DOCTOR LEAFLET

MORPHINE INJECTION (Preservative Free)

COMPOSITION:
Each ampoule of preservative-free Morphine Injection contains 5 ml of 100 mg (20mg/ml) morphine sulphate or 10 ml of 200 mg (20 mg/ml) morphine sulphate.
Morphine Injection contains no preservatives.

ACTION
Morphine is the principal opium alkaloid. Opiate receptors in the central nervous system mediate analgesic activity (see below), and morphine exerts its agonist activity primarily at the mu receptor. Opioid agonists occupy the same receptors as endogenous opioid peptides (enkephalins or endorphins), and both may alter the central release of neurotransmitters from afferent nerves sensitive to noxious stimuli. Opioid antagonists block the opiate receptor, inhibit the pharmacological activity of the agonist and will precipitate withdrawal in dependent patients.

Central opioid receptors located in several specific brain centers are the primary site of action of systemically administered opioids. Opiate receptors in the spinal cord are located in an area of the dorsal horn of the gray matter called the substantia gelatinosa. These are the receptors targeted by intraspinal (epidural and intrathecal) opioid administration. Intraspinal administration provides more profound and longer-lasting analgesia than traditional injectable administration, and at much lower doses. Moreover, side effects that are intolerable with IV administration may diminish with intraspinal administration due to the lower doses used. These advantages have led to the increasing use of this method to treat postoperative and chronic malignant and non-malignant pain.

The physiochemical properties of opioids are the main determinants of their pharmacokinetic profiles during intraspinal use. Morphine is the most hydrophilic of the commonly used opioids, and under physiological conditions is also highly ionized. After epidural injection, the small un-ionized portion is taken up into the cord slowly but is rapidly converted to the ionized form, being trapped in the spinal cord for longer periods than lipophilic agents, such as fentanyl. These characteristics account for the slower onset of action (15-60 min) but longer duration of analgesia (up to 24 hours). Moreover, the hydrophilic nature of morphine minimizes the eggression from the spinal cord and systemic absorption following vascular uptake. In addition, the high concentration of drug in the CSF that is available for cephalad flow results in less segmentalization (the degree to which analgesia is limited to discrete dermatomal segments corresponding to the level of intraspinal injection) than lipophilic agents, but also results in a greater risk of delayed respiratory depression.

Drug distribution following intrathecal administration is similar to that of epidural administration once the opioid is present within the CSF. However, because the opioid is not subject to initial uptake by the epidural vasculature, intrathecal doses are only 1/10 of the epidural dose and the onset of analgesia is faster.

There are several infusion techniques for intraspinal delivery including a single or double intraspinal shot (e.g., after Cesarean sections), multiple intermittent bolus injections (e.g., in the cancer patient), or continuous infusion with or without bolus as-needed injections

(e.g., in the cancer patient requiring exceptionally high doses). Patient controlled analgesia (PCA) is becoming increasingly widespread using on-demand patient-controlled boluses and a lockout period, with or without an underlying continuous basal infusion. Because intraspinal morphine has a long duration of action, it is suitable for either bolus injections or continuous infusion. (Note: Morphine Injection 20mg/ml is only indicated for continuous infusion.)

There are several options for intraspinal delivery systems, which can broadly be divided into two groups implantable drug infusion systems and externalized systems. Each system has its own advantages and disadvantages, and the patients' individual circumstances will determine which delivery system is most appropriate.

Intraspinal administration of opioids for acute postoperative pain is generally limited to procedures that are thoracic, abdominal, urological, orthopedic, or gynecological in nature. When used for chronic pain, intraspinal opioid administration is generally limited to those patients in whom adequate systemic opioids fail to provide adequate analgesia and/or are associated with unacceptable side effects.

Opioids for intraspinal administration must be preservative-free since preservatives can have neurotoxic effects when administered near the spinal cord and result in permanent nerve damage.

