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Review

Review on fentanyl: Mechanism and Pharmacology of fentanyl drug

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Abstract

In this area, smaller quantities of Fentanyl were generally always given with one of a variety of IV hypnotics. The term neurolept anesthesia was essentially a combination of neuroleptic agents with inhalation anesthetics (fentanyl and higher doses of droperidol), with nitrous oxide and oxygen or not. This practice had become fairly common, first in the majority of western countries followed by the vast majority of Eastern European countries. The use of fentanyl in anesthesia became widely accepted with the publication of a paper in December 1969, in The New England Journal of Medicine, that described a study by Lowenstein et al. It wasn't long afterward that many randomized studies were performed over a 3-to-4-year period to assess high-dose morphine/oxygen anesthesia as a Technique For Critically Ill Patients Undergoing open heart surgery-and later major vascular surgery. Some of the increase use of this technique was attributed to remarkable stability of cardiovascular function in this group of critically ill patients.

Fentanyl is indicated for the management of breakthrough pain (which is brief occurrences of intense pain despite taking around-the-clock pain medication). It is only indicated for patients who are 18 years of age or older and are already on regularly scheduled doses of a narcotic (opiate) pain medication within the past seven days, who are tolerant to the effects of the narcotic pain medications. Fentanyl is a narcotic (opiate) analgesic, which is a type of medication that change the way the brain and nervous system respond to pain. Give it with your other pain medication(s). Do not discontinue your other pain medication(s) before or during your use of fentanyl.

Keywords: Fentanyl, Opoid, Narcotic, Analgesic, Anesthetics

INTRODUCTION

Studies were limited to animals for the first three to four years. Following these preliminary investigations, patients with severe valvular disease and subsequently individuals with coronary artery disease were the subjects of a tentative investigation using a high-dose fentanyl/oxygen method[1]. High-dose fentanyl/oxygen anesthesia outperformed high-dose morphine and, in a matter of years, became the preferred method for almost all patients having heart surgery. This led to the evaluation of possible substitutes for fentanyl

as a pure opioid "anesthetic" or as supplements to be used in conjunction with inhaled drugs or intravenous hypnotics at the Janssen Laboratories in Beerse, Belgium. These investigations led to the development, subsequent research, and approval of al-fentanil and sufentanil in the United States[1,2].

Fentanyl's story is one of the most popular opiate analgesics in contemporary anesthesia and pain treatment, opens in Belgium in the late 1950s. At that time, the founder Dr. Paul Janssen, of Janssen Pharmaceutica, now one of the Johnson & Johnson's most lucrative divisions,developed an interest in strong analgesics to manage a hodgepodge of pain syndromes that were ill or inappropriately managed in the moment[2]. The synthesis of a large number of new molecular entities exhibiting opioid analgesic activity and clinically evaluated in multiple animal models. The most recent long-list of the best of the molecules was a drug that went nathalie mountaintop called fentanyl. Back then, Janssen would have compounds after they had been tested against a new molecule in the lab to clinician friends of his who would research the drugs in a clinical setting[2,3]. George De Castro, an anesthesiologist in the Brussels region, entanyl was typically administered in small doses. together with one of several intravenous hypnotics[3].

The technique, called neurolept anesthesia, was the combination of neuroleptic substances and an inhalation anesthetic fentanyl and some pretty hefty doses of droperidol, with or without nitrous oxide and oxygen. This technique that became relatively widespread, initially in most Western and then followed by the majority of the Eastern European countries[3]. Janssen realized that fentanyl, or any of his drugs' ultimate success predicated on acceptance and use in the United States, The top event that raised the increasing use of fentanyl in the operating room was the idea of high-dose opioid anesthesia, which was initially brought into the United Lowenstein and others wrote in a report published in the New England Journal of Medicine in December 1969[3,4]. This study led to many randomized for other protocols in the 3-4 years, assessing highdose morphine/oxygen anesthesia as a Technique For Critically Ill Patients Undergoing open heart surgery; and then later, on major vascular surgery. Part of what makes the technique so popular resulted from impressive cardiovascular stability seen in this group of patients[4].

Oralet was never a runaway blockbuster for premedication but had many supporters around the United States. Other companies have investigated fentanyl in lozenge, nasal spray, buccal patches, dissolvable oral formulations, and multiple transmucosal delivery modalities[4]. Aerosolized fentanyl has been researched for pulmonary trachea and pharyngeal absorption. A sufentanil-releasing implant that can be injected in liquid form is in clinical development. Furthermore, fentanyl is increasingly being assessed in a set of iontophoretic delivery systems. Fentanyl remains one of the biggest drugs to be used in the operating room, specifically, a short intravenous infusion, as premedicant for hine-like effects, i.e., analgesia[4,5].

