

For the use only of a Registered Medical Practitioner or a Hospital or a Laboratory

Rx Milrinone Lactate Injection

Sterile Solution for IV Use

Composition:-

Each ml Contains:-

Milrinone Lactate

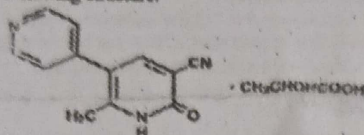
Eq. to anhydrous Milrinone 1 mg.

Water for Injection IP q.s

MILOR मिलौर

DESCRIPTION

Milrinone lactate injection is a member of a class of bipyridine inotropic/vasodilator agents with phosphodiesterase inhibitor activity, distinct from digitalis glycosides or catecholamines. Milrinone lactate is designated chemically as 1, 6-dihydro-2-methyl-6-oxo-[3,4'-bipyridine]-5-carbonitrile lactate and has the following structure:



Milrinone is off-white to tan crystalline compound with a molecular weight of 211.2 and a molecular formula of $C_{11}H_{10}N_2O$. It is slightly soluble in methanol, and very slightly soluble in chloroform and in water. As the lactate salt, it is stable and colourless to pale yellow in solution. Milrinone lactate is available as sterile aqueous solutions of the lactate salt of milrinone for injection or infusion intravenously.

DIVERSE EFFECTS AND PRECAUTIONS

Prolonged oral use of milrinone has increased the mortality rate and milrinone is now only used intravenously for short-term use.

Supraventricular and ventricular arrhythmias, hypotension, angina-like chest pain, and headache have been reported. Hypokalaemia, tremor, and thrombocytopenia may occur. The incidence of arrhythmias may be lower in children whereas the risk of thrombocytopenia may be higher (see Administration in Children, below).

Milrinone should be used with caution in patients with severe obstructive aortic or pulmonary valvular disease or with hypertrophic cardiomyopathy. Since milrinone may facilitate conduction through the atrioventricular node it can increase the ventricular response rate in patients with atrial flutter or fibrillation. Digitalisation should be considered in these patients before milrinone therapy is started. Blood pressure, heart rate, ECG, fluid and electrolyte balance, and renal function should be monitored during milrinone therapy. Milrinone should be given in reduced doses to patients with renal impairment.

PHARMACOLOGY

Pharmacokinetics

Following intravenous injections of 12.5 mcg/kg to 125 mcg/kg to congestive heart failure patients, milrinone had a volume of distribution of 0.38 liters/kg, a mean terminal elimination half-life of 2.3 hours, and a clearance of 0.13 liters/kg/hr. Following intravenous infusions of 0.2 mcg/kg/min to 0.7 mcg/kg/min to congestive heart failure patients, the drug had a volume of distribution of about 0.45 liters/kg, a mean terminal elimination half-life of 2.4 hours, and a clearance of 0.14 liters//. These pharmacokinetic parameters were not dose-dependent, and the area under the plasma concentration versus time curve following injections was significantly dose-dependent.

Milrinone has been shown (by equilibrium dialysis) to be approximately 70% bound to human plasma protein. The primary route of excretion of milrinone in man is via the urine. The major urinary excretions of orally administered milrinone in man are milrinone (83%) and its O-glucuronide metabolite (12%). Elimination in normal subjects via the urine is rapid, with approximately 60% recovered within the first two hours following dosing and approximately 90% recovered within the first eight hours following dosing. The mean renal clearance of milrinone is approximately 0.3 liters/min, indicative of active secretion.

PHARMACODYNAMICS

In patients with heart failure due to depressed myocardial function, milrinone produced a prompt dose and plasma concentration related increase in cardiac output and decreases in pulmonary capillary wedge pressure and vascular resistance, which were accompanied by mild-to-moderate increases in heart rate. Additionally, there is no increased effect on myocardial oxygen consumption. In uncontrolled studies, hemodynamic improvement during intravenous therapy with milrinone was accompanied by clinical symptomatic improvement, but the ability of milrinone to relieve symptoms has not been evaluated in controlled clinical trials. The great majority of patients experience improvements in hemodynamic function within 5 to 15 minutes of the initiation of therapy. In studies in congestive heart failure patients, milrinone when administered as a loading injection followed by a maintenance infusion produced significant mean initial increases in cardiac index of 25 percent, 38 percent, and 42 percent at dose regimens of 37.5 mcg/kg/0.375

