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CASE REPORT

Fatal outcome in a child after ingestion of a transdermal fentanyl patch

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Abstract The case history and toxicological findings of a fatal fentanyl intoxication due to ingestion of a transdermal patch are presented. A 1-year-old otherwise healthy girl was put to bed and 2 h later she was found dead. The autopsy revealed a 25-μg/h (4.2 mg) transdermal fentanyl patch in the stomach. Toxicological analysis by liquid chromatography–tandem mass spectrometry with positive electrospray ionization yielded fentanyl and norfentanyl concentrations in the peripheral blood of 5.6 and 5.9 ng/ml, heart blood 19.0 and 8.9 ng/ml, and liver 235 and 26 ng/g, respectively. The cause of death was determined to be a fentanyl overdose. The investigation established that the child has unintentionally swallowed the patch, which had been lying on the floor.

Keywords Fatal intoxication · Transdermal fentanyl patch · Fentanyl · Norfentanyl · LC–MS–MS

Introduction

Transdermal fentanyl patches have been available since 1991, in Germany since 1995, and deliver fentanyl at a constant rate (12.5, 25, 50, 75, and 100 μg/h). They require replacement every 48 or 72 h. An average transdermal bioavailability of 92% has been estimated [1]. Reduced microcirculation in specific skin diseases [2] and elevated local and systemic body temperatures may affect the absorption of transdermally delivered fentanyl [1]. In line with a broad interindividual variability of the absorption of fentanyl from the patch after 3 days of therapeutic use, a residual dose of 28–84.4% of the original contents was found to be a potential lethal dose for opioid-naive individuals [3].

In the context of transdermal fentanyl patches, intoxication and fatal cases have been reported after accidental transdermal absorption [4], overdose and uncontrolled self-application [5, 6], application of cut patches [7], application at elevated temperatures [8–10], and mistake of patches of different doses [11]. Recreational abuse of transdermal fentanyl patches, in some cases fatal, has been reported involving ingestion [12–14], smoking [15], and injection [16]. In addition, a clinically significant respiratory depression after unintentional exposure to a transdermal fentanyl patch was reported in a 2-year-old boy [17]. Another report presented an adverse event that occurred in a child because a fentanyl patch had been placed on a superficial injury [18].

Due to these reports, the Federal Drug Agency ordered an inquiry in July 2005 and published public health advisory and safety warnings [19] that were included in the package insert of transdermal fentanyl products. It is especially pointed out there that the patients and the caregivers should be instructed in the safe handling of the patches including adequate disposal and unattainability for children.

A number of methods have been developed to determine fentanyl or other central-acting drugs in biological samples. Immunoassay [20–23], high-performance liquid chromatography combined with ultraviolet detection [24], and

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several gas chromatographic methods [25–28] have been described. More recent studies were mostly based on liquid chromatography–mass spectrometry [29] or liquid chromatography–tandem mass spectrometry (LC–MS–MS) techniques [30–33].

The presented case describes (for the first time, to the best of our knowledge) a fatal fentanyl intoxication of a 1-year-old girl after ingestion of a fentanyl patch.

Case history

A 1-year-old girl (height 77 cm, weight 11 kg) was put to bed by her grandmother and the day mother. Two hours later, she was found in a non-reacting state and signs of vomit were found in the bed. An emergency physician was not able to resuscitate her. The corpse was stored in the mortuary of a hospital and was transported the next day to the postmortem examination. Body fluids and tissues were collected at autopsy (22 h postmortem) and stored at −20° C until analysis. The autopsy revealed no signs of violence. However, aspiration of stomach content, lung edema, and edema of the brain were observed and in the stomach a transdermal fentanyl patch was found (Durogesic® SMAT 25 μg/h, Janssen Cilag, Neuss, Germany).

Further investigations showed that the 56-year-old day mother was medicated with transdermal fentanyl 25 μg/h for 5 years. According to the prescription, she replaced the patch every 3 days and disposed it within the package in the household waste. On that day, the used patch was apparently dropped on the floor, without being noticed, from where the child picked it up and ingested it.

Materials and methods

Chemicals and standards

Reference compounds and internal standards (fentanyl, fentanyl-D5, norfentanyl, norfentanyl-D5) were obtained from LGC Promochem (Wesel, Germany) and all other chemicals were of analytical grade.