History

Fentanyl was initially released in 1960 as an analgesic, a pain management medicine, and was parenterally by the FDA in 1972 for intravenous anaesthetic under the trade na Sublimaze®. The fentanyl patch has since been in general use for the management of chronic pain[5] . There has been a long history of cercem to use fentanyl. agentis the understanding that the lipophile of a molecule is a decisive factor in its influencing their timing and potency, leading the urge to produce a more to potentiate these lipid-soluble opioid n the 20 years since, numerous other drugs with a related chemical structure to that of fentanyl, more widely known as fentanyl analogues .Some of these analogues are human-use-registered —alfentanil and sufentanil— whereas The other two (carfentanil and thiofentanil) are commonly used in veterinary. Furthermore, other analogues such as acetylfentanyl and furanylfentanyl have not been recorded for and, therefore, are IMFs for medical use[4,5,6].

Main body

Fentanyl provides potent analgesia via its action on opioid receptors. It maintains its duration of action for several hours, and it has a wider therapeutic index because patients develop tolerance to opioid medications. Label Fentanyl has the potential for addiction and abuse and should not be taken with alcohol or benzodiazepines[6]**.**

Pharmacodynamic

Fentanyl is a potent synthetic opioid, which, similar to morphine, produces analgesia but to a greater extent. This robust pharmacologic agent is typically 50 to 100 times more potent. A dose of only 100 micrograms can produce equivalent analgesia to approximately 10 mg of morphine[5,6]. However, fentanyl exhibits vastly different properties and pharmacokinetics. Clinically, its most common use is as a sedative in intubated patients and in severe cases of pain in patients with renal failure due to its primarily hepatic elimination[6]. At times, fentanyl may also be indicated to treat chronic pain patients who have developed tolerance to opiates. When used as a sedative, drug administration is most commonly via a drip. Lastly, fentanyl use can extend to the treatment of epilepsy. That is, in combination with certain neuroleptic medications as part of therapeutic neuroleptanalgesia[6,7]. This activity outlines the indications, mechanism of action, administration methods,

significant adverse effects, contraindications, monitoring, and toxicity of fentanyl so that providers can direct patient therapy to optimal outcomes[7].

Fentanyl pharmacology

- Like most clinically used opioids, fentanyl produces its pharmacological effects via activation of the mu opioid receptor (MOR).with low affinity for delta and kappa opioid receptors[6,7].
- Fentanyl is a synthetic, lipophilic phenylpiperidine opioid agonist, unlike morphine, which is an alkaloid extracted from the opium poppy.
- Fentanyl is a highly efficacious agonist at the MOR with a 1.35 nM binding affinity (Ki) at recombinant human MORs (Volpe et al., 2011), an affinity similar to that reported[7].
- This potent medication is usually 50 to 100 times more powerful. One hundred micrograms of fentanyl provides the same analgesia as approximately 10 mg of morphine.
- However, fentanyl has very different properties and pharmacokinetics than other opioids[7].

Objectives

1. Least potential indications for pain therapy with fentanyl[5].
2. Least contraindications/adverse events of fentanyl[5].
3. Identify use of interprofessional teams to improve collaborative care and patient outcomes[5,6].
4. Identify the mechanism of action of fentanyl.
5. Review the contraindications and adverse event profile of fentanyl.
6. Explain interprofessional team strategies for improving care coordination and communication to advance fentanyl therapy, improve outcomes, and minimize adverse events and misuse, especially in light of the ongoing opioid crisis [6,7].

Preclinical pharmacology of fentanyl:

MOR belong to the superfamily of G-protein coupled receptors, a class of membrane-bound receptors that exhibit a seven transmembrane-spanning helical domain connected by intra- and extra-cellular loops[8].
The MOR produces its effects via interactions with inhibitory heterotrimeric G-proteins (Gi/o), which are responsible for producing most opioid-related pharmacological effects, including analgesia and euphoria. However, MOR also produce G-protein-independent signaling through beta-arrestin[7,8].

