

Fatal Respiratory Arrest Due to Transdermal Fentanyl

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ABSTRACT Transdermal fentanyl patches (TFP), which provide steady-state fentanyl concentrations for 72 hours, are an attractive alternative treatment compared to multiple daily oral opioids in cancer patients. But the dosage should be gradually increased due to possible undesirable side effects such as excessive sedation, respiratory depression, seizures, coma. There were three TFP of 75 µg.h⁻¹ on the patient's forehead and on the bilateral anterior skin of the head when the patient is brought to the emergency service. The patient with Glasgow coma scale (GCS):5 and pupillary bilateral myotic was immediately intubated, and transferred to the intensive care unit. Naloxone was administered as an antidote. Despite the supportive therapy with vasoactive drugs and antibiotics, the patient did not gain conscious and could not be weaned from the ventilator. Multiorgan failure developed, and the patient suffered cardiac arrest, and died on the 16th day.

Keywords: Transdermal patch; fentanyl; heart arrest

Transdermal fentanyl patch (TFP) was initially studied during the late 1980s' in the postoperative setting, where its safety and efficacy could be evaluated under controlled clinical conditions and with intensive monitoring.¹ Soon thereafter, clinical trials demonstrated that transdermal fentanyl was safe and efficacious for the outpatient treatment of chronic cancer pain.² TFP releases 12, 25, 50, 75, 100 µg.h⁻¹ doses. TFP, which provide steady-state fentanyl concentrations for 72 hours, are an attractive alternative treatment compared to multiple daily oral medications especially in malign and non malign cancer patients.³ But the dosage must be increased by titrating because it is 50-100 times more powerful than morphine and absorbed rapidly. Pharmacologically, fentanyl, like all µ agonists, acts on the central nervous system causing analgesia, sedation, severe respiratory depression, muscle rigidity, seizures, coma and hypotension. Intentional or unintentional misuse, as well as abuse, may lead to significant clinical consequences, including death.⁴

In this case, we presented a 77 year-old patient who underwent 3 patches of TFP (75 µg.h⁻¹) due to squamous cell lung cancer pain and underwent arrest due to opioid overdose.

CASE REPORT

A 77-year-old male patient was brought to our emergency department with complaints of altered consciousness, and respiratory complaints. His consciousness was closed in the emergency department. The first documented

vital findings were: arterial blood pressure: 130/90 mm Hg, pulse: 53 beats/minute, respiratory rate 6-8 breaths, oxygen saturation was 80%, Glasgow Coma Scale: 5. On physical examination, pupillary bilateral myotics and slowly respiration were observed. The patient with low GCS and shallow breathing was intubated successfully without any need of further narcotics. Respiratory support was given to the patient with ambu mask. There wasn't any abnormality in the electrocardiography (ECG). Blood glucose was measured as 90 mg.dl⁻¹ routine. Routine laboratory examination results a renal function (GFR 92.87 mL/min/1.7 m²), creatinine: 2,5 mg/dl, urea: 140 mg.dl⁻¹, procalcitonin: 0.22 µg.dl⁻¹. Sodium, chloride, lactate, and albumin were in normal range. Further blood tests including a full blood count, liver function, and coagulation test showed no abnormalities.

Cranial computed tomography (CT) and dif-fusing magnetic resonance (MR) appeared with a preliminary diagnosis of cerebrovascular event. No acute pathology was seen. On the physical examination of the patient, three TFP of 75 µg are attached to the forehead and the bilateral anterior skin together. Intensive care physician administered at a sufficient amount naloxone (0,4 mg) as antidote.

About the TFP of the patient's body were asked some questions to the patients' relatives. They reported that three TFP in a day of are attached at the same time for pain. The general condition of the patient was rapidly disrupted after this event. The patient had known lung cancer in a variety of squamous cell cancer and hypertension. He had discharged from the chest diseases clinic three days ago, and the patient was using TFP for the first time. The patient's FDG PET / CT had seen as a malignant nodular mass lesion with upper lung lobe apico-posterior FDG uptake and irregular limited nodular lesion with FDG uptake in the right upper lobe.

After receiving the intensive care unit, first treatment included respiratory support with mechanical ventilation. An attempt was made to achieve a mean arterial pressure (MAP) >65 mmHg with noradrenaline infusion. Antibiotic therapy

started in patient with fever. But multiorgan failure occurred. A percutaneous dilatational tracheotomy was performed at 8th day to easy weaning because the previous extubating attempts failed.

