ינואר 2019

רופא/ה, רוקח/ת נכבד/ה,

הנידון: MCR 10, 30, 100 mg Controlled Release Tablets
עדכון עלונים

מעבדות רפא מבקשת להביא לידיעתכם כי עודכנו העלון לרופא והעלון לצרכן של התכשיר.

המרכיב הפעיל: Morphine Sulphate
התוויה: Prolonged relief of severe pain
בעל הרישום: מעבדות רפא בע"מ

השינויים בעלונים:
בהתאם לדרישת משרד הבריאות להוסיף לכל התכשירים מקבוצת האופיואידים תיבות אזהרה לגבי אינטראקציה עם בנזודיאזפינים והתמכרויות, הוסף בעלונים לפני ההתוויה המידע הבא:

בעלון לצרכן:

תרופות ממשפחת האופיואידים עלולות לגרום להתמכרות, בעיקר בשימוש ממושך, והינן בעלות פוטנציאל לשימוש לרעה ולמינון יתר. תגובה למינון יתר יכולה להתבטא בנשימה איטית ואף לגרום למוות.
וודא כי הנך מכיר את שם התרופה, המינון שהנך לוקח, תדירות המתן, משך הטיפול, תופעות הלוואי והסיכונים הפוטנציאלים.
מידע נוסף אודות הסיכון לתלות והתמכרות ניתן למצוא בקישור:
https://www.health.gov.il/UnitsOffice/HD/MTI/Drugs/risk/DocLib/opioids_he.pdf

נטילת תרופה זו עם תרופות ממשפחת הבנזודיאזפינים, תרופות אחרות המדכאות מערכת עצבים מרכזית (כולל סמים) או אלכוהול עלולה לגרום לתחושת ישנוניות עמוקה, קשיי נשימה (דיכוי נשימתי), תרדמת ומוות.

בעלון לרופא:

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES

- Concomitant use of benzodiazepines and opioids may result in profound sedation, respiratory depression, coma, and death *[*see section *4.5]*.
- Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.
- Limit dosages and durations to the minimum required.
- Follow patients for signs and symptoms of respiratory depression and sedation.

כמו כן, בתגובות בין תרופתיות הוספה קבוצת הבנזודיאזפינים כדוגמא לתרופות סדטיביות.

מצ"ב קישור לעלונים בהם מסומנים השינויים. למידע המלא יש לעיין בעלון בשלמותו.

העלונים נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות (www.health.gov.il), וניתן גם לקבלם מודפסים ע"י פניה לחברת מעבדות רפא בע"מ בטל': 02-5893939 או בכתובת דוא"ל RA@rafa.co.il.

בכבוד רב,

מגר' מיכל וויקוביץ
רוקחת ממונה

DOCTOR LEAFLET

MCR CONTROLLED-RELEASE TABLETS

- Narcotic prescription required -

Composition

Active ingredient:

MCR 10 contains: 10 mg Morphine Sulphate. Brown round coated tablets.

MCR 30 contains: 30 mg Morphine Sulphate. Purple round coated tablets.

MCR 100 contains: 100 mg Morphine Sulphate. Grey round coated tablets.

Inactive ingredients:

Hydroxyethylcellulose, cetostearyl alcohol, magnesium stearate, talc, titanium dioxide.

In addition the tablets contain the following:

MCR 10 contains: Lactose (90 mg), iron oxide (red, yellow and black), polyvinyl alcohol, macrogol/PEG.

MCR 30 contains: Lactose (70 mg), indigo carmine, erythrosine, sunset yellow, hypromellose, polyethylene glycol 400.

MCR 100 contains: Iron oxide (yellow and black), indigo carmine, hypromellose, polyethylene glycol 400.

Action

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

Morphine has for many years been regarded as the most effective agent for the relief of severe pain of various etiologies. The disadvantage of conventional oral morphine therapy is its rapid metabolism following absorption, requiring either the administration of tablets every 4 hours or, alternatively, the use of injectable preparations.

