

PRODUCT MONOGRAPH

^NSUFENTA*

Sufentanil Citrate Injection, House Std.

Opioid Analgesic

Adjunct to Anaesthesia

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CLINICAL PHARMACOLOGY

SUFENTA sufentanil citrate is an opioid analgesic. The analgesic potency of sufentanil is approximately 5 to 7 times that of fentanyl. Dosage requirements for equianalgesic effect will be 1/5 to 1/7 those of fentanyl on a $\mu\text{g}/\text{kg}$ basis.

Assays of histamine in patients administered SUFENTA sufentanil citrate have shown no elevation in plasma histamine levels and no indication of histamine release.

Intravenous Use

At intravenous doses of up to $8 \mu\text{g}/\text{kg}$, sufentanil provides profound analgesia; at doses $\geq 8 \mu\text{g}/\text{kg}$, sufentanil produces a deep level of anaesthesia. Sufentanil produces a dose-related attenuation of catecholamine release, particularly norepinephrine.

Intravenous SUFENTA sufentanil citrate has an immediate onset of action, with a distribution of 0.72 minutes, redistribution of 13.7 minutes and an elimination half-life of 148 minutes. It is rapidly and extensively metabolized into a large number of inactive metabolites that are excreted with the urine and feces. The liver and small intestine are the major sites of biotransformation; oxidative O- and N-dealkylation are the primary metabolic pathways. Approximately 80% of the administered dose is excreted within 24 hours and only 2% of the dose is eliminated as unchanged drug. Plasma protein binding of sufentanil is approximately 92.5%.

The pharmacokinetics of intravenous sufentanil can be described as a three-compartment model, with relatively limited accumulation and rapid elimination from tissue storage sites, allowing for relatively more rapid recovery than with fentanyl.

At intravenous dosages of $\geq 8 \mu\text{g}/\text{kg}$, SUFENTA sufentanil citrate produces hypnosis and anaesthesia without the use of additional anaesthetic induction agents. A deep level of anaesthesia is maintained at these dosages, as demonstrated by EEG patterns. Dosages of up to $25 \mu\text{g}/\text{kg}$ attenuate the sympathetic response to surgical stress and maintain cardiovascular stability. The sympathetic response is blocked at doses of sufentanil of $25\text{-}30 \mu\text{g}/\text{kg}$, with dependable cardiovascular stability, infrequent bradycardia and preservation of myocardial oxygen balance.

Pancuronium may produce a dose-dependent elevation in heart rate and blood pressure during SUFENTA sufentanil citrate-oxygen anaesthesia that is not suppressed by the minimal effects of high doses of sufentanil on cardiac function, heart rate or blood pressure. The vagolytic effect of pancuronium may be reduced in patients administered nitrous oxide together with sufentanil. The use of moderate doses of pancuronium or of a less vagolytic neuromuscular blocking agent should maintain stable lower heart rate and blood pressure.

In patients administered high doses of SUFENTA sufentanil citrate, dosage requirements for neuromuscular blocking agents are generally lower as compared to patients given fentanyl or halothane, and comparable to patients given enflurane or isoflurane.

Bradycardia is seen infrequently in patients administered SUFENTA sufentanil citrate-oxygen anaesthesia. The use of nitrous oxide with high doses of sufentanil may decrease mean arterial pressure, heart rate and cardiac output.

In one study of patients undergoing craniotomy, SUFENTA sufentanil citrate at $20 \mu\text{g}/\text{kg}$ has been shown to provide more adequate reduction in intracranial volume than equivalent doses of fentanyl, based upon requirements for furosemide and anaesthesia supplementation. During carotid endarterectomy, sufentanil produced EEG patterns and reductions in cerebral blood flow and oxygen utilization comparable to those of fentanyl.

The intraoperative use of SUFENTA sufentanil citrate at anaesthetic dosages maintains cardiac output, with a slight reduction in systemic vascular resistance during the initial postoperative period. Requirements for postoperative analgesics are generally reduced in patients administered moderate or high doses of sufentanil as compared to patients given inhalation agents.

Decreased respiratory drive and increased airway resistance occur with increased SUFENTA doses. The duration and degree of respiratory depression are dose-related when sufentanil is used at subanaesthetic dosages. At high doses, a pronounced decrease in pulmonary exchange and apnea may be produced.

Epidural Use

Epidural SUFENTA sufentanil citrate produces spinal analgesia of rapid onset (within 5-10 minutes) and moderate duration (generally 4-6 hours). The onset and duration of analgesia appear to be dose-related.

Peak plasma concentrations following single epidural doses of SUFENTA sufentanil citrate are reached within 10 minutes and are 4-6 times lower than those after intravenous administration. Systemic absorption within the first 3 hours after epidural administration is approximately 1/3-1/2 that of an intravenous bolus. Vascular uptake of sufentanil after high thoracic (T3-4) administration is 3-4 times lower than after mid-thoracic to lumbar epidural injection. Coadministration of epinephrine reduces systemic availability of sufentanil, especially in the first hours after injection. Time to peak plasma concentrations and maximum plasma concentrations increase with repeated epidural doses of SUFENTA sufentanil citrate.

Mean sufentanil concentrations in CSF exceeded 2 ng/mL within a few minutes after an epidural injection of 75 µg; peak concentrations in the CSF occurred within 5-90 minutes. Thereafter, the decay of sufentanil concentrations in the CSF was biphasic with an average sufentanil terminal half-life of 165 minutes compared to 355 minutes in plasma.

During labour and vaginal delivery, the addition of 10-30 µg sufentanil to bupivacaine (0.125%-0.25%) provided analgesia of better quality and longer duration versus bupivacaine (0.25%) alone. Apgar scores and neurobehavioural scores of neonates were not affected by the epidural administration of sufentanil to women in labour.

Placental transfer of sufentanil was investigated in women undergoing caesarean section. Within 30-55 minutes of epidural doses of 22-38 µg sufentanil, maternal plasma concentrations varied from ≤0.02-0.16 ng/mL; neonatal concentrations were generally below 0.02 ng/mL with measurable levels up to 0.9 ng/mL found in only a few neonates. Fetal plasma concentrations rapidly equilibrate with maternal concentrations. Individual umbilical vein to maternal plasma concentration ratios averaged 0.4. Plasma protein binding of sufentanil, related to the α₁ acid glycoprotein level, was 90.7% in mothers and 79.3% in neonates.

