

DATA SHEET

RA-MORPH[®]

Morphine Hydrochloride BP Solution 1, 2, 5, and 10 mg/mL

DESCRIPTION

Morphine hydrochloride is 7,8-didehydro-4,5-epoxy-17-methylmorphinan-3,6-diol hydrochloride trihydrate (molecular weight 375.8). It is a white, crystalline powder or colourless, silky crystals. It is soluble 1:21 in water and 1:10 in boiling alcohol. It is practically insoluble in chloroform or ether.

RA-MORPH solutions are clear colourless or pale yellow solutions.

Morphine is liable to precipitate out of solution in an alkaline environment.

RA-MORPH contains Morphine Hydrochloride BP 1, 2, 5, and 10 mg/mL in a sugar and alcohol free vehicle containing the excipients citric acid, sodium citrate dihydrate, disodium edetate and glycerol with sodium methyl hydroxybenzoate 0.2% w/v as preservative and Water for Injections.

PHARMACOLOGY

Pharmacodynamics

Morphine is the principal alkaloid of opium and is a phenanthrene derivative.

Morphine, like other opioids, acts as an agonist interacting with stereo-specific and saturable binding sites/receptors in the brain, spinal cord and other tissues. These sites have been classified as μ receptors and are widely distributed throughout the central nervous system being present in highest concentration in the limbic system (frontal and temporal cortex, amygdala and hippocampus), thalamus, striatum, hypothalamus, midbrain and laminae I, II, IV and V of the dorsal horn in the spinal cord. It has been postulated that exogenously administered morphine exerts its analgesic effect, in part, by altering the central release of neurotransmitter from afferent nerves sensitive to noxious stimuli.

Peripheral threshold or responsiveness to noxious stimuli is unaffected leaving monosynaptic reflexes such as the patella or the Achilles tendon reflex intact.

Morphine exerts its primary effects on the central nervous system and organs containing smooth muscle. Pharmacological effects include analgesia, drowsiness, alteration in mood (euphoria), reduction in body temperature, dose-related depression of respiration, interference with adrenocortical response to stress (at high doses), reduction in peripheral resistance with little or no effect on cardiac index, cough suppressions mediated through a direct effect on the medullary centre and miosis.

Direct stimulation of the chemoreceptor trigger zone may cause emesis and spasmogenic effects on the gastrointestinal tract resulting in decreased peristaltic activity. Urinary retention may occur due to increased bladder sphincter tone.

Pharmacokinetics

Absorption

Morphine is readily absorbed from the gastrointestinal tract. Significant first-pass metabolism occurs in the liver following oral administration; hence, the bioavailability of oral morphine is low and variable.

With repeated regular dosing, oral morphine is about 1/3 as potent as when given by intramuscular injection.

Distribution, Metabolism and Elimination

Morphine is distributed throughout the body, but particularly to parenchymatous tissue such as kidney, lung, liver and spleen. Lower concentrations are found in skeletal muscle and brain tissue. Morphine diffuses across the placenta and trace amounts are found in sweat and breast milk. About 35% is protein bound, mainly to albumin. Morphine is metabolised principally in the liver by conjugation with glucuronic acid at the 3-hydroxyl group, and to a much lesser extent to the 3,6-diglucuronide. Elimination half-life is approximately 1.5-2 hours in healthy subjects and 90% of the dose is recovered in urine within 24 hours. Approximately 7-10% of the dose is recovered in faeces, the majority after conjugation and excretion via bile.

INDICATIONS

Morphine is an analgesic used for the symptomatic relief of moderate to severe pain, especially that associated with neoplastic disease, myocardial infarction, and surgery. In addition to relieving pain, morphine also alleviates the anxiety associated with severe pain.

CONTRAINDICATIONS

Morphine is contraindicated in patients hypersensitive to narcotics; in children under one year of age including premature infants or during labour or delivery of premature infants; following biliary tract surgery or surgical anastomosis; paralytic ileus; in patients who are taking or have taken MAO inhibitors within the previous fourteen days.

Morphine is contraindicated in respiratory depression especially in the presence of cyanosis and excessive bronchial secretion. It should be used with caution in patients with decreased respiratory reserve, acute bronchial asthma or other obstructive airway disease, heart failure secondary to chronic pulmonary disease (cor pulmonale), cardiac arrhythmias, severe CNS depression, acute alcoholism, delirium tremens, head injuries, brain tumour, raised cerebrospinal or intracranial pressure, suspected surgical and acute abdomen, paralytic ileus, delayed gastric emptying, severe liver and renal dysfunction, incipient hepatic encephalopathy and convulsive states such as status epilepticus, tetanus due to stimulatory effects on the spinal cord or strychnine poisoning.