MCR incorporates morphine in a controlled-release system which allows the patient to take the preparation on a 12-hourly basis. The morphine is gradually released and absorbed with controlled bioavailability.

MCR therefore has a significant advantage compared with other, conventional forms of morphine in the relief of severe pain, for those patients who are able to take an oral preparation.

WARNING: RISKS FROM CONCOMITANT USE WITH BENZODIAZEPINES OR OTHER CNS DEPRESSANTS

Concomitant use of opioids with benzodiazepines or other central nervous system (CNS) depressants, including alcohol, may result in profound sedation, respiratory depression, coma, and death [see 'Drug Interactions'].

Reserve concomitant prescribing of these drugs for use in patients for whom alternative treatment options are inadequate.

Limit dosages and durations to the minimum required.

Follow patients for signs and symptoms of respiratory depression and sedation.

Indications

Prolonged relief of severe pain.

Contraindications

Hypersensitivity to any of the tablet constituents.

Respiratory depression, head injury, known or suspected paralytic ileus, 'acute abdomen', delayed gastric emptying, obstructive airways disease, acute or severe bronchial asthma, known morphine sensitivity, acute hepatic disease, concurrent administration of monoamine oxidase inhibitors or within two weeks of discontinuation of their use.

Children under three years of age. Since the controlled release tablets must be swallowed whole, and not broken, chewed, dissolved or crushed, only children who are able to swallow the tables in whole, can use MCR tables.

Not recommended for pre-operative use or for the first 24 hours post-operatively.

Warnings

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, "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 morphine, they gradually increase in intensity, reaching a maximum in 36-72 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 dosage is 30 mg/day. The drug may be discontinued after 2 days at the 30 mg/day dosage level.

Clonidine may reduce anxiety, tachycardia and other autonomic symptoms associated with opioid withdrawal.

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.

Hyperalgesia

Hyperalgesia that will not respond to a further dose increase of morphine sulphate may very rarely occur in particular in high doses. A morphine sulphate dose reduction or change in opioid may be required.

Increased Intracranial Pressure

The respiratory depressant effects and the capacity to elevate cerebrospinal fluid pressure may be markedly exaggerated in the presence of brain tumor, intracranial lesions or preexisting elevated intracranial pressure. Use with extreme caution and only if deemed essential. **The use of morphine in head injury is contraindicated. See Contraindications.** Opioids may obscure the clinical course of patients with head injuries.

Asthma and other Respiratory Conditions

Use with extreme caution in patients with impaired respiratory function. **The use of morphine in obstructive airways disease, acute or severe bronchial asthma is contraindicated. See Contraindications.** Even therapeutic doses of opioids may decrease respiratory drive while simultaneously increasing airway resistance to the point of apnea.

The major risk of opioid excess is 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.

Use with cation in patient with severe cor pulmonale.

Post-Operative Use

MCR tablets 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. **See Contraindications.** If any sign of paralytic ileus becomes apparent, MCR should be immediately discontinued. Due to the possibility of respiratory depression, patients who are scheduled to undergo cordotomy or any other pain-relieving surgical procedure should not receive MCR for 24 hours prior to surgery. Such patients should be transferred to an immediate- release or intravenous morphine preparation to allow for rapid titration.

Following surgery, if further treatment with MCR is warranted, the dosage should be adjusted 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. MCR tablets are not recommended during pregnancy and labour due to the risk of neonatal respiratory depression. 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.

Withdrawal symptoms may be observed in the new born of mothers undergoing chronic treatment.

Use in Labor

Opioids cross the placental barrier and may cause respiratory depression and psycho-physiologic effects in the neonate. Resuscitation may be required; naloxone should be readily available.

Morphine is contraindicated during labor for delivery of a premature infant.

Use in Breastfeeding

MCR is not recommended for use in nursing mothers as morphine is excreted in breast milk.