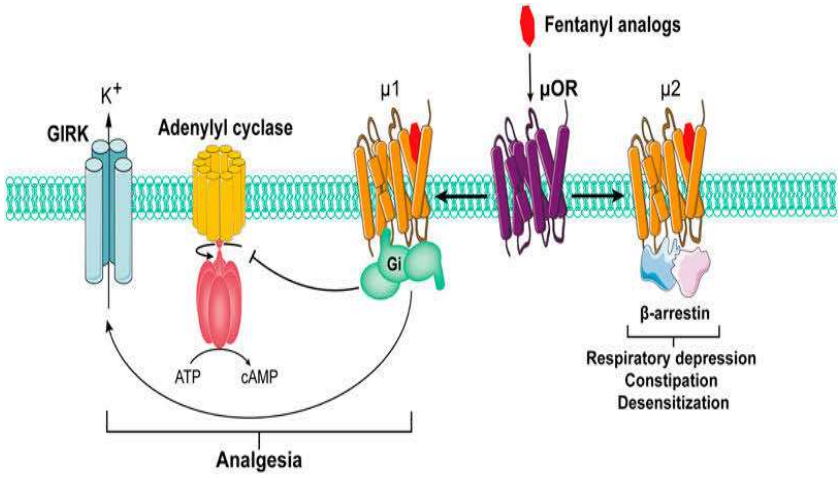
Mode of action

Fentanyl binds to opioid receptors, particularly the mu opioid receptor, which are attached to G-proteins.

Activation of the opioid receptors results in GDP being exchanged for GTP on the G-proteins, resulting in down-regulation of adenylate cyclase and decreased cAMP concentration.

Decreased cAMP concentration lowers the cAMP dependent influx of calcium ions into the cell.

The GTP to GDP exchange causes hyperpolarization of the cell and inhibition of neural activity.



Pharmacokinetics

Absortion

The bioavailability percentages of fentanyl routes of administration are: sublingual tab-54% bioavailable15, transmucosal lozenge-50% bioavailable16, buccal tabs-65% bioavailable17, sublingual spray-76% bioavailable18, and the nasal spray is 20% more bioavailable than outcome of the transmucosal route20 (consistently 64% bioavailable) [8].

The Cmax and the concentrations for orally administered fentanyl are as follows

Cmax concentrations: were calculated as 0.4±0.1ng/mL for the low-200µg dose and 2.5±0.6ng/mL for the high-1600µg dose

Tmax values: 20-40 minutes11.

The AUC values were calculated to be 172±96ng*min/mL for the low-200µg dose and 1508±1360ng*min/mL for the high-1600µg dose1[7,8]

- For fentanyl sublingual spray

Cmax concentraction: were calculated as 0.20±0.06ng/mL for the low-100µg dose and 1.61±0.60ng/mL for the high-800µg dose

Tmax values: 0.69-1.25 hours.12

The AUC values were calculated to be 1.25±0.67ng*h/mL for the low-100µg dose and 10.38±3.70ng*h/mL for the high-800µg dose.12[8]

- For fentanyl transdermal systems

Cmax concentrations: were calculated to be 0.24±0.20ng/mL

Tmax values: of 3.6±1.3 hours for a 25µg/h dose.13

The AUC value was calculated to be 0.42±0.35ng/mL*h.13[7,8]

- For fentanyl nasal spray

Cmax concentration: was calculated to be 815±301pg/mL

Tmax values: of <1 hour, using the maximal concentration of a 200ug/100µL dose.14

The AUC was calculated to be 3772pg*h/mL.14[9]

Distribution

Volume of Distribution

The volume of distribution intravenously is reported as 4L/kg (range 3-8L/kg) Label,19 and the volume of distribution orally is 25.4L/kg.17. In patients with liver impairment, the volume of distribution intravenously is 0.8-8L/kg.19.Fentanyl crosses the blood-brain barrier 9 and the placenta[8,9]

Protein binding

Fentanyl is bound 80-85% to plasma proteins.15,16,17,18,20 One study showed that a solution of fentanyl at 0.1µg/L was bound 77.9±1.1% to human serum albumin and 12.0±5.4% to α-1 acid glycoprotein.7 The same 0.1µg/L concentration of norfentanyl (the primary metabolite of fentanyl) was bound 7.62±1.2% to human serum albumin and 7.24±1.9% to α-1 acid glycoprotein.7[7,9]

Metabolisum

A variety of inactive metabolites are formed by the metabolism of fentanyl.Approximately 99% of fentanyl is metabolized to norfentanyl through N-dealkylation by cytochrome P450[8]. Additionally, fentanyl can undergo amide hydrolysis to form despropionylfentanyl, or be hydroxylated by alkyl hydroxylation to reduce the N-alkyl group to form hydroxyfentanyl, which can also undergo norfentanyl N-dealkylation to form hydroxynorfentanyl. Fentanyl Norfentanyl Despropionylfentanyl Hydroxyfentanyl Hydroxynorfentanyl Route of elimination Approximately 75% of a fentanyl dose is eliminated in the urine within 72 hours, with <7% of the dose excreted unchanged, while approximately 9% is eliminated via feces with <1% unchanged[8,9].