INDICATIONS

Morphine injection 20mg/ml (preservative-free) is a systemic opioid analgesic indicated only for IV, epidural and intrathecal infusion in the treatment of intractable chronic pain. It was developed for use in continuous microinfusion devices and may require dilution before use as dictated by the characteristics of the device and the dosage requirements of the individual patient.
Morphine injection 20mg/ml is primarily intended for patients who are opioid-tolerant.
Morphine sulphate administered epidurally or intrathecally provides pain relief for extended periods without attendant loss of motor, sensory or sympathetic function.

CONTRAINDICATIONS

Hypersensitivity to morphine or other opioids.
Acute respiratory depression, upper airway obstruction.
Diarrhea caused by poisoning, until the toxic material has been eliminated from the gastrointestinal tract, or diarrhea associated with pseudomembranous colitis caused by antibiotics.
Paralytic ileus.
Due to the high concentration of the 20mg/ml injection, this formulation is contraindicated for use during labor.
Due to the high concentration of the 20mg/ml injection, this formulation is contraindicated in all pediatric patients who cannot reliably participate in the correct assessment of their own pain relief.
Administration of morphine by the epidural or intrathecal route is contraindicated in the presence of any active, untreated systemic infection, local infection or inflammation at the injection site, spinal cord disease, coagulation defects caused by anticoagulant therapy or hematological disorders, parenterally administered corticosteroids within a two week period or other concomitant drug therapy or medical condition which would contraindicate the technique of epidural or intrathecal analgesia.

WARNINGS

Patient Monitoring

Morphine injection 20mg/ml is not recommended for single-dose administration due to the very large amount of morphine in the ampoule and the associated risk of overdosage. Single intraspinal doses can be administered more reliably with the standard preparation of Morphine Injections (0.5mg/ml and 1.0mg/ml).

Continuous, intraspinal opioid analgesia for the control of chronic intractable pain is appropriate only when less invasive means of controlling pain have failed, and should always be preceded by a trial of serial intermittent intraspinal doses to assess the efficacy and adverse effects of this mode of administration. Once it has been determined that the patient is a suitable candidate for such chronic therapy, implantation surgery of the microinfusion device can be performed. Epidural and intrathecal administration should be undertaken only by physicians familiar with the techniques and patient management problems associated with intraspinal administration. Severe respiratory depression up to 24 hours following epidural or intrathecal administration have been reported. Therefore, patients must be observed in a fully equipped and staffed environment for at least 24 hours after the initial (single) test dose and, as appropriate, for the first several days after catheter implantation, and/or following substantial dose increments. The facilities must be equipped with resuscitative drugs and equipment including oxygen and naloxone injection, and personnel trained in their use. Reservoir filling must be performed by qualified personnel, using strict aseptic technique. Extreme care must be taken to ensure that the refill dose is injected into the correct port. A period of observation appropriate to the clinical situation should follow each refill or manipulation of the drug reservoir or programming changes. Before discharge, the patient and attendant should receive proper instruction in the proper home care of the device and in the recognition and practical treatment of excessive dosing.

Drug Dependence

Opioid analgesics may cause physical and psychological dependence.

Physical Dependence

Physical dependence is the adaptation of the body to the presence of an opioid drug. This involves physiological changes which explain two phenomena frequently seen with long-term opioid treatment - tolerance and the withdrawal syndrome.

Tolerance is defined as the need to administer a higher dose of the opioid to maintain the same level of analgesia. For most patients, the first indication of tolerance is a decrease in the duration of analgesia for a given dose and the appearance of breakthrough pain. Tolerance may be confused with an increase in the pain intensity of the disease itself (which is the most common reason an increase in dosage is indicated). Irrespective of the underlying cause, it is recommended that the dose be increased and the patient re-titrated until the pain is again controlled.

Withdrawal symptoms, sometimes called the opioid abstinence syndrome, are those manifested by a patient upon cessation of treatment or rapid reduction of dosage. In its mildest form, the opioid abstinence syndrome may be confused with viral, influenza-like syndromes.

In severe withdrawal, early symptoms include yawning, lacrimation, rhinorrhea, restless or "yen sleep", and perspiration. These may be followed by mydriasis, piloerection, flushing, tachycardia, twitching, tremor, restlessness, instability, and anorexia. Ultimately,

symptoms include muscle spasm, fever, nausea, diarrhea, vomiting, and spontaneous orgasm.

