Accidental transdermal fentanyl overdose in a child

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Abstract

Fentanyl is a synthetic opioid that provides analgesia for procedures with moderate to severe pain and also can be used to manage acute or chronic pain. Fentanyl is available in several dosing forms and is more widely used as a transdermal patch for the management of chronic pain at home. Accidental exposure to even one dose of fentanyl, especially by children can result in a fatal overdose leading to disturbances of consciousness and/or respiratory depression. A nine-year-old boy was referred to the pediatric emergency department because of disturbed consciousness and respiratory depression. A patch of fentanyl 100 mcg/h was found on the bruised knee during the examination. For treatment, he got naloxone 0.1 mg, infusion therapy and artificial lung ventilation due to respiratory depression. Signs characteristic of acute toxic leukoencephalopathy and hypoxic-ischemic encephalopathy were found on brain magnetic resonance imaging (MRI). After 29 days in the inpatient unit and 120 days of rehabilitation, the patient was discharged home with moderate neurological impairment. Opioid misuse can cause serious life-threatening consequences especially in children resulting in death or severe neurological impairment. When dealing with cases of fentanyl overdose, doctors should keep in mind not only respiratory depression and hypotension, but the presence of toxic leukoencephalopathy as well. These cases may be preventable through better education of prescribers and patients.

Keywords

Fentanyl; Transdermal patch; Toxic leukoencephalopathy; Opioid overdose; Pediatric

1. Introduction

Fentanyl is a synthetic opioid that has 75 to 125 times the potency of morphine and provides analgesia for procedures with moderate to severe pain [1]. Due to its quick onset (in as little as two to three minutes), relatively brief duration of effects (30 to 60 minutes), and absence of histamine release, this substance is often preferred over longer-acting opioids, such as morphine, for procedural sedation [2, 3]. It is also suitable for treating both acute and chronic pain [4, 5]. It is an opioid agonist-analgetic that activates opiate receptors, resulting in an altered pain response by inhibiting ascending pain pathways, increasing the threshold for pain and providing analgesia, sedation and respiratory depression. It binds to stereospecific receptors at various sites within the central nervous system (CNS), raising the pain threshold and blocking the transmission of pain signals through ascending pathways [4].

Fentanyl is available in several dosing forms such as injection, nasal spray, transdermal patch, sublingual tablet, sublingual spray and transmucosal lozenge (lollipop) [5]. Fentanyl patch—transdermal dosing of fentanyl is used for moderate to severe chronic pain when other pain treatments such as non-opioid pain medicines or immediate-release opioid remedies do not act well enough or are not tolerated [6].

The use of fentanyl has a potential risk for abuse and addiction, increasing likelihood of overdose and fatality [7–9]. Accidental exposure to even one dose of fentanyl, especially by children can result in an overdose with disturbances of consciousness, respiratory depression and/or fatal consequences [10, 11]. Moreover, lethal outcomes have been reported when children who have accidentally ingested transmucosal immediate-release fentanyl products. Deaths due to a fatal overdose of fentanyl have occurred when children and adults were accidentally exposed to fentanyl transdermal patch [4, 12–14].

Additionally, fentanyl overdosage can result in toxic leukoencephalopathy and severe neurological dysfunction [15, 16] which can extend duration of hospitalization and necessitates significant resources for rehabilitation.

We present a case of accidental opioid (fentanyl) intoxication via the transdermal route. Our patient presented with coma, respiratory depression and seizures, and radiological findings of toxic leukoencephalopathy.
2. Case presentation

A nine-year-old boy was rushed to the pediatric emergency department (PED) of our hospital due to changes in the child’s consciousness. His parents told that earlier on the very same day he fell off his scooter and bruised his left temple and knee. In the nighttime, the boy started vomiting, was sleepy and parents could not wake him up. On admission the child’s consciousness was disturbed with a score of 7 according to Glasgow Coma Scale (GCS), the pupils were symmetrical and narrow and do not react to light. His limbs were cold and muscles were hypotonic. There was a clear respiratory depression: bradypnea with 4–5 b/m, cyanosis was observed and saturation on rooms air was 80%. Heart rate was 50 bpm and arterial blood pressure was 70/40 mmHg. A patch of fentanyl 100 mcg/h was found on the bruised knee during the examination. Mom claimed that she applied the patch without knowing about its components and she was unable to account for the origin of the patch. The boy was completely healthy before the accident.