Half life and clerance

Half-life: Fentanyl's half life is 7 hours16. The half life of fentanyl sublingual spray is 5-12 hrs18.
Clearance: Total plasma clearance of fentanyl is 0.5L/hr/kg either (0.3-0.7L/hr/kg)16 or 42L/hr17,20 . After an intravenous administration, surgical patients had a clearance of 27-75L/h, patients with hepatic insufficiency had a clearance of 3-80L/h, and patients with renal insufficiency had a clearance of 30-78L/h[10].

Toxicity

Toxicity Fentanyl is has an IV LD50 of 2.91mg/kg in rats, an oral LD50 of 18 mgkg-1 in rats and 368mg/kg in mice. MSDS Labels have not established an LD50 value in humans. Signs of overdose include respiratory depression but may also include somnolence, stupor, coma, skeletal muscle flaccidity, cold clammy skin, pupillary constriction, pulmonary edema, bradycardia, hypotension, airway obstruction, atypical snoring, death.Label,15,16,17,18,19,20 In the case of overdose, the patient should be given naloxone or nalmehene to reverse the action of the opioids as well as supportive measures maintain the airway or advance life support in case of cardiac arrest[10].

Interaction with food

While you're getting treatment with fentaNYL, it's best to steer clear of alcohol and any medications that have alcohol in them. Mixing these can lead to more side effects on your nervous system, like feeling sleepy, dizzy, lightheaded, having trouble focusing, and struggling with thinking or judgment. In serious cases, this could lead to low blood pressure, trouble breathing, fainting, coma, or even death. Also, avoid grapefruit and grapefruit juice since they can heighten the effects of fentanyl in your system[9,10].

If you have any questions about how to take this or other medications you're prescribed, please reach out to your doctor or pharmacist. Stick to the recommended dose of fentaNYL, and hold off on activities that need mental sharpness, like driving or handling dangerous machinery, until you know how the medication impacts you. It's really important to let your doctor know about all the other medications you're taking, including vitamins and herbs. And please, don't stop any medication without discussing it with your doctor first[10].

With drug

It's important not to use fentanyl alongside certain medications. For example, drugs that block CYP3A4, like some antibiotics and antifungals, as well as protease inhibitors, can raise fentanyl levels in the blood[10]. This can make the effects of the opioid last longer and worsen breathing problems caused by the drug. On the flip side, if someone stops taking a medication that encourages CYP3A4, like carbamazepine or phenytoin, while using fentanyl citrate injections, it might lead to higher levels of fentanyl in their system, increasing the chances of negative side effects. Also, if a person has taken a monoamine oxidase inhibitor in the last two weeks, they should avoid fentanyl altogether[11].

Why this drug is prescribe?

Fentanyl is used to treat breakthrough pain (sudden episodes of pain that occur despite round-the-clock treatment with pain medication) in cancer patients who are at least 18 years old (or at least 16 years old if using Actiq brand lozenges) and receiving regularly scheduled doses of another narcotic (opiate) pain medication who are tolerant (accustomed to the effects of the medication) to narcotic pain medications. Fentanyl belongs to a class of medications called narcotic (opiate) analgesics, which alter how the brain and nervous system respond to pain. It should be used in conjunction with your other pain medication(s); do not stop taking your other prescriptions[9,10,11].

Therapeutic uses

This drug is prescribed to relieve severe chronic pain (such as caused by cancer).
Fentanyl is a type of opioid analgesic.
It acts in the brain to alter how your body perceives and reacts to pain.Do not use the patch type of fentanyl to treat pain that is mild or will pass in a few days.

This drug is not for "as needed" use.Fentanyl injection is to help relieve pain that is severe and happens during and after surgery. It is also used in combination with other medications before or during surgery to make the anesthetic (numbing medication) work more effectively[11,12].

Side effects

Such common side effects are experienced by over 1% of the population with fentanyl, and there are strategies to help manage them, including:

- Skin rashes or itching
- Nausea or vomiting
- Stomach ache
- Tiredness or excess drowsiness
- Weakness or fatigue
- Light headedness or spinning (Vertigo)
- Dizziness
- Mental fog or confusion
- Pain in the head

Serious side effects

Serious side effects happen in less than 1 in 100 people.

CONCLUSION

To sum it up, the research showed that fentanyl really helps reduce acute pain and that patients generally handle it well. The side effects of fentanyl were minor and short-lived. When patients experience less pain, they tend to function better and feel more satisfied with their care. A review by Downey and colleagues pointed out that less pain leads to greater satisfaction and improved communication between patients and their doctors. Most cases discussed in this article used fentanyl as a nasal spray, which offers a different option compared to traditional methods like taking it orally or through an injection. In conclusion, fentanyl is effective in lowering pain intensity for patients in the emergency department, and it often works better than morphine and methoxyflurane for many individuals.

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