The severity of the abstinence syndrome is related to the degree of dependence, the abruptness of withdrawal, and the drug used. In general, withdrawal symptoms develop at the time the next dose would originally have been given. For parenteral morphine, they gradually increase in intensity, reaching a maximum at 24-72 hours and subsiding over 5-10 days.

If a reduction in dosage is required, the opioid abstinence syndrome can usually be avoided by gradually decreasing the dosage in the following fashion. Half the prior daily dosage should be given for the first 2 days. This should be reduced by 25% every 2 days thereafter, until the daily dosage is the equivalent of 10 mg parenteral morphine. The drug may be discontinued after 2 days on this dose. Clonidine may reduce anxiety, tachycardia and other autonomic symptoms associated with opiate withdrawal.

Care must be taken to avoid withdrawal in those patients who have been maintained on parenteral/oral opioids when epidural or intrathecal administration is considered. Low doses of opioids administered epidurally or intrathecally will not prevent withdrawal symptoms from occurring in a physically dependent patient. In such patients, systemic opioids should be tapered slowly while initiating analgesia with intraspinal opioids. One suggestion is that 50% of the 24-hour pre-spinal dose be withdrawn and given as spinal equivalents; thereafter, systemic therapy is reduced 20% daily while intraspinal therapy is increased appropriately.

Withdrawal precipitated by the administration of an opioid antagonist is manifested by the onset of symptoms within minutes; reaching maximum intensity within 30 minutes. Do not administer an opioid antagonist as a means of detecting dependence. If an opioid antagonist must be used to treat serious respiratory depression in a physically dependent patient, administer with extreme care using 10-20% of the usual initial dose (see Overdosage).

Physical dependence does not imply psychological dependence.

Psychological Dependence

Psychological dependence is a pattern of compulsive drug use characterized by a craving for an opioid and the need to use the opioid for effects other than pain relief. This type of dependence is extremely rare in patients taking opioids for the relief of severe pain. It is very occasionally seen in patients who have previously used psychoactive substances for recreational purposes. This must not be confused with the behavior of patients whose pain is inadequately treated, who will also manifest drug-seeking behavior. For these patients titration to pain-controlling dosage is required.

Head Injury and Increased Intracranial Pressure

The respiratory depressant effects and the capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of head injury, brain tumor, other intracranial lesions or preexisting elevated intracranial pressure. Opioids may obscure the clinical course of patients with head injuries. Use with extreme caution and only if deemed essential. Increased intracranial pressure represents a relative contraindication for intraspinal administration.

Asthma and other Respiratory Conditions

Morphine should be used with extreme caution in patients undergoing an acute asthma attack, patients with chronic obstructive pulmonary disease or cor pulmonale, and patients

with a substantially decreased respiratory reserve, preexisting respiratory depression, hypoxia or hypercapnia. In such patients, even usual therapeutic doses of narcotics may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.
Intraspinal administration is relatively contraindicated in patients at high risk for respiratory depression.

Cardiovascular Effects
Opioids may cause hypotension in the postoperative patient, or in those whose ability to maintain blood pressure is compromised by hypovolemia or concurrent administration of phenothiazines or general anesthetics. Opioids may produce orthostatic hypotension in ambulatory patients.
Morphine, like all opioid analgesics, should be administered with caution to patients in circulatory shock since vasodilation produced by the drug may further reduce cardiac output and blood pressure. Shock and severe hypovolemia are relative contraindications for intraspinal administration.

Genitourinary Effects
Following single dose epidural or intrathecal administration of morphine, urinary retention occurs very frequently (some estimates are as high as 80% in males and somewhat lower in females), and may persist for 10-20 hours following injection. Catheterization may be required. Thus, when epidural or intrathecal administration is considered, especially in the perioperative period, consideration should be given to the risks inherent in urethral catheterization, e.g., sepsis.

