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Review

Predictive Factors for Respiratory Depression Following Fentanyl Administration in Pediatric Patients

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Abstract

Fentanyl is a potent opioid agonist developed for analgesic procedures. It is used for both acute and chronic moderate-to-severe pain. Fentanyl has a rapid onset and short duration of action, making it the preferred analgesic option for various situations. It alters pain response by binding to opioid receptors. Fentanyl carries a high risk for overdose, resulting in various complications, such as impaired consciousness and respiratory depression. Deaths due to fentanyl poisoning mainly occur due to respiratory depression. Children are susceptible to accidental exposure to fentanyl overdose, and due to their special developmental needs, the mortality risk due to fentanyl overdose is higher in this population than in adults. However, limited evidence is available regarding fentanyl-induced respiratory depression in children. This review aims to discuss fentanyl-induced respiratory depression in children and its predictive factors. Although opioids act on the same receptor, fentanyl leads to more severe respiratory effects. While morphine and heroin decrease respiratory rate without affecting tidal volume, fentanyl reduces both respiratory rate and tidal volume. The same doses of fentanyl via the same route of administration achieved higher plasma concentrations in children than in adults. Neuromuscular diseases and obstructive sleep apnea increase the risk of fentanyl-induced respiratory depression in children. Predictive factors for fentanyl-induced respiratory depression in children also include age, co-administration of sedatives, and genetic polymorphisms affecting metabolism. Future research should prioritize improving risk assessment tools and validating predictive models to optimize fentanyl use while minimizing harm in pediatric patients.

Keywords: *Fentanyl, Respiratory depression, Fentanyl-induced respiratory depression, Children, Pediatric patients*

Introduction

Fentanyl is a potent synthetic opioid usually used as an analgesic in procedures with moderate to severe pain (1). It is more preferred over longer-acting opioids, such as morphine, for procedural sedation, as fentanyl has a rapid onset (2-3 minutes) and limited duration of action (30 to 60 minutes) (2). It is also associated with no histamine release and is 75–125-fold more potent than morphine (1). Fentanyl can be used in both acute and chronic pain states (3).

Fentanyl exerts its effects by activating opiate receptors, which alter pain perception by elevating the pain threshold and providing analgesia, inhibiting ascending pain pathways, and sedation. It can elevate the pain threshold and inhibit ascending pain pathways by binding to stereospecific receptors at different sites within the central nervous system (CNS) (4). Fentanyl can be administered via various routes, such as intravenous, intranasal, sublingual, transdermal, and transmucosal. In cases of moderate to severe chronic pain, the fentanyl transdermal patch is typically used when alternative pain therapies, including non-opioid analgesics or immediate-release opioid formulations, prove insufficient or are poorly tolerated (5).

Fentanyl has a high risk for addiction and abuse, raising the risk for overdose and mortality (6). Children can be accidentally exposed to fentanyl, which can lead to an overdose resulting in respiratory depression, impaired consciousness, and other serious complications (7-9). According to previous reports, accidental exposure to a fentanyl transdermal patch with fatal overdose has led to deaths in children and adults (10, 11). Furthermore, fentanyl poisoning may lead to advanced neurological deficits and toxic leukoencephalopathy (12), which may prolong hospital stay and require substantial rehabilitation resources.

In the age group under one year, 25 opioid overdoses, with zero reported deaths, were reported from January 2020 to August 2022, according to a Poison Control report (13). However, other case reports outside the poison control report showed that fentanyl overdose can lead to a mortality rate of 50% (14). These cases occurred within the common age range for pediatric ingestions, typically 2–4 years. Previous studies report that approximately 3% of pediatric intensive care unit (PICU) admissions related to toxic ingestions are attributable to opioid exposure (15).

Respiratory depression is the main cause of death in cases of fentanyl poisoning. Fentanyl reduces inspiratory effort and respiratory rate and increases chest wall rigidity, resulting in significant respiratory distress. It is critical to identify predictive factors for fentanyl-induced respiratory depression in children, especially due to their developmental differences. However, studies investigating fentanyl-induced respiratory depression and its predictive factors in children are scarce. This review aims to explore current evidence focusing on the occurrence of respiratory depression after fentanyl administration in pediatric populations and its predictive factors.

