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# Selected Topics: Toxicology

## FENTANYL INTOXICATION CAUSED BY ABUSE OF TRANSDERMAL FENTANYL

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□ **Abstract—Fentanyl has an analgesic effect 100 times greater than that of morphine; therefore, transdermal administration of fentanyl has been widely used to control pain. Due to misconceptions regarding the proper use of fentanyl, its simple method of administration, and the absence of regulatory rules regarding its use, both medical providers and non-medical providers have abused fentanyl. We report on three cases of fentanyl intoxication and suggest solutions to prevent its abuse in the future. Three patients were intoxicated by transdermal fentanyl, which resulted in respiratory depression. Two of these cases were attributed to non-medical use of the drug and the other occurred while using fentanyl as directed by medical personnel. Physicians should use transdermal fentanyl only to control chronic pain, and rules should be established to prevent abuse of fentanyl that occurs due to its ease of use and the absence of any established policy regarding the prescription and disposal of this drug.** 

□ **Keywords—fentanyl; transdermal administration; respiratory insufficiency; opioid; pain**

### INTRODUCTION

Fentanyl acts primarily as a pure and selective opioid $\mu$ receptor agonist that relieves pain with fewer adverse effects and a more potent analgesic effect than morphine. Fentanyl is administered via intravenous, epidural, transdermal, and transmucosal routes.

Transdermal fentanyl is composed of a protective peel strip and four functional layers containing fentanyl. The drug reservoir contains 2.5 mg fentanyl/10 $cm^2$ of patch size, which is delivered via passive diffusion to systemic circulation. Because this transdermal delivery offers improved administration and enables continuous systemic application of fentanyl that produces a constant serum concentration similar to a continuous infusion, it has been widely used since it was first produced in 1991. Due to its pharmacokinetic features, transdermal fentanyl has been used to control chronic pain in patients who cannot control their pain using less potent opioids, but it is not useful for controlling acute pain. However, both medical providers and non-medical personnel have abused fentanyl, and fatal cases have occasionally been reported. We report here on three cases of fentanyl intoxication caused by transdermal fentanyl. We also analyze the pharmacokinetic features of transdermal fentanyl and suggest causes and solutions for the abuse of transdermal fentanyl.

### CASE REPORTS

*Case 1*

A 76-year-old female monk was admitted to our Emergency Department (ED) exhibiting a drowsy mental state that had developed 3 h previously. She had no known medical problems. She had experienced nausea and vomiting for 1 day, and she was in an altered mental state.

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She was initially taken to a public primary health center, where a computed tomography (CT) scan of the brain and laboratory blood tests were conducted. The CT scan of the brain was normal. An initial arterial blood gas (ABG) examination yielded the following values: pH 7.28, $PaCO_2$ 59.1 mm Hg, $PaO_2$ 98.5 mm Hg, $HCO_3$ 24.2 mmol/L, and oxygen saturation 96%. The level of glucose was 215 mg/dL. However, a second ABG examination 1 h after the initial examination showed aggravated respiratory acidosis, and she was then referred to our hospital. Upon arrival at our hospital, her vital signs were as follows: blood pressure 140/90 mm Hg, heart rate 83 beats/min, respiratory rate 6 breaths/min, and temperature 36.8°C. The ABG examination revealed the following: pH 7.36, $PaCO_2$ 50.2 mm Hg, $PaO_2$ 69.2 mm Hg, $HCO_3$ 26.2 mmol/L, and oxygen saturation 93%. At that point she was placed on a mechanical ventilator. Upon physical examination, she was drowsy with contracted pupils (1 mm) and normal light response; however, her lungs were clear. She showed symmetrical motor weakness of approximately grade IV in all extremities, with both a normal deep tendon response and normal sensory responses. Babinski's sign was not observed. Other laboratory findings were within normal limits. A CT scan of the chest showed normal findings. She received conservative treatments and was weaned from the mechanical ventilator on day 2. Upon detailed physical examination, we found two fentanyl patches (20 $cm^2$) (Durogesic®; Ortho-McNeil, Titusville, NJ) attached to her back. She informed the physician that her friend, who had colon cancer, gave her a few patches to decrease back pain that occurred after intense exercise. She was discharged from the hospital after the fourth day without sequelae.

*Case 2*

A 67-year-old man was admitted to our ED in a comatose state. He had been treated for neck pain at a public primary health center and discharged with a prescription for two fentanyl patches (10 $cm^2$) 8 h before arrival at our hospital. He had been found to be unresponsive 2 h before arrival at the hospital and was initially taken to a public primary health center, where he was dead on arrival and underwent cardiopulmonary resuscitation for 20 min. The two attached patches were removed and he was referred to our hospital. On arrival, his vital signs were as follows: blood pressure 120/80 mm Hg under administration of 10 ug/kg/min of dopamine, heart rate 96 beats/min, and temperature 36.0°C. His central venous pressure was 13 mm Hg. He was comatose, with doll's eye signs and no light responses or corneal reflexes. Laboratory findings were within normal limits. The electrocardiogram displayed atrial fibrillation as well as a heart rate of 90 beats/min without ischemic change. Chest radiography revealed chronic bronchial pathology, and a CT scan of the brain revealed multiple lacunar infarctions. He was intensively treated with induced hypothermia; however, he did not recover from his drowsy mental state and was referred to a private hospital on the seventh day.

*Case 3*

A 52-year-old man with no known medical problems presented at an ED exhibiting an altered mental state and apnea. A CT scan of the brain was conducted and revealed normal findings. It was assumed he had suffered a stroke, so he was intubated and administered 50,000 U urokinase and then transferred to our hospital. On arrival, he was comatose with contracted pupils (1 mm), no focal neurologic abnormalities, and his lungs were clear. The ABG examination revealed respiratory acidosis; however, all other laboratory findings were within normal limits. He was placed on mechanical ventilation. Two fentanyl patches (20 $cm^2$) (Durogesic®) were found attached to his neck and removed. He was weaned from the mechanical ventilator on day 2 and discharged from the hospital after 4 days without sequelae. He reported that one of his relatives, who had esophageal cancer, gave him two patches to decrease his neck pain.

## DISCUSSION

Fentanyl is a pure and selective opioid $\mu$ receptor agonist that is 80–100 times more potent than morphine (1). Fentanyl is administered via intravenous, epidural, transmucosal, and transdermal routes. Because it is a highly lipophilic drug, 98.6% of the injected dose is redistributed to highly vascular tissues, such as the brain and heart, within 1 h of intravenous administration, and elimination from the vascular tissue is rapid (2). Therefore, the duration of fentanyl's action is short and it is used for the management of acute pain, such as postoperative pain, via intravenous and epidural routes (2).

Transdermal delivery systems have been developed to deliver a drug at a predictable and approximately constant rate, although there is interpatient variability depending upon patient age, thickness and status of the skin, and body temperature. To be effectively delivered via the transdermal route, a drug has to have a low molecular weight ($<$ 1000 g/mol) and high solubility in water and oil (3). Fentanyl has a molecular weight of 286 g/mol and is also highly lipophilic, therefore, the absorption of fentanyl through a transdermal delivery system is