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Research Article

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An Unusual Homicide Involving Strangulation after Transdermal Fentanyl and Buprenorphine Intoxication

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Abstract

Fentanyl and buprenorphine are powerful opioids used for the induction of anesthesia as well as for severe pain management. Transdermal fentanyl and buprenorphine patches are widely used for outpatient management of chronic pain. However several cases of deaths connected with their administration have been described in literature. We present an unusual and exceptional homicidal death attributed to a combination system of acute transdermal opioids poisoning and strangulation. The concentration of the drugs and their metabolites in femoral blood and urine were capable of causing fatal intoxication. This manner of complex homicide raises the question of the importance of mechanisms involved.

Keywords

Buprenorphine intoxication; Fatal intoxication; Central nervous system

Introduction

Pain is a characteristic of many cancers, particularly in the advanced stages at which the palliative care approach to symptom control achieves the best outcome. A holistic approach generally dictates that the primary objective of any treatment of the cancer per se is symptom control of advanced stages. For these reasons, pain, which invariably increases with progression of disease, should be treated with opioid drugs and not withheld in the terminal stages. Orally administered opioid drugs are used preferentially because of the cost and convenience, but other ways of administration (subcutaneous, rectal, and spinal) are also possible. More recently, transdermal fentanyl and buprenorphine have been evaluated in the treatment of moderate to severe cancer pain.

Fentanyl is a potent scheduled narcotic analgesic (schedule II in USA, schedule I in Italy) that was first discovered by Dr Jansen in 1960 and initially administered and monitored by anesthesiologists in pre/intraoperative patient management [1].

Its use has expanded over the past decade to include outpatient pain management and the first proprietary fentanyl patch was approved by the FDA in 1990. Fentanyl acts on the central nervous system (CNS), inducing states of euphoria and sedation [2] but the danger inherent to fentanyl is its potency (50-100 times greater than morphine) and rapidity of action, causing respiratory depression within a few minutes of administration when in overdosage. Patients should be warned against the use of heating pads, hot tubs, electric blankets, heat lamps, and saunas while wearing transdermal fentanyl patches since the heat produced by these items could potentially boost the amount of fentanyl released from the system. Additionally, fever may enhance fentanyl absorption [3].

Serum fentanyl concentrations become detectable about two hours after placement of transdermal system and attain a range of 0.3-1.2 µg/L within 24 hours after application of a 25 µg/hr transdermal patch; the ranges for the 50, 75 and 100 µg/hr patches are 0.6-1.8, 1.1-2.6, and 1.9-3.8 µg/L respectively. This is followed by continuous sustained systemic release of the drug for 72 h. Following removal of the patch, serum fentanyl levels decline with an average elimination half-life of 17 hours (range 13-22) [4].

When fentanyl patches are used to treat cancer patients, steady state serum concentrations of 2.6 (+/- 1.3 µg/L) are approached by the time the second patch has been applied, and the kinetics of the drug remain stable for the duration of treatment. Regarding the fatal cases, due to self-administered (intravenous injections, patches smoking, accidental ingestion, abuse death) blood concentrations of 3.0 to 28.0 µg/L (average 8.3 µg/L) were reported [5-10].

Other authors described some cases of excessive transdermal use of fentanyl patches, finding a blood levels averaging 23.0 µg/L (12.0-41.0 µg/L) and 233 µg/L (89.0-449.0 µg/L) in urine [2,11-13]. Buprenorphine is an opioid derived from the baine with high affinity and slow dissociation for the µ-receptor and weak k-receptor and ∂ - 2 receptor antagonists, resulting in strong analgesia and long duration of action that makes it very safe to use even at high doses [14]. Buprenorphine can be given by any route, but because there is very great inter-individual variability in bioavailability, hence resultant peak plasma concentrations may vary widely as well. Studies in humans are lacking, but measurements in animal show that after nasal administration bioavailability is very high and maximal plasma concentrations occur almost as rapidly as after parental administration [15,16].