INDICATIONS AND CLINICAL USE

SUFENTA sufentanil citrate is indicated for intravenous administration:

- as a primary anaesthetic agent for the induction and maintenance of anaesthesia with 100% oxygen in patients undergoing major surgical procedures, such as cardiovascular surgery or neurosurgical procedures in the sitting position, for whom myocardial or cerebral oxygen imbalance would be particularly detrimental or for whom extended postoperative ventilation is anticipated.
- as an analgesic adjunct at doses up to 8 $\mu\text{g}/\text{kg}$ in the maintenance of balanced general anaesthesia for major surgical procedures.

SUFENTA sufentanil citrate is indicated for epidural administration:

- for the postoperative management of pain following general surgery, thoracic or orthopedic procedures and caesarean section.
- as an analgesic adjunct to epidural bupivacaine during labour and vaginal delivery.

CONTRAINDICATIONS

SUFENTA sufentanil citrate is contraindicated in patients with known hypersensitivity to fentanyl or to other morphinomimetics.

Intravenous use in labour, or before clamping of the cord during caesarean section is not recommended due to the possibility of respiratory depression in the newborn infant. This is in contrast to the epidural use in labour, during which sufentanil in doses up to 30 μg does not influence the condition of the mother or the newborn.

As with other opiates administered epidurally, SUFENTA sufentanil citrate should not be given to patients exhibiting the following:

- severe hemorrhage or shock;
- septicemia;
- local infection at the site of proposed puncture;
- disturbances in blood morphology and/or anticoagulant therapy or other concomitant drug therapy or medical conditions which could contraindicate the technique of epidural administration.

WARNINGS

SUFENTA SUFENTANIL CITRATE SHOULD BE ADMINISTERED ONLY BY PERSONS SPECIFICALLY TRAINED IN THE USE OF INTRAVENOUS ANAESTHETICS AND MANAGEMENT OF THE RESPIRATORY EFFECTS OF POTENT OPIOIDS AND, WHEN ADMINISTERED EPIDURALLY, PERSONS SPECIFICALLY TRAINED IN THE TECHNIQUES AND PATIENT MANAGEMENT ASSOCIATED WITH EPIDURAL ADMINISTRATION.

COMPLETE RESUSCITATION EQUIPMENT AND AN OPIOID ANTAGONIST SHOULD BE READILY AVAILABLE WHENEVER SUFENTANIL IS USED.

Intravenous administration or inadvertent intravascular injection during epidural administration of SUFENTA sufentanil citrate may cause skeletal muscle rigidity, particularly of the truncal muscles. The incidence of muscular rigidity associated with intravenous SUFENTA sufentanil citrate can be reduced by:

- 1) administration of up to 1/4 of the full paralyzing dose of a non-depolarizing neuromuscular blocking agent just prior to administration of SUFENTA sufentanil citrate at dosages of up to 8 $\mu\text{g}/\text{kg}$;
- 2) incremental administration in divided doses of a full paralyzing dose of neuromuscular blocking agent following loss of the eyelash reflex during induction with thiopental when sufentanil has been used in doses up to 8 $\mu\text{g}/\text{kg}$ in major surgical procedures;
- 3) simultaneous administration of SUFENTA sufentanil citrate and a full paralyzing dose of a neuromuscular blocking agent when SUFENTA sufentanil citrate is used in anaesthetic doses (above 8 $\mu\text{g}/\text{kg}$).

The neuromuscular blocking agent used should be compatible with the patient's cardiovascular status. Adequate facilities should be available for postoperative monitoring and ventilation of patients administered anaesthetic doses of SUFENTA sufentanil citrate. It is essential that these facilities be fully equipped to handle all degrees of respiratory depression. Dosages above 1 $\mu\text{g}/\text{kg}$ sufentanil per hour of surgery frequently produce respiratory depression. In a clinical study involving 616 patients, 69 of the 86 patients (80%) who required naloxone in the immediate postoperative period had received a sufentanil dosage in excess of 1 $\mu\text{g}/\text{kg}$ per hour.

Non-epileptic (myo)clonic movements can occur.

PRECAUTIONS

General

The initial dose of SUFENTA sufentanil citrate should be appropriately reduced in elderly and debilitated patients. The effect of the initial dose should be considered in determining supplemental doses.

Vital signs should be monitored routinely.

Nitrous oxide may produce cardiovascular depression when given with high doses of SUFENTA sufentanil citrate (see CLINICAL PHARMACOLOGY).

High doses of pancuronium may produce increases in heart rate during SUFENTA sufentanil citrate-oxygen anaesthesia. Bradycardia and possibly asystole can occur if the patient has received an insufficient amount of anticholinergic or when SUFENTA sufentanil citrate is combined with non-vagolytic muscle relaxants. Bradycardia can be treated with atropine.

Head Injuries

SUFENTA sufentanil citrate may obscure the clinical course of patients with head injuries.

In patients with compromised intracerebral compliance, the use of rapid bolus injections should be avoided; in such patients the transient decrease in mean arterial pressure has occasionally been accompanied by a short-lasting reduction of the cerebral perfusion pressure.

Impaired Respiration

SUFENTA sufentanil citrate should be used with caution in patients with pulmonary disease, decreased respiratory reserve or potentially compromised respiration. In such patients, opioids may additionally decrease respiratory drive and increase airway resistance.

During anaesthesia, impaired respiration can be managed by assisted or controlled respiration. As with all potent opioids, profound analgesia is accompanied by respiratory depression and diminished sensitivity to CO₂ stimulation which may persist into or recur in the postoperative period. Appropriate postoperative monitoring should be employed to ensure that adequate spontaneous breathing is established and maintained prior to patient discharge from the recovery area.

Respiratory depression caused by opioid analgesics can be reversed by opioid antagonists such as naloxone. Because the duration of respiratory depression produced by SUFENTA sufentanil citrate may last longer than the duration of the opioid antagonist action, appropriate surveillance should be maintained.

