx during autopsy. Blood fentanyl concentrations and additional toxicological findings were obtained from the Toxicology Section of the Centre of Forensic Sciences, which provides the sole toxicology testing for coroner's investigations in the province of Ontario (approximate population 12 million). Further information pertaining to the circumstances of death, autopsy findings, and cause and manner of death was obtained from the Office of the Chief Coroner of Ontario.

The Centre of Forensic Sciences does not use a screening method to detect the presence of fentanyl, thus all cases in which fentanyl was quantitated were cases in which targeted analysis for the drug had been performed. Fentanyl was extracted from blood samples by liquid/liquid extraction and quantitation was performed using gas chromatography–mass spectrometry (GC/MS) in the electron-impact ionization positive ion mode with selected ion monitoring. In all seven cases, toxicological testing also included a general drug screen by gas chromatography (GC) and GC/MS which is capable of detecting approximately 140 chemically-basic drugs; analysis for volatiles (including ethanol); and in six of the cases an enzyme-linked immunoassay screen (ELISA) for the detection of opiates, cannabinoid metabolites, barbiturates, and benzoylecgonine was also conducted.

Case Reports

Case 1

The deceased was a 42-year-old male who was found dead by his neighbor. He was last seen alive at 1 p.m. the previous day, when he was observed to be lying on the floor of his apartment wearing his coat. At 4 p.m. he was seen in the fetal position in bed, the same position in which he was found deceased at 11 p.m. later that night. He had a history of alcohol abuse and had recently had his right toe amputated due to frost bite. He had prescriptions

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for lorazepam and fentanyl (Duragesic®, 50 μg/h). An investigation of the scene identified numerous prescription bottles and drug paraphernalia. Information obtained from a friend of the deceased indicated it was not unusual to find him passed out in the middle of the afternoon, as he was a heavy drinker and substance abuser. Postmortem examination revealed two small pieces of plastic (constituents of a fentanyl patch) in the mouth that were not obstructing the airway. In the posterior oropharynx two further pieces of plastic were found, again these were not obstructing the airway. There were no other significant findings at autopsy. Toxicological analyses revealed a heart blood fentanyl concentration of 22 ng/mL. Amitriptyline (0.4 mg/L) and nortriptyline (0.4 mg/L) were also detected in the blood. Testing also revealed the presence of doxepin and codeine; however, quantitation was not performed based on the case history and on the fentanyl concentration. The cause of death was attributed to fentanyl overdose and the manner of death was accident.

Case 2

The deceased was a 20-year-old female who was known to have ingested fentanyl patches on previous occasions. Although she was prescribed fentanyl (Duragesic®, 100 μg/h), the reason for this prescription was not known. On the evening before death she was observed chewing a fentanyl patch and a fentanyl patch was found at the scene, resealed in its package with black tape. Toxicological analyses revealed a femoral blood fentanyl concentration of 13 ng/mL. Methylenedioxymethamphetamine (MDMA) was also detected at a concentration of 0.17 mg/L. The cause of death was attributed to fentanyl overdose and the manner of death was accident.

Case 3

The deceased was a 51-year-old female who had a long history of prescription drug abuse. She was observed chewing a fentanyl patch and taking other prescription medications prior to falling asleep on the sofa. She was found unresponsive hours later. Paramedics were called but she was pronounced dead at the scene. There were no signs of trauma and no evidence of street drug use; however, there were multiple prescriptions for fentanyl and various benzodiazepines all prescribed by different physicians. The prescriptions for fentanyl were in her husband's name. Toxicological analyses revealed a femoral blood fentanyl concentration of 97 ng/mL. Methadone (0.15 mg/L), citalopram (1.1 mg/L), nortriptyline (1.1 mg/L), temazepam (0.13 mg/L) and diphenhydramine (>2.0 mg/L) were also detected. Testing also revealed the presence of diazepam, nordiazepam, and oxazepam; however, quantitation of these drugs was not performed based on the case history and the other drug findings. The cause of death was attributed to mixed drug overdose and the manner of death was accident.

Case 4

This 46-year-old male with a history of drug abuse had recently been prescribed fentanyl (Duragesic®, 100 μg/h) as an alternative to sustained-release morphine for control of neuralgic-type chronic pain. He was found without vital signs by his wife in the bathroom of their home. Vomitus beneath his face contained the remnants of a Duragesic® patch. Resuscitation attempts were unsuccessful. At autopsy, a perforated duodenal ulcer was detected with approximately 1 L of blood in the abdomen. He was also found to be wearing two Duragesic® patches, one on each buttock. Toxicological analyses revealed a femoral blood fentanyl concentration of 19 ng/mL. Alprazolam (97 ng/mL) was also detected. The cause of death was ruled to be a combination of pathological and toxicological reasons (perforated duodenal ulcer, fentanyl toxicity) and the manner of death was undetermined.