Use in Children

Morphine should be administered with caution and in carefully determined dosages to small children since they may be relatively sensitive to opioids. Since the controlled release tablets must be swallowed whole, and not broken, chewed, dissolved or crushed, only children who are able to swallow the tables in whole, can use MCR tables. **See Contraindications.** The administration of broken, chewed or crushed tablets may lead to a rapid release and absorption of a potentially fatal dose of morphine.

Accidental consumption of MCR tablets, especially in children, can result in a fatal overdose of morphine.

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.

Precautions

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, myxedema, acute alcoholism, delirium tremens, cerebral arteriosclerosis, fever, kyphoscoliosis, Addison's disease, adrenocortical insufficiency, prostatic

hypertrophy or urethral stricture, toxic psychosis, severe CNS depression, coma, gallbladder dysfunction, inflammatory bowel disorders, opioid dependent patients or a history of alcohol or drug abuse.

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

As with all narcotics a reduction in dosage may be advisable in the elderly, in hypothyroidism and in patients with significantly impaired renal or hepatic function.

Renal and hepatic dysfunction may cause a prolonged duration of action and a cumulative effect.

Seizures may become aggravated, or may occur in individuals without a history of convulsive disorders, if dosage is substantially increased because of tolerance.
Use with caution in patients with convulsive disorders. Morphine may lower the seizure threshold in patients with a history of epilepsy.

The cough reflex is suppressed.

Exercise caution when using opioid analgesics post-operatively and in patients with pulmonary disease. Morphine should be used with caution in patients about to undergo surgery of the biliary tract since it may cause spasm of the sphincter of Oddi. Similarly, morphine should be used with caution in patients with diseases of the biliary tract and pancreatitis.

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

Effects on ability to drive and use machines: This drug may produce drowsiness or dizziness and may modify the patient's reactions to a varying extent depending on the dosage and susceptibility. This medicine can impair cognitive function and can affect a patient's ability to drive safely. 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. If affected, patients should not drive or operate machinery.
Concomitant use of alcohol and MCR tablets may increase the undesirable effects of MCR tablets; concomitant use should be avoided.

It is not always possible to ensure bio-equivalence between different brands of prolonged release morphine products. Therefore, if patients (once titrated to an effective dose) need to be changed from MCR preparations to other slow, sustained or prolonged release morphine or other potent narcotic

analgesic preparations, the physician needs to take into account the need for retitration and clinical assessment.

MCR 10 and MCR 30 tablets contain Lactose.
MCR 30 tablets contain sunset yellow (E110) which may cause allergic reactions.

Adverse Reactions

In normal doses, the commonest side effects of morphine are nausea, vomiting, constipation and drowsiness. With chronic therapy, nausea and vomiting are unusual, but should they occur the tablets can be readily combined with an anti-emetic if required. Constipation may be treated with appropriate laxatives.
The following frequencies are the basis for assessing undesirable effects:
Very common (≥ 1/10)
Common (≥ 1/100 to < 1/10)
Uncommon (≥ 1/1,000 to <1/100)
Rare (≥ 1/10,000 to < 1/1,000)
Very rare (<1/10,000)
Not known (cannot be estimated from the available data)

	Very Common	Common	Uncommon	Not known
Immune system disorders			Allergic reaction	Anaphylactic reaction Anaphylactoid reaction
Psychiatric disorders		Confusion Insomnia	Agitation Euphoria Hallucinations Mood altered	Drug dependence Dysphoria Thinking disturbances
Nervous system disorders		Dizziness Headache Involuntary muscle contractions Somnolence	Convulsions Hypertonia Myoclonus Paraesthesia Syncope	Hyperalgesia (see section 4.4)
Eye disorders			Visual disturbance	Miosis
Ear and labyrinth disorders			Vertigo	
Cardiac disorders			Palpitations	Bradycardia Tachycardia
Vascular disorders			Facial flushing Hypotension	Hypertension
Respiratory thoracic and mediastinal disorders			Bronchospasm Pulmonary oedema Respiratory depression	Cough decreased
Gastrointestinal disorders	Constipation Nausea	Abdominal pain Anorexia Dry mouth Vomiting	Dyspepsia Ileus Taste perversion	
Hepatobiliary disorders			Increased hepatic enzymes	Biliary pain Exacerbation of pancreatitis