Other Effects
Patients receiving opioids on a chronic basis and who undergo cordotomy or any other pain-relieving surgical procedure should be monitored closely for respiratory depression; and the morphine dosage should be titrated to the new post-operative requirement.

Use in Pregnancy
Safety of use in pregnancy has not been established. The placental transfer of opioids is rapid. Maternal addiction following illicit use, resulting in withdrawal symptoms in the neonate, is well documented. Withdrawal symptoms include irritability, excessive crying, yawning, sneezing, increased respiratory rate, tremors, hyperreflexia, fever, vomiting, increased stools and diarrhea. These symptoms usually appear during the first days of life. Morphine sulphate should be given to pregnant woman only if clearly needed, and the potential benefit to the mother outweighs the possible hazard to the fetus.

Use in Labor
Due to the high concentration of the 20mg/ml injection, this formulation is contraindicated for use during labor (see Contraindications).

Use in Breastfeeding
Ordinarily, nursing should not be undertaken while a patient is receiving Morphine Injection since morphine sulphate is excreted in maternal milk.

Use in Pediatrics
Due to the high concentration of the 20mg/ml injection, this formulation is contraindicated in all pediatric patients who cannot reliably participate in the correct assessment of their

own pain relief (see Contraindications). Safety and efficacy of epidural and intrathecal injection of morphine in children have not been established.

Use in the Elderly
Morphine should be used with caution in the elderly. Dosage should be carefully controlled and the patient monitored for possible drug interactions. A lower dosage than usual may be necessary because some elderly patients are highly sensitive to the respiratory depressant effect of morphine. Also, geriatric patients are more likely to have prostatic hypertrophy or renal function impairment, and therefore may be more adversely affected by urinary retention. These precautions are particularly relevant when morphine is administered epidurally or intrathecally, since the pharmacodynamics of morphine when administered by these routes are more variable in geriatric patients than in younger patients. Lower doses or longer dosing intervals than those usually recommended for adults may be required, and are usually therapeutically effective, for these patients.

ADVERSE REACTIONS
Epidural or intrathecal administration does not eliminate the risk of severe side effects common to systemic opioid analgesics. For both IV and intraspinal administration, the most serious adverse reactions include respiratory depression and apnea. Less frequently, circulatory depression, respiratory arrest, shock and cardiac arrest may occur. Because of a delay in maximum CNS effects with intravenously administered drug (30 min), rapid administration may result in overdosing. Bolus administration by the epidural or intrathecal route may result in early respiratory depression due to direct venous redistribution of morphine to the respiratory centers in the brain. Late (up to 24 hours) onset of acute respiratory depression has been reported with administration by the epidural or intrathecal route and is believed to be the result of rostral spread. Reports of respiratory depression following intrathecal administration have been more frequent, but the dosage used in most of these cases has been considerably higher than that recommended. This depression may be severe and could require intervention. Intrathecal administration and/or injection into thoracic sites are more likely to cause respiratory depression than epidural administration and/or injection into lumbar sites.

The most frequent adverse reactions are constipation, lightheadedness (especially in ambulatory patients), dizziness, sedation, nausea, vomiting, feeling faint, unusual tiredness or weakness, drowsiness and sweating. Genitourinary reaction such as urinary retention, decreased urination, or hesitance are much more common following epidural or intrathecal administration of morphine (incidence up to 80% in males and somewhat lower in females) and may persist for 10 to 20 hours following single injections. Catheterization may be required. Reduced libido or potency may be more likely to occur after intraspinal administration. In addition, epidural and intrathecal administration is accompanied by a high incidence of pruritus, which is dose related and often occurs on the face. Following intraspinal administration, peripheral edema occasionally occurs.

Patients experiencing these adverse reactions should receive lower doses of the drug and/or symptomatic treatment of the side effect (e.g. laxatives for constipation). During chronic opioid use, tolerance develops to many of the side effects, which gradually subside. In general, side effects of morphine are amenable to reversal by narcotic antagonists, but should only be used after careful consideration of the risks.