PRECAUTIONS

Drug Dependence

Narcotic analgesics have abuse potential, and should only be used with caution in patients with a history of substance abuse and alcohol abuse. Psychological and physical dependence, and tolerance may occur with repeated dosing. Except in patients with terminal conditions, morphine should be restricted to short-term administration for the relief of severe pain not responding to non-narcotic analgesics.

Abrupt withdrawal of morphine in those physically dependent may precipitate withdrawal syndrome, including convulsions. Therefore, patients on prolonged therapy should be withdrawn gradually from the drug if it is no longer required for pain control.

Abuse of Oral Dosage Forms

Abuse of oral dosage forms by parenteral administration can be expected to result in serious adverse events, which may be fatal.

General

Use with extreme caution in patients with head injury and increased intracranial pressure. Respiratory depressant effects and ability to increase cerebrospinal fluid pressure may be exaggerated, and the clinical course obscured.

Therapeutic doses of narcotics may decrease respiratory drive and increase airway resistance to the point of apnoea in patients with acute asthma, chronic obstructive pulmonary disease or cor pulmonale, or those with a substantially decreased pulmonary reserve or respiratory depression. Resuscitative equipment and narcotic antagonists must be readily available.

Morphine should be administered with extreme caution in aged or debilitated patients. Patients with reduced circulating volume, impaired myocardial function or who are receiving sympatholytic drugs should be carefully observed for orthostatic hypotension.

Caution should be taken in prescribing morphine for patients with severely impaired pulmonary, hepatic or renal function and those with hypothyroidism, pancreatitis, biliary tract disorders, adrenocortical insufficiency, prostatic hypertrophy and urethral stricture. Morphine may obscure the diagnosis and clinical course in patients with acute abdominal conditions, and should be used with caution in those with obstructive bowel disorders, or ulcerative colitis. Because of the spasmogenic properties of morphine in the biliary tract and sphincter of Oddi, it should be used only when necessary, and with caution in biliary colic, operations on the biliary tract and acute pancreatitis.

Seizures may result from high doses. Morphine may lower the seizure threshold in patients with a history of seizures. Patients with known seizure disorders should be carefully observed, especially when doses are increased in response to tolerance.

Patients should also be cautioned about the combined effects of morphine with other CNS depressants, including other opioids, phenothiazines, sedative/hypnotics and alcohol.

Morphine should be used with caution pre-operatively or within the first 24 hours, post-operatively.

Gastrointestinal Motility

Decreased gastric emptying associated with morphine may be expected to increase the risks of aspiration either associated with morphine induced CNS depression/coma, or during or after general anaesthesia. As with all oral morphine preparations, RA-MORPH oral solution should be used with caution post-operatively and following abdominal surgery, as morphine impairs intestinal motility and should not be used until the physician is assured of normal bowel function.

Should paralytic ileus be suspected or occur during use, RA-MORPH oral solution should be discontinued immediately.

Cordotomy

Severe pain antagonises the subjective and respiratory depressant actions of morphine. Should pain suddenly subside, these effects may rapidly manifest. Patients who are scheduled for cordotomy or other interruption of pain transmission pathways should not receive RA-MORPH oral solution within 24 hours of the procedure. Pain in the immediate pre-operative period, and any symptoms of opioid withdrawal, should be managed with short-acting analgesic agents. If further treatment with RA-MORPH oral solution is then indicated, the dosage should be adjusted to the new post-operative requirement.

Driving and Operating Dangerous Machinery

Since morphine may cause drowsiness and general impairment of co-ordination, ambulatory patients should be cautioned against driving or operating dangerous machinery.

Use in Pregnancy

Australian Pregnancy Categorisation C: Morphine crosses the placental barrier and its administration during labour may cause respiratory depression in the newborn infant. Morphine should therefore only be used during the last 2-3 hours before expected delivery after weighing the expected benefits for the mother against the potential risk to the foetus.

Morphine has been associated with foetal CNS defects in rodent studies. Safe use in pregnancy prior to labour has not been established in respect to possible adverse effects on foetal development. Morphine may prolong labour by reducing the strength and frequency of uterine contractions.

Infants born of mothers who have been taking morphine chronically may exhibit withdrawal symptoms.

Use in Lactation

Morphine appears in breast milk. Morphine administration to nursing mothers is not recommended.

Paediatric Use

Safety and effectiveness in neonates have not been established.

