FENTANYL INJECTION

PRODUCT INFORMATION

NAME OF THE MEDICINE

Fentanyl citrate is chemically identified as N-(1-phenethyl-4-piperidyl) propionanilide citrate, MW 528.61. The chemical formula is C_{22}H_{28}N_{2}O, C_{6}H_{8}O_{7}. The Australian Approved name is fentanyl citrate. The CAS number is 990-73-8. The structural formula is:

![Structural Formula of Fentanyl Citrate]

DESCRIPTION

Fentanyl injection contains fentanyl citrate 50 µg/mL in citric acid anhydrous, sodium citrate, sodium chloride in Water for Injections BP in glass vials or polyethylene sterile ampoules. Fentanyl injection contains no antimicrobial agent. It should be used only once and any residue discarded. The pH is adjusted with sodium hydroxide and ranges from 4.0 to 7.5.

PHARMACOLOGY

Fentanyl is an opioid analgesic. A dose of 100 µg (0.1 mg or 2.0 mL) is approximately equivalent in analgesic activity to 10 mg of morphine or 75 mg of pethidine. The principal actions of therapeutic value are analgesia and sedation. Alterations in respiratory rate and alveolar ventilation associated with opioid analgesics may last longer than the analgesic effect. As the dose of opioid is increased, the decrease in pulmonary exchange becomes greater. Large doses may produce apnoea. Fentanyl appears to have less emetic activity than either morphine or pethidine. Histamine assays and skin wheal testing in man indicate that clinically significant histamine release rarely occurs with fentanyl. Recent assays in man show no clinically significant histamine release at doses up to 50 µg/kg (0.05 mg/kg or 1 mL/kg). Fentanyl preserves cardiac stability and blunts stress-related hormonal changes at higher doses.
Fentanyl produces minimal cortical depression and may act by filling receptor sites located in the thalamus, midbrain and spinal cord. A specific morphine antagonist (e.g. nalorphine) produces reversal of respiratory, cardiovascular, miotic and motor inco-ordination effects and also produces reversal of analgesia, euphoria and sedation. Rigidity of the diaphragm and intercostal muscles can be eliminated by suxamethonium. Cholinergic effects such as bradycardia are reversed by atropine.

**Pharmacodynamics**

As with longer-acting opioid 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. Fentanyl frequently slows the respiratory rate (see PRECAUTIONS).

2. Altered sensitivity to CO₂ stimulation has been demonstrated for up to four hours following a single intravenous dose of 600 µg (12 mL) fentanyl to healthy volunteers.

3. Duration and degree of respiratory depression is dose related.

4. The peak respiratory depressant effect of a single intravenous dose of fentanyl is noted 5 to 15 minutes following injection. (See also PRECAUTIONS concerning respiratory depression).

**Pharmacokinetics**

The pharmacokinetics of fentanyl can be described by a three-compartment model, with a distribution time of 1.7 minutes, redistribution of 13 minutes and a terminal elimination half-life of 219 minutes. The volume of distribution for fentanyl is 4 L/kg.

The onset of action is almost immediate when the drug is given intravenously; 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 µg. Following intramuscular administration, the onset of action is from seven to eight minutes and the duration of action is one to two hours.

Fentanyl plasma protein binding capacity increases with increasing ionisation of the drug.

Alterations in pH may affect its distribution between plasma and the central nervous system. It accumulates in skeletal muscle and fat, and is released slowly into the blood.

Fentanyl is primarily transformed in the liver and demonstrates a high first pass clearance with approximately 75% of an intravenous dose excreted in urine, primarily as metabolites with less than 10% representing the unchanged drug. Approximately 9% of the dose is recovered in the faeces, primarily as metabolites.
INDICATIONS

Short duration analgesia during pre-medication, induction and maintenance of anaesthesia, and in the immediate post-operative period.

Opioid analgesic supplement to general and regional anaesthesia.

Combination with a neuroleptic as an anaesthetic pre-medication for the induction of anaesthesia, and as an adjunct in the maintenance of general and regional anaesthesia.