The following adverse reactions have also been reported occasionally:

Central Nervous System
Euphoria, dysphoria, delirium, insomnia, agitation, anxiety, fear, hallucinations, disorientation, confusion, lethargy, impairment of mental and physical performance, coma, mood changes, weakness, headache, visual disturbances, tremor, psychic dependence, and miosis. Convulsions or myoclonus may rarely occur when high doses of morphine are given IV or intraspinally.

Gastrointestinal
Dry mouth, anorexia and biliary tract spasm. Patients with chronic ulcerative colitis may experience increased colonic motility. Toxic dilatation has been reported in patients with acute ulcerative colitis.

Cardiovascular
Facial flushing, hypotension (more frequent), hypertension, peripheral circulatory collapse, tachycardia, bradycardia, arrhythmia, palpitations, chest wall rigidity, and syncope. While low doses of intravenously administered morphine have little effect on cardiovascular stability, high doses are excitatory, resulting from sympathetic hyperactivity and increase in circulating catecholamines.

Allergic
Urticaria, other skin rashes, diaphoresis, laryngospasm, edema, and rarely hemorrhagic urticaria. A case of thrombocytopenia induced by morphine has been reported. Wheals, phlebitis and pain may occur at the site of IV injection. Effects induced by histamine release e.g., decreased blood pressure, fast heartbeat, increased sweating, redness or flushing of the face, wheezing or troubled breathing.

Other
When morphine is used intraspinally, the possibility of surgical complications and drug delivery system complications should be kept in mind. Examples of the former include bleeding, infection of the spinal catheter, tissue damage and CSF leaks. Examples of the latter include mechanical difficulties due to cathether kinking, dislodgement or obstruction, pump/battery failure, and programming errors.

PRECAUTIONS
It is recommended that administration of morphine injection by epidural or intrathecal routes be limited to the lumbar area. Intrathecal use has been associated with a higher incidence of respiratory depression than epidural use.

The diagnosis or clinical course of acute abdominal conditions may be obscured by opioids.

Exercise caution in elderly and debilitated patients and in patients sensitive to CNS depressants, including those with cardiovascular disease, hypothyroidism, acute alcoholism, delirium tremens, cerebral arteriosclerosis, fever, kyphoscoliosis, Addison's disease, prostatic hypertrophy or urethral stricture, toxic psychosis, severe CNS depression, coma, gallbladder/biliary tract/pancreas dysfunction, or a history of drug abuse.

Renal and hepatic dysfunction may cause a prolonged duration of action and a cumulative effect. Hence, care should be exercised in these conditions, particularly with repeated dosing.

Seizures may become aggravated, or may occur in individuals without a history of convulsive disorders if dosage is substantially increased because of tolerance. Patients with known seizure disorders should be carefully observed.

The cough reflex is suppressed.

Exercise caution when using opioid analgesics post-operatively especially following gastrointestinal tract surgery.

Use with caution in patients with atrial flutter and other supraventricular tachycardias. Vagolytic action may increase the ventricular response rate.

Patients with reduced circulating blood volume, impaired myocardial function or on sympatholytic drugs should be observed carefully for orthostatic hypotension. To decrease the possibility of the development of hypotension, the minimal effective dose should be given.

This drug may produce drowsiness or dizziness. Therefore, patients should be warned that their ability to perform potentially hazardous tasks requiring mental alertness or physical coordination, such as driving a vehicle or operating machinery, may be impaired.

Drug Interactions
Caution should be exercised if morphine is to be used concurrently with monoamine oxidase inhibitors (e.g., phenelzine), and within two weeks of their discontinuation, since severe reactions have been reported with other opioid analgesics, especially pethidine. In such patients, it is recommended that a small test dose of morphine (1/4 of the usual dose) or several small incremental test doses over a period of several hours first be administered to permit observation of any interaction.

Administration of an opioid antagonist such as naloxone or naltrexone will block the therapeutic effect of morphine, and will precipitate withdrawal symptoms in patients physically dependent on opioids; such symptoms may persist for up to 48 hours and be difficult to reverse. Similarly, administration of a mixed agonist/antagonist opioid analgesic (e.g,. pentazocine, buprenorphine) to a patient receiving therapy with a pure agonist opioid such as morphine may reduce the analgesic effect, or precipitate withdrawal.