Patients should be closely monitored for at least 2 hours following each administration of an epidural injection of SUFENTA sufentanil citrate as respiratory depression may occur.

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

Patients on chronic opioid therapy or with a history of narcotic abuse may require increased amounts of sufentanil.

Careful titration of dosage may be required in patients with conditions such as uncontrolled hypothyroidism or alcoholism (see DRUG INTERACTIONS; alcohol can potentiate the respiratory depression of narcotics). In such cases, prolonged postoperative monitoring is required.

Drug Interactions

Cytochrome P450 3A4 Enzyme Inhibitors

Sufentanil is metabolized mainly via the human cytochrome P450 3A4 enzyme. However, no *in vivo* inhibition by erythromycin (a known cytochrome P450 3A4 enzyme inhibitor) has been observed. Although clinical data are lacking, *in vitro* data suggest that other potent cytochrome P450 3A4 enzyme inhibitors (e.g. ketoconazole, itraconazole, ritonavir) may inhibit the metabolism of sufentanil. This could increase the risk of prolonged or delayed respiratory depression. The concomitant use of such drugs requires special patient care and observation; in particular, it may be necessary to lower the dose of SUFENTA sufentanil citrate.

Interaction with Other Central Nervous System Depressants

An additive effect with SUFENTA sufentanil citrate may be exhibited in patients receiving barbiturates, tranquilizers, opioids, general anaesthetics or other CNS depressants (e.g. alcohol). In such cases of combined treatment, the dose of SUFENTA sufentanil citrate and/or these agents should be reduced.

MAO Inhibitors

It is usually recommended to discontinue MAO inhibitors 2 weeks prior to any surgical or anaesthetic procedure.

Interaction with Beta-Blockers

As with all opioids, a decrease in heart rate and/or blood pressure may be seen when sufentanil is administered to patients who are on beta-blocker medication.

Impaired Hepatic or Renal Function

In patients with liver or kidney dysfunction, SUFENTA sufentanil citrate should be administered with caution due to the importance of these organs in the metabolism and excretion of SUFENTA sufentanil citrate.

Use in Pregnancy

SUFENTA sufentanil citrate has been shown to have an embryocidal effect in rats and rabbits when given in doses 2.5 times the upper human dose for a period of 10 days to over 30 days. These effects were probably due to maternal toxicity (decreased food consumption with increased mortality) following prolonged administration of the drug. No evidence of teratogenic effects have been observed after administration of SUFENTA sufentanil citrate in rats or rabbits. Since the safety of SUFENTA sufentanil citrate in pregnant women has not been established, this drug should be used in pregnancy only if the expected benefits are considered to outweigh any potential risks.

Labour and Delivery

Although the use of epidurally administered SUFENTA sufentanil citrate is indicated for labour and delivery (see INDICATIONS AND CLINICAL USE and DOSAGE AND ADMINISTRATION), caution should be exercised in the presence of fetal distress. The use of intravenous SUFENTA sufentanil citrate in labour and delivery is not recommended (see CONTRAINDICATIONS).

Nursing Mothers

It is not known whether this drug is excreted in human milk. Because fentanyl analogues are excreted in human milk, caution should be exercised when SUFENTA sufentanil citrate is administered to a nursing woman.

Pediatric Use

The safety and efficacy of intravenous SUFENTA sufentanil citrate in children, particularly under 2 years of age, has been documented only in a limited number of cases. Likewise, documented use of epidural SUFENTA sufentanil citrate in pediatric cases is limited.

Drug Abuse and Dependence

Sufentanil can produce drug dependence of the morphine type and, therefore, has the potential for being abused.

Effects on Driving Ability and Use of Machinery

Patients should be advised to allow sufficient time to elapse before operating a car or heavy machinery.

ADVERSE REACTIONS

Intravenous Use

The most frequent adverse reactions in 320 patients administered SUFENTA sufentanil citrate intravenously were:

- hypotension (7%);
- hypertension (3%);
- chest wall rigidity (3%);
- bradycardia (3%).

Other adverse reactions that may occur (reported incidence of less than 1%) are:

- cardiovascular: tachycardia, arrhythmia;
- gastrointestinal: nausea, vomiting;
- respiratory: apnea, postoperative respiratory depression, bronchospasm;
- dermatological: itching;
- central nervous system: chills;
- miscellaneous: intraoperative muscle movement.

Postmarketing adverse reports include: laryngospasm, dizziness, myoclonic movements and respiratory depression.

Allergic reactions and asystole have been reported; but since several drugs were coadministered during anaesthesia, it is uncertain whether there is a causal relationship to the drug.

Epidural Use

The frequency of adverse experiences associated with the use of epidural SUFENTA sufentanil citrate was evaluated in 1,478 postoperative patients and 14,467 parturients. The most frequently reported adverse experiences were somnolence or sedation, pruritus, nausea, vomiting and urinary retention.

During clinical trials, slow respiratory rate (<10 breaths/min) and apneic periods were noted in 3.5% and 2.5% of postoperative patients, respectively. These episodes developed early after drug administration and were resolved within 1 hour. Concomitant use of epinephrine may reduce the incidence and severity of respiratory depression. No respiratory depressive episodes were observed in patients receiving epidural SUFENTA sufentanil citrate during labour and delivery.

Other observed adverse experiences include:

- cardiovascular: hypotension (2%);
- central nervous system: motor block (18%, labour patients only), dizziness (2%), euphoria (2%);
- urinary system disorders: urinary incontinence (1%);
- miscellaneous: fever (1%), shivering (2%), pain at injection site (1%), miosis (1%).

Adverse experiences that occurred in less than 1% of patients are:

- bradycardia, hypopnea, rash, headache, confusion.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Symptoms

Overdosage would be manifested by an extension of the pharmacological actions of SUFENTA sufentanil citrate (see CLINICAL PHARMACOLOGY) as with other potent opioid analgesics. Depending on the individual sensitivity, the clinical picture is determined primarily by the degree of respiratory depression, which varies from bradypnea to apnea.

The intravenous LD₅₀ of sufentanil in male rats is 12.5 mg/kg.