mcg/kg/min, 50 mcg/0.5 mcg//, and 75 mcg/kg/0.75 mcg/kg/min, respectively. Over the same range of loading injections and maintenance infusions, pulmonary capillary wedge pressure significantly decreased by 20 percent, 23 percent, and 36 percent, respectively, while systemic vascular resistance significantly decreased by 17 percent, 21 percent, and 37 percent. Mean arterial pressure fell by up to 5 percent at the two lower dose regimens, but by 17 percent at the highest dose. Patients evaluated for 48 hours maintained improvements in hemodynamic function, with no evidence of diminished response (tachyphylaxis). A smaller number of patients have received infusions of milrinone for periods up to 72 hours without evidence of tachyphylaxis.

The duration of therapy should depend upon patient responsiveness.

Milrinone has a favorable inotropic effect in fully digitalized patients without causing signs of glycoside toxicity. Theoretically, in cases of atrial flutter/fibrillation, it is possible that milrinone may increase ventricular response rate because of its slight enhancement of AV node conduction. In these cases, digitalis should be considered prior to the institution of therapy with milrinone.

Improvement in left ventricular function in patients with ischemic heart disease has been observed. The improvement has occurred without inducing symptoms or electrocardiographic signs of myocardial ischemia. The steady-state plasma milrinone concentrations after approximately 6 to 12 hours of unchanging maintenance infusion of 0.5 mcg/kg/min are approximately 200 ng/mL. Near maximum favorable effects of milrinone on cardiac output and pulmonary capillary wedge pressure are seen at plasma milrinone concentrations in the 150 ng/mL to 250 ng/mL range.

USES AND ADMINISTRATION

Milrinone is a phosphodiesterase inhibitor similar to amrinone with positive inotropic and vasodilator activity. It

is, however, reported to have greater positive inotropic activity than amrinone. It is given intravenously, as the lactate, in the short-term management of severe heart failure unresponsive to other forms of therapy and in acute heart failure after cardiac surgery. In some longer-term studies milrinone was given by mouth, but an increased mortality rate was reported. Doses of milrinone lactate are expressed in terms of the base; milrinone lactate 1.43 mg is equivalent to about 1 mg of milrinone. The initial loading dose is the equivalent of milrinone 50 micrograms/kg given over 10 minutes followed by a continuous maintenance infusion. The maintenance infusion may be titrated between 375 and 750 nanograms/kg per minute but a total daily dose of 1.13 mg/kg should not be exceeded. Dosage should be reduced in patients with renal impairment (see below).

ADMINISTRATION IN CHILDREN

Milrinone has been used in children with septic shock or heart failure after cardiac surgery. Pharmacokinetic studies^{1, 2} have suggested that steady-state plasma concentrations of milrinone are lower in children than in adults given similar doses, and that milrinone clearance is faster in children. Higher doses in proportion to body-weight may therefore be necessary in children than in adults. For neonates and children aged 1 month to 18 years with heart failure, low cardiac output after cardiac surgery, or shock, the BNFC recommends an initial dose of 50 to 75 micrograms/kg by intravenous infusion over 30 to 60 minutes, followed by continuous intravenous infusion at a dose of 30 to 45 micrograms/kg per hour (500 to 750 nanograms/kg per minute). The infusion may be continued for 2 to 3 days, but is usually given for 12 hours after cardiac surgery.

Milrinone also appears to be effective for the prevention of low cardiac output in children undergoing cardiac surgery.³ It has been tried for the prevention of low systemic blood flow in premature infants, but further studies are needed to confirm its role.⁴ A study⁵ of adverse effects in children given milrinone has suggested that arrhythmias are less common than in adults whereas thrombocytopenia is more common.