Skin and subcutaneous tissue disorders		Hyperhidrosis Rash	Urticaria	
Renal and urinary disorders			Urinary retention	Ureteric spasm
Reproductive system and breast disorders				Amenorrhoea Decreased libido Erectile dysfunction
General disorders and administration site conditions		Asthenic conditions Pruritus	Peripheral oedema	Drug tolerance Drug withdrawal syndrome

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form

http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.gov.il

Drug Interactions

Morphine sulphate should not be co-administered with monoamine oxidase inhibitors or within two weeks of such therapy.

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 such as benzodiazepines , tricyclic antidepressants and other CNS depressants including alcohol (concomitant use of alcohol and MCR tablets should be avoided), anticholinergics or neuromuscular blocking agents, muscle relaxants, antihypertensives and gabapentin . Respiratory depression, hypotension, profound sedation, coma, severe constipation, or urinary retention may result.

Medicinal products that block the action of acetylcholine, for example antihistamines, anti-parkinsons and anti-emetics, may interact with morphine sulphate to potentiate anticholinergic adverse events.

The depressant effects of morphine may be enhanced by chloral hydrate, glutethimide, beta-adrenergic blockers (propranolol) and furazolidone.

Plasma concentrations of morphine sulphate may be reduced by rifampicin.

Cimetidine inhibits the metabolism of morphine sulphate.

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.

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

Although there are no pharmacokinetic data available for concomitant use of ritonavir with morphine sulphate, ritonavir induces the hepatic enzymes responsible for the glucuronidation of morphine sulphate, and may possibly decrease plasma concentrations of morphine sulphate.

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

For the correct and effective use of morphine it is critical to adjust the dosing regimen for each patient individually. The following dosage recommendations are, therefore, only suggested approaches to what is actually a series of clinical decisions in the management of the pain of an individual patient.

The dosage of morphine is individualized according to the severity of the pain, the patient's age and metabolism, previous history of analgesic therapy, and response to morphine.

The correct dosage for any individual patient is that which is sufficient to control pain with no, or tolerable, side effects for a full 12 hours.

MCR should be taken on a regular 12-hourly schedule, at the minimum dose required to achieve acceptable analgesia. For patients who experience end-of-dosing failure, an 8-hourly schedule may be employed.

MCR tablets should be swallowed whole and not chewed, crushed, dissolved or broken. Taking broken, chewed or crushed tablets could lead to the release of a toxic dose of morphine.

The MCR formulation is designed to embody release characteristics appropriate to a 12-hour dosing interval. In adjusting dosing requirements, it is recommended that the dosing interval never be extended beyond 12 hours, because the administration of inappropriately-large single doses may lead to acute overdosage.

It is recommended that patients receiving MCR be supplied with a concurrent prescription for immediate-release morphine, which is then readily available to the patient if breakthrough pain is experienced.

Initial Dose and Titration

In opioid-naive patients, for ease of titration, it is recommended that the initial daily dosage of morphine be established using morphine immediate-release tablets (MIR) using a 4-hourly schedule. The total daily dose should then be divided into two and administered as MCR tablets 12-hourly.

Because of the difficulty of titrating MCR, opioid-naive patients who are started directly on MCR therapy should initially receive a conservative dose of 10-20 mg, 12-hourly, in order to avoid overdosage. The majority of patients will then require an upward titration.

Most patients are controlled on 30-100 mg of MCR 12-hourly. However, smaller doses such as 10 mg 12-hourly may be adequate in some patients, while higher doses may be needed in others. 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.

During the course of treatment the patient may experience breakthrough pain due to an increase in the level of pain or the development of tolerance to the drug. If this breakthrough pain occurs often, an increase in the dosage may be required. If other measures to relieve pain (e.g., nerve blocks) are employed, the morphine dosage should be reduced to an appropriate level (see Physical Dependence).