Instantly, single dose of naloxone 0.1 mg/kg was administered with infusion therapy and oxygen therapy. The pupils became wider, and muscle tone increased, but respiratory depression remained, leading to endotracheal intubation and artificial ventilation of the lungs. Dopamine infusion was administered to treat persistent hypotension. Immediately, a computerized tomography (CT) scan of the head and cervical spine was performed but no signs of acute traumatic injury were found. An increased alpha amylase of 2121 U/L was detected in the blood test. As the possibility of traumatic pancreatic injury was being considered, an abdominal ultrasound was conducted, which revealed no evidence of any traumatic injury to the abdominal organs. The duration of the ventilation was one day. Since the patient’s breathing and protective reflexes fully recovered, the patient was extubated because further ventilation would have required additional sedation. After extubating, spontaneous breathing was sufficient, there was no need for oxygen and hemodynamics was stable. However, GCS remained 6–7. Reactions to stimuli with tension and tachycardia up to 200 bpm were observed. The head MRI revealed irregular areas in the white matter of the hippocampus region and parahippocampal gyrus bilaterally. Even if these signs are characteristic of acute toxic leukoencephalopathy, hypoxic-ischemic encephalopathy could not be completely excluded either.

The child was treated for 29 days, and later transferred to a children’s rehabilitation hospital. On the day of referral, he was conscious and communicating verbally, nevertheless, he remained with memory, attention concentration disorders and rapid fatigue.

In the rehabilitation hospital, the patient was treated for 120 days. Throughout the rehabilitation period, there was an improvement in the boy’s Barthel index score from 0 to 25 points—from total dependency to severe dependency [17].

Further recommendations were given to relatives on the improvement of child developmental (cognitive, language, social) skills.

3. Discussion

Opium derivatives have been used for centuries, but their potential was not realized until the 1970s when morphine and its derivates were used for neurolept and balanced anesthesia as well as a complete anesthetic in cardiovascular surgeries. Prior to that, morphine was administered as a preanesthetic, postanesthetic analgesic and anesthetic supplement. In the 1950s, researchers began looking for new non-barbiturate intravenous anesthetics, which led to the discovery of dextromoramide, a more potent analgesic than available options. The synthesis of fentanyl by Janssen in 1960 paved the way for a deeper understanding of the structure-activity relationships of opioid analgesics and stimulated the development of compounds with even greater potency and safety [18].

The transdermal therapeutic system (TTS) fentanyl has been designed for rate-controlled drug delivery. This offers a practical treatment regimen for a medication that was previously limited by a short therapeutic effect and lack of suitability for oral delivery, while also providing a non-invasive parenteral route of administration. TTS fentanyl has been approved by the United States Food and Drug Administration (FDA) for the management of chronic pain in patients requiring opioid analgesics [19]. The transdermal therapeutic system (TTS) fentanyl has been designed for rate-controlled drug delivery. It provides a convenient regimen for the use of a drug previously limited by a short duration of action and a non-invasive parenteral route for a drug that is unsuitable for oral administration. TTS fentanyl has been approved by the United States Food and Drug Administration for the management of chronic pain in patients requiring opioid analgesics [19].

It is a rectangular, transparent unit composed of a protective peel strip and four functional layers. The amount of fentanyl released from each system (25 mcg/hour per 10 cm2) is proportional to the surface area [19].

Fentanyl is a high-potency opioid that finds applications in managing acute and chronic pain. However, its misuse, whether deliberate or accidental and abuse may result in severe clinical outcomes, including death. The transdermal use of fentanyl, which is associate with potential risks and adverse effects, which have been highlighted by FDA and Health Canada. Despite these warnings, serious consequences including fatalities due to misuse or abuse of the drug continue to occur [19].

There are different types of transdermal delivery system available, such as the original reservoir transdermal device and the more recent matrix patch, which have different functional layers and protective features to ensure consistent and safe diffusion of fentanyl. Additionally, a needle-free, patient-controlled, postoperative pain management treatment called the fentanyl iontophoretic transdermal system (ITS) is also available [20], although the Ionsys brand name has been discontinued in the U.S. [21].

