PRODUCT MONOGRAPH

®FENTANYL CITRATE INJECTION USP

(fentanyl 50 mcg/mL as fentanyl citrate)

Opioid Analgesic–Adjunct to Anesthesia

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Fentanyl Citrate Injection USP
(fentanyl 50 mcg/mL as fentanyl citrate)

THERAPEUTIC CLASSIFICATION

Opioid Analgesic–Adjunct to Anesthesia

ACTION AND CLINICAL PHARMACOLOGY

Fentanyl, although chemically unrelated to morphine, produces pharmacologic effects and degree of analgesia similar to morphine. On a weight basis, however, fentanyl is 50 to 100 times more potent than morphine, but its duration of action is shorter than that of meperidine or morphine. A parenteral dose of 100 mcg (2.0 mL) of fentanyl is approximately equivalent in analgesic activity to 10 mg of morphine or 75 mg of meperidine.

The principal actions of therapeutic value are analgesia and sedation (see DETAILED PHARMACOLOGY).

**Human Pharmacology**

Fentanyl has been reported to be an opioid analgesic with a rapid onset and a short duration of action.

Alterations in respiratory rate and alveolar ventilation, associated with opioid analgesics may last longer than the analgesic effect. As the dose of the opioid is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnea. Fentanyl appears to have less emetic activity than other opioid analgesics. Histamine assays and skin wheal testing in man, as well as *in vivo* testing in dogs, indicate that clinically significant histamine release rarely occurs with fentanyl. Assays in man demonstrate no clinically significant histamine release in dosages up to 50 mcg/kg (0.05 mg/kg: 1 mL/kg). Fentanyl preserves cardiac stability and at higher doses, inhibits stress-related hormonal changes.

Fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. It may also produce other signs and symptoms characteristic of opioid analgesics including euphoria, miosis, bradycardia and bronchoconstriction.

The onset of action of fentanyl is almost immediate when the drug is given *intravenously*; however the maximal analgesic and respiratory depressant effects may not be noted for several minutes. The usual duration of action of analgesic effect is 30 to 60 minutes after a single IV dose of up to 100 mcg (0.1 mg; 2.0 mL).

Following *intramuscular* administration, onset of action is from 7 to 8 minutes, and the duration of action is 1 to 2 hours.

Following *epidural* administration, onset of analgesia occurs between 5 and 10 minutes and the duration of action is generally 2 to 5 hours. Analgesia can be maintained with on-demand or
continuous epidural administration.

As with longer acting opioid analgesics, the duration of respiratory depressant effect may be longer than the analgesic effect. The following observations have been reported concerning altered respiratory response to CO₂ stimulation following administration of fentanyl to man:

1. Diminished sensitivity to CO₂ stimulation may persist longer than depression of respiratory rate. Altered sensitivity to CO₂ stimulation has been demonstrated for up to four hours following a single intravenous dose of 600 mcg (0.6 mg; 12 mL) of fentanyl to healthy volunteers. Fentanyl frequently slows the respiratory rate, duration and degree of respiratory depression being dose related.

2. The peak respiratory depressant effect of a single intravenous dose of fentanyl is noted 5 to 15 minutes following injection (see WARNINGS and PRECAUTIONS).

Fentanyl, in commonly used clinical doses (less than 10 mcg/kg) has little or no effect on myocardial or hemodynamic function except for vagally induced bradycardia.

The effects of low doses of fentanyl (0.07 mcg/mL and 0.36 mcg/mL) on hemoglobin affinity for oxygen have been studied in comparison to other analgesics. It has been reported that such doses shifted the hemoglobin dissociation curve to the left, but a higher dose (0.71 mcg/mL) failed to alter this curve.

In patients scheduled for coronary artery bypass, fentanyl at doses of 37 mcg/kg followed by 53 mcg/kg IV, showed instances of hemolysis; however the clinical significance is still to be defined.

The circulatory effects of fentanyl at 5 sequential doses of 1 mcg/kg IV were studied in conscious and anesthetized subjects. In conscious patients, fentanyl did not affect the pressure or heart rate, while in anesthetized patients, a 20% fall in blood pressure and heart rate was noted.

Fentanyl has been used in fourteen neonates undergoing major surgical procedures; doses of 10 mcg/kg, 25 mcg/kg or 50 mcg/kg were given IV. An extremely prolonged ventilatory depression, 1.5 to 2 times the normal adult value and transient rebounds in plasma levels were noted.

**Pharmacokinetics**

With doses of approximately 3 to 30 mcg/kg IV in humans, the serum curves could be described in terms of a three-compartment open model.

At all doses, plasma levels have been reported to fall rapidly in the first 5 minutes to approximately 20% of the peak value.

The elimination half-life is approximately:
- from 0.73 to 1.63 minutes for the first distribution phase;
- from 5.1 to 21 minutes for the second phase;
- from 86.6 to 346.5 minutes for the third phase.
Urinary excretion was very low during the first two hours.