Conversion from other Opioid Analgesics

Patients who have previously received other opioids to control their pain may be started directly on MCR therapy using the conversion table below:

	Oral	Parenteral
morphine	1	3
methadone	1.5	3
pethidine	0.1	0.4
pentazocine	0.17	0.5
codeine	0.15	
oxycodone	1	
buprenorphine	35	
nalbuphine		3

1 Calculate the total daily dosage of each opioid (mg)

2 Multiply by the conversion factor shown (this gives the daily total in oral morphine equivalents)

3 Divide by two and administer MCR tablets 12-hourly

4 If the patient is receiving more than one opioid, the morphine equivalents of each opioid should be summed to give the total daily dosage of morphine.

The conversion table is only meant to serve as a guide. In all circumstances, the patient's response following conversion from other opioids must be carefully monitored and the dosage of MCR adjusted accordingly. To reduce the dangers of overdosage the conversion factors have been estimated conservatively for use in one direction - from other opioids to MCR. For this reason the table should not be used where the intention is to convert from MCR to other drugs. The conservative nature of the factors presented means that it is likely that further upward titration may be necessary.

Conversion between MCR and MIR

When converting between these forms, the total daily dosage of morphine should remain the same. Therefore, when changing from MCR to MIR, the total daily dosage of MCR should be divided into 6 daily doses of MIR.

When changing from MIR to MCR, the total daily dosage of MIR should be divided into two and administered as MCR 12-hourly.

Conversion from Parenteral Morphine to MCR

A 1:3 ratio of parenteral to oral morphine equivalence is suggested. This ratio is conservative and may underestimate the amount of morphine required. If this is the case, the dose of MCR can be gradually increased to achieve acceptable analgesia.

Children:

For children with severe cancer pain, a starting dose in the range of 0.2 to 0.8 mg morphine per kg body weight 12 hourly is recommended. Doses should then be titrated as for adults. Since the controlled release tablets must be swallowed whole, and not broken, chewed, dissolved or crushed, only children who are able to swallow the tables in whole, can use MCR tables.

Post-operative pain:

MCR tablets are not recommended in the first 24 hours post-operatively or until normal bowel function has returned; thereafter it is suggested that the following dosage schedule be observed at the physician's discretion:

1. MCR 10 tablets (1-2 tablets) 12 hourly to patients under 70 kg.
2. MCR 30 tablets 12 hourly to patients over 70 kg.
3. Elderly - a reduction in dosage may be advisable in the elderly.
4. Children - not recommended.

Supplemental parenteral morphine may be given if required but with careful attention to the total dosages of morphine, and bearing in mind the prolonged effects of morphine in this controlled release formulation.

Overdose

Signs of morphine toxicity and overdose are pin-point pupils, skeletal muscle flaccidity, bradycardia, respiratory depression, hypotension, somnolence and central nervous system depression which can progress to stupor or coma. Circulatory failure and deepening coma may occur in more severe cases. Overdose can result in death. Rhabdomyolysis progressing to renal failure has been reported in opioid overdose.

Crushing and taking the contents of a prolonged release dosage form may lead to the release of morphine in an immediate fashion; this might result in a fatal overdose.

Treatment of morphine overdose:
Primary attention should be given to the establishment of a patent airway and institution of assisted or controlled ventilation.

Oral activated charcoal (50g for adults, 1 g/kg for children) may be considered if a substantial amount has been ingested within one hour, provided the airway can be protected.

The pure opioid antagonists are specific antidotes against the effects of opioid overdose. Other supportive measures should be employed as needed.

In the case of massive overdose, administer naloxone 0.8 mg intravenously. Repeat at 2-3 minute intervals as necessary, or by an infusion of 2 mg in 500 ml of normal saline or 5% dextrose (0.004 mg/ml).

The infusion should be run at a rate related to the previous bolus doses administered and should be in accordance with the patient's response. However, because the duration of action of naloxone is relatively short, the patient must be carefully monitored until spontaneous respiration is reliably re-established. MCR tablets will continue to release and add to the morphine load for up to 12 hours after administration and the management of morphine overdose should be modified accordingly.