Treatment

Intravenous administration of an opioid antagonist such as naloxone should be employed as a specific antidote to manage respiratory depression. The duration of respiratory depression following overdosage with sufentanil may be longer than the duration of action of the opioid antagonist; additional doses of the latter may therefore be required.

Administration of an opioid antagonist should not preclude more immediate countermeasures. In the event of overdose, oxygen should be administered and ventilation assisted or controlled as indicated for hypoventilation or apnea. A patent airway must be maintained, and a nasopharyngeal airway or endotracheal tube may be indicated. If depressed respiration is associated with muscular rigidity, a neuromuscular blocking agent may be required to facilitate assisted or controlled respiration. Intravenous fluids and vasopressors for the treatment of hypotension and other supportive measures may be employed.

DOSAGE AND ADMINISTRATION

The dosage of SUFENTA sufentanil citrate should be individualized in each case according to body weight, physical status, underlying pathological condition, use of other drugs and type of surgical procedure and anaesthesia. In obese patients (more than 20% above ideal total body weight), the dosage of SUFENTA sufentanil citrate should be determined on the basis of lean body weight. Dosage should be reduced in elderly and debilitated patients (see PRECAUTIONS).

Vital signs should be monitored routinely.

Intravenous Use

See dosage range chart for the use of SUFENTA sufentanil citrate by intravenous injection:

- 1) in doses of up to 8 $\mu\text{g}/\text{kg}$ as an analgesic adjunct to general anaesthesia;
- 2) in doses $\geq 8 \mu\text{g}/\text{kg}$ as a primary anaesthetic agent for induction and maintenance of anaesthesia with 100% oxygen.

Usage in Children

For induction and maintenance of anaesthesia in children less than 12 years of age undergoing cardiovascular surgery, an anaesthetic dose of 10-25 $\mu\text{g}/\text{kg}$ administered with 100% oxygen is generally recommended. Supplemental dosages of 25-50 μg are recommended for maintenance based on response to initial dose and as determined by changes in vital signs indicating surgical stress or lightening of anaesthesia. Since experience with the use of SUFENTA sufentanil citrate, particularly in the young age group, is limited, anaesthetists should be guided by progressive experience with the use of the drug in children.

Premedication

The selection of preanaesthetic medications should be based upon the needs of the individual patient.

Neuromuscular Blocking Agents

The neuromuscular blocking agent selected should be compatible with the patient's condition, taking into account the hemodynamic effects of a particular muscle relaxant and the degree of skeletal muscle relaxation required (see CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS).

In patients administered high (anaesthetic) doses of SUFENTA sufentanil citrate, it is essential that qualified personnel and adequate facilities are available for the management of postoperative respiratory depression (see WARNINGS and PRECAUTIONS).

Epidural Use

Proper placement of the needle or catheter in the epidural space should be verified prior to SUFENTA injection to preclude inadvertent intravascular or intrathecal administration. If analgesia is inadequate, the placement and integrity of the catheter should be verified prior to the administration of any additional epidural medication.

Postoperative Management of Pain

An initial dose of 30-60 μg SUFENTA sufentanil citrate may be expected to provide adequate pain relief for up to 4-6 hours. Additional boluses of up to 25 μg SUFENTA sufentanil citrate may be administered at not less than one-hour intervals if there is evidence of lightening of analgesia.

Analgesic Adjunct During Labour and Delivery

The recommended initial dose for SUFENTA sufentanil citrate, administered with 0.125%-0.25% bupivacaine, is 10 μg . If required, two subsequent injections of the combination may be given; supplemental doses should be separated by intervals of at least one hour. It is recommended that the total sufentanil dose administered not exceed 30 μg .

ADULT DOSAGE RANGE CHART - INTRAVENOUS USE
See chart below.

ADMINISTRATION WITH NITROUS OXIDE/OXYGEN				
INDICATION	APPROXIMATE DURATION OF ANAESTHESIA	INITIAL DOSE	MAINTENANCE INCREMENTS (included in total dosage)	TOTAL DOSAGE (A cumulative dosage in the range of 0.5-1.0 $\mu\text{g}/\text{kg}$ per hour is recommended.)
AS AN ADJUNCT TO MAJOR SURGERY	at least one hour	A minimum of 0.5 $\mu\text{g}/\text{kg}$ is necessary to control or abolish cardiovascular responses to laryngoscopy and intubation. The initial dosage should represent at least 75% of the total dosage administered during the case.	10-25 μg as needed when movement and/or changes in vital signs indicate surgical stress or lightening of analgesia. Supplemental doses should be individualized and adjusted to the remaining operative time anticipated.	0.5-2 $\mu\text{g}/\text{kg}$ administered as an analgesic adjunct with nitrous oxide/oxygen in patients undergoing general surgery in which endotracheal intubation and mechanical ventilation are required.
AS AN ADJUNCT TO MORE COMPLICATED MAJOR SURGERY	at least two hours		25-50 μg as determined by changes in vital signs that indicate stress or lightening of analgesia. Supplemental dosages should be individualized and adjusted to the remaining operative time anticipated.	2-8 $\mu\text{g}/\text{kg}$ administered as an analgesic adjunct with nitrous oxide/oxygen in patients undergoing more complicated major surgical procedures. At dosages in this range, SUFENTA sufentanil citrate has been shown to attenuate sympathetic reflex activity in response to surgical stimuli, maintain cardiovascular stability and provide relatively rapid recovery.
ADMINISTRATION WITH 100% OXYGEN				
INDICATION	INITIAL DOSE		MAINTENANCE INCREMENTS (included in total dosage)	TOTAL DOSAGE
AS A PRIMARY ANAESTHETIC AGENT	The initial dose should be individualized with due consideration given to patient status, concomitant medications and anticipated level of surgical stimulation. See total dosage guidelines.		25-50 μg as determined by changes in vital signs that indicate stress and lightening of anaesthesia.	8-30 $\mu\text{g}/\text{kg}$ (anaesthetic doses) administered with 100% oxygen and a muscle relaxant. SUFENTA sufentanil citrate has been found to produce sleep at dosages $\geq 8 \mu\text{g}/\text{kg}$ and to maintain a deep level of anaesthesia without the use of additional anaesthetic agents. At dosages in this range of up to 25 $\mu\text{g}/\text{kg}$, catecholamine release is attenuated. High doses are indicated in patients undergoing surgical procedures such as cardiovascular surgery and neurosurgery in the sitting position, in whom myocardial or cerebral oxygen imbalance would be detrimental. Postoperative mechanical ventilation and observation are essential at these dosages due to extended postoperative respiratory depression.

