

An Overview on Propofol–Fentanyl Anesthesia for Complex Spine Surgery

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Abstract:

Background: Complex spine surgery often requires prolonged anesthesia, stable hemodynamic control, effective analgesia, rapid recovery, and preservation of intraoperative neurophysiological monitoring. Propofol is a widely used intravenous hypnotic because of its favorable pharmacokinetic and pharmacodynamic profile, rapid onset and recovery, low incidence of postoperative nausea and vomiting, and suitability for total intravenous anesthesia and neurosurgical procedures. It also decreases cerebral blood flow, intracranial pressure, and cerebral metabolic rate, while remaining generally compatible with evoked-potential monitoring. However, propofol may produce dose-dependent cardiovascular depression, particularly hypotension and bradycardia. Fentanyl is a potent synthetic μ -opioid receptor agonist commonly used as an analgesic and anesthetic adjunct. In neuroanesthesia, it provides effective analgesia and attenuates sympathetic responses to laryngoscopy and surgical stimulation, while having relatively limited direct effects on somatosensory and motor evoked-potential monitoring at usual anesthetic doses. Nevertheless, careful titration is necessary because excessive fentanyl administration can cause respiratory depression, hypercapnia, hypotension, and other opioid-related adverse effects. The complementary hypnotic properties of propofol and potent analgesic effects of fentanyl therefore make their combination relevant to anesthetic management during complex spine surgery.

Keywords: Propofol; Fentanyl; Complex spine surgery; Total intravenous anesthesia; Neuroanesthesia; Neuromonitoring; Hemodynamic stability; Analgesia.

Introduction:

Modern management of pain after spinal surgery therefore emphasizes multimodal analgesia rather than exclusive dependence on opioids. Multimodal strategies combine medications and techniques with different mechanisms of action to provide effective analgesia while limiting opioid-related adverse effects. Depending on the type of surgery and patient characteristics, these strategies may include paracetamol, nonsteroidal anti-inflammatory drugs or cyclooxygenase-2 inhibitors, ketamine, local or regional anesthetic techniques, and carefully titrated opioids when required. Procedure-specific evidence indicates that adequate perioperative analgesia is closely associated with earlier mobilization and discharge after complex spinal surgery (1).

Propofol (2,6-diisopropylphenol) is a potent intravenous hypnotic drug that was developed by Imperial Chemical Industries Limited (London, UK), patented by John (Iain) Glen and Roger James in 1977, and commercially launched in 1986 in Europe and 1989 in the US (2).

Like most anaesthetics, propofol is a γ -aminobutyric acid (GABA) receptor agonist. It has a favourable pharmacokinetic (PK) and pharmacodynamic (PD) profile, which has resulted in it becoming the most commonly used intravenous anaesthetic for the past three decades. Rapid and smooth induction with nearly no excitation phenomena, relatively short context-sensitive time, rapid terminal half-life time and low incidence of

postoperative nausea and vomiting (PONV) make it a very versatile hypnotic drug. It is used for sedation and anaesthesia for almost all types of surgery, but is particularly well-suited for anaesthesia in patients undergoing ambulatory and neurosurgery where rapid psychomotor recovery are of utmost importance. Its efficacy and utility has also been proven for sedation of patients in the intensive care unit (ICU) and conscious sedation of patients undergoing diagnostic or invasive procedures (3).

The adverse effects of propofol are well-documented, with the most common being pain on injection. Other adverse effects are cardiovascular (bradycardia, hypotension) and metabolic (hyperlipidaemia secondary to infusion of lipid formulation) (4).

Role of Propofol in Neurosurgery and the Central Nervous System

The role of propofol has been established since 2015. Propofol decreases cerebral blood flow, intracranial pressure, and cerebral metabolic rate, while maintaining dynamic and static autoregulation and vascular responsiveness to carbon dioxide. (5).

Effect on Neuromonitoring

Propofol is generally compatible with intraoperative neurophysiological monitoring and is commonly used during TIVA because it avoids the marked suppression of evoked potentials produced by volatile anaesthetics. Nevertheless, increasing propofol concentrations can dose-dependently reduce signal amplitude, so a stable infusion is preferred during critical monitoring periods (6).

Cardiovascular System

Propofol has extensive effects on the cardiovascular system. The most prominent effect is systemic blood pressure reduction accompanied by a decrease in cardiac output. This effect is dose-dependent and even occurs at sedative doses. It is more pronounced in elderly and physiologically compromised patients. The effect is, at least partially, mediated by a significant decrease of sympathetic tone accompanied by a decrease in vascular resistance. Furthermore, propofol also inhibits the physiological baroreflex responses, thereby enhancing cardiovascular depression (7).

