

**Public Assessment Report  
for paediatric studies submitted in accordance  
with Article 45 of Regulation (EC) No1901/2006, as  
amended**

**Corotrop (AT, CZ, DE, SE), Corotrope (BE, FR, GR, HU,  
LU, NL, PL, PT, SK, ES), Primacor (UK)**

**INN: Milrinone**

**AT/W/0004/pdWS/001**

|  |            |
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| <b>Rapporteur:</b>                       | AT         |
| <b>Finalisation procedure (day 120):</b> | 09.04.2011 |
| <b>Date of finalisation of PAR</b>       | 09.06.2011 |

## ADMINISTRATIVE INFORMATION

|  |                               |
|--|-------------------------------|
| Invented name of the medicinal product(s):       | See section VI                |
| INN (or common name) of the active substance(s): | Milrinone                     |
| MAH (s):   | See section VI                |
| Pharmaco-therapeutic group (ATC Code):           | C01CE02                       |
| Pharmaceutical form(s) and strength(s):          | Solution for infusion: 1mg/ml |

## I. EXECUTIVE SUMMARY

This is an assessment of data for Milrinone, as part of the Article 45 EU worksharing procedure for assessment of paediatric studies completed since the Paediatric Regulation entered into force (26 Jan 2007). AT is Rapporteur for this procedure.

As requested by the EMEA in a letter dated 3<sup>rd</sup> February 2010 and in accordance with Article 45 of Regulation EC No 1901/2006 as amended, the Marketing Authorization Holders submitted the following clinical studies, for assessment:

1. **Evan Zucker, Sydney Heyman and Savas Ozdemir.** Reversed Ventilation Perfusion Mismatch Involving a paediatric Patient in Congestive Heart Failure. *The Journal of Nuclear Medicine* 1997 Nov; 38 (11).
2. **Chu CC. et al.** Effect of milrinone on postbypass pulmonary hypertension in children after tetralogy of Fallot repair. *Clin Med J* 2000, 63, 294-300.
3. **Hoffman, TM et al.** Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. *Circulation* 2003; 107: 996-1002
4. **Barton P. et al.** Haemodynamic effect of IV milrinone lactate in paediatric patients with septic shock: a prospective, double-blinded, randomized, placebo-controlled, interventional study. *Chest* 1996, 109, 1032-12.
5. **Rosenzweig EB et al.** Intravenous arginin-vasopressin in children with vasodilatory shock after cardiac surgery. *Circulation* 1999, 100, II 182-6.
6. **Feneck RO. et al.** Intravenous milrinone following cardiac surgery: effect of bolus infusion followed by variable dose maintenance infusion. *J Cardiothorac Anthes* 1992, 6, 554-562.
7. **Wright EM et al.** Milrinone in the treatment of low output states following cardiac surgery. *Eur J Anaesthesiol* 1992, 5 21-26.
8. **Chang AC et al.** Milrinone: systemic and pulmonary haemodynamic effects in neonates after cardiac surgery. *Crit Care Med* 1995, 23, 1907-14.
9. **Lindsay CA. et al.** Pharmacokinetics and pharmacodynamics of milrinone lactate in paediatric patients with septic shock. *J Pediatr* 1998; 132; 329-34.
10. **Ramamoorthy C et al.** Pharmacokinetics and side effects of milrinone in infants and children after open heart surgery. *Anesth Analg* 1998, 86, 283-9.
11. **Rinder CS et al.** Platelet activation and aggregation during cardiopulmonary bypass. *Anesthesiology* 1991, 75, 388-393.
12. **Wernovsky G et al.** Postoperative course and haemodynamic profile after the arterial switch operation in neonates and infants: a comparison of low-flow cardiopulmonary bypass and circulatory arrest. *Circulation*, 1995, 92, 2226-2235.
13. **Sanofi-Synthelabo Inc.** PRIMACORP: Prophylactic Intravenous use of milrinone after cardiac operation in Paediatrics  
2001 Aug.
14. **Charpie JR et al.** Serial blood lactate measurements predict early mortality following neonatal repair or palliation for complex congenital heart disease. *Circulation suppl* 1, 1999, 100 (18) 1399.
15. **Charpie JR et al.** Serial blood lactate measurements predict early outcome after neonatal repair or palliation for complex congenital heart disease. *J Thorac Cardiovasc Surg* 2000, 120, 73-80.