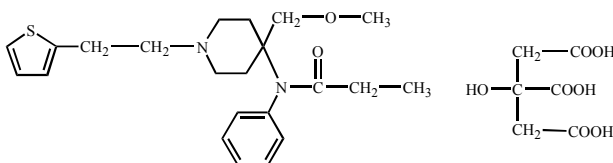
NOTE: The suggested intravenous administration rate for SUFENTA sufentanil citrate is 250-300 $\mu\text{g}/\text{minute}$.

PHARMACEUTICAL INFORMATION**Drug Substance**

Common Name: sufentanil citrate

Chemical Name: N-[4-(methoxymethyl)-1-[2-(2-thienyl)ethyl]-4-piperidiny]-N-phenylpropanamide 2-hydroxy-1,2,3-propanetricarboxylate (1:1)

Structural Formula:



Molecular Formula: $C_{22}H_{30}N_2O_2S \cdot C_6H_8O_7$

Molecular Weight: 578.68

Description: Sufentanil citrate is a white to slightly yellowish powder with a melting range of 133°C-140°C and a pKa of 8.01. It is freely soluble in methanol, soluble in water and sparingly soluble in ethanol. The log partition coefficient (n-octanol/aqueous buffer solution at pH 10.8) is 3.95.

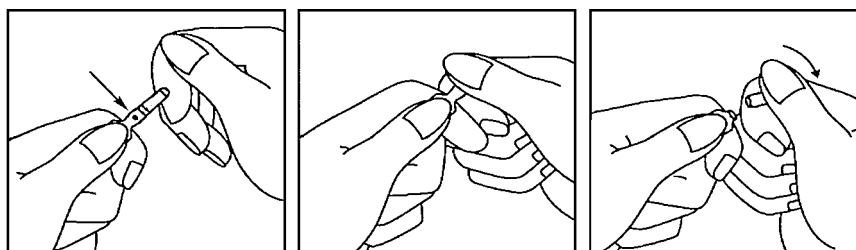
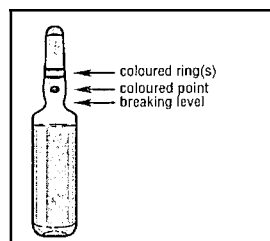
Composition

SUFENTA sufentanil citrate injection is a sterile, preservative-free, isotonic, aqueous solution. The solution contains sufentanil citrate equivalent to 50 μ g of sufentanil base per mL, sodium chloride and water for injection. SUFENTA sufentanil citrate has a pH range of 4.5 - 7.0.

Instructions for use/handling

1. Maintain the ampoule between thumb and index, leaving the tip of the ampoule free.
2. With the other hand, hold the tip of ampoule putting the index against the neck of ampoule, and the thumb on the coloured point in parallel to the identification coloured ring(s).

3. Keeping the thumb on the point, sharply break the tip of ampoule while holding firmly the other part of the ampoule in the hand.



Stability and Storage Recommendations

SUFENTA ampoules should be stored at controlled room temperature (15-30°C). Protect from light.

Incompatibilities

SUFENTA is an injectable solution and must not be mixed with other products. If desired, SUFENTA may be mixed with sodium chloride or glucose intravenous infusions. Such dilutions are compatible with plastic infusion sets, they should be used within 24 hours of preparation.

AVAILABILITY OF DOSAGE FORMS

SUFENTA sufentanil citrate is a colourless, sterile, preservative-free, isotonic, aqueous solution containing sufentanil citrate equivalent to 50 µg per mL of sufentanil base for intravenous and epidural injection. It is supplied in 1 mL and 5 mL ampoules. For packaging configurations, please consult published price list.

PHARMACOLOGY

Analgesic Activity

The narcotic analgesic effect of intravenous sufentanil has been studied in mice, rats and dogs. In mice, sufentanil had in the hot plate test an ED₅₀ of 0.0028 mg/kg, compared to an ED₅₀ of 0.026 mg/kg for fentanyl and 6.45 mg/kg for morphine. In rats, the ED₅₀ on the tail withdrawal test is 0.00071 mg/kg. Sufentanil was found to be 4,520 times more potent than morphine and 16 times more potent than fentanyl. In dogs, the minimal effective analgesic dose, defined as the dose needed to intubate an awake, unpremedicated dog without producing heart rate or blood pressure changes, was 0.00025 mg/kg for sufentanil, 0.012 mg/kg for fentanyl, 0.15 mg/kg for morphine and 0.45 mg/kg for meperidine. Sufentanil was 1,875 times more potent than meperidine, 625 times more potent than morphine and 5 times more potent than fentanyl.

The analgesic effect of epidural sufentanil has been studied in a variety of species. In rats, the ED₅₀ on the tail withdrawal test was 0.26 and 0.59 µg/rat for significant and surgical analgesia, respectively. Sufentanil was >30 times more active than morphine after epidural administration. In guinea pigs, the epidural morphine:fentanyl:sufentanil potency ratio was 1:3:20 for threshold electric current that evoked a vocalization response. An epidural dose of 2.5 µg sufentanil suppressed the noxiously evoked activity of wide-dynamic-range neurons for more than 2 hours in cats.

In rats, the analgesic potency of epidural sufentanil was comparable to intravenous and intrathecal but 3 times more potent than subcutaneous sufentanil. The order of onset of analgesia was intrathecal > epidural > subcutaneous sufentanil. For the dissociation from central behavioural effects, especially blockade of the pinna reflex, the epidural route produced a greater selectivity than the other routes.

After repeated epidural sufentanil administration to rats and dogs, tolerance was observed to develop to the analgesic and behavioural effects of sufentanil.

