

Data Sheet

FENTANYL INFUSION

Fentanyl Citrate 10 µg/ml (Syringes and Bags), 20 µg/ml (Syringes)

Presentation

Fentanyl infusion 10 µg/ml contains fentanyl citrate and is available as follows:

- 100 µg (as fentanyl base) in 10 ml syringes
- 500 µg (as fentanyl base) in 50 ml syringes
- 1000 µg (as fentanyl base) in 100 ml flexible bags.

Fentanyl infusion 20 µg/ml contains fentanyl citrate and is available as follows:

- 1000 µg (as fentanyl base) in 50 ml syringes.
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Uses

Actions

Fentanyl is a potent narcotic analgesic with a rapid onset and short duration of action. The principal actions of therapeutic value are analgesia and sedation. At a dose of 100 micrograms, the analgesic activity of fentanyl is approximately equivalent to 10 mg of morphine or 75 mg of pethidine. Fentanyl differs from morphine by its short duration of analgesic activity, lack of emetic activity, and minimal hypotensive activity.

The actions of fentanyl are qualitatively similar to those of morphine and pethidine, i.e. analgesia, euphoria, miosis, bradycardia, respiratory depression, bronchoconstriction, muscle rigidity and suppression of cough reflexes. These effects can be reversed by specific narcotic antagonists, e.g. naloxone. As with morphine, fentanyl-induced bradycardia from vagal stimulation is blocked or reversed by atropine. Alterations in respiratory rate and alveolar ventilation, associated with narcotic analgesics may last longer than the analgesic effect. As the dose of the narcotic is increased, the decrease in pulmonary exchange becomes greater. Larger doses may produce apnoea. The behavioural effects of fentanyl and morphine are similar in mice, and with toxic doses death is due to respiratory depression. The respiratory depressant properties of fentanyl appear to be due to a central effect by decreasing the sensitivity of the respiratory centre to carbon dioxide. In an experiment in cats, no effect on neuromuscular transmission was observed in the presence of severe respiratory depression.

Histamine assays and skin wheal testing in man, as well as *in vivo* testing in dogs, indicate that histamine release rarely occurs with fentanyl. Experiments in dogs, have shown that intravenously administered fentanyl at doses 2-4 times the recommended human dose, had minimal effect on blood pressure and heart rate. Much higher doses of fentanyl citrate, ranging from 100-400 micrograms/kg, produce an immediate fall in blood pressure, followed by partial recovery, and a sustained hypotensive effect lasting up to 30 minutes.

Pharmacokinetics

The onset of action of fentanyl is almost immediate when the medicine is given intravenously. However, the maximal analgesic and respiratory depressant effect may not be noted for several minutes. The usual duration of action of analgesic effect is 30 to 60 minutes after a single I.V. dose of up to 100 micrograms.

As with longer acting narcotic analgesics, the duration of the respiratory depressant effect of fentanyl 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.
2. Fentanyl frequently slows the respiratory rate, but this effect is seldom noted for longer than 30 minutes regardless of the dose administered.
3. Altered sensitivity to CO₂ stimulation has been demonstrated for up to four hours following a single intravenous dose of 600 micrograms fentanyl to healthy volunteers.
4. Duration and degree of respiratory depression is dose-related.
5. The peak respiratory depressant effect of a single intravenous dose of fentanyl is noted 5 to 15 minutes following injection.

(See also **Warnings and Precautions** concerning respiratory depression.)

Fentanyl produces a minimum of cortical depression, and it is suggested that it exerts its action by filling receptor sites located in the thalamus, mid-brain, and spinal cord. A specific narcotic antagonist, e.g. naloxone, produces reversal of respiratory, cardiovascular, miotic, and motor incoordination effects, as well as analgesia, euphoria, and sedation. Rigidity of the diaphragm and intercostal muscles can be eliminated by succinylcholine. Cholinergic effects, e.g. bradycardia, are reversed by atropine. Fentanyl is metabolised primarily in the liver. In humans, *in vitro* experiments have demonstrated that fentanyl is metabolised mainly by cytochrome P450 3A4 (CYP 3A4) to norfentanyl *via* oxidative N-dealkylation.