Methods

A comprehensive literature search was conducted in Medline (via PubMed), Scopus, and Web of Science databases up to August 17, 2025. Medical Subject Headings (MeSH) and relevant free-text keywords were used to identify synonyms. Boolean operators (AND', OR') were applied to combine search terms in alignment with guidance from the Cochrane Handbook for Systematic Reviews of Interventions. Key search terms included: "Fentanyl" OR "Opioids" AND "Respiratory Depression" OR "Fentanyl-induced Respiratory Depression" AND "Pediatrics" OR "Children". Summaries and duplicates of the found studies were exported and removed by EndNoteX8. Any study that discusses the predictive factors for respiratory depression following fentanyl administration in pediatric patients and is published in peer-reviewed journals was included. All languages are included. Full-text articles, case series, and abstracts with related topics are included. Case reports, comments, and letters were excluded.

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Discussion

Fentanyl Overview

Fentanyl is metabolized rapidly, as it is detected in the plasma within 90 seconds after administration (5, 16). The fentanyl metabolite levels in the plasma peak at approximately 90 minutes (16). Thereafter, metabolite levels decline slowly with a mean terminal half-life of 375 minutes (16). The majority of fentanyl products are metabolized after 72 hours, with terminal elimination half-lives ranging from 219 to 853 minutes (17). The body eliminates fentanyl mainly by excreting its metabolites in urine. It is metabolized into norfentanyl by hepatic phase 1 cytochrome-P450 (CYP)-mediated reactions (17) and oxidative N-dealkylation at the piperidine ring (18). Despropionylfentanyl, hydroxyfentanyl, and hydroxynorfentanyl are other minor metabolites formed by other pathways. Carboxamide hydrolysis results in the formation of despropionylfentanyl, while both hydroxyfentanyl and hydroxynorfentanyl metabolites are hydroxylated at the propionyl moiety (19).

Fentanyl is a synthetic, lipophilic phenylpiperidine opioid, which explains its rapid onset, short duration, and rapid CNS permeability. It acts through activation of the mu-opioid receptor (MOR) (20), with a 1.35 nM binding affinity (Ki) at human recombinant MORs (21). Fentanyl has a low affinity for delta and kappa opioid receptors (20). Fentanyl concentrations ranging between 0.3 and 0.7 ng/ml provide analgesia without adverse effects, while a concentration >3 ng/ml results in CNS and respiratory depression in opioid-naïve patients (22, 23). Fentanyl poisoning has been associated with increased risk of intubation and prolonged intensive care unit (ICU) stay (24). Deaths from fentanyl poisoning have been reported with post-mortem serum concentrations ranging from 3 to 383 ng/ml (25). Other side effects of fentanyl poisoning include pruritus, orthostatic hypotension, nausea, constipation, urinary urgency or retention, and cough suppression. Intravenous (IV) usage may lead to chest wall rigidity (4). The peak of respiratory depression occurs about 25 minutes after a single IV dose and may persist for 2–3 hours (16, 26).

The pharmacokinetic curve of fentanyl involves an initial rapid distribution phase followed by a prolonged terminal elimination phase (16). Sudden elevations in fentanyl plasma concentrations may occur; thus, the pharmacokinetic curve of fentanyl may have several peaks. Typically, the initial peak of fentanyl in plasma occurs within five minutes after IV administration (27). Some studies reported that fentanyl plasma concentrations were associated with secondary peaks in hospitalized patients receiving IV fentanyl (5). These secondary peaks were observed approximately 45–60 minutes following administration (28, 29). Furthermore, more delayed secondary plasma peaks were observed in some patients (210 minutes) (30). These secondary plasma peaks are of clinical significance, as new-onset respiratory distress has been observed during the secondary peak, which sometimes necessitated naloxone rescue (29).