**Metabolism and Excretion:** The concentration of fentanyl excreted unchanged in the urine is usually about 8 to 10%. The liver is the most important metabolizing organ, whereas extrahepatic metabolism occurs only to a very minor degree in the kidney.

The metabolites of fentanyl are reported to be: phenylacetic acid, norfentanyl (4-N-(Npropionyl-3H-anilino)piperidine), propionic acid and despropiofentanyl (1-2 (phenethyl)-4-Nanilino-piperidine).

**INDICATIONS AND CLINICAL USE**

Fentanyl Citrate Injection USP, administered by intravenous or intramuscular injection, is indicated:

- For analgesic action of short duration during the anesthetic periods, premedication, induction and maintenance, and in the immediate postoperative period (recovery room) as the need arises;

- For use as an opioid analgesic supplement in general or regional anesthesia;

- For administration with a neuroleptic such as droperidol injection as an anesthetic premedication, for induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia; and

- For use as an anesthetic agent with oxygen in selected high-risk patients, such as those undergoing open heart surgery or certain complicated neurological or orthopedic procedures.

Fentanyl Citrate Injection USP, by epidural administration, is indicated for the postoperative management of pain following general surgical procedures and cesarean sections.

**CONTRAINDICATIONS**

Fentanyl is contraindicated in patients with known hypersensitivity to the drug. As with other opiates administered epidurally, fentanyl should not be given to patients exhibiting the following:

- Septicemia
- Severe hemorrhage or shock
- Local infection at the site of proposed puncture
- Disturbances in blood morphology and/or anticoagulant therapy or other concomitant drug therapy or medical conditions which could contraindicate the technique of epidural administration.
Fentanyl Citrate Injection USP

WARNINGS

As with other CNS depressants, patients who have received fentanyl should have appropriate surveillance. Resuscitative equipment and an opioid antagonist such as naloxone should be readily available to manage apnea (see PRECAUTIONS and OVERDOSAGE).

Fentanyl citrate injection should be administered only by persons specifically trained in the use of intravenous anesthetics and management of the respiratory effects of potent opioids.

If fentanyl is administered with a tranquilizer such as droperidol, the user should familiarize himself with the special properties of each drug, particularly the widely differing durations of action. In addition, when such a combination is used, fluids and other countermeasures to manage hypotension should be available (see PRECAUTIONS).

As with other potent opioids, the respiratory depressant effect of fentanyl may persist longer than the measured analgesic effects. The total dose of all opioid analgesics administered should be considered by the practitioner before ordering opioid analgesics during recovery from anesthesia. It is recommended that opioids, when required should be used in reduced doses, initially as low as one-fourth to one-third those usually recommended.

Fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. In addition, skeletal muscle movements of various groups in the extremities, neck and external eye have been reported during induction of anesthesia with fentanyl; these reported movements have, on rare occasions, been strong enough to pose patient management problems. The effect is related to the speed of injection and its incidence can be reduced by the use of slow intravenous injection. Once the effect occurs, it is managed by the use of assisted or controlled respiration and, if necessary, by a neuromuscular blocking agent compatible with the patient's condition.

Where moderate or high doses are used (above 10 mcg/kg), there must be adequate facilities for postoperative observation and ventilation, if necessary, of patients who have received fentanyl. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

Fentanyl may also produce other signs and symptoms characteristic of opioid analgesics including euphoria, miosis, bradycardia and bronchoconstriction.

Head Injuries and Increased Intracranial Pressure
Fentanyl should be used with caution in patients who may be particularly susceptible to respiratory depression such as comatose patients who may have a head injury, brain tumour, other intracranial lesions, or a pre-existing increase in intracranial pressure. In addition, fentanyl may obscure the clinical course of patients with head injury.

Acute Abdominal Conditions
The administration of opioids may obscure the diagnosis or clinical course of patients with acute abdominal conditions.
Pregnant Women
The safe use of fentanyl has not been established with respect to possible adverse effects upon fetal development. Therefore, it should not be used in women of childbearing potential unless, in the judgement of the physician, the potential benefits outweigh the possible hazards.

PRECAUTIONS

General
Vital signs should be monitored routinely. Fentanyl may produce bradycardia, which may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias.

Fentanyl should be administered with caution to patients with liver and kidney dysfunction because of the importance of these organs in the metabolism and excretion of drugs.

Pediatrics
The safety of fentanyl in children younger than 2 years of age has not been established.

Pregnant Women
There are insufficient data regarding placental transfer and fetal effects; therefore, safety for the infant in obstetrics has not been established.

Nursing Women
It is not known whether fentanyl is excreted in human milk. Caution should be exercised when fentanyl is administered to a nursing mother.

Special Risk Patients
The initial dose of fentanyl should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining incremental doses. Nitrous oxide has been reported to produce cardiovascular depression when given with higher doses of fentanyl.