Use with caution and in reduced dosage in patients concurrently receiving other opioid analgesics, general anesthetics, antihistamines, phenothiazines, barbiturates, other tranquilizers, sedative-hypnotics, tricyclic antidepressants and other CNS depressants including alcohol, anticholinergics or neuromuscular blocking agents. Concurrent therapy may increase the risk of respiratory depression, hypotension, profound sedation, coma, severe constipation, or urinary retention.

Concurrent use of opioid analgesics with antidiarrheals may increase the risk of severe constipation, as well as CNS depression.

Patients receiving concurrent antihypertensive medication and opioid analgesics should be monitored closely, due to the increased risk of orthostatic hypotension.

Because morphine may decrease the clearance of zidovudine, concurrent use should be avoided because the toxicity of either or both of these medications may be potentiated.

Case reports have described CNS toxicity (confusion, disorientation, respiratory depression, apnea, seizures) following concurrent administration of cimetidine and opioid analgesics, though no clear-cut cause and effect relationship has been established.

Diagnostic Interference
Because opioids may increase biliary tract pressure with resultant increases in plasma amylase or lipase, measurements of their levels may be unreliable for 24 hours following administration.

DOSAGE AND ADMINISTRATION
Morphine sulphate preservative-free Injection is intended for IV, epidural or intrathecal administration.

General Dosing Information - Intraspinal Administration
Epidural or intrathecal administration of opioid analgesics should be performed only by physicians experienced in these techniques. Solutions containing a preservative must not be injected via these routes. Upon initiation of continuous intraspinal therapy and following any subsequent dosage increments that are substantial, patients should be monitored in an adequate setting for at least 24 hours (see Warnings). Such facilities should have available resuscitative equipment and medications, including oxygen and a specific antagonist (naloxone HCl injection), for the management of respiratory depression or other complications that may arise.

For epidural or intrathecal administration, injection into the lumbar area may be preferred because of the increased risk of respiratory depression with injection into the thoracic area. Also, the epidural route is preferred, whenever possible, because of the increased risk of respiratory depression with intrathecal administration (see Precautions)..

Prior to the initial epidural administration, proper placement of the needle or catheter in the epidural space must be verified. Aspiration to check for blood or cerebrospinal fluid may be performed; however, the fact that intravascular administration is possible even when aspiration for blood is negative must be kept in mind. Alternatively, administration of 5 ml (3ml for obstetrical patients) of preservative-free 1.5% lidocaine hydrochloride with epinephrine 1:200,000 injection may be used to verify placement in the epidural space. Tachycardia occurring after injection of the test medication indicates that the medication has entered the circulation; sudden onset of segmental anesthesia indicates that the medication has been administered intrathecally.

Following epidural or intrathecal injection of an opioid analgesic, administration of low doses of naloxone via continuous IV infusion for 24 hours may decrease the incidence of potential side effects without interfering with the analgesic effectiveness of the medication.

The desired amount of morphine should be withdrawn from the ampoule through a microfilter. To minimize risk from glass or other particles, the product must be filtered

thorough a 5 micro (or smaller) microfilter before injecting into the microinfusion device. If dilution is required, 0.9% sodium chloride injection is recommended.

Specific Dosing Regimens

For the correct and effective use of morphine it is critical to adjust the dosing regimen for each patient individually according to the severity of pain, the patient's metabolism and condition, previous history of analgesic therapy, concomitant medications, and response to morphine. The following dosage recommendations are, therefore, only suggested approaches to what is actually a series of clinical decisions in the management of pain of an individual patient.

Parenteral Administration

For patients with severe chronic pain in whom the oral route is not feasible (e.g., bowel obstruction), parenteral opioids are needed. Since intermittent injections are expensive, uncomfortable, induce "clock watching" and are associated with the "bolus effect" (peak levels associated with intolerable adverse effects and trough levels associated with inadequate analgesia), a continuous IV infusion is preferable. Continuous IV infusions (CIVI) are especially suitable for patients who already require IV access and maintenance for other reasons. Opioid therapy with CIVI should usually be attempted prior to initiating intraspinal therapy since this route of administration is less invasive, less expensive and is associated with a lower risk of serious complications.