Blood buprenorphine concentrations vary both from the routes of administration and from dosage (i.e. an intravenous dose of 0.3 mg of buprenorphine showed an average plasma concentration of 0.5 µg/L within 2 hours after administration, the sublingual administration of 2 mg of buprenorphine produced an average peak plasma concentrations of 1.6 µg/L with 1.3 hours) [17,18].

In fatal cases post-mortem blood concentrations of buprenorphine and its metabolite range respectively from 1.1 to 29.0 µg/L (average 8.4 µg/L) and from 0.2 to 12.6 µg/L (average 2.6 µg/L) [19,20].

A transdermal patch formulation of buprenorphine with three different patch strengths: 35, 52.5 and 70 µg/h (Transtec®) is widely available across Europe. Each matrix patch continuously delivers buprenorphine for up to 96 h (4 days) across the skin and into the systemic circulation, corresponding to 0.8, 1.2 and 1.6 mg/day for

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the 35, 52.5 and 70 µg/h patch strengths, respectively. With the first application to the skin, plasma concentrations of buprenorphine increased steadily with time, and the minimum effective therapeutic dose (100 pg/ml) was reached at some 21 h and 11 h following the application of a single 35 and 70 µg/h patch, respectively. After about 60 h, peak plasma concentrations (Cmax) of 305 and 624 pg/ml were reached for the 35 and 70 µg/h strength patch, respectively [21].

Of very important note is that because buprenorphine is a mixed opioid agonist/antagonist, it does have a dosage ceiling. Therefore, those patients who are already on large doses of chronic opioids are not considered appropriate candidates for transdermal buprenorphine therapy [22].

The first fatalities were reported in France (the drug was licensed for 1st time in France in 1996) and then few cases of fatal intoxication by different routes were reported [21,23,24]. No cases have been published regarding fatal intoxication due to transdermal application of buprenorphine patches.

In this paper we describe an unusual murder of a woman, treated with transdermal opioids for cancer pain at terminal stages, committed by her husband combining an overdose of fentanyl/buprenorphine transdermal patches and strangulation.

Case History

A 78-year old white female and her husband were both found dead lying on their bed. A letter was also found in which he wrote the reasons for this terrible act. The woman had been diagnosed with terminal breast cancer and was using fentanyl patches for treatment of pain. At the death scene on the woman's body there were 53 fentanyl and buprenorphine patches,13 Duragesic 50 µg/h, 18 Transtec 30 -52,5 µg/h-and 22 Transtec 20-35 µg/h-respectively, spread across the chest (Figure 1), back, abdomen and lower limbs.

External examination revealed a cyanosed face, rhinorrhagia and multiple petechial hemorrhages on the facial skin and in the conjunctivae and sclera.

On the woman's neck there was a single horizontal ligature mark. Neck dissection revealed areas of soft tissue bruising and blood staining of the deeper muscles. Internal examination showed subpleural petechial hemorrhages and congestion of inner organs.

A large and tough irregular mass in the right breast (13×5.5 cm) was also noted and subsequent histological studies revealed extensive areas of breast carcinoma with skin infiltration. Metastatic lesions were not found. A careful examination of the body revealed no apparent injection sites. Microscopic examination of the lungs showed congestion and edema and the analysis of skin samples of the neck revealed a vital reaction due to infiltration of granulocytes next to vessel walls. Femoral blood and urine was also collected for toxicological analyses. The husband was found dead on the bed next to the woman with a noose around his neck made by the intersection of three self-locking plastic cable ties drawn by two side rings (Figure 2). The autopsy highlighted the presence of blood infiltration in neck's tissues with sub pleural and subepicardic petechiae. On the body of the subject was not recognized any other cause injury. The death was attributed to mechanical asphyxia by strangulation.