The patient's cardiac was arrested on the 16th day, but he did not respond to cardiopulmonary re-suscitation, and he was exitus.

DISCUSSION

This case describes the family attitude in which the patient's family administered three TFP once a day to the patient while TFP is prescribed a application once in every three days. The sequence of events and the absence of other factors that could have resulted in the clinical scenario presented here strongly point toward the systemic effects of a fentanyl overdose.

TFP have been widely used in the treatment of cancer pain. But some side effects and intoxications as a result of misuses have been reported. Ergil et al. reported a patient has an oropharyngeal carcinoma resistant to other analgesics, developed respiratory depression and get a mechanical ventilation support 10 hour after administration of TFP.⁵ Desio et al. reported a 21 years old woman who administered TFP by intravenous use (a case of fentanyl abuse accomplished by the aspiration of the drug contents out of a TFP, and the injection into a permanent central venous catheter) and developed respiratory arrest for 2 times.⁶ Also, Jumbelic reported 8 cases resulting in death after the use of fentanyl TFP.⁷ In our case, patient has a respiratory depression with one a day three dose TFP, and he needed to ventilator support, and respiratory system tried to be recovered with naloxone administration.

Fentanyl is a pure selective µ receptor agonist which can be administer intravenous, epidural, transdermal, buccal, oromucosal, intranasal and spinal. Fentanyl is rapidly absorbed into the skin, forming a depot of drug in the upper layers of the skin.⁸ With its high lipid solubility, transdermal fentanyl easily passes through the blood brain barrier. Therefore, initial therapy is not to exceed a dose of 25 µg.h⁻¹, and for opioid-tolerant patients,

doses prescribed can be 50, 75, and 100 $\mu\text{g}\cdot\text{h}^{-1}$.⁹ Respiratory depression occurs at a fentanyl concentration range of 1-5 $\mu\text{g}\cdot\text{L}^{-1}$, loss of consciousness occurs at $34 \pm 7 \mu\text{g}/\text{L}$ and the minimum effective concentration to produce an analgesic effect is $0.63 \pm 0.25 \mu\text{g}\cdot\text{L}^{-1}$.¹⁰ Although we did not measure fentanyl plasma concentrations, we believe that this mechanism was responsible for increased systemic fentanyl levels and the observed symptoms of opioid overdose in this patient.

Some physician knowledge of appropriate TFP use is generally poor, and recent reports raise concerns about the use of these delivery systems without an adequate understanding of their pharmacology and toxicology.¹¹ Some side effects and intoxications because of misuses have been reported. In an autopsy study, 25 cases of deadly fentanyl intoxications and the postmortem tissue distribution have been described.¹² Their patients were suffering from severe oncological disease or former drug addicts who misused it for various reasons. In this case, although they do not know that they overdosed it, they have brought the patient to the hospital with an early alert with impairment of the general condition of the patient.

The side effects of TFP are similar to other opioids side effects. These side effects occur earlier and more commonly in elderly patients. In our case, 77 years-old-male patients, the toxic side effects occur early after first use.

Naloxone is very effectively reverses the respiratory depression during of opioids, and supports diagnose.¹³ In our patient responded to administra-

tion of 0.4 mg naloxone, but did not provide spontaneous respiration.

Transdermal fentanyl patch is widely used for cancer pains which don't respond or inadequate response for analgesic treatment to other analgesics. Dose should be increased gradually and further caution should be exercised in patients who are not known whether they have used narcotic analgesics previously. Physicians should also consider that the patch should have been plastered on unusual locations. These analgesic patches should be kept in mind while taking cancer history of elderly patients presented with altered mental status or cardiopulmonary arrest.

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: Yeşim Ş Bayraktar; **Design:** Faruk Çiçekçi; **Control/ Supervision:** Jale B Çelik, Ateş Duman; **Data Collection and/or Processing:** Yeşim Ş Bayraktar, Faruk Çiçekçi; **Analysis and/or Interpretation:** Yeşim Ş Bayraktar, Faruk Çiçekçi; **Literature Review:** Yeşim Ş Bayraktar, Faruk Çiçekçi; **Writing the Article:** Yeşim Ş Bayraktar, Faruk Çiçekçi.

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