Fentanyl

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QUALITATIVE AND QUANTITATIVE COMPOSITION
Each ml contains 50 µg Fentanyl (as fentanyl citrate).

PHARMACEUTICAL FORM
Fentanyl is a sterile, preservative-free, isotonic aqueous solution for intravenous use.

CLINICAL PARTICULARS
Therapeutic indications
Fentanyl is indicated:
- for use as a narcotic analgesic supplement in general or regional anaesthesia.
- for administration with a neuroleptic as an anesthetic 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 undergoing major surgery.

Posology and method of administration
The dosage of Fentanyl should be individualized according to age, body weight, physical status, underlying pathological condition, use of other drugs, and type of surgery and anesthesia.
The initial dose should be reduced in the elderly and in debilitated patients. The effect of the initial dose should be taken into account in determining supplemental doses.
To avoid bradycardia, it is recommended to administer a small intravenous dose of an anti-cholinergic just before induction.
A neuroleptic may be given to prevent nausea and vomiting.
- *Use as an analgesic supplement to general anesthesia*
Low dose: 2 µg/kg.
Fentanyl in small doses is most useful for minor, but painful, surgery.
Moderate dose: 2-20 µg/kg.
Where surgery becomes more complicated, a larger dose will be required. The duration of activity is dependent on dosage.
High dose: 20-50 µg/kg.
During major surgical procedures, in which surgery is longer, and during which the stress response would be detrimental to the wellbeing of the patient, dosages of 20-50 µg/kg Fentanyl with nitrous oxide/oxygen have been shown to have an attenuating effect. When dosages in this range have been used during surgery, post-operative ventilation and observation are essential in view of the possibility of extended post-operative respiratory depression.
Supplemental doses of 25-250 µg (0.5-5 ml) should be tailored to the needs of the patient and to the anticipated time until completion of the operation.
- *Use as an anesthetic agent*
When attenuation of the response to surgical stress is especially important, doses of 50-100 µg/kg may be administered with oxygen and a muscle relaxant. This technique provides anaesthesia without necessitating the use of additional anaesthetic agents. In certain cases, doses up to 150 µg/kg may be required to produce this anaesthetic effect. Fentanyl has been used in this fashion 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.
- *Use in the elderly*
As with other opioids, the dose should be reduced in elderly or debilitated patients.
- *Use in children*
For induction and maintenance in children aged 2-12 years, a dose of 2-3 µg/kg is recommended.

Contraindications
Known intolerance to either of its components or to other morphino-mimetics.

Special warnings and special precautions for use
As with all potent opioids:
Respiratory depression is dose related and can be reversed by specific narcotic antagonists such as naloxone, but additional doses of the latter may be necessary because the respiratory depression may last longer than the duration of action of the opioid antagonist.
Profound analgesia is accompanied by marked respiratory depression, which can persist or recur in the postoperative period.
Therefore, patients should remain under appropriate surveillance.
Resuscitation equipment and narcotic antagonists should be readily available. Hypoventilation during anaesthesia may alter the patient's responses to CO_2, thus affecting respiration postoperatively.
Induction of muscle rigidity, which may also involve the thoracic muscles, can occur, but can be avoided by the following measures: slow I.V. injection (ordinarily sufficient for lower doses), premedication with benzodiazepines and the use of muscle relaxants.
Non-epileptic myoclonic movements can occur.
Bradycardia, and possibly asystole, can occur if the patient has received an insufficient amount of anticholinergic, or when Fentanyl is combined with non-vagolytic muscle relaxants. Bradycardia can be treated with atropine.
Opioids may induce hypotension, especially in hypovolemic patients. Appropriate measures to maintain a stable arterial pressure should be taken.
The use of rapid bolus injections of opioids should be avoided in patients with compromised intracerebral compliance; in such patients the transient decrease in the mean arterial pressure has occasionally been accompanied by a short-lasting reduction of the cerebral perfusion pressure.
Patients on chronic opioid therapy or with a history of opioid abuse may require higher doses.
It is recommended to reduce the dosage in the elderly and in debilitated patients. Opioids should be titrated with caution in patients with any of the following conditions: uncontrolled hypothyroidism; pulmonary disease; decreased respiratory reserve; alcoholism; or impaired hepatic or renal function. Such patients also require prolonged post-operative monitoring.
If Fentanyl is administered with a neuroleptic, the user should be familiar with the special properties of each drug, particularly the differences in duration of action. When such a combination is used, there is a higher incidence of hypotension. Neuroleptics can induce extrapyramidal symptoms that can be controlled with anti-Parkinson agents.