For patients transferring from oral opioids, standard equianalgesic tables should be consulted for calculating the total daily opioid dose in parenteral morphine equivalents. For CIVI, the daily parenteral morphine dose should be added to solution (e.g., 500ml saline) and delivered over the ensuing 24 hours (e.g., 20ml/hour). A loading bolus of 15 mg may be given by slow IV injection at the start of the infusion. Arrangements for rescue medication for breakthrough pain should always be ensured. It is important to remember that all conversion tables/ratios are meant to serve only as a guide and the dosage must always be adjusted according to the patient's response. Following assessment, the initial dose should be titrated up or down accordingly, until analgesia is adequate and side effects minimal. Following initiation of the infusion and after any subsequent changes in the infusion rate that are substantial, the patient should be monitored closely for several hours in a setting where an opioid antagonist, oxygen and resuscitative equipment, and personnel trained in their use, are available.

During the course of treatment the patient may experience a recurrence of pain due to an increase in the level of pain because of disease progression or the development of tolerance to the drug. If this occurs, an increase in the dosage may be required. As there is no upper limit to the amount of morphine that may be given in intractable oncologic pain, the quantity administered should be that which produces adequate analgesia with no or tolerable side effects.

In published reports of adults with severe, chronic pain, maintenance dosages of CIVI usually have ranged from 0.8-80mg/hr although even higher dosages (eg, 150mg/hour) occasionally have been required. In a limited number of children with severe, chronic cancer pain, maintenance dosages of 0.025-2.6mg/kg/hr have been infused IV (median 0.04-0.07).

Intraspinal Administration

In most cases the patient who initiates therapy with continuous intraspinal opioids will have been treated previously (unsuccessfully) with opioids either orally or parenterally. A patient's intraspinal analgesic requirements can be estimated by using the following conversion ratio:

300 mg oral morphine equals
100 mg parenteral morphine equals
10 mg epidural morphine equals
1 mg intrathecal morphine

(For patients who previously took opioids other than morphine, standard equianalgesic tables should be consulted for calculating the total daily opioid dose in morphine equivalents.) It is important to remember that all conversion tables/ratios are meant to serve only as a guide and the dosage must always be adjusted according to the patient's response. Patients whose pain is unusually severe or has a marked neuropathic component will often require higher intraspinal doses, while elderly patients will usually require lower intraspinal doses.

In all cases, the starting dose must be individualized, based upon in-hospital evaluation of the response to serial single-dose epidural/intrathecal bolus injections of regular Morphine Injections (preservative free) 0.5mg/ml and 1.0mg/ml, with close observation of the analgesic efficacy and adverse effects prior to surgery involving the continuous microinfusion device.

The usual starting dose for continuous epidural infusion, based upon limited data in patients who have some degree of opioid tolerance is 4.5 to 10mg/day. (The recommended initial epidural dose in patients who are not tolerant to opioids ranges from 3.5 to 7.5mg/day. **However, continuous intraspinal opioid administration in opioid-naive patients is not generally recommended!!)** The dose requirements may increase significantly during treatment. The upper daily limit for each patient must be individualized. The published literature suggests that most patients with severe chronic intractable pain will eventually require 10-100 mg/day.

The recommended initial lumbar intrathecal dose range in patients with no tolerance to opioids is 0.2 to 1mg/day. **However, continuous intraspinal opioid administration in opioid-naive patients is not generally recommended!!** The published range of doses for individuals who have some degree of opioid tolerance varies from 1 to 10mg/day. Limited experience with continuous intrathecal infusion of morphine has shown that the daily doses have to be increased over time. The upper daily dosage limit for each patient must be individualized. In a minority of patients a daily dose of 10-20mg may be necessary. Doses greater than 20mg/day are rarely necessary and should be employed with caution since they may be associated with a higher likelihood of serious side effects such as myoclonus and respiratory depression.