Methods

Preliminary screening tests performed in urine indicated the presence of buprenorphine by an immunochemistry technique (EMIT Siemens Viva-E®, Siemens Healthcare Diagnostics, Camberley, UK).

Further analysis performed by head space gas chromatography-flame ionization detector (GC Fison 8000, Perkin Elmer) did not indicate presence of ethanol in blood.

Qualitative procedures

A general unknown screen was performed on urine and femoral blood "by solid phase extraction (SPE) and gas chromatography-mass spectrometry (GC-MS). The GC-MS instrument consisted of an Agilent 7890A GC system equipped with an Agilent 7683 B series autosampler (Agilent Technologies, Palo Alto, Ca, USA), and interfaced to a single quadrupole Agilent 5975 C mass spectrometer (Agilent Technologies, Palo Alto, Ca, USA). The column used was an Agilent HP-5MS, 30 m length, 0.25 mm i.d. and 0.25 µm film thickness (Agilent Technologies, Palo Alto, Ca, USA). The gas carrier (He) flow was constant at 1 mL/min. The oven temperature was set initially at 100°C for 1 min, and programmed to 300°C at 20°C/min. Injector and transfer line temperature were respectively 300°C and 230°C.

Full scan acquisition mode was used and fentanyl, buprenorphine and nor-buprenorphine were identified on the basis of the Wiley Mass Spectral library 2011. No other drugs were found.

Fentanyl, buprenorphine and norbuprenorphine identification was then confirmed in the same specimens by electron ionization and selected ion monitoring (SIM) acquisition mode, monitoring three ions for each analyte. The ions of interest were 245, 146, 189 for fentanyl; 450, 482 and 506 for buprenorphine, 468, 557 and 542 for nor-buprenorphine.

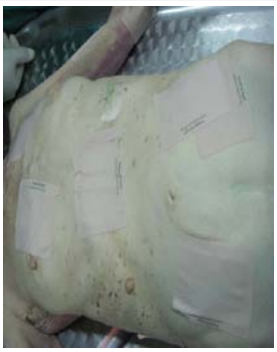

Figure 1: Photo of the deceased woman showing multiple patches over the chest and abdomen.

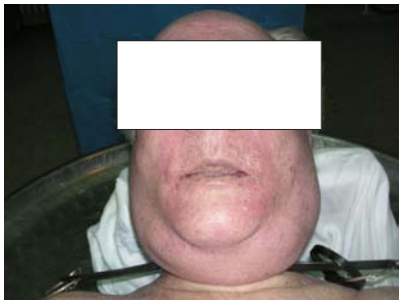

Figure 2: Photo of the deceased man showing the plastic cable tied around his neck.

Quantitative procedure

An internal standard (nalorphine) was added to 1.0 ml aliquots of femoral blood and urine, and then the specimens were extracted by means of SPE-Bond Elut LRC-Certfy, derivatisation with MSTFA (Sigma–Aldrich - St.Louis, MO, USA) and analysed by GC/MS at the same conditions mentioned above. Quantification of each analyte was performed using the fully validated method.

Method validation

LOD (limit of detection) and LOQ (limit of quantification), defined as the lowest concentrations that produce signal/noise ratios values of at least 3 and 10 respectively, were calculated analyzing urine and blood samples added with decreasing amounts of each drug. Linearity was evaluated analyzing different calibration levels, and applying the least-square regression method to build the calibration curve, and for each level 5 replicates were carried out. Accuracy and precision were evaluated using three quality controls (QC). Imprecision, as degree of repeatability, was estimated as the average of relative standard deviation (% RSD) values calculated for QC samples with 5 replicates. The intra-day and inter-day imprecision's were calculated in the same day and in 5 different days during a month, respectively.

Acceptable linear regression was obtained for each calibration curve (R^2=0.992; 0.997; 0.989 respectively). Inter-day precision and accuracy were always lower than 10% for all of the analytes. The LOQ was 0.10 µg/L for fentanyl and 0.25 µg/L for both buprenorphine and nor buprenorphine; the LOD was set at the same concentrations.