Fentanyl is associated with a lot of adverse effects. Its administration may cause some people to become drowsy, dizzy or lightheaded, or feel a false sense of well-being. Nausea or vomiting may occur, especially during the first days of treat-
ment. Severe constipation is related to long-time fentanyl use [6, 22]. Opioid-induced respiratory depression (OIRD) is one of the most dangerous and life-threatening complications of opiate consumption. OIRD via activation of μ-opioid receptors at specific sites in the CNS including pre-Bötzinger complex, a respiratory rhythm-generating area in the pons [8]. OIRD is a combination of decreased respiratory drive, decreased level of consciousness and upper airway obstruction due to a decrease in the supraglottic airway tone. It can be fatal, if not detected and treated early [10]. In most studies, the respiratory effects of opioids are quantified by the observed changes in breathing frequency and/or oxygen saturation [11]. Animal studies show that intravenously administered fentanyl produces more rapid depression of respiration than equipotent doses of heroin or morphine [7].

The increase in the population level exposure to fentanyl is due to the raising availability and prescriptions of transdermal patch formulations [23]. Fentanyl-related deaths are increasing worldwide [24]. A strong correlation between the annual rates of transdermal fentanyl utilization and fatal fentanyl overdoses has been noted [23].

In our case fentanyl patch was used as an ordinary wound dressing, and according to the mother, the composition of it was unknown. Worldwide, there are cases of fentanyl patch misuse by adults, using fentanyl patches for pain relief prescribed to somebody else [14], children, ingesting already used fentanyl patch [13], or opioid intoxication after accidental attachment of somebody else’s (usually grandmother’s) fentanyl patch to a child’s skin while sleeping in the same bed [12, 15]. There are several cases found in the literature about accidental fentanyl patch overdose in children. A previously healthy 19-month-old girl was admitted to pediatric emergency department for unresponsiveness. A fentanyl patch was found on her lower lumbar spine. The MRI revealed signs of toxic leukoencephalopathy [15]. A 3-year-old girl was found unresponsive at home. A fentanyl patch had been attached to the child’s lower back. Head CT showed global cerebral edema. The patient turned out to be brain dead [12]. There are also fatal outcomes from fentanyl patch ingestion. A 1-year-old girl was found dead at home. The autopsy revealed transdermal fentanyl patch in her stomach [13]. Case of fatal overdose of transdermal fentanyl delivery system in adult (a 58-year-old man) described as a fentanyl misuse. The man used fentanyl patch, prescribed for his relative for pain relief [14]. Fentanyl overdose by consuming already used fentanyl patches can be life-threatening, because every transdermal device, even after being used, contains a significant quantity of fentanyl [25]. Respiratory depression remains the main hazard of opiate use, because of the obvious risk of fatal outcome [11]. Nevertheless, a direct toxic effect of opiates on the brain cells called toxic leukoencephalopathy can be observed [15, 26, 27].

Leukoencephalopathy is a syndrome of neurologic deficits, including alteration of mental status, caused by pathologic changes in the cerebral white matter. The term, toxic leukoencephalopathy, encompasses a wide variety of exposures and clinical presentations [16]. The classic findings on MRI include abnormally high T2 signal in symmetric distribution in the cerebellar and posterior cerebral hemispheres, including the posterior limbs of the internal capsule [15, 16]. The molecular mechanisms and demyelinating process are not fully understood, but a neurotoxic effect of opioids may have to be considered, as well as there can be a combination of mitochondrial injury and hypoxia [15, 27]. Fentanyl overdose may result in fatal outcome [12], outcome with neurological deficit of different stages [14] or full recovery [15]. The patient was discharged from the hospital with a moderate neurological deficit. In our case, fentanyl caused respiratory depression leading to moderate hypoxia and hypotension. However, MRI findings are characteristic of toxic leukoencephalopathy. This explains the delayed recovery phase and neurological deficit of the patient on discharge, although we can’t completely rule out the effects of cerebral hypoxia and hypoperfusion. First and foremost, the management of fentanyl poisoning, whether transdermal or another route, should focus on ventilatory support and oxygenation [19]. The competitive opioid antagonist naloxone must be administered to reverse the effects of opioid-induced respiratory depression. Naloxone is a short-acting opioid antagonist with a brief duration of action that is capable of reversing respiratory depression and sedation within 8–13 min. If necessary, it can be administered repeatedly [28]. In our case a single dose of naloxone was administered without on going doses or naloxone drip. This is a question of concern. Ventilation, oxygenation and circulation of the patient were ensured. As the effects of naloxone are temporary and may not outlast the duration of action of certain opioids, particularly in toxic doses, clinicians should also consider initiating naloxone infusions [29]. Naloxone can be used also in children to prevent the adverse effects of opiate induced respiratory depression [30].