During the course of treatment the patient may experience a recurrence of pain due to an increase in the level of pain because of disease progression or the development of tolerance to the drug. If this occurs, an increase in the dosage may be required. As there is no upper limit to the amount of morphine that may be given in intractable oncologic pain, the quantity administered should be that which produces adequate analgesia with no or tolerable side effects.

If other measures to relieve pain (e.g.nerve blocks, cordotomy) are employed, the morphine dosage should be reduced to an appropriate level.

In debilitated or geriatric patients, epidural or intrathecal administration should be undertaken only with extreme caution, using relatively small doses.

Safety and efficacy of epidural or intrathecal administration in children have not been determined, and usage in this population is not generally recommended.

Overdosage

Manifestations

Morphine overdosage is initially characterized by sedation, confusion and delirium. If such symptoms become apparent, morphine should be withdrawn and the patient monitored. Later manifestations of serious morphine overdosage include respiratory depression (reduced respiratory rate and/or tidal volume, Cheyne-Stokes respiration, cyanosis), extreme somnolence progressing to stupor or coma, flaccidity of skeletal muscle, cold or clammy skin, pinpoint pupils, and sometimes hypotension and bradycardia. Severe overdosage may result in apnea, circulatory collapse, cardiac arrest and death. (Note: Respiratory depression may be delayed in onset up to 24 hours following epidural or intrathecal administration.)

Treatment

Primary attention should be given to establishing adequate respiratory exchange through the provision of a patent airway and institution of assisted or controlled ventilation. If depressed respiration is associated with muscular rigidity, an IV neuromuscular blocking agent may be required.

Because of the risk of systemic withdrawal, an opioid antagonist - preferably naloxone - should only be administered for symptomatic respiratory or cardiovascular depression. If the patient is arousable and the peak plasma levels of the opioid have already been reached the patient should be monitored until his/her condition improves. If the patient is unarousable or respiratory depression is severe, naloxone I.V. should be used to improve ventilation using small bolus injections of dilute solution (0.4mg in 10ml saline), which are titrated against the respiratory rate. (In children some authorities have recommended a naloxone dose of 0.005-0.01 mg/kg.) Since the duration of action of intrathecal or epidural morphine exceeds that of naloxone, administration of the antagonist should be repeated to maintain adequate respiration and the patient should be kept under observation. Patients should be observed for evidence of renarcotization.

In individuals who are physically dependent upon morphine, the administration of the usual dose of naloxone will precipitate an acute withdrawal syndrome. The severity of the syndrome is dependent on the degree of physical dependence and the dose of naloxone given. If at all possible, avoid the use of an antagonist in such individuals. However, if absolutely necessary, administer the naloxone with extreme caution, using only 10-20% of the usual initial dose given.

Employ supportive measures as indicated. Observe the patient for a rise in temperature or pulmonary complications that may require antibiotic therapy.

PHARMACEUTICAL PRECAUTIONS

Protect from light and store at room temperature. Discard any unused portion. Do not autoclave. Protect from freezing.

Parenteral solutions should be inspected visually for particulate matter and discoloration prior to administration whenever container and solution permit. Do not use if the injection is darker than pale yellow or if it contains a precipitate.
Morphine sulphate has been reported to be physically or chemically incompatible with solutions containing aminophylline, amobarbital sodium, chlorothiazide sodium, phenytoin sodium, heparin sodium, meperidine hydrochloride, methicillin sodium, nitrofurantoin sodium, pentobarbital sodium, phenobarbital sodium, sodium bicarbonate, sodium iodide, and thiopental sodium.

Each ampoule of Morphine Injection 20mg/ml (preservative free) contains a large amount of potent narcotic which may be potentially abused. Due to the limited indications for this product, the risk of overdosage and risk of its diversion and abuse, it is recommended that special measures be taken to control this product within the hospital or clinic. Accidental dermal exposure should be treated by the removal of any contaminated clothing and rinsing the affected area with water.

PRESENTATION
Each ampoule contains 20mg/ml morphine sulfate (preservative-free) in a volume of 5 ml (100mg/5ml) or 10 ml (200mg/10/ml).