INTERACTIONS WITH OTHER MEDICINES

Acidifying/alkalising Agents

The clearance of morphine may be increased by acidifying agents and decreased by alkalising agents. Morphine's actions on gastrointestinal motility may influence absorption of other drugs.

Amphetamines, Chlorpromazine and Methocarbamol

The analgesic effect of morphine is potentiated by amphetamines, chlorpromazine and methocarbamol.

CNS Depressants

CNS depressants, such as other opioids, anaesthetics, sedatives, hypnotics, barbiturates, phenothiazines, tranquilisers, chloral hydrate and glutethimide may enhance the depressant effects of morphine. Monoamine oxidase inhibitors (including procarbazine hydrochloride), pyrazolidone antihistamines, cimetidine, beta-blockers and alcohol may also enhance the depressant effect of morphine. The interactive effects may include respiratory depression, hypotension, profound sedation and coma.

Coumarin Derivatives

Morphine may increase the anticoagulant activity of coumarin and other anticoagulants.

Monoamine Oxidase Inhibitors (MAOIs)

Non-selective MAOIs intensify the effects of morphine and other opioid drugs which can cause anxiety, confusion and significant respiratory depression, sometimes leading to coma. Morphine should not be given to patients taking non-selective MAOIs or within 14 days of stopping such treatment. It is not known whether there is an interaction between the selective MAOIs (e.g. moclobemide, selegiline) and morphine, therefore caution is advised with this drug combination.

Ritonavir

Ritonavir may increase the activity of glucuronyl transferases, and co-administration with morphine may result in decreased morphine serum levels and possible loss of analgesic efficacy.

ADVERSE EFFECTS

The major hazards associated with morphine, as with other narcotic analgesics, are respiratory depression and, to a lesser degree, circulatory depression. Respiratory arrest, shock and cardiac arrest have occurred following use of morphine.

Most Common Adverse Effects Requiring Medical Attention

The most frequently observed side effects of narcotic analgesics such as morphine are sedation, nausea and vomiting, constipation and sweating.

Sedation

Most patients experience initial drowsiness partly for pharmacokinetic reasons and partly because patients often recuperate from prolonged fatigue after the relief of persistent pain. Drowsiness usually clears in three to five days and is usually not a reason for concern providing that it is not excessive, or associated with unsteadiness or confusional symptoms. If excessive sedation persists, the reason for it

must be sought. Some of these are: concomitant sedative medications, hepatic or renal failure, exacerbated respiratory failure, higher doses than tolerated in an older patient, or the patient is actually more severely ill than realised. If it is necessary to reduce the dose, it can be carefully increased again after three or four days if it is obvious that the pain is not being well controlled. Dizziness and unsteadiness may be caused by postural hypotension particularly in elderly or debilitated patients. It can be alleviated if the patient lies down. Because of the slower clearance in patients over 50 years of age, an appropriate dose in this age group may be as low as half or less the usual dose in the younger age group.

Nausea and Vomiting

Nausea and vomiting occur frequently after single doses of narcotics or as an early unwanted effect of regular narcotic therapy. When instituting prolonged therapy for chronic pain, the routine prescription of an antiemetic should be considered. Patients taking the equivalent of a single dose of 20 mg or more of morphine usually require an antiemetic during early therapy. Small doses of prochlorperazine or haloperidol are the most frequently prescribed antiemetics. Nausea and vomiting tend to lessen in a week or so but may persist due to narcotic-induced gastric stasis. In such patients, metoclopramide is often useful.

Constipation

Practically all patients become constipated while taking narcotics on a persistent basis. Elderly or bedridden patients may become impacted. It is essential to caution patients in this regard and to institute an appropriate regimen of bowel management at the start of prolonged narcotic therapy. Dietary modification, suitable exercise and softeners, laxatives and other appropriate measures should be used as required.

Other Adverse Reactions Include

Cardiovascular Disorders

Supra-ventricular tachycardia, hypotension, postural hypotension, palpitations, faintness, syncope.

Central Nervous System Disorders

Euphoria, dysphoria, weakness, insomnia, dizziness, confusional symptoms, vertigo.

Occasionally:: hallucinations, visual disturbances, headache, involuntary muscle contraction, asthenia, somnolence, thought abnormalities.

Uncommonly:: malaise, mood changes, seizures, miosis, paraesthesia, agitation.

Gastrointestinal Disorders

Dry mouth, anorexia, dyspepsia, ileus, constipation, abdominal pain and cramps, taste alterations, gastrointestinal disorders, biliary tract cramps.

Uncommonly: elevated hepatic enzymes.

Genitourinary Disorders

Urinary retention or hesitance, amenorrhoea, erectile dysfunction, reduced libido or potency.