Maintaining airway patency and ensuring adequate respiration and hemodynamic stability are the mainstay of initial care of any opioid-intoxicated patient. Thereafter, naloxone should be administered as soon as possible. Naloxone is a competitive mu-opioid receptor antagonist, which rapidly reverses central and peripheral opioid effects (4). It can be administered via any route, including subcutaneous, intramuscular, intravenous, intranasal, sublingual, endotracheal, and inhalational (31).

Fentanyl-Induced Respiratory Depression

Opioids can lead to respiratory depression by various mechanisms such as impairing inspiratory rhythmogenesis and airway patency, inhibiting inspiratory effort, and disrupting chemosensory feedback, resulting in decreased respiratory rate and apneas (32-34). This results from activating MOR in the medullary (pre-Bötzinger) and pontine (KF, DLP) respiratory centers (35). Although opioids act on the same receptor (MOR), fentanyl leads to more severe respiratory effects. While morphine and heroin decrease respiratory rate without affecting tidal volume, fentanyl reduces both respiratory rate and tidal volume (6). Furthermore, fentanyl is associated with a more reduced minute ventilation than morphine or heroin at equipotent doses (6),

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Fentanyl is seventy-fold more potent in reducing minute ventilation than other opioids. In addition, suppressing fentanyl-induced respiratory depression in mice requires a tenfold dose of naltrexone (3 mg/kg) compared with morphine, which requires 0.3 mg/kg of naloxone (6).

Studies have evaluated the differences between different opioids in reducing cerebral blood flow in mice. Although heroin significantly and rapidly reduced brain oxygen levels (within 5 minutes at a 0.2 mg/kilogram dose), fentanyl has a 10-20-fold greater potency in reducing brain oxygen levels compared to heroin (35). It can reduce brain oxygen levels at low doses within the first minute, which peaks in the second minute after injection (36). Furthermore, fentanyl is 400-fold more potent in reducing brain oxygenation compared to morphine and oxycodone (37).

Unlike morphine, heroin, and levallorphan, fentanyl may lead to "wooden chest syndrome" (35). Fentanyl leads to rigidity when administered with a dose of 15 µg/kg ideal body weight, involving a bolus dose of 250 mcg (35). A dose of 1 mg per 70 kg body weight was noted to cause rigidity in 50%. Notably, rigidity appears before apnea. Typically, rigidity is observed in 60–90 seconds following a 250-mcg bolus dose, while respiratory depression and apnea occur within 7-9 minutes following bolus injection (38). About two-thirds of individuals who die from fentanyl overdose are found with the needle still inserted, the tourniquet applied, and the syringe in hand (39). Witnesses often describe abrupt muscle rigidity, seizure-like movements, rapid onset of facial and oral cyanosis, and gurgling respirations (39). Such presentations are commonly reported by first responders and emergency department clinicians managing fentanyl overdoses.

Furthermore, fentanyl, at very low doses, reduces nucleus accumbens oxygen levels (37). This effect increases with the increase in doses. Besides the nucleus accumbens, the subcutaneous space showed reduced oxygen levels following fentanyl administration (37). Thus, fentanyl-induced oxygen drop in brain tissue is mainly caused by a reduction in blood oxygen levels and respiratory depression. Additionally, the area under the curve for oxygen decrease showed that the combination of heroin and fentanyl is 10-fold more potent than fentanyl alone and 5-fold more potent than heroin alone (37). This extended period of cerebral hypoxia is clinically significant, as brain cells can withstand brief reductions in oxygen supply but sustain more severe injury when the hypoxia is prolonged (40).

Fentanyl-Induced Respiratory Depression in Children

Fentanyl can provide an effective and rapid analgesia for pediatric populations via various routes, such as intranasal, intravenous, and transdermal. However, it is associated with a high risk of opioid-induced respiratory depression due to its high potency and lipophilicity, resulting in a narrow safety margin. Thus, a minor alteration in the exposure or patient susceptibility may significantly lead to respiratory depression. Accordingly, it is critical to identify predictive factors for respiratory depression in pediatric populations following fentanyl administration to achieve safer dosing, monitoring, and prevention.