Chronic Obstructive Pulmonary Disease
Fentanyl should be used with caution in patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, and others with potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists.

Appropriate surveillance should be maintained because the duration of respiratory depression of doses of fentanyl employed during anesthesia may be longer than the duration of the opioid antagonist action. Consult individual prescribing information (levallorphan, nalorphine and naloxone) before employing opioid antagonists.

Conduction Anesthesia
Certain forms of conduction anesthesia, such as spinal anesthesia and some peridural anesthetics
can alter respiration by blocking intercostal nerves.

Through other mechanisms, fentanyl can also alter respiration (see ACTION AND CLINICAL PHARMACOLOGY). Therefore, when fentanyl is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological actions involved, and be prepared to manage them in the patients selected for these forms of anesthesia.

**Dependence Liability**

Fentanyl can produce drug dependence of the morphine-type and therefore has the potential of being abused. Psychic dependence, physical dependence, and tolerance may develop upon repeated administration.

**DRUG INTERACTIONS**

When a neuroleptic such as droperidol is used with fentanyl, pulmonary arterial pressure may decrease. This fact should be considered by those who conduct diagnostic and surgical procedures where interpretation of pulmonary arterial pressure measurements might determine final management of the patient. Vital signs should be monitored routinely.

When either high doses or anesthetic doses of fentanyl are employed, even relatively small dosages of diazepam may cause cardiovascular depression.

Other CNS depressant drugs (e.g. barbiturates, tranquilizers, opioids and general anesthetics) will have additive or potentiating effects with fentanyl. When patients have received such drugs, the dose of fentanyl required will be less than usual. Likewise, following the administration of fentanyl, the dose of other CNS depressant drugs should be reduced.

When fentanyl is used with a neuroleptic, such as droperidol, hypotension can occur. If this occurs, the possibility of hypovolemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient to improve venous return to the heart should be considered when operative conditions permit. Care should be exercised in moving and positioning of patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other countermeasures do not correct hypotension, the administration of pressor agents other than epinephrine should be considered. Because of the α-adrenergic blocking action of droperidol, epinephrine may paradoxically decrease the blood pressure in patients treated with droperidol.

When droperidol is used with fentanyl and the EEG is used for postoperative monitoring, it may be found that the EEG pattern returns to normal slowly.

Severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics. Since the safety of fentanyl in this regard has not been established, its use in patients who have received MAO inhibitors within 14 days is not recommended.
Serotonergic Drugs
Coadministration of fentanyl with a serotonergic agent, such as a Selective Serotonin Reuptake Inhibitor or a Serotonin Norepinephrine Reuptake Inhibitor, may increase the risk of serotonin syndrome, a potentially life threatening condition (see also ADVERSE REACTIONS).

ADVERSE REACTIONS

As with other opioid analgesics, the most common serious reactions reported to occur with fentanyl are: respiratory depression, apnea, muscle rigidity and bradycardia. If these remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur.

Pruritus, occurring mainly in the face and chest area, is observed frequently following the administration of fentanyl by the epidural route. Other adverse reactions that have been reported are: cough, hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, diaphoresis, itching, drowsiness and urinary retention.

It has been reported that secondary rebound respiratory depression may occasionally occur postoperatively. Patients should be monitored for this possibility and appropriate countermeasures taken as necessary.

When a neuroleptic such as droperidol is used with fentanyl, the following adverse reactions can occur: chills or shivering, restlessness, and postoperative hallucinatory episodes (sometimes associated with transient periods of mental depression); extrapyramidal symptoms (dystonia, akathisia and oculogyric crisis) have been observed up to 24 hours postoperatively. When they occur, extrapyramidal symptoms can usually be controlled with antiparkinson agents. Postoperative drowsiness is also frequently reported following the use of droperidol.

Elevated blood pressure, with or without pre-existing hypertension, has been reported following administration of fentanyl combined with droperidol. This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also frequently attributed to anaesthetic and surgical stimulation during light anesthesia.

Although fentanyl has been reported to induce grand mal seizures with IV administration at doses of 100 mcg, there was no electroencephalographic documentation. Some authors suggest that rigidity is a more likely explanation for the myoclonic movements, since none of the patients showed any neurologic disorders after their reported seizures.

Post-marketing reports describe patients with symptoms suggestive of, or diagnostic of, serotonin syndrome following the concomitant use of fentanyl with a serotonergic drug, such as a Selective Serotonin Reuptake Inhibitor or a Serotonin Norepinephrine Reuptake Inhibitor (see also PRECAUTIONS, DRUG INTERACTIONS).
OVERDOSAGE

For management of a suspected drug overdose, contact your regional Poison Control Centre immediately.

Symptoms: The manifestations of fentanyl overdose are an extension of its pharmacologic actions.