16. **Kikura M et al.** The effects of milrinone on platelets in patients undergoing cardiac surgery. *Anest Analg* 1995, 81, 44 -48.
17. **Bailey JM et al.** The pharmacokinetics of milrinone in paediatric patients after cardiac surgery. *Anaesthesiology* 1999, 90, 1012-18.
18. **Kestin AS et al.** The platelet function defect of cardiopulmonary bypass. *Blood*, 1993, 82, 107-117.
19. **Cai J. et al.** Nitric oxide and milrinone: combined effect on pulmonary circulation after Fontan-type procedure: a prospective, randomized study. *Ann Thorac Surg* 2008, 86, 882-8.
20. **McNamara et al.** Milrinone improves oxygenation in neonates with severe persistent pulmonary hypertension. *Journal of Critical Care* 2006, 21, 217-233.
21. **Duggal B. et al.** Milrinone and low cardiac output following cardiac surgery in infants: is there a direct myocardial effect? *Pediatr Cardiol* 2005, 26, 642-45.
22. **Paradisis M. et al.** Randomized trial of milrinone versus placebo for prevention of low systemic blood flow in very preterm infants. *J Pediatr* 2009, 154, 189-95.
23. **Bailey J.M. et al.** A population pharmacokinetic analysis of milrinone in paediatric patients after cardiac surgery. *Journal of Pharmacokinetics and Pharmacodynamics* 2004, 31(1)43-59.
24. **Paradisis M. et al.** Population pharmacokinetics and dosing regimen design of milrinone in preterm infants. *Arch Dis Child Foetal Neonatal Ed* 2007, 92, 204-209.
25. **Watson S. et al.** Use of milrinone in paediatric care unit. *Paediatrics* 1999, 104, 674-82.
26. **Bassler D. et al.** Neonatal persistent pulmonary hypertension treated with milrinone: four case reports. *Biol Neonate* 2006, 89, 1-5.
27. **Price J.F. et al.** Outpatient continuous parenteral inotropic therapy as bridge to transplantation in children with advanced heart failure. *Journal of Cardiac Failure* 2006, 12, 139-43.
28. **Berg A.M. et al.** Home inotropic therapy in children. *J. Heart Lung Transplant.* 2007, 26(5), 453-57.
29. **Toyoshima LK et al.** In vivo dilatation of the foetal and postnatal ductus arteriosus by inhibition of phosphodiesterase 3 in rats. *Biol Neonate* 2006, 89, 251-56.

SmPC and PL changes are proposed in sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3.

After evaluating the presented data we conclude that the administration of milrinone in children in Europe in the following indication can be recommended:

- *In paediatric population <National approved name> is indicated for the short-term treatment (up to 35 hours) of severe congestive heart failure unresponsive to conventional maintenance therapy (glycosides, diuretics, vasodilators and/or angiotensin converting enzyme (ACE) inhibitors), and for the short-term treatment (up to 35 hours) of paediatric patients with acute heart failure, including low output states following cardiac surgery.*

Dosage recommendations (incl. maximal treatment duration of 35 hours), special warnings (esp. paediatric patients with renal impairment, with patent ductus arteriosus,) adverse events (esp. patent ductus arteriosus, intraventricular haemorrhage) and pharmacological properties concerning paediatric population have to be added to the specific sections of SmPC and PIL.

## II. RECOMMENDATION<sup>1</sup>

### Final proposed SmPC changes

#### 4.1 Therapeutic indications

*In paediatric population <National approved name> is indicated for the short-term treatment (up to 35 hours) of severe congestive heart failure unresponsive to conventional maintenance therapy (glycosides, diuretics, vasodilators and/or angiotensin converting enzyme (ACE) inhibitors), and for the short-term treatment (up to 35 hours) of paediatric patients with acute heart failure, including low output states following cardiac surgery.*

#### 4.2 Posology and method of administration

##### Paediatric population:

*In published studies selected doses for infants and children were:*

- *Intravenous loading dose: 50 to 75 µg/kg administered over 30 to 60 minutes.*
- *Intravenous continuous infusion: To be initiated on the basis of hemodynamic response and the possible onset of undesirable effects between 0.25 to 0.75 µg/kg/min for a period up to 35 hours.*

*In clinical studies on low cardiac output syndrome in infants and children under 6 years of age after corrective surgery for congenital heart disease 75 µg/kg loading dose over 60 minutes followed by a 0.75 µg/kg/min infusion for 35 hours significantly reduced the risk of development of low cardiac output syndrome.*

*Results of pharmacokinetic studies (see section 5.2) have to be taken into consideration.*

##### Renal impairment:

*Due to lack of data the use of milrinone is not recommended in paediatric population with renal impairment (for further information please see section 4.4).*

##### Patent ductus arteriosus:

*If the use of milrinone is desirable in preterm or term infants at risk of/with patent ductus arteriosus, the therapeutic need must be weighed against potential risks (see section 4.4, 4.8, 5.2, and 5.3).*

#### 4.4 Special warnings and precautions for use

##### Paediatric population:

*The following should be considered in addition to the warnings and precautions described for adults:*

*In neonates, following open heart surgery during <National approved name> therapy, monitoring should include heart rate and rhythm, systemic arterial blood pressure via umbilical artery catheter or peripheral catheter, central venous pressure, cardiac index, cardiac output, systemic vascular resistance, pulmonary artery pressure, and atrial pressure. Laboratory values that should be followed are platelet count, serum potassium, liver function, and renal function.*

<sup>1</sup> The recommendation from section V can be copied in this section.