Fentanyl pharmacokinetics differ according to age, with a high exposure risk in children (41). It has been reported that the same doses of fentanyl via the same route of administration achieved higher plasma concentrations in children than in adults (42). This can be explained by the low volume of distribution and plasma clearance of children, especially neonates and preterm, which precipitate prolonged exposure and larger effective brain exposure for a given dose (42). However, routine pediatric dosing is weight-adjusted, which tends to normalize plasma concentrations relative to adults in controlled clinical settings, but weight-based dosing does not eliminate pharmacokinetic variability from prematurity, illness, inflammation, or transdermal mishaps (43). Transdermal fentanyl patches used at home can be seriously harmful for children, as accidental application to a child or heat exposure can significantly elevate the maximum concentration and flux of fentanyl, resulting in delayed but severe respiratory depression (8, 10).

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Besides pharmacokinetics, the pharmacodynamics of fentanyl are significantly influenced by pediatric physiology. The elevated cerebral oxygen consumption and developmental differences in cerebrovascular responsiveness and chemoreflexes that limit cerebrovascular reserve in children, particularly infants, determine fentanyl pharmacodynamic vulnerability. Based on a physiologically based model developed by Chakravartula et al., children have a greater risk of developing rapid and deep reductions in brain and blood oxygen levels than adults, even at equivalent fentanyl plasma concentrations and similar minute-ventilation depressions. This is due to their developmental differences (42).

It has been reported that neuromuscular diseases, chronic pulmonary disease, and obstructive sleep apnea (OSA) decrease respiratory reserve and impair arousal responses, thus increasing the risk of fentanyl-induced respiratory depression (44, 45). The role of OSA in developing respiratory depression following fentanyl administration in children has been debatable in previous studies. However, clinically and practically, OSA is considered a significant predictive factor for respiratory depression in children receiving opioids, including fentanyl (44). Another predictive factor for respiratory depression following fentanyl administration in children is age. Children, especially infants and neonates, show a great risk of developing adverse respiratory outcomes after receiving opioids due to their underdeveloped respiratory regulation (42).

Furthermore, the coadministration of other sedatives, such as benzodiazepines and antihistamines, can significantly increase the risk of opioid-induced respiratory depression in pediatric populations (46). Agents that decrease fentanyl exposure, such as CYP3A inhibitors, can significantly and unexpectedly increase fentanyl plasma concentrations (47). To minimize the risk of fentanyl-induced respiratory depression in children, continuous monitoring by capnography and pulse oximetry should be performed.

Implications of Predictive Factors for Fentanyl-Induced Respiratory Depression

Predictive factors for respiratory depression following fentanyl administration in children can help early identification of high-risk patients, which aids in tailoring dosing regimens and monitoring strategies to the individual patient; improving patient safety by decreasing the risk of hypoxia, brain injury, or death; optimizing anesthesia and analgesia protocols; and reducing burden on healthcare by reducing the risk of prolonged hospital stay and ICU admissions. Identifying predictive factors for fentanyl-induced respiratory depression can also provide a basis for future research and more personalized medicine.

Conclusion

Fentanyl remains a cornerstone analgesic in pediatric practice; however, its narrow therapeutic margin necessitates vigilance for respiratory depression, particularly in vulnerable populations. This review highlights that predictive factors, including developmental pharmacokinetic and pharmacodynamic differences, higher cerebral oxygen demand in children, and pre-existing neurological or respiratory conditions, significantly influence the risk of fentanyl-induced respiratory compromise. Future research should prioritize refining risk stratification tools and validating predictive models to optimize fentanyl use while minimizing harm in pediatric patients.

Disclosure

Conflict of interest

There is no conflict of interest.

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Ethical considerations

This study is a literature review of previously published literature and does not involve any original data collection involving human or animal subjects. Therefore, ethical approval was not required.

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Data availability

Data that support the findings of this study are embedded within the manuscript.

Author contribution

All authors contributed to conceptualizing, data drafting, collection, analysis and final writing of the manuscript.

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