Treatment: In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A patent airway must be maintained; an oropharyngeal airway or endotracheal tube might be indicated. If depressed respiration is associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. The patient should be carefully observed for 24 hours, body warmth and adequate fluid intake should be maintained. If hypotension occurs and is severe or persists, the possibility of hypovolemia should be considered and managed with appropriate parenteral fluid therapy. A specific opioid antagonist such as nalorphine, levallorphan or naloxone should be available for use, as indicated to manage respiratory depression. This does not preclude the use of more immediate countermeasures. The duration of respiratory depression following overdosage of fentanyl may be longer than the duration of opioid antagonist action. Consult the package insert of the individual opioid antagonists for details about use.

It is not known whether fentanyl is dialyzable.

DOSAGE AND ADMINISTRATION

Fentanyl Citrate Injection USP is administered by intravenous, intramuscular or epidural injection.

Dosage should be individualized. Some of the factors to be considered in determining the dose are: age, body weight, physical status, underlying pathological condition, use of other drugs and the surgical procedure involved. Vital signs should be monitored routinely.

Adult Dosage

Premedication

As premedication (to be appropriately modified in the elderly, debilitated and those who have received other depressant drugs), 0.7 to 1.4 mcg/kg (0.014 to 0.028 mL/kg) may be administered intramuscularly 30 to 60 minutes prior to surgery.

Adjunct to General Anesthesia

See Dosage Range Chart (Table 1).

Adjunct to Regional Anesthesia

With regional anesthesia, 0.7 to 1.4 mcg/kg (0.014 to 0.028 mL/kg) may be administered intramuscularly or slowly intravenously, over one to two minutes, when additional analgesia is required.
As a General Anesthetic
When attenuation of responses to surgical stress is especially important, fentanyl in doses of 50 to 100 mcg/kg (1 to 2 mL/kg) may be administered with oxygen and a muscle relaxant to produce anesthesia without the use of additional anesthetic agents.

In certain cases, doses up to 150 mcg/kg (3 mL/kg) may be necessary to produce the anesthetic effects.

Table 1: Dosage Range Chart: Adjunct to General Anesthesia

<table>
<thead>
<tr>
<th>Low Dose</th>
<th>Moderate Dose</th>
<th>High Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 mcg/kg (0.002 mg/kg; 0.04 mL/kg) Fentanyl Citrate Injection USP.</td>
<td>(Major Surgical Procedure) 2 to 20 mcg/kg (0.002 to 0.02 mg/kg; 0.04 to 0.4 mL/kg) Fentanyl Citrate Injection USP.</td>
<td>(Open Heart and Certain Complicated Procedures Involving Prolonged Surgery) 20 to 50 mcg/kg (0.02 to 0.05 mg/kg; 0.4 to 1 mL/kg) Fentanyl Citrate Injection USP.</td>
</tr>
<tr>
<td>Fentanyl in small doses is useful for minor but painful surgical procedures. In addition to the analgesia during surgery, fentanyl may also provide some pain relief in the immediate postoperative period.</td>
<td>Where surgery becomes more major, a larger dose is required. With this dose, in addition to adequate analgesia, one would expect to see some abolition of the stress response. However, respiratory depression will be such that artificial ventilation during anesthesia is necessary, and careful observation of ventilation postoperatively is essential.</td>
<td>During open heart surgery and certain more complicated neurosurgical and orthopedic procedures where surgery is more prolonged, and in the opinion of the anesthesiologist, the stress response to surgery would be detrimental to the wellbeing of the patient, dosages of 20 to 50 mcg/kg (0.02 to 0.05 mg/kg; 0.4 to 1 mL/kg) of Fentanyl Citrate Injection USP with nitrous oxide/oxygen have been shown to attenuate the stress response as defined by increased levels of circulating growth hormone, catecholamine, ADH and prolactin.</td>
</tr>
</tbody>
</table>

When dosages in this range have been used during surgery, postoperative ventilation and observation are essential due to extended postoperative respiratory depression. The main objective of this technique would be to produce "stress free" anesthesia.

Additional doses are infrequently needed in these minor procedures. Maintenance Dosage 10 to 25 mcg (0.01 to 0.025 mg; 0.2 to 0.5 mL) Fentanyl Citrate Injection USP administered intravenously or intramuscularly when movement or changes in vital signs indicate surgical stress or lightening of analgesia. Maintenance Dosage (ranging from 25 mcg [0.025 mg; 0.5 mL] to one half of the initial loading dose) Fentanyl Citrate Injection USP will be dictated by changes in vital signs which indicate stress and lightening of analgesia. However, the additional dosage selected must be individualized especially if the anticipated remaining operative time is short.