CONTRAINDICATIONS

1. Known hypersensitivity or intolerance to fentanyl or other opioid analgesics.
2. Bronchial asthma
   (See also PRECAUTIONS)
3. Head injuries and increased intracranial pressure
   As for any opioid analgesic, fentanyl should not be used in patients susceptible to respiratory depression, such as comatose patients who may have head injuries or brain tumour (see also PRECAUTIONS). Fentanyl may obscure the clinical course of patients with head injury.
4. Concomitant MAO inhibitors
   Severe and unpredictable potentiation by MAO inhibitors has been reported with opioid analgesics and the use of fentanyl in patients who have received MAO inhibitors within 14 days is not recommended (see INTERACTIONS 3).
5. Myasthenia gravis
   Fentanyl may cause muscle rigidity upon IV administration. Therefore, the need for reversal with muscle relaxants contraindicates its use in patients with a history of myasthenia gravis.
6. Children two years of age or younger
   Safe conditions for use have not been established.
7. Use in patients after operative interventions in the biliary tract

PRECAUTIONS

1. ADEQUATE FACILITIES SHOULD BE AVAILABLE FOR POST-OPERATIVE MONITORING AND VENTILATION.

   RESUSCITATIVE EQUIPMENT, OXYGEN AND AN OPIOID ANTAGONIST SHOULD BE READILY AVAILABLE TO MANAGE APNOEA.

   FENTANYL SHOULD ONLY BE USED BY EXPERIENCED DOCTORS AND IN PATIENTS WHO ARE UNDER CONSTANT SUPERVISION.
2. **Concomitant neuroleptics**
   If fentanyl is administered with neuroleptics, the user should be familiar with the special properties of each drug, particularly with regard to durations of action. In addition, when such a combination is used, fluids and other countermeasures to manage hypotension should be available.

3. **Total opioid dose**
   As with other potent opioids, the respiratory depressant effect of fentanyl persists longer than the measured analgesic effect. The total dose of all opioid analgesics should be considered before additional opioid analgesics are given during recovery from anaesthesia. It is recommended that post-operative opioids, when required, should be used initially in reduced doses, as low as 1/4 to 1/3 of those usually recommended.

4. **Muscle rigidity**
   Fentanyl may cause muscle rigidity, particularly involving the muscles of respiration. This effect is related to the dose and speed of injection and may be reduced by slow intravenous injection. If this effect occurs, it may be managed by the use of assisted or controlled respiration and, if necessary, by administration of a neuromuscular blocking agent compatible with the patient's condition.

   Nonepileptic myoclonic movements can occur.

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

   Patients on chronic opioid therapy or with a history of opioid abuse may require higher doses to achieve an adequate therapeutic effect.

6. **Respiratory depression**
   Depression of respiration is the most marked and dangerous side effect of fentanyl. In the post-operative period, patients may exhibit delayed depression of respiration. Patients should be monitored for this possibility and appropriate countermeasures taken as necessary (see PRECAUTION 7).

7. **Impaired respiration**
   Fentanyl should be used with caution in patients with severe impairment of pulmonary function because of the possibility of respiratory depression (e.g. chronic obstructive pulmonary disease, patients with decreased respiratory reserve, or any patient with potentially compromised respiration).

   In such patients, opioids may further decrease respiratory drive and increase airway resistance. During anaesthesia, this can be managed by assisted or controlled respiration.

8. **Use of opioid antagonists for respiratory depression**
   Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists.
However, appropriate surveillance should be maintained because the duration of respiratory depression of doses of fentanyl employed during anaesthesia is usually longer than the duration of opioid antagonist action. Consult individual product information (nalorphine or naloxone) before employing opioid antagonists.

9. **Impaired liver and kidney function**
   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.

10. **Bradycardia**
    Fentanyl may produce bradycardia, and possibly asystole. Bradycardia may be treated with atropine; however, fentanyl should be used with caution in patients with cardiac bradyarrhythmias.