For less severe overdose, administer naloxone 0.2 mg intravenously followed by increments of 0.1 mg every 2 minutes if required.

Naloxone should not be administered in the absence of clinically significant respiratory or circulatory depression secondary to morphine overdose. Naloxone should be administered cautiously to persons who are known, or suspected, to be physically dependent on morphine. In such cases, an abrupt or complete reversal of opioid effects may precipitate an acute withdrawal syndrome.

Pharmacological properties

Pharmacodynamic properties

Pharmacotherapeutic group: natural opium alkaloid

ATC code: N02A A01

Morphine acts as an agonist at opioid receptors in the CNS particularly Mu and to a lesser extent Kappa receptors. Mu receptors are thought to mediate supraspinal analgesia, respiratory depression and euphoria, and Kappa receptors, spinal analgesia, miosis and sedation.

Central Nervous System

The principal actions of therapeutic value of morphine are analgesia and sedation (i.e., sleepiness and anxiolysis). Morphine produces respiratory depression by direct action on brain stem respiratory centres.

Morphine depresses the cough reflex by direct effect on the cough centre in the medulla. Antitussive effects may occur with doses lower than those usually required for analgesia. Morphine causes miosis, even in total darkness. Pinpoint pupils are a sign of narcotic overdose but are not pathognomonic (e.g., pontine lesions of haemorrhagic or ischaemic origin may produce similar findings). Marked mydriasis rather than miosis may be seen with hypoxia in the setting of morphine overdose.

Gastrointestinal Tract and Other Smooth Muscle

Morphine causes a reduction in motility associated with an increase in smooth muscle tone in the antrum of the stomach and duodenum. Digestion of food in the small intestine is delayed and propulsive contractions are decreased. Propulsive peristaltic waves in the colon are decreased, while tone is increased to the point of spasm resulting in constipation. Morphine generally increases smooth muscle tone, especially the sphincters of the gastrointestinal and biliary tracts. Morphine may produce spasm of the sphincter of Oddi, thus raising intrabiliary pressure.

Cardiovascular System

Morphine may produce release of histamine with or without associated peripheral vasodilation. Manifestations of histamine release and/or peripheral vasodilation may include pruritus, flushing, red eyes, sweating, and/or orthostatic hypotension.

Endocrine System

Opioids may influence the hypothalamic-pituitary-adrenal or -gonadal axes. Some changes that can be seen include an increase in serum prolactin, and decreases in plasma cortisol and testosterone in association with inappropriately low or normal ACTH, LH or FSH levels. Some premenopausal women may have low oestrogen levels. Clinical symptoms may be manifest from

these hormonal changes.

Other Pharmacological Effects

In vitro and animal studies indicate various effects of natural opioids, such as morphine, on components of the immune system; the clinical significance of these findings is unknown.

Pharmacokinetic properties

Morphine is well absorbed from MCR tablets and, in general, peak plasma concentrations are achieved 1- 5 hours following administration. The availability is complete when compared to an equivalent dose of immediate release oral solution. Morphine is subject to a significant first-pass effect which results in a lower bioavailability when compared to an equivalent intravenous dose.

The major metabolic transformation of morphine is glucuronidation to morphine 3-glucuronide and morphine-6- glucuronide which then undergo renal excretion. These metabolites are excreted in bile and may be subject to hydrolysis and subsequent re-absorption.

Patients are titrated to appropriate pain control using the wide range of strengths of MCR tablets. Consequently, there is a large inter-patient variation in required dosage.

Storage conditions:

Store below 25°C.

Presentation

MCR-10: 50 controlled-release tablets

MCR-30: 50 controlled-release tablets

MCR-100: 20 controlled-release tablets

Registration holder:

Rafa laboratories Ltd. P.O.Box 405, Jerusalem 9100301

Registration numbers:

MCR 10: 0664722515
MCR 30: 0580122516
MCR 100: 0316525386

The format of this leaflet was determined by the Ministry of Health and its content was checked and approved in April 2016.