Case 5

The deceased in this case, a 42-year-old female, had a history of alcoholism and had been observed drinking in the early hours of the morning before falling asleep on a living room chair. Later that morning she was noted to be unresponsive. Emergency services were called and instructions on how to position the woman were given via telephone. Upon arrival, paramedics secured her airway at the scene via endotracheal intubation. During this procedure they found a "foreign object" lodged in the back of her mouth that was removed easily with fingers. During a search of the deceased's property an open Duragesic® package was located in the front pocket of a pair of jeans. She was transferred to hospital but resuscitative attempts were unsuccessful. In addition to alcoholism, the deceased's medical history included a self inflicted abdominal stab wound in a past suicide attempt and a fractured left humerus as a result of an assault that required open reduction and internal fixation. Medications found with the deceased included a Flovent® (GlaxoSmithKline, Mississauga, Ontario, Canada, fluticasone) inhaler, Naprosyn® (Roche Mississauga, Ontario, Canada, naproxen), and Tylenol® (Janssen-Ortho) No.3 (acetaminophen with codeine). The pharmacy listed on these medications was contacted and provided information that previous prescriptions in the deceased's name also included lorazepam and chlordiazepoxide. There was no apparent history of a prescription for fentanyl. Postmortem examination revealed no evidence of trauma or assault and no needle track marks. No obvious pathology was noted. An examination of the foreign body found it to be tough transparent plastic measuring approximately 5 × 3 cm. It appeared to have a cavity and had been thoroughly chewed. It was concluded that it was consistent with the size and texture of a Duragesic® patch. In this case a blood sample taken on admission to hospital was available for toxicological analysis in addition to femoral and heart blood samples taken at autopsy. The fentanyl concentrations in these three samples were 14, 28, and 32 ng/mL respectively. The blood ethanol concentration was 160 mg/100 mL and the urine ethanol concentration was 238 mg/100 mL. The only other findings were trace levels of chlorpheniramine, amitriptyline, nortriptyline, codeine, and dextromethorphan. The cause of death was attributed to combined fentanyl and ethanol overdose and the manner of death was accident.

Case 6

This 32-year-old male, a known chronic alcoholic and drug abuser, was a passenger in a car when the driver noticed he appeared unwell. The vehicle was stopped and paramedics were called. When they arrived at the scene he was without vital signs and could not be resuscitated. The driver of the vehicle stated that the deceased had been consuming large quantities of alcohol whilst in the car and that they had argued when he refused to provide him with additional alcohol. In addition, the driver stated that the deceased also chewed two Duragesic® patches whilst in the vehicle. An investigation of the car revealed an open box of Duragesic® patches (50 μg/h) that were prescribed to the driver. Toxicological analyses revealed a heart blood fentanyl concentration of 7 ng/mL. Blood and urine ethanol concentrations of 209 and 287 mg/100 mL respectively were also detected. The only

other toxicological finding was the indication of cannabinoid metabolites in the blood. There were no major findings at autopsy and the cause of death was attributed to fentanyl and ethanol overdose and the manner of death was accident.

Case 7

The deceased was a 41-year-old male who had a history of drug abuse and a chronic pain condition. He was being treated with Duragesic® patches (25 μg/h) for the latter although he was known to be a challenging patient due to his history of drug abuse. On the day of his death he reportedly consumed one beer and was then witnessed to chew a fentanyl patch before going to sleep. He was observed breathing heavily and 2 h later was found cold and unresponsive. Paramedics were called but he could not be resuscitated and was pronounced dead in the local emergency department.

Toxicological analyses revealed a heart blood fentanyl concentration of 8 ng/mL. Blood and urine ethanol concentrations of 171 and 243 mg/100mL, respectively, were also detected. The only other toxicological finding was the indication of cannabinoid metabolites in the blood. At autopsy, the only postmortem findings were an acute upper gastrointestinal bleed and peripancreatic hemorrhage therefore the cause of death was attributed to fentanyl and ethanol overdose. The manner of death was considered accidental.

Results & Discussion

During the time period between 2002 and 2004 a total of 112 fentanyl-related deaths were identified. Seven of these deaths occurred following the oral administration of fentanyl patches. Although isolated reports of oral/transmucosal abuse of fentanyl patches have been previously reported in the literature, this is the largest reported collection of cases presented by a single laboratory to date. The seven decedents described in the current study comprise three females and four males with ages ranging from 20 to 51 years. Postmortem blood fentanyl concentrations were determined for all cases and ranged from 7 to 97 ng/mL. In four previously reported cases where postmortem blood fentanyl concentrations following the oral abuse of transdermal patches have been provided, blood concentrations ranged from 2.5–31 ng/mL with a mean of 14 ng/mL (2,5–7). In addition, the postmortem fentanyl concentrations in the seven cases in this study are consistent with fatal levels reported following other routes of administration (1,2,11).

In four of the seven cases the decedents had their own prescription for fentanyl, although each of these individuals was also known to have a history of drug abuse. In one case the deceased had ingested her husband's prescription, in a second case the individual used a friend's prescription and in the final case the source of the fentanyl could not be determined. Oral abuse of fentanyl in combination with ethanol was common as was the use/abuse of other drugs, as illustrated by the case histories provided.