Respiratory Disorders

Respiratory depression, bronchospasm, cough decreased.

Endocrine Disorders

Uncommonly:: peripheral oedema, pulmonary oedema, syndrome of inappropriate antidiuretic hormone secretion characterised by hyponatraemia secondary to decreased free-water excretion may be prominent (monitoring of electrolytes may be necessary).

General Disorders

Allergic reaction, anaphylactic and anaphylactoid reactions, drug dependence, facial flushing, pruritus, urticaria, other skin rashes, hypertonia, oedema.

Withdrawal (Abstinence) Syndrome

Physical dependence with or without psychological dependence tends to occur on chronic administration. An abstinence syndrome may be precipitated when narcotic administration is discontinued or narcotic antagonists administered.

The following withdrawal symptoms may be observed after narcotics are discontinued: body aches, diarrhoea, gooseflesh, loss of appetite, nervousness or restlessness, runny nose, sneezing, chills, tremors or shivering, stomach cramps, nausea, trouble with sleeping, unusual increase in sweating and yawning, weakness, tachycardia and unexplained fever. With appropriate medical use of narcotics and gradual withdrawal from the drug, these symptoms are usually mild.

DOSAGE AND ADMINISTRATION

Dosage must be titrated to the patient's needs because of the wide inter-individual variability in plasma concentration required to achieve analgesia.

The usual adult dosage is 5-20 mg (2.5-10 mL of the 2 mg/mL mixture) every 4 hours. The initial dose will depend largely on the patient's previous treatment and should be the lowest compatible with pain control. Treatment should start at a dosage of 5 mg every 4 hours, with further increments as required. With repeat administration, tolerance may develop and the dose may need to be increased gradually in order to control the pain.

Dosage should be lower in elderly patients, those with respiratory, hepatic or renal impairment and in patients receiving CNS depressants.

Dosage in children should be adjusted according to body weight, 0.1-0.2 mg/kg every 4 hours.

OVERDOSAGE

Symptoms and Signs

Serious morphine overdosage is characterised by 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, and sometimes hypotension and bradycardia, and pin point pupils (dilated if hypoxia is severe). Severe overdosage may result in apnoea, circulatory collapse, cardiac arrest and death.

Treatment

Primary attention should be given to the establishment of adequate respiratory exchange through the provision of a patent airway and controlled or assisted ventilation. The narcotic antagonist naloxone hydrochloride is a specific antidote against respiratory depression due to overdosage or as a result of unusual sensitivity to morphine. An appropriate dose of one of the antagonists should therefore be administered, preferably by the intravenous route. The usual initial intravenous (I.V.) adult dose of naloxone is 0.4 mg or higher (please refer to Naloxone Data Sheet for specific directions). Concomitant efforts at respiratory resuscitation should be carried out. Since the duration of action of morphine may exceed that of the antagonist, the patient should be under continued surveillance and doses of the antagonists should be repeated as needed to maintain adequate respiration.

An antagonist should not be administered in the absence of clinically significant respiratory or cardiovascular depression. Oxygen, intravenous fluids, vasopressors and other supportive measures should be used as indicated.

In an individual physically dependent on narcotics, the administration of the usual dose of narcotic antagonist will precipitate an acute withdrawal syndrome. The severity of this syndrome will depend on the degree of physical dependence and the dose of antagonist administered. The use of narcotic antagonists in such individuals should be avoided if possible. If a narcotic antagonist must be used to treat serious respiratory depression in the physically dependent patient, the antagonist should be

administered with extreme care by using dosage titration, commencing with 10 to 20% of the usual recommended initial dose.

Evacuation of gastric contents may be useful in removing unabsorbed drug.

Toxicity

Morphine toxicity may result from overdosage but because of the great inter-individual variation in sensitivity to opioids it is difficult to determine an exact dose of any opioid that is toxic or lethal.

The presence of pain or tolerance tends to diminish the toxic effects of morphine. Published data suggest that in a morphine naive, pain-free individual, the lethal dose would be in excess of 120 mg. Patients on chronic oral morphine therapy have been known to take in excess of 3000 mg/day with no apparent toxicity.

PRESENTATION AND STORAGE CONDITIONS

Morphine Hydrochloride 1 mg/mL, 2 mg/mL, 5 mg/mL, 10 mg/mL each available in a 200 mL bottle.

Store below 30°C. Do not refrigerate. Protect from light. Discard any unused solution 6 months after opening.

MEDICINE CLASSIFICATION

Controlled Drug B1

NAME AND ADDRESS OF THE SPONSOR

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