PRESCRIBING INFORMATION

[Pr] FENTANYL CITRATE INJECTION, USP

50 mcg/mL (fentanyl)

THERAPEUTIC CLASSIFICATION
Narcotic Analgesic
Adjunct to Anesthesia

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PACKAGE INSERT

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ACTION AND CLINICAL PHARMACOLOGY

Fentanyl is a synthetic narcotic analgesic with actions qualitatively similar to those of morphine and meperidine. A 100 mcg dose 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. Alterations in respiratory rate and alveolar ventilation, associated with narcotic analgesics, may last longer than the analgesic effect. As the narcotic dose is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnea. Fentanyl appears to have less emetic activity than other narcotic analgesics. Histamine assays and skin-wheal testing in man, as well as *in vivo* testing in dogs, indicate that histamine release rarely occurs with fentanyl. Recent assays in man show no clinically significant histamine release in dosages up to 50 mcg/kg. Fentanyl preserves cardiac stability and obtunds stress-related hormonal changes at higher doses.

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

The onset of action of fentanyl is almost immediate following IV administration, however, the maximal analgesic and respiratory depressant effect may not be noted for several minutes. The usual duration of action of the analgesic effect is 30 to 60 minutes after a single IV dose of up to 100 mcg.

Following IM administration, the onset of action is from 7 to 8 minutes and the duration of action is 1 to 2 hours. With epidural use, the onset of action is between 5 and 10 minutes following administration and the duration of action is generally 2 to 5 hours. When administered epidurally, concentrations of fentanyl in plasma (C_{max}) are roughly one-third of those found after IV administration.

As with longer acting narcotic analgesics, the duration of fentanyl's respiratory depressant effect may be longer than the analgesic effect. The following observations have been reported concerning altered respiratory response to CO_2 stimulation following fentanyl administration to man:

Diminished sensitivity to CO_2 stimulation may persist longer than depression of respiratory rate (Altered sensitivity to CO_2 stimulation has been demonstrated for up to 4 hours following a single IV dose of 600 mcg fentanyl to healthy volunteers). Fentanyl frequently slows the respiratory rate; duration and degree of respiratory depression are dose-related. The peak respiratory effect of a single IV dose of fentanyl is noted 5 to 15 minutes following injection (see also **WARNINGS** and **PRECAUTIONS**).

INDICATIONS AND CLINICAL USES

IV or IM Route: For analgesic action of short duration during the anesthetic periods, premedication, induction and maintenance. Also indicated for use as a narcotic analgesic supplement in general or regional anesthesia.

Fentanyl may be administered with a neuroleptic such as droperidol as an anaesthetic premedication for the induction of anesthesia and as an adjunct in the maintenance of general and regional anesthesia.

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

Epidural Route: For the postoperative management of pain following general surgical procedures and caesarean sections.

CONTRAINDICATIONS

Hypersensitivity to Fentanyl: As with other opiates given epidurally, fentanyl should not be given to patients exhibiting the following : severe hemorrhage or shock, septicemia, local infection at the site of proposed puncture, disturbances of blood morphology and/or anticoagulant therapy or other concomitant drug therapy or medical conditions which could contraindicate the technique of epidural administration.

WARNINGS

Patients who have received fentanyl should have appropriate surveillance. Resuscitative equipment and a narcotic antagonist (e.g. naloxone) should be readily available to manage apnea.

If fentanyl is administered with a neuroleptic 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. **As with other potent narcotics, fentanyl's respiratory depressant effect persists longer than the measured analgesic effect. Consider the total dose of all narcotic analgesics administered before ordering such drugs during recovery from anesthesia. It is recommended that narcotics, when required, should be used in reduced doses initially, as low as ¼ to ⅓ those usually recommended.**

Fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. The effect is related to the speed of injection and its incidence can be reduced by the use of slow IV 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 of fentanyl are used (above 10 mcg/kg) there must be adequate facilities for postoperative observation and also for ventilation, if it becomes necessary. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression.

Drug dependence: Fentanyl can produce drug dependence of the morphine type and therefore has the potential for being abused.

MAO inhibitors: Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics. Since fentanyl's safety in this regard has not been established, its use in patients who have received MAO inhibitors within 14 days is not recommended.

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 or brain tumor. In addition, fentanyl may obscure the clinical course of patients with head injury.

Children: Fentanyl's safety in children under 2 years of age has not been established.

Pregnancy: Fentanyl's safe use 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 the potential benefits outweigh the possible hazards. There is insufficient data regarding placental transfer and fetal effects, therefore, safety for the infant in obstetrics has not been established.