Improving education at all levels, for both physicians and patients, could prevent a significant proportion of opioid misuse and therapeutic errors, including those related to fentanyl patches [19, 21]. As naloxone is the drug used to temporarily reverse the effects of opioid overdosage and can save lives in overdose situations take home naloxone program (THN) was established in several countries [28, 31, 32]. These programs have expanded and scaled up in different European countries and are now being prioritized in the US and Canada due to the significant increase in fatal opioids overdoses in recent years [32, 33]. Guidelines have been developed to support the prescription of naloxone for people at high risk of opioid overdose [28]. Take-home naloxone programs increase accessibility to naloxone among people who use opioids and their friends or family, as well as permitting first responders to use naloxone. These programs have also encouraged authorities to change the prescription-only status of naloxone to increase its availability as an opioid reversal drug [32]. The distribution of take-home naloxone kits, which typically include two doses of intramuscular naloxone, rescue-breathing masks and pamphlets on overdose management, has been shown to effectively reduce fentanyl-related deaths [24]. In British Columbia, for instance, the distribution of THN kits reversed 85 opioid overdoses in 20 months [31].

Fentanyl consumption in Lithuania is increasing from 0.684 Defined Daily Dose (DDD) in 2017 to 0.861 DDD in 2020 [34]. The number of deaths increased from 1.17 deaths per 100,000 inhabitants in 1990 to 4.85 deaths per 100,000 inhabitants in 2019 in all age groups as well [35]. Although
there are no official statistics, every year we record at least a few cases of unintentional opiate poisoning in children. The cases of accidental fentanyl overdose in our department are extremely rare. In any case, when a child presents in coma, physicians must always remember the possibility of opioid intoxication including transdermal fentanyl patch, therefore a thorough physical examination and a full history are extremely important. As the fentanyl consumption in Lithuania increases it would be important to develop preventive programs to help to reduce opioid overdose and its consequences.

4. Conclusions

Even though fentanyl is a high potency opioid that is widely used for management of acute and chronic pain as well as for sedation and general anesthesia, it also can expose patient patients to the risk of abuse and misuse or opioid addiction. Fentanyl misuse can lead to overdose, respiratory depression, death or severe neurological damage, especially in children. When dealing with cases of fentanyl overdose, doctors should keep in mind not only respiratory depression and hypotension, but the presence of toxic leukoencephalopathy as well. As the rates of transdermal fentanyl utilization increase, the rates of fentanyl overdose and overdose-related deaths increase consequently. Naloxone is a drug used to reverse the effects of opioid overdose and can save lives in overdose situations. Given overdose is common, therefore the tools for increasing public access to the drug as well as training programs for community and medical providers can increase access to naloxone among people who use opioids and their friends or family and save lives in case of opioid overdose.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

DEG and SK—were taking care of the patient, diagnosed the case and where the main initiators of the manuscript. TK—collected the material about the patient. DEG—wrote the first version of the manuscript. LG and IR—revised the drafted work, contributed in analysis and interpretation of clinical data. All authors contributed to the preparation of the manuscript. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

As the manuscript does not include any information about personal data allowing identification of a person, an ethical approval is not required. Lithuanian University of Health Sciences, Kaunas region bioethics committee: kaunorbtek@lsmuni.lt. The patient’s parents gave their consent for publication of the case in medical literature.

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CONFLICT OF INTEREST

The authors declared no conflict of interest.

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