ADMINISTRATION IN RENAL IMPAIRMENT

Doses of milrinone should be reduced in patients with renal impairment. The following doses for maintenance infusion are recommended based on creatinine clearance (CC):

CC 50 mL/minute: 430 nanograms/kg per minute

CC 40 mL/minute: 380 nanograms/kg per minute

CC 30 mL/minute: 330 nanograms/kg per minute

CC 20 mL/minute: 280 nanograms/kg per minute

CC 10 mL/minute: 230 nanograms/kg per minute

CC 5 mL/minute: 200 nanograms/kg per minute

HEART FAILURE

Milrinone is one of several drugs that may be used in heart failure, but because of an increased mortality rate reported following long-term oral use it is usually only given intravenously for short-term management of heart failure unresponsive to other treatments. The PROMISE (Prospective Randomized Milrinone Survival Evaluation) study

1 showed that oral milrinone increased morbidity and mortality in patients with severe chronic heart failure.

However, more recently, longer-term continuous intravenous use for up to 8 weeks has been studied in patients awaiting heart transplantation and appeared to be well tolerated.

2 Intermittent uses on several days a week has also been tried.

3 In patients with acute exacerbation of heart failure, a prospective study 4 found no benefit from the routine use of short-term intravenous milrinone.

WARNINGS

Whether given orally or by continuous or intermittent intravenous infusion, milrinone has not been shown to be safe or effective in the longer (greater than 48 hours) treatment of patients with heart failure. In a multicenter trial of 1088 patients with Class III and IV heart failure, long-term oral treatment with milrinone was associated with no improvement in symptoms and an increased risk of hospitalization and death. In this study, patients with Class IV symptoms appeared to be at particular risk of life-threatening cardiovascular reactions. There is no evidence that milrinone given by long-term continuous or intermittent infusion does not carry a similar risk. The use of milrinone both intravenously and orally has been associated with increased frequency of ventricular arrhythmias, including nonsustained ventricular tachycardia. Long-term oral use has been associated with an increased risk of sudden death. Hence, patients receiving milrinone should be observed closely with the use of continuous electrocardiographic monitoring to allow the prompt detection and management of ventricular arrhythmias.

ANIMAL TOXICITY

Oral and intravenous administration of toxic dosages of milrinone to rats and dogs resulted in myocardial degeneration/fibrosis and endocardial hemorrhage, principally affecting the left ventricular papillary muscles. Coronary vascular lesions characterized by periaortic edema and inflammation have been observed in dogs only. The myocardial/endocardial changes are similar to those produced by beta-adrenergic receptor agonists such as isoproterenol, while the vascular changes are similar to those produced by minoxidil and hydralazine. Doses within the recommended clinical dose range (up to 1.13 mg/day) for congestive heart failure patients have not produced significant adverse effects in animals.

PREGNANCY CATEGORY C

Oral administration of milrinone to pregnant rats and rabbits during organogenesis produced no evidence of teratogenicity at dose levels up to 40 mg/kg/day and 12 mg/kg/day, respectively. Milrinone did not appear to be teratogenic when administered intravenously to pregnant rats at doses up to 3 mg/kg/day (about 2.5 times the maximum recommended clinical intravenous dose) or pregnant rabbits at doses up to 12 mg/kg/day, although an increased resorption rate was apparent at both 8 mg/day and 12 mg/day (intravenous) in the latter species. There are no adequate and well-controlled studies in pregnant women. Milrinone should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

OVERDOSAGE

Doses of milrinone may produce hypotension because of its vasodilator effect. If this occurs, administration of milrinone should be reduced or temporarily discontinued until the patient's condition stabilizes. No specific antidote is known, but general measures for circulatory support should be taken.

STORAGE: - Store in dry place at 20° to 25°C. Protect from light. Do not freeze.

Improper Storage may be Deteriorate the product

MEDICINE: - Keep out of reach of children.

Presentation: - Each pack contain

Milrinone Lactate Injection is supplied as 10 ml single dose vials in a box

Manufactured by Pace Biotech

(A WHO-GMP Certified Company)

Surajpur, Panta Sahib, Dist.- Sambar (H.P.)-173001

Marketed by :



TNT PHARMACEUTICALS

SCO No-30, Rally, Sec-12/A

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