Interaction with other medicaments and other forms of interaction
Drugs such as barbiturates, benzodiazepines, neuroleptics, halogenic gases and other, non-selective CNS depressants (e.g. alcohol) may potentiate the respiratory depression of narcotics.
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.
Fentanyl, a high clearance drug, is rapidly and extensively metabolized mainly by CYP3A4. Itraconazole (a potent CYP3A4 inhibitor) at 200 mg/day given orally for 4 days had no significant effect on the pharmacokinetics of IV Fentanyl.
Oral ritonavir (one of the most potent CYP3A4 inhibitors) reduced the clearance of IV Fentanyl by two thirds; however, peak plasma concentrations after a single dose of IV Fentanyl were not affected.
When Fentanyl is used in a single dose, the concomitant use of potent CYP3A4 inhibitors such as ritonavir requires special patient care and observation. With continuous treatment, a dose reduction of Fentanyl may be required to avoid accumulation of Fentanyl, which may increase the risk of prolonged or delayed respiratory depression.
It is usually recommended to discontinue MAO-inhibitors 2 weeks prior to any surgical or anesthetic procedure. However, several reports describe the uneventful use of Fentanyl during surgical or anesthetic procedures in patients on MAO-inhibitors.

Pregnancy and lactation
There are no adequate data from the use of Fentanyl in pregnant women. Studies in animals have shown some reproductive toxicity (see Preclinical safety data). The *potential risk* for humans is unknown.
Administration during childbirth (including cesarean section) is not recommended because Fentanyl crosses the placenta and because the fetal respiratory carrier is particularly sensitive to opiates. If Fentanyl is nevertheless administered, an antidote for the child should always be at hand.
Fentanyl is excreted into human milk. Therefore, nursing is not recommended for 24 hours following the administration of this drug. The risk/benefit of breastfeeding following fentanyl administration should be considered.

Effects on ability to drive and use machines
Patients should only drive or operate a machine if sufficient time has elapsed after the administration of Fentanyl.

Undesirable effects
Adverse events reported in association with intravenous fentanyl use in clinical trials are listed below:
Central & Peripheral Nervous System Disorders
Common: Muscle rigidity (which may also involve the thoracic muscles)/ myoclonic movements, dizziness
Cardiovascular Disorders, General
Common: Hypotension
Heart Rate and Rhythm Disorders
Common: Bradycardia
Respiratory System Disorders
Common: Apnea, respiratory depression
Uncommon: Laryngospasm
Gastro-Intestinal System Disorders
Very Common: Nausea, vomiting
Body as a Whole - General Disorders
Uncommon: Allergic reactions (such as anaphylaxis, bronchospasm, pruritus, urticaria)
In addition to the adverse reactions reported in clinical trials, the following adverse reactions have also been reported in post-marketing and occur rarely: asystole.
Secondary rebound respiratory depression after the operation has been observed in rare instances.
When a neuroleptic is used with Fentanyl, the following adverse reactions may be observed: chills and/or shivering, restlessness, post-operative hallucinatory episodes; and extrapyramidal symptoms.

