



Transient Aphasia Induced by Fentanyl: A Potential Neurological Adverse Effect

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Abstract

Fentanyl, a potent synthetic mu-opioid receptor agonist, is widely used for pain management. Due to its high lipophilicity and low molecular weight, fentanyl can rapidly cross the blood-brain barrier, facilitating its swift entry into the central nervous system (CNS). While many of its adverse drug reactions (ADRs) are well-documented, neurological effects such as aphasia remain exceedingly rare.

We report the case of a 55-year-old female who developed aphasia after receiving fentanyl for postoperative pain. This case was taken from the surgery department as part of the Pharmacovigilance elective under the Department of Pharmacology.

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Introduction

The World Health Organization (WHO) defines an adverse drug reaction (ADR) as "a response to a medication that is noxious and unintended and occurs at doses normally used in humans [1]." In developed countries, ADRs rank among the leading causes of mortality and morbidity [2]. They contribute significantly to increased mortality rates, hospital admissions,

prolonged hospitalization, elevated healthcare costs, and the removal of drugs from the market. The manifestations of ADRs are influenced by various factors, including genotype, age, gender, race, underlying medical conditions, drug class, administration route, and drug-drug interactions. Following post-marketing surveillance, various drugs have been linked to ADRs categorized as types A and B, with less frequent

occurrences of types C and D, according to Rawlins' classification system [3]. Type A (augmented) reactions are more prevalent, whereas Type B (bizarre) reactions, while rare, are severe and pose considerable clinical challenges due to their unpredictability and potential recurrence at any dosage [4].

Opioids are among the oldest and most potent pharmacological agents for treating severe pain; however, their use is associated with serious side effects such as respiratory depression, addiction, drowsiness, nausea, and constipation. While their efficacy in acute pain management is well established, their long-term use for chronic pain remains a growing concern and is under critical scrutiny [5]. Amongst the opioids, fentanyl is a synthetic opioid agonist which acts on the mu-opioid receptor. It is 100 times more potent than morphine. The activation of the mu-opioid receptors are responsible for causing analgesic effect [6].

Fentanyl has been associated with ADRs ranging from minor side effects like itching and nausea to serious, life-threatening complications such as respiratory depression and cardiac arrest. Central nervous system manifestations include delirium, sedation, nausea, vomiting, and constipation. Notably, dizziness and respiratory depression are serious concerns, with the latter increasing the risk of apnea and death when administered beyond safe therapeutic limits. Fentanyl-induced respiratory depression is exacerbated by vagus nerve stimulation, which can also lead to bradycardia [7].

In this case report, we present a rare ADR of fentanyl, namely aphasia. Aphasia is defined as "an acquired language disorder often due to brain injury that affects expressive and receptive language [8]." According to the Vigibase database, nervous system disorders make 14% of all the ADRs associated with fentanyl use. However, only 170 cases out of more than 60,000 cases have been associated with aphasia [9]. This makes it a very rare adverse event and hence is worth reporting.

Case Report

A 55-year-old woman with no known comorbidities presented to the surgery outpatient department (OPD) with complaints of abdominal pain and constipation

for two days. A biopsy was performed, which was suggestive of high-grade dysplasia. The patient subsequently underwent a right-sided hemicolectomy with a side-to-side ileocolic anastomosis. Following surgery, she experienced severe pain at the surgical site, for which an intravenous fentanyl infusion was administered at a rate of 2 mL per hour. On the same day, she developed aphasia, and her Glasgow Coma Scale (GCS) score dropped to nine (E2V2M5). (The highest possible GCS is 15, and the lowest is 3). Bilateral pupils were round, equal, and reactive to light. There was no respiratory distress, and her SpO₂ was 97%. An urgent neurology consult was sought, and it was advised to discontinue fentanyl. Magnetic resonance imaging (MRI) of the brain and magnetic resonance angiography (MRA) of the head and neck were performed, both of which were normal. The patient was subsequently shifted to the intensive care unit (ICU) for monitoring. By the next day, her GCS score improved to 14 (E4V4M6) and later to 15. She was transitioned to intravenous infusion of tramadol with ketamine at a rate of 8 mL per hour and remained comfortable. On discontinuation of the drug, the patient was recovering thereby indicating a reversible aphasia. The Naranjo score was 6 (probable), indicating a probable causal relationship between fentanyl and the observed adverse event.

Ten elements make up the validated, structured Naranjo Probability Scale, which is used to determine the probability that an adverse event is caused by a particular medication. According to the direction and strength of the evidence, each item is given a score based on the response—"Yes," "No," or "Do not know"—with corresponding point values of -1, 0, +1, or +2. The probability of an ADR is classified as definite (scoring ≥ 9), probable (score 5–8), possible (score 1–4), or doubtful (score ≤ 0) based on the cumulative score. The total score, which represents the degree of causation vary from -4 to +13 [10].

Discussion

World Health Organization (WHO) defines adverse drug reaction (ADR) as "a response to a medication that is noxious and unintended and occurs at doses normally used in man." ADRs are common in all hospitals, whether they are primary care or tertiary care. ADRs not only impact patients' quality of life but also increase the burden on the healthcare system. Their

elevated mortality and morbidity make them a major public health concern [11].