Fentanyl has been used for open heart surgery and certain other major surgical procedures in patients for whom protection of the myocardium from excess oxygen demand is indicated, and for certain complicated neurological and orthopedic procedures.
Postoperative Pain
For the postoperative management of pain following general surgical procedures and cesarean sections, fentanyl may be administered by the epidural route at a dose of 100 mcg (0.1 mg; 2 mL). The 2 mL fentanyl should be diluted with 8 mL of 0.9% sodium chloride resulting in a final concentration of 10 mcg/mL. If required, additional boluses of 100 mcg on demand or by continuous infusion at rate of 1 mcg/kg/hr. CAUTION: Such admixtures should be used within 24 hours because of the risk of microbial contamination during preparation.

It is essential that qualified personnel and adequate facilities are available for the management of respiratory distress.

Pediatric Dosage
For induction and maintenance in children 2 to 12 years of age, a reduced dose as low as 2 to 3 mcg/kg (0.04 to 0.06 mL/kg) of body weight is recommended.
STORAGE AND STABILITY

Store between 15 and 30°C. Protect from light. Protect from freezing. Discard unused portion.

SPECIAL HANDLING INSTRUCTIONS

Fentanyl Citrate Injection USP may be diluted with Sodium Chloride Injection USP 0.9%. Admixtures should be used within 24 hours.

As with all parenteral products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitate, discolouration and leakage prior to administration whenever solution and container permit. Solution showing haziness, particulate matter, precipitate, discolouration or leakage should not be used. Discard unused portion.

Pharmacy Bulk Vial
The use of Pharmacy Bulk Vials is restricted to hospitals with a recognized parenteral admixture program. The Pharmacy Bulk Vial is intended for single puncture, multiple dispensing and for the preparation of admixtures only. Dispensing from a Pharmacy Bulk Vial should be completed as soon as possible after initial entry.

Fentanyl citrate is reported to be physically incompatible with methohexital sodium, pentobarbital sodium, and thiopental sodium.

DOSAGE FORM, COMPOSITION AND PACKAGING

Fentanyl Citrate Injection USP is a preservative free, sterile aqueous solution. Each mL of solution contains: fentanyl 50 mcg (as citrate), citric acid and/or sodium hydroxide to adjust pH and water for injection.

Fentanyl Citrate Injection USP is supplied in 2 mL ampoules, boxes of 10.

Fentanyl Citrate Injection USP is also supplied in 5 mL and 10 mL single use glass vials, boxes of 10, 20 mL single use glass vials, boxes of 5, and 50 mL Pharmacy Bulk Vials, boxes of 1.

LATEX-FREE STOPPER - Stopper contains no dry natural rubber.
PHARMACEUTICAL INFORMATION

Drug Substance

Chemical Group: Fentanyl citrate is an anilinopiperidine-derivative opioid analgesic.

Proper Name: Fentanyl citrate.

Chemical Name: Propanamide, N-phenyl-N-[1-(2-phenylethyl)-4-piperidinyl]-, 2-hydroxy-1,2,3-propanetricarboxylate (1:1).

Structural Formula:

![Structural Formula Image]

Molecular Formula: C_{22}H_{28}N_{2}O \cdot C_{6}H_{5}O_{7}

Molecular mass: 528.60

Free Base Molecular mass: 336.5

Description: Fentanyl citrate is a white to pale yellow crystalline powder. It is partially soluble in water, soluble in methanol, and slightly soluble in ethanol, chloroform and in ether.

DETAILED PHARMACOLOGY

Animal Pharmacology

Mice

Fentanyl was effective in a modified Haffner tail clamp test in mice, to detect analgesic activity. The ED_{50} for fentanyl was reported to be 0.8 mg/kg SC and that for morphine, 15 mg/kg SC. The onset of the analgesic effect occurred in 4 minutes with fentanyl and the duration was 30 minutes.

In mice, fentanyl induced an increase in spontaneous motor activity, Straub tail reaction, increased muscle tone, respiratory depression and convulsions.
Fentanyl induced a constipating effect in mice. In approximately equivalent analgesic doses, morphine appeared to have a greater constipating effect.

**Rats**
Fentanyl exhibited activity in the tail withdrawal test in rats, a test measuring the time elapsing for a rat to remove its tail from a water bath heated to 55°C. Fentanyl was found to be 269 times more potent than morphine after subcutaneous administration and had a faster onset and shorter duration of action than morphine.

At high doses (25 to 400 mcg/kg) fentanyl has been reported to affect cerebral circulation and metabolism in rats. Seizures are noted in about 25% of rats receiving either 200 mcg or 400 mcg/kg.

**Rabbits**
Fentanyl has been shown to produce analgesia in rabbits as evidenced by the failure of a painful stimulus applied to the trigeminal nerve to produce desynchronization of the EEG. Depression of the cortical activating system was evidenced by the increased cortical potentials seen after administration of fentanyl.

**Cats**
Fentanyl, like other potent opioid analgesic, produces skeletal muscle rigidity. This muscular rigidity can be blocked or reversed by succinylcholine.

Fentanyl in doses of 10, 20, 40, 80 and 160 mcg/kg has been demonstrated to have no effect on neuromuscular transmission in anesthetized cats.