LC–MS–MS equipment and conditions

The LC–MS–MS analysis was performed on a Shimadzu (Duisburg, Germany) high-pressure gradient system coupled to an Applied Biosystems (Darmstadt, Germany) triple–quadrupole mass spectrometer API 2000 equipped with electrospray ionization (ESI; Turboionspray®). A Phenomenex (Aschaffenburg, Germany) Luna 5 μ C18 (2) 100A column (150×2 mm) was used at a constant flow rate of 0.4 ml/min for LC separation. The mobile phase was a mixture of ammonium acetate buffer (pH 3.8, 10 mM) and methanol and was programmed as follows: solvent A 95% ammonium acetate buffer with 5% methanol, solvent B 95% methanol with 5% ammonium acetate buffer; 65% B initially, ramping to 100% B from 1 to 4 min. The mass spectrometer was run in multiple reaction monitoring (MRM) mode detecting two MRM transitions of $[M+H]^+$ pseudo molecular ions (Table 1).

Sample preparation

An aliquot of 200 μl serum/blood was transferred to a 2-ml polypropylene vial prepared with 100 μl water, 30 μl of the internal standards (1 ng/μl), and 10 mg $NaHCO_3$. Liquid–liquid extraction (LLE) was performed with 1 ml 1-chlorbutane/methylene chloride (9:1) by gentle shaking for 10 min. After centrifugation and evaporation of the organic layer, the residue was redissolved with 200 μl of high-performance liquid chromatograph eluent, was filtrated and 25 μl was injected.

Tissue and stomach contents were homogenized using an Ultra Turrax (5 g substrate + 20 g 0.1 M phosphate buffer, pH 8), and 1 g of the homogenate was treated as described above (deuterated internal standards were 50 ng/g).

The fentanyl patch from the stomach was shaken overnight in 20 ml methanol, and a dilution (1:500) of the extract was directly injected. Further investigations on the liberation of fentanyl from a patch into an acidic aqueous solution were carried out by gently shaking a Durogesic® SMAT 25 μg/h patch in 20 ml 0.1 M hydrochloric acid (pH 1) at room temperature and injecting an appropriated dilution in duplicate.

Table 1 MS–MS parameters for the detection of fentanyl and norfentanyl

	Precursor	Product	DP	CE	CXP
Fentanyl	337	188	21	33	4
	337	105	21	53	2
Fentanyl-D5	342	188	31	33	4
	342	105	31	53	2
Norfentanyl	233	84	21	27	2
	233	177	21	21	6
Norfentanyl-D5	238	84	21	27	2
	238	182	21	21	6

Focusing potential 330 V, entrance potential 9 V, cell entrance potential 14 V, dwell time 60 ms, ion spray voltage +5,500 V, nitrogen nebulizer gas 40 psi, nitrogen auxiliary gas (60 psi heated to 400°C), nitrogen curtain gas (25 psi), and nitrogen collision-activated dissociation gas (set on 3)

DP Declustering potential, *CE* collision energy, *CXP* collision cell exit potential

Method validation

Drug-free serum samples were spiked with 0–50 ng/ml fentanyl and norfentanyl, and 30 ng/ml of the deuterated internal standards and calibration curves were generated using linear regression (fentanyl: $y=0.0304x+0.0219$, $r=0.998$; norfentanyl: $y=0.0343x+0.0415$, $r=0.997$). LLE recoveries were 86 and 43%, while variation coefficients were 4.4 and 3.6% for fentanyl and norfentanyl, respectively. The limits of detection (s/n=3 for the strongest MRM transition) were 0.03 and 0.10 ng/ml, and the limits of quantification (s/n=10) were 0.11 and 0.33 ng/ml for fentanyl and norfentanyl, respectively.

Quantification of tissues and stomach contents was performed by means of standard addition of 100 and 200 ng/g for fentanyl and 50 and 100 ng/g for norfentanyl.

Matrix-dependent ionization suppression in ESI was observed but can be compensated by using deuterated internal standards.

Results

Apart from fentanyl and norfentanyl, neither other drugs nor ethanol could be detected by the routinely used toxicological screening methods. The results of LC–MS–MS investigations for fentanyl and norfentanyl are given in Table 2 and Fig. 1.

To simulate the drug delivery rate from Durogesic® SMAT 25 μg/h into gastric fluid (physiological range, pH 1–3), the extraction of fentanyl into an acidic aqueous solution was exemplarily determined. About 9% of the total fentanyl amount could be extracted after 10 min, 17% after 30 min, and 39% after 2 h (Fig. 2). After 24 h, about 74% of the active agent was extracted.

However, the gastric content pH in the presented case was about 3–4, and the child obviously ingested a used fentanyl patch.

Table 2 Distributions of fentanyl and norfentanyl in tissues and fluids

	Fentanyl	Norfentanyl
Femoral blood (ng/ml)	5.6	5.9
Heart blood (ng/ml)	19.0	8.9
Liver (ng/g)	235	26
Kidney (ng/g)	37	33
Urine	Positive	Positive
Stomach content (ng/g)	4,460[a]	–
Durogesic® SMAT patch (μg)	197	–

[a] Gastric content (76.5 g) was collected (0.34 mg fentanyl).