Cardiovascular and Respiratory Effects

Sufentanil was administered to awake, unsedated, nonventilated dogs in increasing dosages from 0.16-10 $\mu\text{g}/\text{kg}$. Sufentanil produced dose-related decreases in heart rate up to 5 $\mu\text{g}/\text{kg}$. No further decrease was seen at 10 $\mu\text{g}/\text{kg}$. Diastolic aortic blood pressure decreased significantly after the injection of 0.32 $\mu\text{g}/\text{kg}$ and respiratory rate decreased after 2.5 $\mu\text{g}/\text{kg}$. Arterial pO_2 decreased following 5 and 10 $\mu\text{g}/\text{kg}$ and arterial pCO_2 increased from 0.16 $\mu\text{g}/\text{kg}$ reflecting respiratory depressant activity.

Starting at 2.5 $\mu\text{g}/\text{kg}$, AV dissociations and ventricular extrasystoles were observed in several dogs. Doses of 1.2 $\mu\text{g}/\text{kg}$ and higher induced metabolic acidosis. Salivation and convulsions were observed after 5 and 10 $\mu\text{g}/\text{kg}$. The effects of sufentanil on peripheral circulation were studied in mongrel dogs. Sufentanil produced a slight decrease in skeletal muscle surface pH, and a decrease in mixed venous arterial pH, whereas morphine produced a prompt and highly significant decrease in muscle pH and a 20% decrease in calculated blood volume. No adverse effects were noted for sufentanil or morphine following propranolol-induced beta-blockade. In propranolol-sufentanil treated dogs, peripheral perfusion was adequate, with only a minor decrease in muscle pH and mixed venous pH, similar to that noted in animals treated with sufentanil alone. In comparison, propranolol-morphine treated animals showed severe impairment of peripheral perfusion.

At analgesic doses in rats, epidural sufentanil produces no detectable effects on respiration. Epidural sufentanil was associated with early respiratory depression at 4 times the analgesic dose. In contrast, late respiratory depression was measured up to 7 hours after injection with morphine. The effects of epidural sufentanil and morphine on respiration was further evaluated in rats by whole body plethysmography, measuring tidal volume and frequency of breathing in rats exposed to 8% CO_2 . The dose at which compounds reduce the minute volume of respiration by 25% (ID_{25}) was compared with the dose for significant analgesia (ED_{50} for a TWR latency >6.0 sec). A 133-fold difference between ID_{25} and ED_{50} was observed for morphine; whereas for sufentanil the difference was 12.

Cardiovascular Effects of High-dose Sufentanil

The early (30 minutes) hemodynamic effects of high doses of i.v. sufentanil 0.01 mg/kg and i.v. morphine 4 mg/kg have been investigated in mongrel dogs ventilated with 50% N₂O/50% O₂. Results are summarized below:

Sufentanil

Moderate, insignificant decrease in mean arterial pressure (MAP).

30% decrease in cardiac index (CI) due to more than 50% decrease in heart rate (HR) - partly compensated for by increased stroke volume index (SVI).

Central venous pressure (CVP) and pulmonary capillary wedge pressure (PCWP) increased immediately (returned to control with time).

Peak left ventricular dP/dt decreased 20-50% (both groups).

Rate-pressure product (RPP) decreased to less than 50% of control values (both groups).

Mixed venous oxygen tension (PvO₂), O₂ transport and consumption significantly decreased.

Morphine

During the first 5 min MAP fell to below 50% of the control value.

CI was reduced to 50% of control due to significant decreases in HR and SVI; calculated SVR I was unchanged.

Within 30 minutes, some of the above changes returned to control levels.

CVP and PCWP decreased (returned to control with time).

PvO₂, O₂ transport and consumption immediately decreased but gradually returned toward control values.

The authors concluded that apart from initial, transient changes, sufentanil provided stable cardiovascular dynamics. Morphine was characterized by changes in several hemodynamic parameters.

Cardiovascular Effects of High-dose Sufentanil in Propranolol-treated Dogs

The immediate cardiovascular effects of sufentanil 0.01 mg/kg and morphine 4 mg/kg in dogs pretreated with 2 mg/kg propranolol were compared. Their study was based upon the recommended use of high-dose analgesic anaesthesia for high-risk patients, many of whom were being treated with beta-blockers. Sudden withdrawal of beta-blockers prior to surgery can result in tachyarrhythmias or myocardial infarction. In addition, high-risk patients may have pre-existing disorders (angina, arrhythmia, hypertension) that preclude the use of analgesic anaesthetic agents that may produce adverse cardiovascular effects.

SUMMARY OF RESULTSSufentanilMorphine

40% decrease in CI (both drugs)

MAP, CVP, MPAP -
no significant
change
PCWP increased 50%

MAP decreased 65%
MPAP, 14% decrease
and PCWP, 33% decrease

HR decreased 30%

No further decrease
in HR apart from 16%
decrease resulting
from propranolol

SVRI increased by 51%

SVRI decreased by 32%

PVRI - no change

PVRI significantly
increased

RVSWI - no effect

RVSWI - no effect

LVSWI - minor decrease
of 20%

LVSWI - 80% decrease

O₂ transport index and RPP declined significantly (both drugs)O₂ consumption reduced 20%O₂ consumption unchanged

The authors concluded that sufentanil was associated with cardiovascular stability in the presence of total beta-blockade induced by propranolol.

Massive doses (up to 0.16 mg/kg) of sufentanil in mongrel dogs administered after severe asphyxia had no significant delay in the classical effects of asphyxia. Large doses of sufentanil (up to 40 µg/kg/min) had little effect on cardiovascular dynamics in atropinized dogs. Small decreases in heart rate, blood pressure and cardiac output were observed in nonatropinized dogs irrespective of infusion rate.

Effect on Cerebral Blood Flow (CBF) and Oxygen Consumption (CMRO₂)

The effect of 5, 10, 20, 40, 80 and 160 µg/kg of sufentanil on CBF and CMRO₂ was investigated in male Wistar rats anaesthetized with halothane and ventilated with 70% N₂O/30% O₂. MAP, PaO₂, PaCO₂ and temperature were similar in all groups, but CBF decreased significantly in the sufentanil groups compared to a control group ventilated with 70% N₂O/30% O₂. Reduction in CMRO₂ of up to 36% occurred in groups receiving 20 µg/kg.