In anesthetized cats, fentanyl produced a central sympatho-inhibitory effect with the main site of action being the medulla oblongata.

**Dogs**
In dogs, fentanyl induced decreased motor activity, ataxia, decreased responsiveness to auditory and painful stimuli, respiratory depression, salivation and defecation. Nalorphine, 1 mg/kg IV caused an immediate reversal of the central depression induced by fentanyl, indicating that the compound was acting by an opioid-like mechanism.

Fentanyl was administered to anesthetized dogs in increasing dosages from 2.5 mcg to 160 mcg/kg IV. These doses caused no change in left ventricular pressure. Doses up to 30 mcg/kg increased left ventricular maximum dP/dt, heart rate and cardiac afterload. Higher doses decreased pressure-time index and myocardial oxygen consumption by approximately 30%. Higher doses of fentanyl, administered rapidly, produced a fall in mean peripheral arterial pressure.

Other studies conducted in anesthetized dogs demonstrate that fentanyl at 25 mcg/kg IV decreases lactate production in the ischemic ventricle. This decrease in myocardial lactate production indicates that the compound decreased myocardial oxygen demand.
Cardiovascular dynamics are not compromised in anesthetized dogs receiving large doses of fentanyl or fentanyl plus nitrous oxide.

Fentanyl, administered to isolated dog Purkinje and ventricular muscle fibers, was devoid of any action on cardiac transmembrane potentials.

When fentanyl was administered to anaesthetized dogs with experimental coronary occlusion at a dose of 50 mcg/kg IV, it markedly decreased heart rate, left ventricular maximum dP/dt and cardiac output. These effects were reversed by the administration of atropine. Fentanyl was effective in preventing the occurrence of ventricular fibrillation in these animals.

Intra-arterial injections of fentanyl in anesthetized dogs in doses of 10 and 50 mcg caused no changes in femoral blood flow. Intra-arterial injection of 200 mcg of fentanyl caused a decrease in vascular resistance indicating that higher doses of the compound possess a vasodilator component.

In anaesthetized dogs, fentanyl significantly lowered pulmonary arterial pressure as well as pulmonary arterial driving pressure with little change in pulmonary vascular resistance and compliance. This reduction of pulmonary arterial pressure by fentanyl is caused by a decrease in pulmonary blood flow resulting from a decrease in cardiac output and mean arterial pressure.

After coronary artery occlusion, fentanyl at a dose of 100 mcg/kg did not affect either regional myocardial blood flow or myocardial infarct size in dogs.

At doses of 50 mcg/kg in anesthetized dogs, fentanyl has been reported to produce a constriction of the renal vascular bed.

The interaction of fentanyl with diazepam and pancuronium was investigated in anesthetized dogs. Fentanyl alone in dose of 500 mcg/kg IV decreased heart rate, cardiac output and arterial pressure. The administration of diazepam 0.5 mg/kg IV after fentanyl caused some reversal of the decrease in heart rate and cardiac output. The subsequent administration of pancuronium completely reversed the decreased heart rate, cardiac output and arterial pressure. A decrease in cardiac output and arterial pressure leads to decreased pulmonary arterial pressure and blood flow.

Guinea pigs
Fentanyl possesses a spasmogenic effect on the sphincter of Oddi in guinea pigs.

TOXICOLOGY

Fentanyl has been studied by the oral, intravenous, intramuscular or subcutaneous routes in mice, dogs, rats and cats.

Laboratory animals tolerate relatively large doses of fentanyl in comparison to the dose recommended for human use.
Acute Toxicity

Table 2
Acute Toxicity of Fentanyl

<table>
<thead>
<tr>
<th>Species</th>
<th>Route</th>
<th>LD&lt;sub&gt;50&lt;/sub&gt; (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mice</td>
<td>IV</td>
<td>11.2 (7.4-16.8)</td>
</tr>
<tr>
<td></td>
<td>SC</td>
<td>62.0 (27.0-142.0)</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>6.0 (4.6-7.7)</td>
</tr>
<tr>
<td>Rats</td>
<td>IV</td>
<td>6.0 (4.6-7.7)</td>
</tr>
<tr>
<td></td>
<td>SC</td>
<td>12.0 (7.9-19.6)</td>
</tr>
<tr>
<td></td>
<td>Oral</td>
<td>18.0 (9.4-32.4)</td>
</tr>
</tbody>
</table>

Mice
Following subcutaneous administration of fentanyl citrate at doses ranging from 1 to 300 mg/kg in mice, the following effects were noted: increase in spontaneous motor activity, circling, increased response to touch, Straub tail reaction, mydriasis, increased muscle tone, respiratory depression, convulsions, followed by death.

The onset of these effects was seen with doses of fentanyl citrate of 1 mg/kg within 1-2 minutes after injection. The duration of behavioural changes with a dose of 1 mg/kg was approximately one hour, and from 4 to 6 hours with high doses.

