

Fentanyl citrate solution for injection

Core Safety Profile

4.2 Posology and method of administration

Fentanyl should be given only when in an environment where the airway can be controlled and by personnel who can control the airway (see section 4.4).

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 anaesthesia.

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.

4.3 Contraindications

Known intolerance to fentanyl or to other morphino-mimetics.

4.4 Special warnings and precautions for use

Fentanyl should be given only in an environment where the airway can be controlled and by personnel who can control the airway.

As with all potent opioids:

Respiratory depression is dose related and can be reversed by a specific narcotic antagonist 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. Hyperventilation during anaesthesia may alter the patient's responses to CO₂, 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 (myo)clonic movements can occur.

Bradycardia, and possibly cardiac arrest, 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, [*such as droperidol*], the user should be familiar with the special properties of each drug, particularly the difference 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.

As with other opioids, due to the anti-cholinergic effects, administration of Fentanyl may lead to increases of bile duct pressure and, in isolated cases, spasms of the Sphincter of Oddi might be observed.

In patients with myasthenia gravis, careful consideration should be applied in the use of certain anticholinergic agents and neuromuscular-blocking pharmaceutical agents prior to, and during, the administration of a general anaesthetic regimen which includes administering intravenous Fentanyl.

Paediatric Population

Techniques that involve analgesia in a spontaneously breathing child should only be used as part of an anaesthetic technique, or given as part of a sedation/analgesia technique with experienced personnel in an environment that can manage sudden chest wall rigidity requiring intubation, or apnoea requiring airway support.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of Other Drugs on Fentanyl

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.

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.

Co-administration of fluconazole or voriconazole and Fentanyl may result in an increased exposure to 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 anaesthetic procedure. However, several reports describe the uneventful use of Fentanyl during surgical or anaesthetic procedures in patients on MAO-inhibitors.

Effect of Fentanyl on Other Drugs

Following the administration of Fentanyl, the dose of other CNS-depressant drugs should be reduced.

Plasma concentrations of etomidate increased considerably (by a factor 2-3) when combined with fentanyl. The total plasma clearance and volume of distribution of etomidate are decreased by a factor 2 to 3 without a change in half-life when administered with Fentanyl.

Simultaneous administration of Fentanyl and intravenous midazolam results in an increase in the terminal plasma half-life and a reduction in the plasma clearance of midazolam. When these drugs are co-administered with Fentanyl their dose may need to be reduced.

4.6 Pregnancy and lactation

There are no adequate data from the use of Fentanyl in pregnant women. Fentanyl can cross the placenta in early pregnancy. Studies in animals have shown some reproductive toxicity (see Section 5.3, Preclinical safety data). The potential risk for humans is unknown.

Administration (I.M. or I.V.) 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.

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.

4.7 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.

4.8 Undesirable effects

The safety of Fentanyl IV was evaluated in 376 subjects who participated in 20 clinical trials evaluating Fentanyl IV as an anaesthetic. These subjects took at least 1 dose of Fentanyl IV and provided safety data. Based on pooled safety data from these clinical trials, the most commonly reported ADRs (with % incidence) were (with % incidence): Nausea (26.1); Vomiting (18.6); Muscle Rigidity (10.4); Hypotension (8.8); Hypertension (8.8); Bradycardia (6.1); and Sedation (5.3).

Including the above-mentioned ADRs, the following table displays ADRs that have been reported with the use of Fentanyl IV from either clinical trials or post-marketing experiences.

The displayed frequency categories use the following convention: Very common ($\geq 1/10$); common ($\geq 1/100$ to $< 1/10$); uncommon ($\geq 1/1,000$ to $< 1/100$); rare ($\geq 1/10,000$ to $< 1/1,000$); very rare ($< 1/10,000$); and not known (cannot be estimated from the available clinical trial data).

Table 1: Adverse Drug Reactions

System Organ Class	Adverse Drug Reactions			
	Frequency Category			
	Very Common	Common	Uncommon	Not Known

System Organ Class	Adverse Drug Reactions			
	Frequency Category			
	Very Common	Common	Uncommon	Not Known
Immune System Disorders				Hypersensitivity (such as anaphylactic shock, anaphylactic reaction, urticaria)
Psychiatric Disorders			Euphoric Mood	
Nervous System Disorders		Dyskinesia; Sedation; Dizziness	Headache	Convulsions; Loss of Consciousness; Myoclonus
Eye Disorders		Visual Disturbance		
Cardiac Disorders		Bradycardia; Tachycardia; Arrhythmia		Cardiac Arrest
Vascular Disorders		Hypotension; Hypertension; Vein Pain	Phlebitis; Blood Pressure Fluctuation	
Respiratory, Thoracic and Mediastinal Disorders		Laryngospasm Bronchospasm Apnoea	Hyperventilation Hiccups	Respiratory Depression
Gastrointestinal Disorders	Nausea; Vomiting			
Skin and Subcutaneous Tissue Disorders		Dermatitis Allergic		Pruritus
Musculoskeletal and Connective Tissue	Muscle Rigidity			

System Organ Class	Adverse Drug Reactions			
	Frequency Category			
	Very Common	Common	Uncommon	Not Known
Disorders				
General Disorders and Administration Site Conditions			Chills; Hypothermia	
Injury, Poisoning and Procedural Complications		Confusion Postoperative	Airway Complication of Anaesthesia; Agitation Postoperative	

4.9 Overdose

Signs and 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 bradypnoea to apnoea.

Treatment

In the presence of hypoventilation or apnoea, 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.

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; 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.