Indications

Fentanyl is indicated for:

- analgesic action in the post-operative period as the need arises;
- use as a narcotic analgesic supplement in general and regional anaesthesia.

Dosage and Administration

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

Usual Dosage in Adult

Administered post-operatively as a slow intravenous infusion at a rate prescribed by the attending physician (typically 500 – 1000 µg over a 24-hour period) or by patient-controlled infusion device, where the dose per activation and the lockout period are set by the attending physician.

An infusion may be started during surgery as an adjunct to general anaesthesia with a dose of 100 µg, increased as required until the desired effect is achieved.

Usual Dosage in Children

For analgesia maintenance in children 2-12 years of age, a reduced dose as low as 20 to 30 micrograms per 10 kg is recommended.

(See **Warnings and Precautions** for use of fentanyl with other CNS depressants and in patients with altered response.)

Contraindications

Fentanyl is contraindicated in patients with known intolerance to fentanyl. Fentanyl should not be administered to children two years of age or younger, because safe conditions for use have not been established. (See **Warnings and Precautions - Use in children**). Fentanyl should not be administered to patients suffering from bronchial asthma. As for any narcotic analgesic, it should not be used in patients who may be particularly susceptible to respiratory depression, such as comatose patients who may have a head injury or brain tumour (See **Warnings and Precautions**). Severe and unpredictable potentiation by MAO inhibitors has been reported with narcotic analgesics.

There is no evidence that fentanyl is potentiated by MAO inhibitors, but since such potentiation is found with other narcotic analgesics, the use of Fentanyl in patients who have received MAO inhibitors within 14 days is not recommended (See **Interactions**).

Fentanyl may cause thoracic muscle rigidity upon intravenous administration. Therefore, the need for reversal with muscle relaxants contraindicates its use in patients with a history of myasthenia gravis.

Warnings and Precautions

Drug Dependence

Fentanyl can produce drug dependence of the morphine type and therefore has the potential for being abused. Fentanyl may be habit forming. Patients on chronic opioid therapy or with a history of opioid abuse may require higher doses.

Hypoventilation (Respiratory Depression)

Profound analgesia is accompanied by marked respiratory depression, which can persist or recur in the post-operative period. Hyperventilation during anaesthesia may alter the patient's responses to CO₂, thus affecting respiration post-operatively. Therefore, patients should remain under appropriate surveillance.

Fentanyl should be used with caution in patients with severe impairment of pulmonary function because of the possibility of respiratory depression, e.g. patients with chronic obstructive pulmonary disease, patients with decreased respiratory reserve, or any patient with potentially compromised respiration. In such patients, narcotics may additionally decrease respiratory drive and increase airway resistance. During anaesthesia, this can be managed by assisted or controlled respiration.

Respiratory depression caused by narcotic analgesics can be reversed by narcotic antagonists. Appropriate surveillance should be maintained because the duration of respiratory depression of doses of fentanyl employed during anaesthesia may be longer than the duration of narcotic antagonist action. Consult individual prescribing information (naloxone) before employing narcotic antagonists. See also discussion of narcotic antagonists in **Overdosage**.)

Resuscitative equipment and a narcotic antagonist should be readily available to manage apnoea.

Muscle Rigidity

Fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the speed of injection and its incidence can be reduced by a slow intravenous injection (ordinarily sufficient for lower doses) premedication with benzodiazapines and the use of muscle relaxants.

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.

Non-epileptic (myo)clonic movements can occur.

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 tumour. In addition, fentanyl may obscure the clinical course of patients with a head injury.

Rapid bolus infusion 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.

Cardiac Effects

Fentanyl may produce bradycardia and possibly asystole if the patient has received an insufficient amount of anticholinergic, or when fentanyl is combined with non-vagolytic muscle relaxants. Bradycardia may be treated with atropine. However, fentanyl should be used with caution in patients with cardiac bradyarrhythmias.