In the lethal dose range, blanching of the cornea and initial depression followed by stimulation were reported. Some deaths were also observed at doses of 3-4 mg/kg of fentanyl citrate, which are approximately one-fifteenth the calculated LD<sub>50</sub>. A biphasic mortality dose-response curve was also observed following intravenous administration.

Rats
Doses of 25 to 400 mcg/kg fentanyl citrate were given as an IV bolus to rats. Twenty-five percent of animals receiving the highest dosage exhibited changes compatible with seizure activity. These seizures may be abolished by naloxone.

Dogs
Repeated intravenous administration of fentanyl citrate at doses of 10, 20 and 40 mcg/kg, spaced 15-30 minutes apart, showed a reduction in respiratory minute volume. Maximum depression was seen within one minute after administration and recovery occurred within 5 minutes.

Intramuscular administration of fentanyl citrate at doses of 12.5, 25, 50, 100, 200 and 1000 mcg/kg produced similar effects at all dose levels, namely decreased motor activity, ataxia, bradycardia, respiratory depression, salivation and defecation. No mortality was reported.

From the studies reported on these species, the rat seems to be very sensitive to fentanyl, while dogs and mice are more tolerant.

Tolerance Studies
Rats
Rats given fentanyl, 40 mcg/kg every second day for a total of 10 days, developed tolerance within 2 days. The degree of tolerance increased until at least the tenth day, and persisted for at
least 24 days after the initial administration.

In a series of experiments in rats, conducted over a period of 15 weeks, with doses of fentanyl ranging from 2.5 to 20 mcg/kg IV, it has been found that the discriminative stimulus properties of fentanyl are not subject to any detectable tolerance.

**Dogs**

The effect of fentanyl on electric stimulation-induced cardiovascular changes has been studied in anesthetized dogs. In untreated dogs, electric stimulation of a branch of the radial nerve elicits an increase in heart rate (HR) and mean arterial pressure (AP). Fentanyl, 100 mcg/kg IV, decreased the HR and AP responses by 85 and 70%, respectively, 5 minutes after injection. The evoked cardiovascular responses returned to pretreatment levels 90 minutes after drug administration. In a second group of dogs, fentanyl 100 mcg/kg IV was administered subsequent to bolus graded doses (ranging from 1.5 to 63 mcg/kg), administered at 20 minutes intervals. The graded doses of fentanyl induced acute tolerance, so that 5 minutes after the injection of the 100 mcg/kg IV dose, the drug had little effect upon the stimulation induced cardiovascular changes, namely, the increase in AP was not affected and the increase in HR was only slightly attenuated. Ninety minutes after the injection of the 100 mcg/kg dose of fentanyl, both the HR and AP responses were enhanced indicating a rebound phenomenon. The study indicates that conditioning an animal for three hours with fentanyl induces tolerance to the depressant effect of the drug upon evoked cardiovascular reflexes.

**Cumulative Effects**

Multiple administration of fentanyl at doses of 40 mcg/kg in rats lead to cumulative analgesic effects (rat tail flick method) after the fourth administration.

**Reproduction and Teratology**

Fentanyl was administered continuously to Sprague-Dawley rats, using chronically implanted osmotic minipumps. The drug was given at doses of 10, 100 and 500 mcg/kg/day for two weeks prior to breeding and throughout pregnancy until day 21, when the dams were sacrificed. At the highest dose, 4/28 rats died within 24 hours after implantation of the pump.

No other drug-related adverse effects have been reported. Rats gained similar amounts of weight during pregnancy and blood gas values were normal. Fentanyl has been found to be devoid of adverse reproductive and teratogenic effects.
REFERENCES

Preclinical


Clinical


PART III: CONSUMER INFORMATION

FENTANYL CITRATE INJECTION USP
(fentanyl 50 mcg/mL as fentanyl citrate)

This leaflet is part III of a three-part "Product Monograph" published when Fentanyl Citrate Injection USP was approved for sale in Canada and is designed specifically for Consumers. This leaflet is a summary and will not tell you everything about Fentanyl Citrate Injection USP. Contact your doctor or pharmacist if you have any questions about the drug.

ABOUT THIS MEDICATION

What the medication is used for:
Fentanyl Citrate Injection USP is indicated for the following uses:
When injected in a vein
- For pain relief of short duration during prior to, during and immediately after general or regional anesthesia.

When injected in the spine
- For pain relief after surgery, and during labour and vaginal delivery.

What it does:
Fentanyl Citrate Injection USP will provide pain relief when injected in a vein prior to, during and immediately after general or regional anesthesia. When injected in the spine, it provides pain relief.