Overdose
Symptoms
An overdosage of Fentanyl manifests itself as an extension of its pharmacologic actions. Depending on the individual sensitivity, the clinical picture is determined primarily by the degree of respiratory depression, which varies from bradypnea to apnea.
Treatment
In the presence of hypoventilation or apnea, oxygen should be administered and respiration should be assisted or controlled as indicated. A specific narcotic antagonist, such as naloxone, should be used as indicated to control respiratory depression. This does not preclude the use of more immediate countermeasures. The respiratory depression may last longer than the effect of the antagonist; additional doses of the latter may therefore be required.
Depressed respiration associated with muscular rigidity, an intravenous neuromuscular blocking agent might be required to facilitate assisted or controlled respiration.
The patient should be carefully observed; body warmth and adequate fluid intake should be maintained. If hypotension is severe or if it persists, the possibility of hypovolemia should be considered, and if present, should be controlled with appropriate parenteral fluid administration.

PHARMACOLOGICAL PROPERTIES
Pharmacodynamic properties
Fentanyl is a potent, narcotic analgesic. Fentanyl can be used as an analgesic supplement to general anesthesia or as the sole anesthetic. Fentanyl preserves cardiac stability and obtunds stress-related hormonal changes at higher doses. A dose of 100 µg (2.0 ml) is approximately equivalent in analgesic activity to 10 mg of morphine. The onset of action is rapid. However, the maximum analgesic and respiratory depressant effect may not be noted for several minutes. The usual duration of action of the analgesic effect is approximately 30 minutes after a single i.v. dose of up to 150 µg. Depth of analgesia is dose-related and can be adjusted to the pain level of the surgical procedure. Fentanyl has a broad safety-margin. In rats the ratio LD_{50}/ED_{50} for the lowest level of analgesia is 277, as compared with 69.5 and 4.6 for morphine and pethidine respectively.
Like other narcotic analgesics, Fentanyl, depending upon the dose and speed of administration, can cause muscle rigidity, as well as euphoria, miosis and bradycardia.
Histamine assays and skin-wheal testing in man, as well as *in vivo* testing in dogs, have indicated that clinically significant histamine release is rare with Fentanyl.
All actions of Fentanyl are immediately and completely reversed by a specific narcotic antagonist such as naloxone.

Pharmacokinetic properties
After intravenous injection, Fentanyl plasma concentrations fall rapidly, with sequential distribution half-lives of about 1 minute and 18 minutes and a terminal elimination half-life of 6 hours. Fentanyl has a Vc (volume of distribution of the central compartment) of 13 L, and a total Vdss (distribution volume at steady-state) of 336 L. The plasma-protein binding of Fentanyl is about 84 %.
Fentanyl is rapidly metabolized, mainly in the liver. Fentanyl clearance is 574 ml/min. Approximately 75 % of the administered dose is excreted within 24 hours and only 10 % of the dose is eliminated as unchanged drug.

Preclinical safety data
In vitro fentanyl showed, like other opioid analgesics, mutagenic effects in a mammalian cell culture assay, only at cytotoxic concentrations and along with metabolic activation. Fentanyl showed no evidence of mutagenicity when tested in *in vivo* rodent studies and bacterial assays. There are no long-term animal studies to investigate the tumor-forming potential of fentanyl.
Some tests on female rats showed reduced fertility as well as embryo-retardant. These findings were related to maternal toxicity and not a direct effect of the drug on the developing embryo. There was no evidence of teratogenic effects.

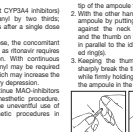
PHARMACEUTICAL PARTICULARS
List of excipients
The inactive ingredients of the injectable solution are sodium chloride and water for injections.

Compatibility
The injectable solution must not be mixed with other products.
If desired, Fentanyl may be mixed with sodium chloride or glucose intravenous infusions. Such dilutions are compatible with plastic infusion sets. These should be used within 24 hours of preparation.

Special precautions for storage
Keep ampoule in the outer carton.
Store between 15° and 30°C.
Keep out of reach of children.

Nature and contents of container
Fentanyl is supplied in 2 ml and 10 ml ampoules.

Instructions for use/handling
1. Maintain the ampoule between the thumb and index finger, leaving the tip of the ampoule free.
2. With the other hand, hold the tip of ampoule by putting the index finger against the nack of the ampoule and the thumb on the colored point in parallel to the identification colored ring(s).
3. Keeping the thumb on the point, sharply break the tip of the ampoule while firmly holding the other part of the ampoule in the hand.



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