Marked depression in EEG tracing with low frequency, high amplitude and burst suppression occurred in the sufentanil groups. Short periods of epileptoid patterns and spikes were seen in the 80 and 160 $\mu\text{g}/\text{kg}$ groups.

EEG Effects

The effects of morphine, fentanyl, sufentanil and alfentanil on the EEG were investigated in Beagle dogs. All compounds increased the amplitude of the EEG, decreased the frequency of the EEG and produced spindle-like bursts of biphasic waves. Frontal cortex changes in the total power were the shortest (18 minutes) after 0.004 mg/kg fentanyl. Sufentanil produced the shortest effects in the amygdala (18 minutes); longer lasting effects (60 minutes) occurred in the frontal cortex and hippocampus.

In rabbits, equipotent doses of sufentanil (0.01 mg) induced a deeper narcotic effect (burst suppression) than fentanyl (0.1 mg). Otherwise, conventional EEG and amplitude frequency spectra were reported to be equal for both drugs.

Drug Interaction Studies

Mongrel dogs received a loading dose of sufentanil (0.01 mg/kg) followed by an i.v. injection of succinylcholine (1 mg/kg). Animals were ventilated with 50% N₂O/50% O₂, and analgesia was maintained with a slow i.v. infusion of 0.00025 mg/kg sufentanil. Ten minutes later, an i.v. test dose of 1 mg/kg succinylcholine was given, followed 45 minutes later by an i.v. dose of 0.1 mg/kg pancuronium bromide, and another 45 minutes later by an i.v. dose of 0.16 mg/kg propranolol. Sufentanil in combination with succinylcholine seemed to induce some slight positive inotropic effects. A pronounced stimulating effect on cardiac and hemodynamic parameters was seen with the addition of pancuronium bromide, possibly due to its sympathomimetic action. Propranolol caused a significant increase in pulmonary artery pressure, left ventricular end-diastolic pressure and pulmonary vascular resistance. There was a decrease in cardiac output and left ventricular stroke work.

Miscellaneous Studies

In dogs and rats, the narcotic effects of sufentanil were reversed by nalorphine. In dogs, the ED₅₀ values for the antagonism of apomorphine-induced emesis were 0.00028 mg/kg for sufentanil, 0.0012 mg/kg for fentanyl and 0.68 mg/kg for morphine. Plasma levels of histamine were unaffected by i.v. administration of sufentanil (0.15 mg/kg) in dogs. *In vitro*, sufentanil (500 mg/mL) failed to induce hemolysis in human blood.

Metabolism and Pharmacokinetics

The pharmacokinetics of sufentanil were determined using a sensitive radioimmunoassay. In rats receiving tritiated sufentanil, the excretion of radioactivity was very rapid and complete. After 24 hours, 86.8% of the administered radioactivity had been excreted; 10.6% was excreted in the second day of dosing. Excretion was predominantly in the feces (61.6%) and in the urine (37.8%). Sufentanil was rapidly metabolized to a large number of metabolites, with oxidative N-dealkylation at the piperidine nitrogen being the major pathway. In dogs, 60% of the dose was excreted in the urine and 40% in the feces. Biliary excretion was shown to be an important elimination pathway, as suggested by the large fraction of metabolites excreted in the feces. In rats, 93.1% of sufentanil was bound to plasma protein, compared to 92.8% in dogs and 92.5% in man.

Placental transfer of sufentanil was determined in Wistar rats. Placental concentrations were 25% higher than those in maternal blood. The ratio of maternal to umbilical blood levels averaged 1.2. Placental concentrations were 2-2.5 times higher than fetal radioactivity levels. Total radioactivity recovered from placentae, uteri, fetal membranes and fetuses represented 0.1-0.4% of maternal dose over the course of the 120 minute test period.

Plasma levels and tissue distribution of ³H-sufentanil were determined in Wistar rats. Radioactivity gradually became undetectable in plasma following an initial rapid distribution phase lasting up to approximately 2 hours. The terminal elimination had a half-life of 8 hours. Plasma levels of unchanged sufentanil declined triexponentially with $t_{\tau} = 1.6$ minutes, $t_{\alpha} = 10.6$ minutes and $t_{\beta} = 63$ minutes. Total plasma clearance averaged 69.1 mL/min/kg. Peak radioactivity levels reported were in the lung, adrenals, kidney and liver. Twenty-nine to fifty-two percent of the dose was recovered in the small intestine 1-2 hours after injection. A peak level of 36% was found in the large intestine at 8 hours. Sixty-five percent of unchanged drug was measured in the brain at 8 hours.

TOXICOLOGY

SUFENTA sufentanil citrate has been administered by the intravenous or epidural routes either acutely or subacutely to mice, rats, guinea pigs and dogs. The chronic toxicity of subcutaneous sufentanil was evaluated in the rat.

Acute Toxicity

<u>Animals</u>	<u>No. Animals/Dose</u>	<u>LD₅₀ (mg/kg) 14 Days</u>
Albino mice	10 M	16.8 (10.6 - 26.6)
	10 F	18.0 (13.7 - 23.5)
Wistar rats	10 M	12.5 (7.87 - 19.7)
	10 F	9.34 (5.88 - 14.8)
Guinea pigs	10 M	11.8 (7.87 - 17.7)
	10 F	13.0 (8.17 - 20.6)
Dogs	4 M	10.1 (3.82 - 26.9)
	4 F	19.5 (9.14 - 41.8)

Signs of toxicity: convulsions, exophthalmos, excitation, palpebral ptosis, loss of righting reflex, tremors, dyspnea and cyanosis (high dose in mice), diuresis and diarrhea (in rats), cyanosis and hypothermia (in guinea pigs), sedation or prostration (in dogs).

The acute LD₅₀ (14 days after administration) in Wistar rats after epidural sufentanil administration was >320 µg/rat (>1.28 mg/kg). No pathological changes in the brain and spinal cord were noted.