Discussion

In opioid-naive patients, the minimum effective analgesic serum concentration of fentanyl ranges from 0.2 to 1.2 ng/ml. The frequency of adverse events—mainly respiratory depression—increases at serum levels above 2 ng/ml [1].

In the transdermal delivery system, the amount of fentanyl delivered is proportional to the surface area of the patch. Delivery rates of 25, 50, 75, and 100 μg/h lead to effective analgesic serum concentrations of fentanyl of 0.3–1.2, 0.6–1.8, 1.1–2.6, and 1.9–3.8 ng/ml, respectively [34].

Anderson and Muto [35] analyzed 25 deaths after transdermal fentanyl application. When fentanyl was not considered to be the cause of death, heart blood and liver tissue concentrations ranged from <2 to 7 ng/ml (mean 3.6 ng/ml) and from 5.8 to 31 ng/g (mean 14.6 ng/g), respectively. When fentanyl was considered to be the cause of death, heart blood and liver tissue concentrations ranged from 16 to 139 ng/ml (mean 50 ng/ml) and from 69 to 352 ng/g (mean 167 ng/g), respectively. The authors concluded that, in the case of transdermally delivered fentanyl, blood and liver tissue concentrations above 7 ng/ml and 69 ng/g, respectively, may indicate a fentanyl overdose.

In some neonates, intravenously administered fentanyl in doses as little as 25–50 μg/kg required artificial respiration [36], and children generally seem to be more susceptible to opioids [18].

Pharmacokinetic data showed that 15 μg/kg of orally administered fentanyl leads to maximum serum concentrations (C_{max}) of 1.1–3.0 ng/ml (mean 1.6 ng/ml) after 0.5–3.0 h (mean 1.7 h) [37].

In the case reported here, only 197 μg of remaining fentanyl in the patch was determined. Postmortem processes (autopsy not until 22 h after death) and alteration of the patch due to storage conditions may have reduced the remaining fentanyl amount. However, a remaining dose of at least 2.4 mg (57%) after the regular use of 3 days has been considered. According to the data presented by Streisand et al. [37] and the observed delivery rate from Durogesic® SMAT patch during extraction into H_2O/HCl (Fig. 2), toxic serum fentanyl concentrations could be expected within a few hours. Furthermore, the observed high fentanyl concentrations in the liver tissue of 235 ng/g were interpreted as a result of first-pass effects. The femoral and heart blood fentanyl concentrations of 5.6 and 19.0 ng/ml, respectively, are out of the therapeutic range, especially in a case of an opioid-naive child, and leave no doubt that a fentanyl overdose followed by aspiration of gastric content was the cause of death.

This and other reports make it clear that used transdermal fentanyl patches can be (unintentionally) misused.