Cardiac contractility remains preserved. Propofol only has direct negative inotropic actions at concentrations exceeding the clinical range, an effect that is similar in failing and non-failing human hearts. The negative inotropic effect is mediated through a concentration-dependent decrease in the uptake of Ca^{2+} into the sarcoplasmic reticulum, which is simultaneously accompanied by an increase of myofilament sensitivity to Ca^{2+} , partially counteracting the effect. The haemodynamic response lags behind the hypnotic effect of propofol. While the hypnotic half-time plasma effect site equilibration time ($T_{1/2k_{eo}}$) is 2.5 min, independent of age, haemodynamic half-time plasma effect site equilibration time is 5 min in young patients, and up to 10 min in elderly patients (2).

Fentanyl

Definition

Fentanyl is a potent synthetic opioid analgesic and a strong agonist at the mu-opioid receptor, widely used as an analgesic and anaesthetic adjunct (8).

Chemistry

The chemical structure of fentanyl, a substance with the chemical name *N*-(1-phenethyl-4-piperidyl) propionamide and the formula $\text{C}_{22}\text{H}_{28}\text{N}_2\text{O}$, is a monocarboxylic acid amide. It contains a relatively simple skeleton with four important parts, namely the amide group, aniline, piperidine ring, and alkyl chain linked to a tertiary nitrogen (Figure 1) (9).

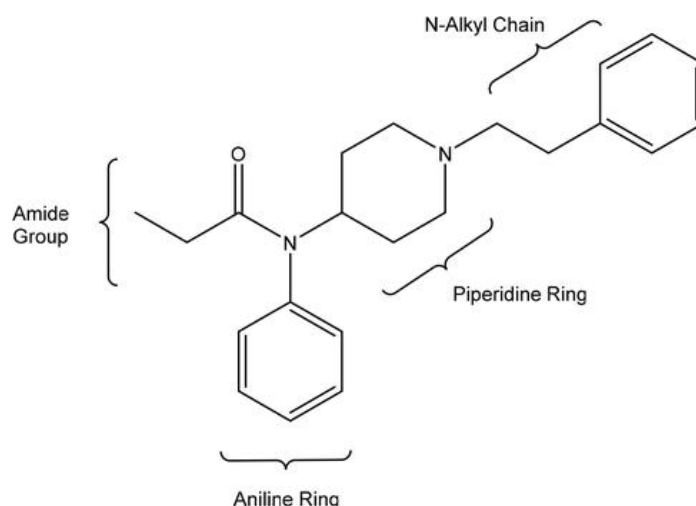


Figure 1. Structure of fentanyl (9).

It was patented in 1965 under the number U.S. Pat. No. 3,164,600 ('600) (10).

Dose and Administration

Fentanyl is typically administered intravenously (IV), intramuscularly (IM), transdermally (TD) as skin patches, intranasally (IN) in the form of a volatile nasal spray, and intrathecally (IT). It is also available as a buccal soluble thin film, which can dissolve in the mouth, similar to the sublingual tablets. However, in contrast to other opiates, it is less common to find forms of synthetic drugs such as oral tablets or powders. A new medication currently being used to address the gastrointestinal (GI) side effects without counteracting its primary analgesic aims acts selectively on the GI mu-opioid receptors and can aid in alleviating constipation while still providing pain relief, a dilemma previously treated off-label in some hospitals by suspending a vial of naloxone in ice water and taking the mix enterally. The transdermal patch is for the long-term management of pain. This article focuses on injectable fentanyl; more detailed coverage of the transdermal formulation is available in the StatPearls specific article on transdermal fentanyl (8).

Fentanyl comes in an injectable form of 50 mcg/mL. Dosing is as follows by indication (8):

- **Preoperative analgesia**
 - 50 to 100 mcg IV/IM for a single dose 30 to 60 minutes before surgery; consider lower dosing in patients 65 and older.
- **Anesthesia adjunct**
 - 2 to 50 mcg/kg/dose IV for a single dose
 - 2 to 20 mcg for low dosing; 20 to 50 mcg for higher dosing. Low dosing is favored in patients 65 and older.
- **Regional anesthesia adjunct**
 - 50 to 100 mcg IV/IM for a single; consider lower dosing in patients 65 and older.
- **General anesthesia**
 - 20 to 50 mcg/kg/dose IV for a single dose; consider lower dosing in patients 65 and older.
 - For high-risk patients undergoing complicated surgical procedures, use with oxygen and a muscle relaxant; doses up to 150 mcg/kg/dose may be necessary.