11. **Sphincter of Oddi Spasm**
    As has been observed with all opioid analgesics, episodes suggestive of sphincter of Oddi spasm may occur with fentanyl.

12. **Adjunct to conduction anaesthesia**
    Certain forms of conduction anaesthesia, such as spinal anaesthesia and some peridural anaesthetics, 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 anaesthesia, the anaesthetist should be familiar with the physiological alterations involved and be prepared to manage them in patients selected for these forms of anaesthesia.

13. **Monitoring**
    Vital signs should be monitored routinely.

14. **Elderly, debilitated patients**
    The initial fentanyl dose should be reduced in elderly and debilitated patients. Elderly patients may be more susceptible to adverse effects, such as respiratory depression and cardiovascular effects. They may also have age related kidney function impairment, resulting in lower clearance rates of fentanyl. 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 postoperative monitoring.

15. **Hypotension**
    Opioids may induce hypotension, particularly in hypovolaemic patients. Appropriate measures should be taken to maintain stable arterial pressure.
Use in Pregnancy  Category C

Opioid analgesics may cause respiratory depression in the newborn infant. These products should only be used during labour after weighing the needs of the mother against the risk to the foetus. If fentanyl is nevertheless administered, an antidote should always be at hand for the child. The safe use of fentanyl has not been established with respect to possible adverse effects upon foetal development. Therefore it should be used in women of childbearing potential only when in the judgement of the physician the potential benefits outweigh the possible hazards.

Withdrawal symptoms in newborn infants have been reported with prolonged use of opioids.

Use During Lactation

Fentanyl may enter the maternal milk. Therefore, breastfeeding is not recommended for 24 hours following the administration of this drug.

Use in Children

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

Interactions with Other Drugs

1. Other CNS depressants
   Other CNS depressant drugs, e.g. barbiturates, tranquilizers, benzodiazepines, alcohol, neuroleptics, opioids and general anaesthetics, 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 (see PRECAUTIONS).

2. Fentanyl/neuroleptic combination (see also ADVERSE REACTIONS)
   When a neuroleptic such as droperidol is used with fentanyl, pulmonary arterial pressure may be decreased. Hypotension can occur and, possibly, hypovolaemia (which should be managed with appropriate parenteral fluids).

   Repositioning of 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 together with other countermeasures do not correct hypotension, the administration of pressor agents other than adrenaline should be considered. Because of the α-adrenergic blocking action of droperidol, adrenaline 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.
3. **MAO inhibitors**
   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, the use of fentanyl in patients who have received monoamine oxidase inhibitors within 14 days is not recommended (see CONTRAINDICATIONS 4).

4. **Nitrous oxide**
   Nitrous oxide has been reported to produce cardiovascular depression when given with high doses of fentanyl.

5. **Amiodarone**
   Profound bradycardia, sinus arrest and hypotension have occurred when patients receiving amiodarone have been given fentanyl for anaesthesia.

6. **Adrenergic Blockers and Calcium Channel Blockers**
   The combination of calcium channel blockers and beta-adrenergic blockers during fentanyl anaesthesia should be used with caution since severe hypotension has been reported to occur.

Coadministration of the following drugs may enhance or prolong the effects of fentanyl: azole antifungals, macrolide antibiotics and protease inhibitors such as Ritonavir.

Coadministration of the following drugs may decrease the plasma concentration of fentanyl: phenytoin.

Coadministration of sibutramine hydrochloride with fentanyl may increase the risk of serotonin syndrome (hypertension, hypothermia, myoclonus and mental status changes).

The concurrent administration of fentanyl and naltrexone precipitates opioid withdrawal symptoms.

**ADVERSE EFFECTS**

**More common**
Respiratory depression, apnoea, muscular rigidity, myclonic movements and bradycardia, tachycardia, vein pain, dermatitis allergic.