Results

Our findings demonstrate for fentanyl a postmortem concentration of 11 µg/L and 35 µg/L in femoral blood and in urine, respectively. The postmortem concentration for buprenorphine was 25 µg/L and 140 µg/L; for the metabolite (norbuprenorphine) 13 µg/L and 31 µg/L in femoral blood and in urine, respectively. The results of toxicological analysis of the decedents' blood and urine are presented in table 1.

Discussion

The toxicological findings show excessive use of fentanyl and buprenorphine and together with the presence of multiple patches would indicate that fatal intoxication was a likely cause of death. The blood concentrations are consistent with fatalities attributed to these drugs after excessive use of transdermal fentanyl patches [25-27]. The buprenorphine levels we found are much higher than opiate-dependent subjects' plasma levels where the range reported is 1-8 µg/L [28]. However since macroscopic features suggested that strangulation occurred in a woman with amounts of opioids, hence death was more likely due to a combination of mechanical asphyxia due to strangulation and opioid intoxication. The very high opioid concentrations suggest that the woman may have been in a coma when strangulation occurred. The woman was terminally ill and the crime scene investigation led the authors to suppose that her husband first applied the opioid transdermal patches to impair her consciousness and then strangled the victim, in order to conduct a mercy killing. Then the man committed suicide by autostrangulation with plastic cable ties.

Table 1: Toxicological analysis of the decedents' blood and urine.

	Femoral blood level (µg/L)	Urine level (µg/L)
Fentanyl	11	35
Buprenorphine	25	141
Nor-buprenorphine	13	31

A review of the literature shows that deaths due to opioid poisoning present an asphyxia syndrome on autopsy (distal cianosis, multivisceral congestion, pulmonary edema), with a lack of signs of violence and no other cause of death [29].

This asphyxia is usual in cases of death involving central respiratory depressants.

Multiple case reports of deaths and suicide attributed to buprenorphine or fentanyl are reported. The large majority of the deaths due to buprenorphine are related to misuse with intravenous administration and/or combination with psychotropic medications, mostly benzodiazepines [30].

While toxicity and death from fentanyl intoxication with TD fentanyl patches has also been reported due to patch overuse, as well as inappropriate use of patches (i.e., injecting the contents of a reservoir patch), placing patches on inappropriate anatomic sites, inhaling the contents of the patches, chewing or eating patches, or drinking the contents of the patch used as an infusion [31].

References

1. http://www.usdoj.gov/dea/concern/fentanylp.html.
2. Anderson DT, Muto JJ (2000) Duragesic transdermal patch: postmortem tissue distribution of fentanyl in 25 cases. J Anal Toxicol 24: 627-634.
3. Skaer TL (2006) Transdermal opioids for cancer pain. Health Qual Life Outcomes 4: 24.
4. Physicians' desk reference(1998) Montvale: Medical Economics Company.
5. Marquardt KA, Tharratt RS (1994) Inhalation abuse of fentanyl patch. J Toxicol Clin Toxicol 32: 75-78.
6. Smialek JE, Levine B, Chin L, Wu SC, Jenkins AJ (1994) A fentanyl epidemic in Maryland 1992. J For Sci 39: 159-164.
7. Garriott JC, Rodriguez R, Dimaio VJ (1984) A death from fentanyl overdose. J Anal Toxicol 8: 288-289.
8. Levine B, Kauffman G, Kaplan YH (1987) The determination and distribution in a post-mortem case. Annual Meeting of the American Academy of Forensic Sciences, San Diego.
9. Pare EM, Monforte JR, Gault R, Mirchandani H (1987) A death involving fentanyl. J Anal Tox 11: 272-275.
10. Felgate HE (1998) A suicide involving fentanyl. Bul Int Asso For Tox 19: 32-33.
11. Edinboro LE, Poklis A, Trautman D, Lowry S, Backer R, et al. (1997) Fatal fentanyl intoxication following excessive transdermal application. J Forensic Sci 42: 741-743.
12. Wu Chen NB, Donohue ER, Denton JS (1999) Fentanyl intoxication: suicide by transdermal patch, Annual Meeting of the American Academy of Forensic Sciences, Orlando.
13. Baselt RC (2004) Disposition of Toxic drugs and chemicals in man. (7thedn) Biomedical Publication, Foster City, California.
14. Walsh SL, Preston KL, Stitzer ML, Cone EJ, Bigelow GE (1994) Clinical pharmacology of buprenorphine: ceiling effects at high doses. Clinical Pharmacol Ther 55: 569-580.
15. Kornick CA, Santiago-Palma J, Moryl N, Payne R, Obbens EA (2003) Benefit-risk assessment of trandermal fentanyl for the treatment of chronic pain. Drug Saf 26: 951-973.
16. Lindhardt K, Ravn C, Gizurarson S, Bechgaard E (2000) Intranasal absorption