- ***Post-operative pain control***
 - 50 to 100 mcg IV/IM every 1 to 2 hours as needed; alternately 0.5 to 1.5 mcg/kg/hour IV as needed. Consider lower dosing in patients 65 and older.
 - PCA (patient-controlled analgesia): 10 to 20 mcg IV every 6 to 20 minutes as needed; start at the lowest effective dose for the shortest effective duration - refer to institutional protocols.
- ***Moderate to severe acute pain (off-label)***
 - 1 to 2 mcg/kg/dose intranasally each hour as needed; the maximum dose is 100 mcg. Use the lowest effective dose for the shortest effective duration.

Pharmacogenomics

Genetic variation affecting opioid receptors and fentanyl metabolism may contribute to variability in analgesic response and adverse effects. At present, pharmacogenomic testing is not routinely used to determine perioperative fentanyl dosing, so dosing remains individualized according to clinical response and monitoring (11).

Role of Fentanyl in Neurosurgery and the Central Nervous System

In neuroanaesthesia, fentanyl provides potent analgesia and blunts sympathetic responses to laryngoscopy and surgical stimulation. It should be carefully titrated because excessive opioid effect can cause respiratory depression and hypercapnia, which may adversely affect cerebral physiology; close haemodynamic and ventilatory monitoring is therefore essential (12).

Effect on Neuromonitoring

At usual anaesthetic doses, fentanyl has relatively limited direct effects on somatosensory and motor evoked-potential monitoring compared with hypnotic or volatile agents. Large boluses should still be avoided during critical recordings because associated haemodynamic or ventilatory changes may indirectly affect signal quality (12).

Adverse Effects

Fentanyl's side effects are similar to those of heroin, which produce euphoria, confusion, respiratory depression (which, if extensive and untreated, may lead to arrest), drowsiness, nausea, visual disturbances, dyskinesia, hallucinations, delirium, a subset of the latter known as "narcotic delirium," analgesia, constipation, narcotic ileus, muscle rigidity, constipation, addiction, loss of consciousness, hypotension, coma, and even death (13).

Alcohol and other drugs (i.e., cocaine, heroin) can synergistically exacerbate fentanyl's side effects, creating multi-layered clinical scenarios that can be complex to manage. These substances, taken together, generate undesirable conditions that complicate the patient's prognosis (14).

Contraindications

The use of fentanyl is contraindicated in patients in the following situations (8):

- After operative interventions in the biliary tract, these may slow hepatic elimination of the drug.
- With respiratory depression or obstructive airway diseases (i.e., asthma, COPD, obstructive sleep apnea, obesity hyperventilation, also known as, Pickwickian syndrome)
- With liver failure
- With known intolerance to fentanyl or other morphine-like drugs, including codeine, or any components in the formulation

- With known hypersensitivity (i.e., anaphylaxis) or any common drug delivery excipients (i.e., sodium chloride, sodium hydroxide).

The drug fentanyl should not be used concomitant with certain medications such as CYP3A4 inhibitors like macrolide antibiotics or azole-antifungal agents, and protease inhibitors may increase plasma concentrations of fentanyl, extending the opioid drug action and exacerbating the opioid-induced respiratory depression (OIRD). On the other hand, the cessation of a CYP3A4 inducer medication (i.e., carbamazepine, phenytoin) in patients treated with fentanyl citrate injections may potentially increase fentanyl plasma concentrations prolonging the opioid adverse reactions. If the patient has used a monoamine oxidase inhibitor in the previous 14 days, fentanyl is contraindicated (8).

Toxicity

Typically, a fentanyl overdose manifests as an extrapolation of its pharmacological side effects. Although the clinical scenarios may vary among patients, one of the main concerns is the level of expression of OIRD. In such cases, oxygen administration and respiratory assistance are a priority. An opioid drug antagonist such as naloxone can help to correct OIRD symptoms. Commonly, repeated doses are necessary since, over time, respiratory depression may overcome the effects of the antagonist drug, particularly with opiates such as fentanyl, in which increased receptor affinity may be present as compared to other opiates. Thus, the therapeutic approach should continue until a normal respiratory rate coincides with appropriate oxygen saturation levels (15).

Naloxone/naltrexone are robust opioid antagonists that function by blocking μ -receptors. The FDA has approved these antidote medications for emergency treatment of patients with known or suspected opioid overdose experiencing respiratory and/or central nervous system (CNS) depression. Common routes of naloxone administration include IV, IM, IN, or subcutaneous (SC). Researchers have recently posed a caveat regarding the intranasal route for naloxone administration. Since the incidence of obstructive nasal pathology is relatively high in patients who experience serious OIRD, there is documentation of relevant instances of treatment failures when using the IN formulations (8).

Also, an IV neuromuscular blocker may be employed in cases of severe muscular rigidity to assist the controlled respiration treatments (16).

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