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; it rarely occurs with intramuscular administration. If respiratory depression occurs during anaesthesia, assisted or controlled respiration will provide adequate ventilation without reversing analgesia. Respiratory depression can be immediately reversed by opioid antagonists (e.g. nalorphine) which, it should be noted, will also reverse analgesia. Secondary rebound respiratory depression has been observed after the operation in rare instances.
Muscular rigidity may be associated with reduced pulmonary compliance and/or apnoea, laryngospasm or bronchospasm. Prompt reversal of this effect can be achieved with the intravenous administration of an appropriate single dose of a muscle relaxant such as suxamethonium. 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 the 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.

Less common
Hypotension, hypertension, dizziness, blurred vision, miosis, nausea, emesis, laryngospasm, diaphoresis, itching, euphoria, seizures, spasm of the sphincter of Oddi, anaphylaxis, headache, loss of consciousness, myoclonus, phlebitis, hyperventilation, hiccups, hypothermia, airway complications of anaesthesia, agitation postoperative. Motor stimulation and bronchospasm may occur with high doses of fentanyl. Less frequently, cardiac arrhythmias, postoperative mental depression, paradoxical CNS excitation or delirium may occur.

Fentanyl/neuroleptic combination
When a neuroleptic such as droperidol is used with fentanyl, the following adverse reactions can occur: chills and/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 anaesthesia.

DOSAGE AND ADMINISTRATION

Dosage should be individualised according to age, bodyweight, physical status, underlying pathological condition, use of other drugs, type of anaesthesia to be used and the surgical procedure involved (see also PRECAUTIONS). Fentanyl injection contains no antimicrobial agent. It should be used only once and any residue discarded.

Adults:
Premedication (To be appropriately modified in the elderly, debilitated and those who receive other depressant drugs): 50 to 100 µg (1 to 2 mL) may be administered intramuscularly 30 to 60 minutes prior to surgery.

Adjunct to general anaesthesia
Induction: 50 to 100 µg (1 to 2 mL) IV initially, repeat at two to three minute intervals until desired effect is achieved. A reduced dose of 25 to 50 µg (0.5 to 1 mL) is recommended in elderly and poor risk patients.
Maintenance
25 to 50 µg (0.5 to 1 mL) IV or IM, when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia.

Adjunct to regional anaesthesia
50 to 100 µg (1 to 2 mL) may be administered IM or slowly IV when additional analgesia is required.

Postoperatively (recovery room)
50 to 100 µg (1 to 2 mL) may be administered IM for the control of pain, tachypnoea and emergence delirium. The dose may be repeated in one or two hours as needed.

Children:
For induction and maintenance in children 2 to 12 years of age, a reduced dose of 20 to 30 µg (0.4 to 0.6 mL) per 10 kg is recommended.

Impaired renal function
Fentanyl should be used with caution.

Impaired hepatic function
Fentanyl should be used with caution.

Incompatibilities
Fentanyl is incompatible with thiopentone sodium and methohexitone sodium.

OVERDOSAGE

Symptoms
Narcosis (which may be preceded by marked skeletal muscle rigidity), cardiorespiratory depression accompanied by cyanosis, followed by a fall in body temperature, circulatory collapse, coma and possibly death.

Treatment
In the presence of hypoventilation or apnoea, oxygen should be administered and respiration assisted or controlled as necessary. A patent airway must be maintained.

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 severe or persistent hypotension occurs, the possibility of hypovolaemia should be considered and managed with appropriate parenteral fluid therapy.
A specific opioid antagonist, such as nalorphine 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 is usually longer than the duration of opioid antagonist action.

PRESENTATIONS AND STORAGE CONDITIONS

Fentanyl citrate 50 µg/mL in Polyamp DuoFit®: 10 x 2 mL and 10 x 10 mL

The 2mL Polyamp® presentation should be stored below 25°C.
The 10mL Polyamp® presentation should be stored below 30°C.

NAME AND ADDRESS OF THE SPONSOR

AstraZeneca Pty Ltd
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POISON SCHEDULE OF THE MEDICINE

Controlled Drug (S8)

Date of TGA approval: 9 November 1995
Date of most recent amendment: 8 September 2011

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