PRECAUTIONS

Geriatrics, Debilitated and Other Poor-Risk Patients: The initial dose of fentanyl should be appropriately reduced in elderly or debilitated patients. Consider the effect of the initial dose in determining incremental doses. Nitrous oxide has been reported to produce cardiovascular depression when given with higher doses of fentanyl.

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. Therefore, when fentanyl is used to supplement these forms of anesthesia, the anesthetist should be familiar with the physiological alterations involved and be prepared to manage them in the patients selected for these forms of anesthesia. When used with a neuroleptic such as droperidol, blood pressure may be altered and hypotension can occur. Monitor vital signs routinely.

Patients with Chronic Obstruction Pulmonary Disease: Use fentanyl with caution in patients with decreased obstructive pulmonary disease, patients with decreased respiratory reserve and others with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anesthesia, this can be managed by assisted or controlled respiration. Respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists.

Maintain appropriate surveillance since the duration of respiratory depression with the doses of fentanyl employed during anesthesia may be longer than the duration of the narcotic antagonist action. Consult individual prescribing information before employing narcotic antagonists such as naloxone.

CNS Depressants: When a neuroleptic such as droperidol is used with fentanyl, pulmonary arterial pressure may be decreased. 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. When either high or anesthetic doses of fentanyl are employed, even relatively small doses of diazepam may cause cardiovascular depression. Other CNS depressant drugs (i.e., barbiturates, psychotherapeutic agents, narcotics and general anesthetics) will have additive or potentiating effects with fentanyl. When patients have received such drugs, the dose of fentanyl required will be far less than usual. Likewise, following fentanyl administration, reduce the dose of other CNS depressant drugs.

Patients with Liver and Kidney Dysfunction: Administer fentanyl with caution to patients with liver and kidney dysfunction because of the importance of these organs in drug metabolism and excretion.

Patients with Cardiac Bradyarrhythmias: Fentanyl may produce bradycardia, which may be treated with atropine. However, fentanyl should be used with caution in patients with cardiac bradyarrhythmias.

Use in Conjunction with a Neuroleptic: 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. Consider repositioning the patient to improve venous return to the heart when operative conditions permit. Exercise care in moving and positioning patients because of the possibility of orthostatic hypotension. If volume expansion with fluids plus other counter-measures does not correct hypotension, consider the administration of pressor agents other than epinephrine. Because of droperidol's alpha-adrenergic blocking action, 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, the EEG pattern may return to normal slowly.

ADVERSE REACTIONS

As with other narcotic analgesics, the most common serious adverse reactions reported with fentanyl are respiratory depression, apnea, muscular rigidity and bradycardia. If these conditions remain untreated, respiratory arrest, circulatory depression or cardiac arrest could occur.

After fentanyl is administered epidurally, pruritus is observed quite frequently, mainly in the face and chest area.

Other adverse reactions that have been reported are:

Cardiovascular: hypotension.

CNS: dizziness, blurred vision.

Gastrointestinal: nausea, emesis.

Musculoskeletal: laryngospasm.

Respiratory: postoperative secondary rebound respiratory depression (see **WARNINGS**).

Miscellaneous: diaphoresis.

When a neuroleptic such as droperidol is used with fentanyl, the following adverse reactions can occur:

CNS: chills and/or shivering, restlessness and postoperative drowsiness and hallucinatory episodes (sometimes associated with transient periods of mental depression).

Extrapyramidial Symptoms: dystonia, akathisia and oculogyric crisis.

Cardiovascular: elevated blood pressure, with and without preexisting hypertension. (This might be due to unexplained alterations in sympathetic activity following large doses; however, it is also

frequently attributed to anesthetic and surgical stimulation during light anesthesia).

SYMPTOMS AND TREATMENT OF OVERDOSE

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

In the presence of hypoventilation or apnea, administer oxygen and assist or control respiration as indicated.

Maintain a patent airway; an oropharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, an IV neuromuscular blocking agent might be required to facilitate assisted or controlled respiration. Observe the patient carefully for 24 hours; maintain body warmth and adequate fluid intake. If hypotension occurs and is severe or persists, consider the possibility of hypovolemia and manage with appropriate parenteral fluid therapy. A specific narcotic antagonist such as naloxone or nalorphine should be available for use as indicated to manage respiratory depression. A specific narcotic antagonist such as naloxone may also be used to manage respiratory depression following epidural use of fentanyl with the same caution required as in the case of parenteral administration. This does not preclude the use of more immediate counter-measures. The duration of respiratory depression following fentanyl overdosage may be longer than the duration of narcotic antagonist action.