When it should not be used:
- Fentanyl Citrate Injection USP should not be used in patients with a known history of allergic reactions or sensitivity to this drug or other agents in the same drug family.
- To prevent breathing problems in the newborn baby, fentanyl should not be injected into a vein (intravenous use) during labour or cesarean section before the umbilical cord has been cut. Injection around the spinal cord (epidural use), however, is permitted.
- Fentanyl Citrate Injection USP should not be injected around the spinal cord (epidural use) if there is shock, severe bleeding, systemic infection, or infection around the injection site. This use should also be avoided if you bleed easily or you are taking a blood-thinner.

What the medicinal ingredient is:
Fentanyl

What the nonmedicinal ingredients are:
Each mL of solution contains: fentanyl 50 mcg (as citrate), citric acid and/or sodium hydroxide to adjust pH and water for injection.

What dosage forms it comes in:
Fentanyl Citrate Injection USP is supplied in 2 mL ampoules, boxes of 10.

Fentanyl Citrate Injection USP is also supplied in 5 mL and 10 mL single use glass vials, boxes of 10, 20 mL single use glass vials, boxes of 5, and 50 mL Pharmacy Bulk Vials, boxes of 1.

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions
- Fentanyl Citrate Injection USP should only be administered by persons with the appropriate training and experience with this kind of drug.
- Complete resuscitation (life-saving) equipment and an antidote to rapidly counteract the effects of the drug should always be available.

BEFORE being given Fentanyl Citrate Injection USP, talk to your doctor if:
- You plan on operating a car or heavy machinery after receiving the drug.
- You are an elderly person.
- You have a condition with any part of your body, such as your heart, lung, liver, or thyroid.
- You are taking any medication, such as blood thinners, and/or pain killers.
- You have heavy alcohol use.
- You use any drugs not given you by a doctor.
- You are pregnant or breast feeding.
- You have a known allergic reaction to this drug or any other pain medications or any other general anesthetics.
- You have had a head injury (history and/or current), or if you experience difficulties breathing.

INTERACTIONS WITH THIS MEDICATION

Your doctor should tell you what medication you may or may not use after your surgery or childbirth.

Before taking Fentanyl Citrate Injection USP, tell your doctor about any other medications that you are using including certain antidepressants (selective serotonin reuptake inhibitors (SSRI)) and serotonin/norepinephrine reuptake inhibitors (SNRI).

Drugs that may interact with Fentanyl Citrate Injection USP include: antifungals (ketoconazole, itraconazole), antivirals (ritonavir), sleeping pills (barbiturates), tranquilizers, pain medication (opioids), general anesthetics, or other depressants of the central nervous system, antidepressants (MAO inhibitors), and medicines for high blood pressure (beta-
blockers). Other agents that may also interact are grapefruit juice and alcohol.

Grapefruit juice and alcohol may also change the effect of Fentanyl Citrate Injection USP.

**PROPER USE OF THIS MEDICATION**

Fentanyl Citrate Injection USP can only be used by a doctor in a facility with life-saving equipment.

**Usual dose:**
The dose given to you by your doctor will depend on such factors as how much you weigh, your current health status, any diseases you may currently have, and the kind of surgical procedure you will be undergoing.

**AFTER SURGERY**

**SIDE EFFECTS AND WHAT TO DO ABOUT THEM**

For the following serious side effects, you must seek immediate emergency medical treatment.
- Low (fainting) or high blood pressure (headaches/dizziness)
- Difficulty breathing
- Slow or rapid or irregular heartbeat
- Difficulty urinating

If the following serious side effects are severe, seek medical assistance
- Sleepiness
- Itching
- Nausea and vomiting
- Chills
- Rash
- Headache
- Confusion

In rare cases, muscle stiffness and swollen face have been reported. Call your doctor if you have these conditions.

Since Fentanyl Citrate Injection USP is commonly used together with general anesthetics and other drugs, other side effects may occur.

This is not a complete list of side effects. For any unexpected effects while taking Fentanyl Citrate Injection USP, contact your doctor or pharmacist.

**HOW TO STORE IT**

To store this medicine:
- Keep out of the reach of children.
- Store between 15 and 30°C. Protect from light. Protect from freezing. Discard unused portion.

**REPORTING SUSPECTED SIDE EFFECTS**

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

- Report online at www.healthcanada.gc.ca/medeffect
- Call toll-free at 1-866-234-2345
- Complete a Canada Vigilance Reporting Form and:
  - Fax toll-free to 1-866-678-6789, or
  - Mail to: Canada Vigilance Program
    Health Canada
    Postal Locator 0701E
    Ottawa, Ontario
    K1A 0K9

Postage paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada Web site at www.healthcanada.gc.ca/medeffect.

**NOTE:** Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

**MORE INFORMATION**

This document, plus the full Product Monograph prepared for health professionals, can be obtained by contacting the sponsor, Sandoz Canada Inc., at:

1-800-361-3062

or by written request at:
145, Jules-Léger
Boucherville, (QC), Canada
J4B 7K8

or by email at:
medinfo@sandoz.com

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