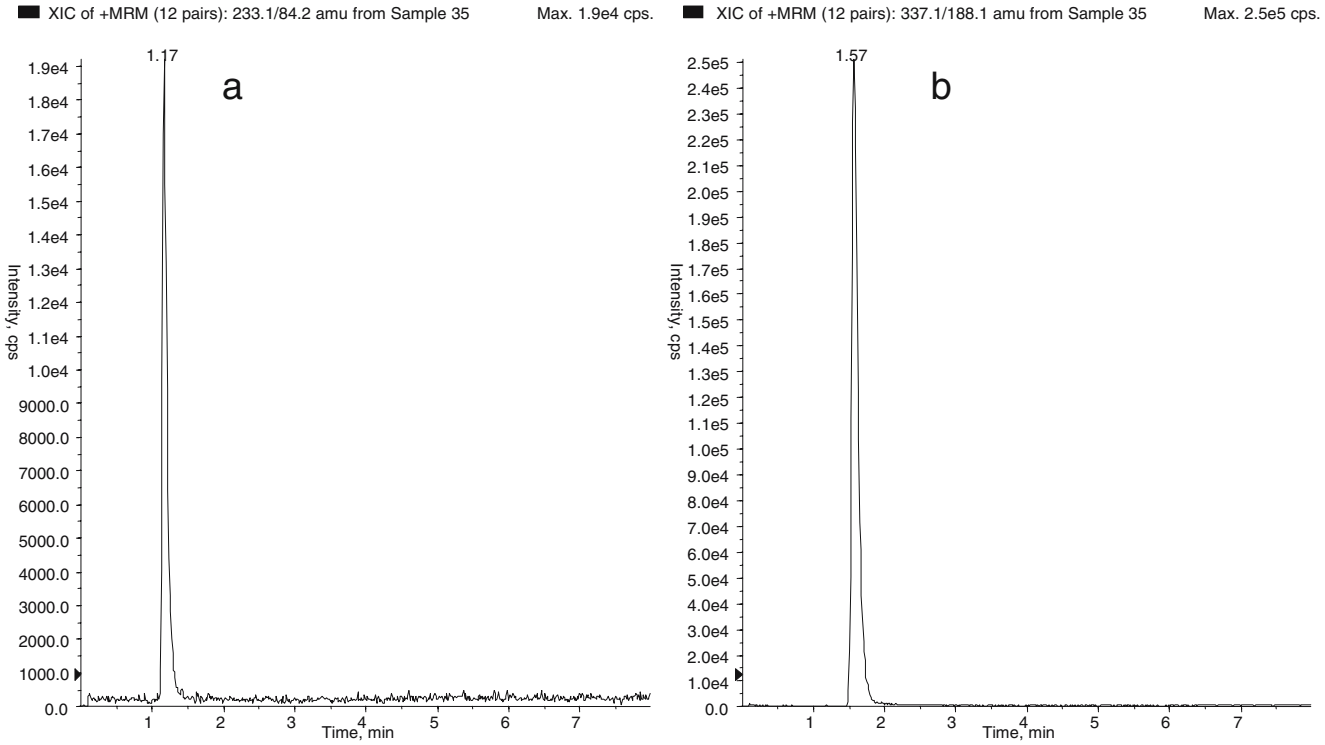

Fig. 1 Extracted ion chromatograms of the heart blood sample. **a** 8.9 ng/ml norfentanyl (MRM 233/84). **b** 19.0 ng/ml fentanyl (MRM 337/188)

Conclusion

A fatal fentanyl intoxication of a 1-year-old child after oral intake of a used 25-μg/h patch is reported. In line with other reports [12–14], this case exemplifies the potential lethal complication resulting from oral administration of transdermal fentanyl patches. The inherent danger derived from used patches, in which a significant residual amount of fentanyl is usually present, is emphasized. Not only should the package insert address those warnings but the prescribing physicians should also individually instruct the patients and their caregivers according to these risks. Likewise, regulatory controls addressing the disposal of used fentanyl patches should also be considered [5, 38].

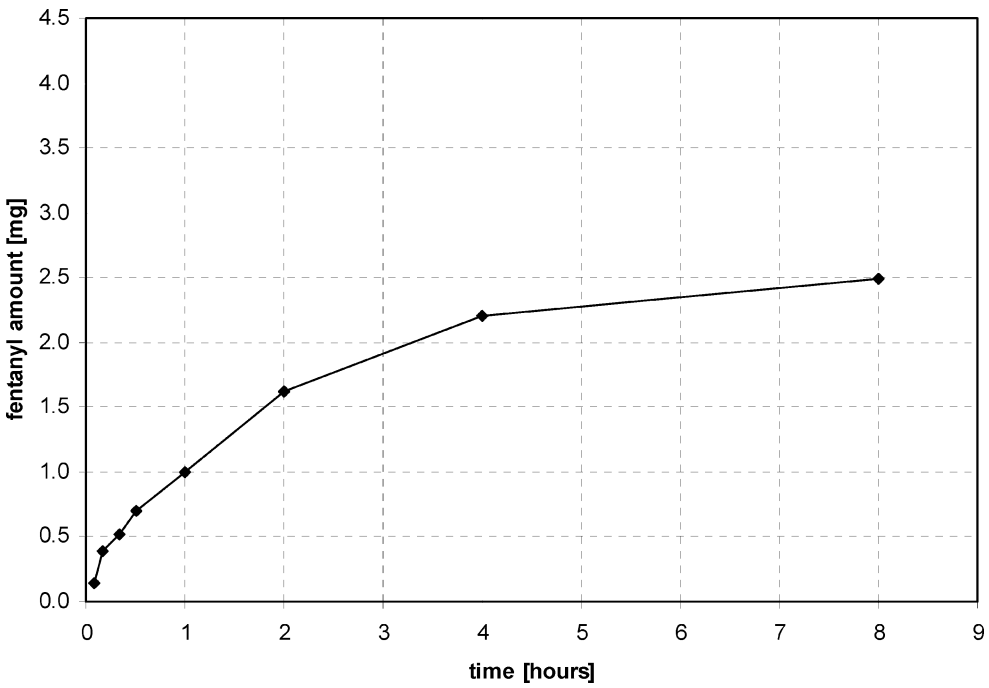

Fig. 2 Fentanyl delivery rate from Durogesic® SMAT 25-μg/h patch (total amount, 4.2 mg fentanyl) during extraction into H_2O/HCl (0.1 M, pH 1) at room temperature

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