Subacute ToxicityFour-week Intravenous Toxicity Study in Wistar Rats

Rats (10 M, 10 F/group) received sufentanil intravenously once a day, 6 days a week, during 4 weeks at 0, 0.31, 1.25 and 5 mg/kg doses. The findings were: increased mortality in sufentanil-treated groups, loss of righting reflex, muscle rigidity and exophthalmos, lower food consumption and body weight gain in all dosed animals; decrease in BUN and SGOT in females at all doses; increase in specific gravity of urine in mid-dosed but not high-dosed males; decrease in creatinine in urine in low-dosed females only; increase in urine pH in high-dosed females.

One-month Intravenous Toxicity Study in Beagle Dogs

Dogs (3 M, 3 F/group) received sufentanil intravenously once a day, 6 days a week, during 1 month at doses of 0, 0.02, 0.16 and 1.25 mg/kg. The findings were: no mortality in any group; ataxia, hypoxia, mydriasis and sleep noted in all treated animals; symptoms disappeared after 1 hour in the low-dosed group, after 2 hours in the mid-dosed group and after 2-3 hours in the high-dosed group; decreased appetite and body weight loss in all treated animals; salivation (mid- and high-dosed); emesis (high-dosed); increased heart rate (high-dosed); mild hypertension (mid- and high-dosed); higher leucocyte values in all treated animals but still within normal limits; slightly high coagulation time values in all

treated groups; high SGPT values in all treated groups; more dilated sinusoids and smaller hepatocytes in some treated animals (not dose-related); thymic involution in many dosed animals; atrophic effect on uterus along with thin-layered vaginal epithelium.

Epidural Toxicity

Subacute administration of epidural sufentanil was investigated in Wistar rats (0.63 or 320 $\mu\text{g}/\text{rat}$ x 5 days), Beagle dogs (10, 50 or 100 $\mu\text{g}/\text{day}$ x 15 days) and guinea pigs (2.5 $\mu\text{g}/\text{day}$ x 28 days). No signs of sufentanil-related pathological changes were observed except a dilated urinary bladder in the rat study at 320 $\mu\text{g}/\text{rat}$. In all 3 studies inflammation with fibrous tissue around the catheter, independent of the use of sufentanil, was noted on histopathological examination. No neurological adverse effects were observed. The reported behavioural changes were typical for the administration of high doses of an opiate analgesic.

Chronic Toxicity

Six-month Subcutaneous Toxicity Study in Wistar Rats

Male and female Wistar rats (20 M, 20 F/group) were administered daily subcutaneous doses of 0, 0.16, 0.63 or 2.5 mg/kg sufentanil for 6 months. Mortality due to suffocation occurred at all doses but was slightly elevated in males in the 2.5 mg/kg group. Dose-dependent and opiate-related changes included: loss of righting reflex, pinna and corneal reflex blockade, muscle rigidity and decrease in food consumption and body weight gain. Hematological changes included: decreased thrombocytes in males (WNL), increased segmented neutrophils and decreased lymphocytes in males and females. Serum analysis revealed decreased calcium, total protein, and albumin in males; decreased cholesterol, triglycerides, phospholipids and increased BUN, total bilirubin, creatinine and AST in males and females. On urinalysis, decreased creatinine and specific gravity were seen in males and increased pH, volume and incidence of bacteria and triphosphate crystals were noted in males and females. However, there was no clear evidence of specific nephrotoxicity. Organ weights were generally decreased; however, increased adrenal weight was noted in all dosed groups. Histopathological examination revealed changes to the adrenals, male and female genital tracts, mammary glands and thymus. Chronic inflammation and foamy cells were observed in the lungs of rats in the 0.16 and 0.63 mg/kg dose groups.

Reproduction and Teratology Studies

Male and Female Fertility Study in Wistar Rats

Eighty dosed males were coupled with nondosed females, and nondosed males were coupled with 80 dosed females. The doses used were: 0, 0.005 mg/kg, 0.02 mg/kg and 0.08 mg/kg. Dosed females received a single i.v. injection/day, 7 days a week for a minimum of 14 days and throughout gestation. Dosed males received the drug 5 days a week for a minimum of 56 days and further until mating. Pregnancy rate was comparable between groups; litter size was normal at low- and mid-doses but significantly decreased at high-dose due to maternal toxicity; an increase in fetal resorptions was also noted at high dose. No evidence of teratogenicity was seen, and there were no adverse effects on male or female fertility.

Intravenous Embryotoxicity and Teratogenicity Study in Wistar Rats

Sufentanil was administered intravenously from day 6 through day 15 of gestation at doses of 0, 0.005, 0.02 and 0.08 mg/kg. Mortality was higher in the dams of the mid- and high-dosed groups, and there was a decrease in pregnancy rates in the same groups. There was no difference between groups with regard to litter size, number of live, dead or resorbed fetuses. Decreased birth weight, attributed to maternal toxicity, was observed at 0.02 and 0.08 mg/kg. No drug-related abnormality was noted in the fetus.

Intravenous Embryotoxicity and Teratogenicity in New Zealand White Rabbits

Sufentanil was administered intravenously to female rabbits from day 6 through day 18 of pregnancy at doses of 0, 0.005, 0.02 and 0.08 mg/kg. Mortality increased in the mid- and high-dosed group adult animals. There was a decrease in pregnancy rate at high-dose, but no effect on mean litter size, number of live, dead and resorbed fetuses. Twenty-four hour survival rate decreased significantly at mid- and high-doses. No abnormalities were found in the fetuses.

Intravenous Embryotoxicity and Teratogenicity Study in Wistar Rats

Peri- and Postnatal Toxicity Study

Sufentanil was administered intravenously to female rats at doses of 0.005, 0.02 and 0.08 mg/kg from day 16 of pregnancy through a 3-week lactation period. There was no difference noted between groups on mortality, pregnancy rate or gestation period. Litters were comparable between groups. There was a slightly lower weight gain during a 3-week neonatal period at 0.02 mg/kg. Almost no pups survived from the 0.08 mg/kg dose group. Survival rate decreased in all treated groups. These effects were thought to be related to anoxia or death of fostering mothers during the lactation period. No abnormalities were observed.

Mutagenicity

The micronucleus test in 30 female rats revealed that single intravenous doses of sufentanil as high as 80 μ g/kg produced no structural chromosome mutations. The Ames *Salmonella typhimurium* metabolic activating test also revealed no mutagenic activity.

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