*Frequency of assessment is determined by baseline values, and it is necessary to evaluate the neonate's response to changes in therapy.*

*Literature revealed that in paediatric patients with impaired renal function, there were marked impairment of milrinone clearance and clinically significant side effects, but the specific creatinine clearance at which doses must be adjusted in paediatric patients is still not clear, therefore the use of milrinone is not recommended in this population (see section 4.2).*

*In paediatric patients milrinone should be initiated only if the patient is hemodynamically stable.*

*Caution should be exercised in neonates with risk factors of intraventricular haemorrhage (i.e. preterm infant, low birth weight) since milrinone may induce thrombocytopenia. In clinical studies in paediatric patients, risk of thrombocytopenia increased significantly with duration of infusion. Clinical data suggest that milrinone-related thrombocytopenia is more common in children than in adults (see section 4.8).*

*In clinical studies milrinone appeared to slow the closure of the ductus arteriosus in paediatric population. Therefore, if the use of milrinone is desirable in preterm or term infants at risk of/with patent ductus arteriosus, the therapeutic need must be weighed against potential risks (see section 4.2, 4.8, 5.2, and 5.3).*

#### 4.8 Undesirable effects

##### Blood and lymphatic system disorders

Uncommon: thrombocytopenia\*

Not known: reduction of red blood count and/or haemoglobin concentration

*\*In infants and children, risk of thrombocytopenia increased significantly with duration of infusion. Clinical data suggest that milrinone-related thrombocytopenia is more common in children than in adults (see section 4.4).*

##### Cardiac disorders

Common: ventricular ectopic activity, non-sustained and sustained ventricular tachycardia (see section 4.4), supraventricular arrhythmias

Uncommon: ventricular fibrillation, angina pectoris, chest pain

Very rare: torsades de pointes

The incidence of both supraventricular and ventricular arrhythmias has not been related to the dose or plasma level of milrinone. Life-threatening arrhythmias have commonly been linked to underlying factors such as existing arrhythmias, metabolic abnormalities (e.g. hypokalaemia), abnormal digoxin levels and catheterisation. *Clinical data suggest that milrinone-related arrhythmias are less common in children than in adults.*

##### Paediatric population:

##### Nervous system disorders

Not known: intraventricular haemorrhage (see section 4.4)

##### Congenital, familial, and genetic disorders

Not known: patent ductus arteriosus\*\*\* (see section 4.2, 4.4, 5.2, and 5.3)

*\*\*\*The critical consequences of the patent ductus arteriosus are related to a combination of pulmonary overcirculation with consecutive pulmonary oedema and haemorrhage and of*

*reduced organ perfusion with consecutive intraventricular haemorrhage and necrotizing enterocolitis with possible fatal outcome as described in literature.*

*Long-term safety data for paediatric population are not yet available.*

## 5.1 Pharmacodynamic properties

### Paediatric population:

*Literature review identified clinical studies with patients treated for low cardiac output syndrome following cardiac surgery, septic shock or pulmonary hypertension. The usual dosages were a loading dose of 50 to 75 µg/kg administered over 30 to 60 minutes followed by an intravenous continuous infusion of 0.25 to 0.75 µg/kg/min for a period up to 35 hours. In these studies, milrinone demonstrated an increase of cardiac output, a decrease in cardiac filling pressure, and decrease in systemic and pulmonary vascular resistance, with minimal changes in heart rate and in myocardial oxygen consumption.*

*Studies of a longer use of milrinone are not sufficient to recommend an administration of milrinone during a period of more than 35 hours.*

*Some studies explored the paediatric use of milrinone in patients with nonhyperdynamic septic shock (Barton et al., 1996; Lindsay et al., 1998); the effect of milrinone on postbypass pulmonary hypertension after tetralogy of Fallot repair (Chu et al., 2000); the combined effect of nitric oxide and milrinone on pulmonary circulation after Fontan-type procedure (Cai et al., 2008).*

*The results of these studies were inconclusive. Therefore, the use of milrinone in these indications cannot be recommended.*

## 5.2. Pharmacokinetic properties

### Paediatric population:

*Milrinone is cleared more rapidly in children than in adults, but infants have significantly lower clearance than children, and preterm infants have even lower clearance. As a consequence of this more rapid clearance compared to adults, steady-state plasma concentrations of milrinone were lower in children than in adults. In paediatric population with normal renal function steady-state milrinone plasma concentrations after 6 to 12 hours continuous infusion of 0.5 to 0.75 µg/kg/min were about of 100 to 300 ng/ml.*