of buprenorphine: in vivo bioavailability study in sheep. Int J Pharm 205: 159-63.

17. Watson PJQ, McQuay HJ, Bullingan RE, Allen MC, Moore RA (1982) Single dose comparison of buprenorphine 0.3 and 0.6 mg I.V. given after operation: clinical effects and plasma concentrations. Brit J Anaesth 54: 37-43.
18. Kuhlman JJ, Lalani S, Magluiolo J, Levine B, Darwin WD (1996) Human pharmacokinetics of intravenous sublingual and buccal buprenorphine. J Anal Tox 20: 369-378.
19. Karch SB (2009) Karch's pathology of drug abuse. (4thedn), Taylor & Francis Group, CRC Press.
20. Tracqui A, Kinzt P, Ludes B (1998) Buprenorphine-related deaths among drug addicts in France a report of 20 fatalities. J Anal Tox 22: 430-434.
21. Kress H(2009) Clinical update on the pharmacology, efficacy and safety of transdermal Buprenorphine. Europ J Pain 13: 219-230.
22. Evans HC, Easthope SE (2003) Transdermal buprenorphine. Drugs 63: 1999-2010.
23. Kintz P (2002) A new series of 13 buprenorphine-related deaths. Clin Biochem 35: 513-516.
24. Gaulier JM, Marquet P, Lacassie E, Dupuy JL, Lachatre G (2000) Fatal intoxication following self-administration of a massive dose of buprenorphine. J Forensic Sci 45: 226-228.
25. Grobosch T, Weniger ST, Lampe D (2007) Fentanyl analytics in a case of fatal misuse of transdermal fentanyl. Instrumentation 74: 59-63.
26. Moon JM, Chun BJ (2011) Fentanyl intoxication caused by abuse of transdermal fentanyl. J Emerg Med 40: 37-40.
27. Jumbelic MI (2010) Deaths with transdermal fentanyl patches. Am J Forensic Med Pathol 31: 18-21.
28. De Los Cobos JP, Martin S, Etcheberrigaray A, Trujols J, Batlle F, et al. (2000) A controlled trial of daily versus thrice weekly buprenorphine administration for the treatment of opioid dependence. Drug Alcohol Depend 59: 223-233.
29. Ferrant O, Papin F, Clin B, Lacroix C, Saussereau, et al. (2011) Fatal poisoning due to snorting buprenorphine and alcohol consumption. Forensic Sci Int 204: 8-11.
30. Lai SH, Yao YJ, Lo DS (2006) A survey of buprenorphine related deaths in Singapore. Forensic Sci Int 162: 80-86.
31. Barrueto FJ, Howland MA, Hoffman RS, Nelson LS (2004) The fentanyl tea bag. Vet Hum Toxicol 46: 30-31.

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