A summary of the blood fentanyl concentrations in relation to the cause of death is provided in Table 1. There were two cases identified in which fentanyl alone was considered to have caused death. Three deaths were attributed to combined fentanyl and ethanol intoxication and in all three cases the blood alcohol concentration exceeded 150 mg/100 mL. Interestingly, the highest fentanyl concentration observed following oral/transmucosal administration (97 ng/mL) was determined in the single case where death was attributed to mixed drug toxicity. Finally, one death was attributed to fentanyl toxicity in combination with a significant underlying medical cause. All seven cases were considered to have been due to accidental drug overdose, with no indication that any of the decedents ingested the Duragesic® patches for the purposes of suicide.

TABLE 1—*Blood fentanyl concentrations (ng/mL) categorized according to medical cause of death.*

	Cause of Death			
	Fentanyl Overdose	Mixed Drug Toxicity	Fentanyl and Ethanol Toxicity	Fentanyl and Medical Cause
Range	13–22	97	7–28	19
n	2	1	3	1

Clinical studies have demonstrated oral/transmucosal fentanyl preparations to be an efficient means of administration and fentanyl in this form is available via prescription for clinical use (e.g. Actiq®) (12). It is not surprising therefore, that abuse of fentanyl via this route of administration has been observed. Indeed, the term "Perc-O-Pops" has been used by illicit fentanyl users of Actiq®, and Duragesic® patches are known as "Chiclets" because of their chewing gum shape (7). Studies have shown the mean overall bioavailability for oral/transmucosal fentanyl is approximately 50%, given its susceptibility to both intestinal and hepatic first-pass metabolism. Most absorption occurs transmucosally (25%) whereas only half of the remaining, swallowed dose (25%), will be absorbed and enter the systemic circulation (13,14). Consequently, when used clinically, administration is most effective when the patient maximizes transmucosal absorption rather than immediately swallowing the fentanyl and instructions are provided to patients to dissolve the preparations slowly and avoid chewing the lozenge. Such practices are not unknown to the drug-abuse population attempting to maximize fentanyl delivery. For example, in one reported case of fentanyl patch abuse, the subject stated that she opted to keep the patches in her oral cavity for up to 4 h as she achieved quicker and more effective pain control in this way (8). Given the variable dose-delivery following oral/transmucosal fentanyl administration, it follows that the maximum blood concentrations of fentanyl achieved and therefore any potential toxic effects could be dramatically affected by whether the user swallows the patch contents or if they retain it in the oral cavity for prolonged periods of time. This could be an important factor in explaining the wide range of postmortem fentanyl concentrations observed in this study. Other explanations for the large variation in concentrations observed in the present study may include tolerance, site dependant differences in postmortem fentanyl concentrations, possible differences in the time interval between consumption and death and the possibility of multiple routes of administration prior to death. For example, in one case, the deceased was using two transdermal patches in addition to the orally administered patch; thus both of these routes of administration contributed to the overall fentanyl concentration observed.

Of interest are the results from case 5 which provide both heart and femoral postmortem blood samples in addition to an antemortem blood sample. The fentanyl concentrations in this case are significantly higher in the postmortem samples compared to the antemortem sample. The difference in these results could be due to a number of factors including; incomplete distribution of fentanyl or postmortem redistribution. Due to the fact that such data are only available in one case and additional information including the exact time of death and time of antemortem sample collection is unknown, it is not possible to draw any conclusions regarding these

TABLE 2—*Variability in postmortem blood concentrations in relation to the possible dose of oral/transmucosal fentanyl.*

Case Number	Fentanyl Dose (mg)	Postmortem Fentanyl Concentration (ng/mL)
7	2.5	8
1	5.0	22
2	10	13
4	10*	19
6	10	7

*Plus 2 × 50 (μg/h) transdermal patches found on body

differing drug concentrations. In addition, although postmortem redistribution may be a factor there is wide variability in the literature regarding postmortem fentanyl site dependent differences (1,11).

In five of the reported cases information regarding the amount of fentanyl consumed was available based on the number and dose of the fentanyl patches found with the deceased (Table 2). The variability observed in the postmortem blood fentanyl concentrations where apparently similar doses of fentanyl have been ingested demonstrates that calculation of dose administered from a determined blood concentration is not advisable in postmortem cases. Aside from inter-individual differences in the pharmacokinetics of the drug and the rapidity of death, the amount of fentanyl that undergoes first-pass metabolism due to the time the patch is held in the oral cavity can also contribute to these varying postmortem concentrations.

Conclusions

These case studies provide valuable information regarding the oral/transmucosal abuse of transdermal fentanyl patches and the wide range of fentanyl concentrations that can arise in deaths following this type of administration. Even though the oral/transmucosal abuse of fentanyl appears to be a relatively rare means of abuse of Duragesic® patches, the present cases illustrate that toxicologists, pathologists, coroners and police officers should consider the possibility of oral abuse and its potentially fatal outcome.

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