DOSAGE AND ADMINISTRATION

(50 mcg = 0.05 mg = 1 mL). Individualize the dosage of fentanyl. Some of the factors to be considered in determining the dose are age, body weight, physical status, underlying pathological condition, use of other drugs, type of anesthesia to be used and the surgical procedure involved. Monitor vital signs routinely.

Adults: Premedication: (to be appropriately modified in the elderly, debilitated and those who have received other depressant drugs): 50 to 100 mcg may be administered IM 30 to 60 minutes prior to surgery.

Adjunct to General Anesthesia: See **DOSAGE CHART** (Table 1). Adjunct to Regional Anesthesia: 50 to 100 mcg may be administered IM or slowly IV over 1 to 2 minutes when additional analgesia is required.

Postoperative Management of Pain: 100 mcg may be administered epidurally. The 2 mL fentanyl should be diluted with 8 mL of 0.9 % normal saline resulting in a final concentration of 10 mcg/mL. Additional boluses may be administered if there is evidence of lightening of analgesia.

Children: For induction and maintenance in children 2 to 12 years of age, a reduced dose as low as 20 to 30 mcg per 9-11 kg is recommended. See **DOSAGE CHART** (Table 1).

As a General Anesthetic: When attenuation of the responses to surgical stress is especially important, doses of 50 to 100 mcg/kg may be administered with oxygen and a muscle relaxant. This technique has been reported to provide anesthesia without the use of additional anesthetic agents. In certain cases, doses up to 150 mcg/kg may be necessary to produce this anesthetic effect. It 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 particularly indicated and for certain complicated neurologic and orthopedic procedures.

As noted above, it is essential that qualified personnel and adequate facilities be available for the management of respiratory depression.

TABLE 1

DOSAGE CHART

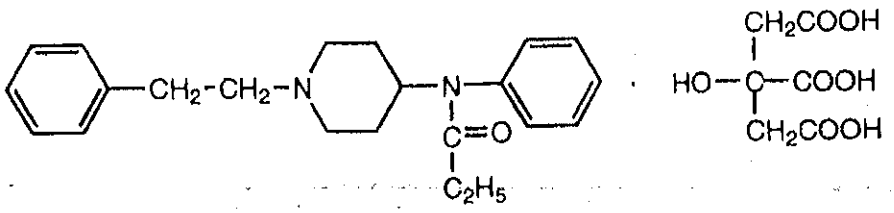
LOW DOSE	MODERATE DOSE	HIGH DOSE
2 mcg/kg (0.04 mL/kg) fentanyl injection. Fentanyl in small doses is most useful for minor, but painful surgical procedures. In addition to the analegesia during surgery, fentanyl may also provide some pain relief in the immediate postoperative period.	2 - 20 mcg/kg (0.04 - 0.4 mL/kg) fentanyl injection. 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.	20 - 50 mcg/kg (0.4 - 1 mL/kg) fentanyl injection. 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 well being of the patient, dosages of 20 - 50 mcg/kg (0.4 - 1 mL/kg) of fentanyl injection 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. 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.
MAINTENANCE DOSE		
Additional doses of fentanyl injection are infrequently needed in these minor procedures.	10 - 25 mcg (0.2 - 0.5 mL) may be administered IV or IM when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia.	Maintenance dosage (ranging from 25 mcg (0.5 mL) to ½ the initial loading dose) will be dictated by the 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.
EPIDURAL DOSE		
1.5 mcg/kg may be administered epidurally.		

PHARMACEUTICAL INFORMATION

Drug Substance

Common Name: Fentanyl Citrate is the citrate salt of N-phenyl-N[1-(2-phenylethyl)-4-piperidinyl] propanamide.

Chemical Structure:



Molecular Formula: $C_{28}H_{36}N_2O_8$

Molecular Weight: 528.6

Description: White granules or a white crystalline powder, odourless, with a bitter taste. Solubility; 1 in 10 parts of methanol, 1 in 40 parts of water, 1 in 140 parts of ethanol, 1 in 350 parts of chloroform, slightly soluble in ether.

Composition: Fentanyl Citrate Injection, USP is a sterile, unpreserved solution containing 0.0785 mg/mL of Fentanyl Citrate which provides 0.05 mg (50 microgram) Fentanyl per mL in sterile Water for Injection.

Stability and Storage Recommendations: Store between 15-30°C. Protect from light.

AVAILABILITY OF DOSAGE FORMS

Fentanyl Citrate Injection, USP is supplied in 2 mL, 5 mL, 10 mL and 20 mL ampoules; cartons of 5. The dosage form contains no bacteriostat or preservative and is intended only for use as single dose injection. Discard any unused portion in an appropriate manner.

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