Opioids may induce hypotension, especially in hypovolaemic patients. Appropriate measures to maintain a stable arterial pressure should be taken.

Others

As has been observed with all narcotic analgesics, episodes suggestive of sphincter of Oddi spasm may occur with fentanyl.

Vital signs should be monitored carefully.

Use in the Elderly or Debilitated Patients

It is recommended to reduce the dosage of fentanyl 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, impaired hepatic or renal function. Such patients also require prolonged post-operative monitoring.

Use in Children

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

Pregnancy and Lactation

Use in Pregnancy

Category C.

There are no adequate data from the use of fentanyl in pregnant women. Studies in animals have shown some reproductive toxicity. The potential risk for humans is unknown. *In vitro* fentanyl, like other opioid analgesics, showed 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 tumour-forming potential of fentanyl.

Some tests on female rats showed reduced fertility as well as embryo mortality. 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.

Administration during childbirth (including caesarean section) is not recommended because fentanyl crosses the placenta and because the foetal respiratory centre is particularly sensitive to opiates. If fentanyl is nevertheless administered, an antidote for the child should always be at hand.

Use in Lactation

Fentanyl is excreted into human milk. Therefore, breastfeeding is not recommended for 24 hours following the administration of this medicine.

The risk/benefit of breast-feeding following fentanyl administration should be considered.

Effects on the Ability to Drive and Use Machines

Patients should only drive or operate a machine if sufficient time has elapsed after the administration of fentanyl.

Adverse Effects

As with other narcotic analgesics, the most common serious adverse reactions reported to occur with fentanyl are respiratory depression, apnoea, muscular rigidity (which may also involve the thoracic muscles), myoclonic movements, and bradycardia.

If these remain untreated, respiratory arrest, circulatory depression, or cardiac arrest could occur.

Respiratory depression is more likely to occur with intravenous administration if a dose is given too rapidly. If respiratory depression occurs during anaesthesia, assisted or controlled respiration will provide adequate ventilation without reversing analgesia.

Respiratory depression can be immediately reversed by narcotic antagonists (naloxone) which, it should be noted, will also reverse analgesia.

Muscular rigidity is a common side effect and in some instances may be associated with reduced pulmonary compliance and/or apnoea, laryngospasm and bronchospasm. Prompt reversal of this effect can be achieved with the intravenous administration of an appropriate single dose of a muscle relaxant such as succinylcholine. Assisted or controlled respiration is required to provide ventilation after the use of muscle relaxants. Bradycardia and other cholinergic effects may occur, and can be controlled with an appropriate dose of atropine. The inclusion of atropine or other anticholinergic agents in the pre-anaesthetic regimen tends to reduce the occurrence of such effects.

Other adverse reactions that have been reported are hypotension, dizziness, blurred vision, nausea, emesis, laryngospasm, diaphoresis, itching and euphoria.

When a neuroleptic such as droperidol is used with fentanyl, the following adverse reactions can occur: chills and/or shivering, restlessness, and post-operative hallucinatory episodes sometimes associated with transient periods of mental depression, and extrapyramidal symptoms (dystonia, akathisia, and oculogyric crisis) have been observed up to 24 hours post-operatively. Extrapyramidal symptoms can usually be controlled with anti-Parkinson agents. Post-operative drowsiness is also frequently reported following the use of droperidol.

Elevated blood pressure with and 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 anaesthesia.

Allergic reactions (such as anaphylaxis, bronchospasm, pruritis, urticaria) and asystole have been reported. Since several medicines were co-administered during anaesthesia, it is uncertain whether there is a causal relationship to fentanyl.

Secondary rebound respiratory depression after the operation has been observed in rare instances.

Interactions

Medicines, such as, CNS depressants, barbiturates, benzodiazepines, neuroleptics, narcotics, alcohol and general anaesthetics, will have additive or potentiating effects with fentanyl.