Opioids are substances that bind to opioid receptors in the human body. They are considered the most potent painkillers. Opioid receptors are G protein-coupled and include mu (μ), delta (δ), kappa (κ), nociceptin/orphanin (N/OFQ), and zeta (ZOR). Mu receptors primarily mediate pain relief and euphoria; delta receptors contribute to both analgesia and mood regulation; kappa receptors provide pain relief but may also cause dysphoria; and nociceptin receptors influence pain, memory, and anxiety [12].

Fentanyl is rapidly distributed in the Central Nervous System (CNS) resulting in neural circuit dysfunction and neuro-inflammation, which is labelled as a potential mechanism for ADR's related to the CNS [13]. According to VigAccess (launched by the WHO in 2015 to provide public access to information on ADRs), a total of 272,573 cases of fentanyl-related ADRs have been reported. The following figure (Figure 1) illustrates the various categories of reported ADRs [9].

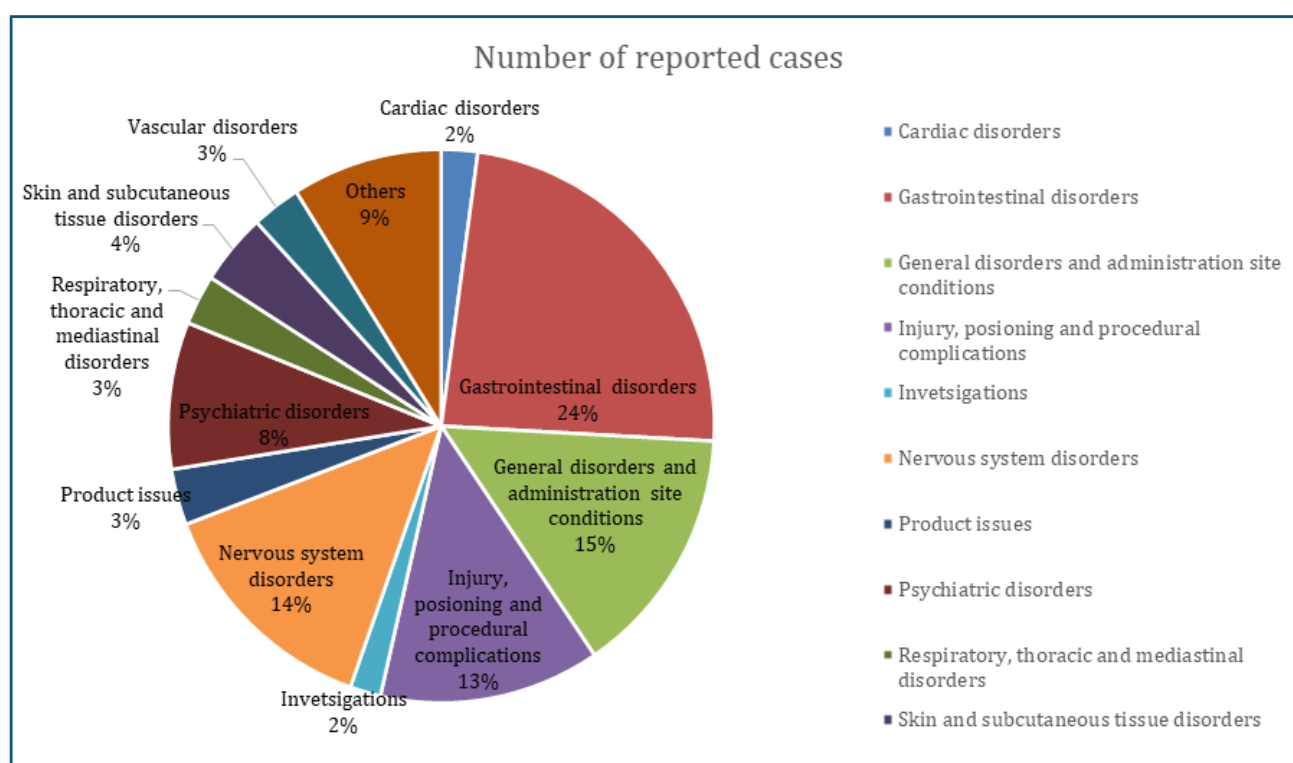


Figure 1: Distribution of ADR's Associated with Fentanyl

In our patient, aphasia occurred following fentanyl administration and could not be attributed to any other cause. The transient episode of aphasia resolved upon discontinuation of fentanyl. Hence, we believe that the aphasia is a rare complication of fentanyl and that reporting this case is critical to raising awareness.

Conclusion

This case highlights a rare but potentially serious adverse drug reaction—aphasia—associated with fentanyl administration. Although fentanyl is a widely used and effective opioid analgesic, especially in postoperative pain management, its use warrants close monitoring due to its diverse and sometimes unpredictable effects on the central nervous system. The temporal relationship between drug administration and the onset of aphasia, along with resolution following drug withdrawal and a Naranjo score of 6 (probable), strongly suggests a causative link. While common ADRs of fentanyl are well-documented, rare manifestations like aphasia may go unrecognized, leading to delayed diagnosis or unnecessary investigations. This case underscores the importance of vigilant pharmacovigilance, timely recognition of atypical ADRs, and the need for individualized

opioid management strategies. Increased awareness and reporting of such rare events can contribute to improved patient safety and informed clinical decision-making.

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Conflict of interest

There is no conflict of interest

Consent

Consent has been taken.

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