When patients have received such medicines, the dose of fentanyl required will be less than usual. Likewise, following the administration of fentanyl the dose of other CNS depressant medicines should be reduced. Post-operative narcotics including fentanyl and other depressants should be given initially in reduced doses, as low as $\frac{1}{4}$ to $\frac{1}{3}$ of those usually recommended. As with other narcotics, the respiratory depressant effect of fentanyl persists

longer than the measured analgesic effect. The total dose of all narcotic analgesics should be considered before ordering narcotic analgesics during recovery from anaesthesia.

Certain forms of conduction anaesthesia, such as spinal anaesthesia and some peridural anaesthetics, can alter respiration by blocking intercostal nerves. Through other mechanisms (see **Actions**) fentanyl can also alter respiration. Therefore, when fentanyl is used to supplement these forms of anaesthesia, the anaesthetist should be familiar with the special properties of each medicine (particularly with the widely differing durations of actions), the physiological alterations involved and be prepared to manage them in patients selected for these forms of anaesthesia.

When fentanyl is used with a neuroleptic such as droperidol, blood pressure may be altered and hypotension can occur. If this occurs, the possibility of hypovolaemia should also be considered and managed with appropriate parenteral fluid therapy. Repositioning the patient improves venous return to the heart and should be considered when operative conditions permit. Care should be exercised in moving and positioning patients because of the possibility of orthostatic hypotension. If volume expansion with fluids together with other countermeasures do not correct hypotension, the administration of pressor agents other than adrenaline should be considered. Because of the alpha-adrenergic blocking action of droperidol, adrenaline may paradoxically decrease the blood pressure in patients treated with droperidol. Pulmonary arterial pressure may also be decreased. This should be considered when interpreting pulmonary arterial pressure measurements as it might determine the final management of the patient.

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

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

Fentanyl is metabolised mainly *via* the human cytochrome P450 3A4 enzyme. It is a high clearance medicine which is rapidly and extensively metabolised. Oral administration of itraconazole (a potent inhibitor of CYP3A4) at 200 mg/day given orally for 4 days did not have a statistically 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, after a single dose of IV fentanyl, the peak plasma concentrations 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. When fentanyl is given continuously with these medicines, a reduction in the dose of fentanyl may be required. This will avoid the accumulation of fentanyl and hence reduces the risk of prolonged or delayed respiratory depression.

There are no data on the *in vivo* interactions between fentanyl and other medicines inhibiting CYP3A4 (e.g. ketoconazole, erythromycin, diltiazem and cimetidine).

Overdosage

Symptoms

The oral LD₅₀ for fentanyl in rats is 18.0 mg/kg. The intravenous LD₅₀ is 2.3 mg/kg, and the intramuscular LD₅₀ is 1.0 mg/kg in rats. The toxic dose in man is unknown.

The manifestations of fentanyl overdosage are an extension of its pharmacological actions. In sufficient overdosage, fentanyl would produce narcosis, which may be preceded by marked skeletal muscle rigidity. Cardio-respiratory depression accompanied by cyanosis occurs, followed by a fall in body temperature, circulatory collapse, coma and death.

Treatment

In the presence of hypoventilation or apnoea, 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.

A specific narcotic antagonist, such as 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 narcotic antagonist action. Consult the package insert of the individual narcotic antagonists for details about use. 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 hypovolaemia should be considered and managed with appropriate parenteral fluid therapy.

Pharmaceutical Precautions

Shelf Life

12 months for syringes 10 µg/ml and 20 µg/ml when stored below 25 °C.

24 months for flexible bags when stored below 25 °C .

Medicine Classification

Controlled Drug B3

Package Quantities

10 µg/ml, 10 ml and 50 ml syringes. 100 ml flexible bags.

20 µg/ml, 50 ml syringes

Further Information

Fentanyl injection contains sodium chloride as required for isotonicity. All products are for single use only.

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