*Following intravenous infusion of 0.5 to 0.75 µg/kg/min to neonates, infants and children after open heart surgery, milrinone has a volume of distribution ranging from 0.35 to 0.9 litres/kg with no significant difference across age groups. Following intravenous infusion of 0.5 µg/kg/min to very preterm infants to prevent systemic outflow after birth, milrinone has a volume of distribution of about 0.5 litres/kg.*

*Several pharmacokinetic studies showed that, in paediatric population, clearance increases with increasing age. Infants have significantly lower clearance than children (3.4 to 3.8 ml/kg/min versus 5.9 to 6.7 ml/kg/min). In neonates milrinone clearance was about 1.64 ml/kg/min and preterm infants have even lower clearance (0.64 ml/kg/min).*

*Milrinone has a mean terminal half-life of 2 to 4 hours in infants and children and a mean terminal elimination half-life of 10 hours in preterm infants.*

*It was concluded that the optimal dose of milrinone in paediatric patients in order to obtain plasma levels above the threshold of pharmacodynamic efficacy appeared higher than in adults,*

but that optimal dose in preterms in order to obtain plasma levels above the threshold of pharmacodynamic efficacy appeared lower than in children.

*Patent ductus arteriosus:*

Milrinone is cleared by renal excretion and has a volume of distribution that is restricted to extracellular space which suggests that the fluid overload and hemodynamic changes associated with patent ductus arteriosus may have an effect on distribution and excretion of milrinone (see section 4.2, 4.4, 4.8, and 5.3).

5.3. Preclinical safety data

*Juvenile animals:*

A preclinical study was performed to clarify the ductus-dilating effects of PDE 3 inhibitors in near-term rat pups and their differential effects in near-term and preterm foetal rats. Postnatal ductus arteriosus dilatation by milrinone was studied with three doses (10, 1 and 0.1mg/kg). The dilating effects of milrinone in the foetal ductus constricted by indomethacin were studied by simultaneous administration of milrinone (10, 1 and 0.1mg/kg) and indomethacin (10 mg/kg) to the mother rat at D21 (near-term) and D19 (preterm). This in vivo study has shown that milrinone induces dose-dependent dilation of the foetal and the postnatal constricted ductus arteriosus. Dilating effects were more potent with injection immediately after birth than at 1 hour after birth. In addition, study showed that the premature ductus arteriosus is more sensitive to milrinone than the mature ductus arteriosus (see section 4.2, 4.4, 4.8, and 5.2).

**1. WHAT TM IS AND WHAT IT IS USED FOR**

TM can be used in children for:

- Short term treatment (up to 35 hours) of severe congestive heart failure (where the heart cannot pump enough blood to the rest of the body) when other medicines have not worked
- Short term treatment (up to 35 hours) of acute heart failure after a heart operation i.e. when your heart is having difficulty pumping blood around your body.

**2. BEFORE YOU TAKE TM**

The following should be considered in addition to warnings and precautions described for adults:

**Take special care with TM:**

**Using TM in children:**

Before giving TM infusion, your doctor will check a lot of parameters such as heart rhythm and blood pressure. He/she will order blood tests as well.

The infusion will not start if your child's heart rhythm and blood pressure is not stable.

Please tell your doctor if:

- your child has kidney problems
- your child is a preterm infant or has a low birth weight
- your child has a certain heart problem named Patent Ductus Arteriosus: a connection between 2 major blood vessels (aorta and pulmonary artery) which persists though it should be closed.

In these cases, your doctor will decide if your child will be treated with TM.

**3. HOW TO TAKE TM**

**Use in children:**

- Your doctor should give your child a first dose ranging between 50 and 75 micrograms for every kilogram of his weight, over a period of 30 to 60 minutes.
- This is then followed by a dose ranging from 0.25 to 0.75 micrograms for every kilogram of his/her weight per minute according to your child's response to the treatment and occurrence of side effects. TM can be given for up to 35 hours.

*During infusion, your child will be closely monitored: your doctor will check a lot of parameters such as heart rhythm and blood pressure and blood will be taken to evaluate the response to therapy and occurrence of side effects.*

#### **4. POSSIBLE SIDE EFFECTS**

*In addition to side effects observed in adults, the following were reported in children:*

*Frequency not known:*

- *bleeding into the fluid-filled areas (ventricles) surrounded by the brain (intraventricular haemorrhage)*
- *a heart problem known as Patent Ductus Arteriosus: a connection between 2 major blood vessels (aorta and pulmonary artery) which persists though it should be closed. This can cause excess fluid in the lungs, bleedings, destruction of the bowel or part of the bowel and possibly be fatal.*

*Moreover, compared to adults, decrease in the number of platelets in the blood seems to occur more often in children and the risk of this side effect is increased with the duration of the TM infusion. Heart rhythm troubles seem to occur less often in children than in adults.*

### **III. INTRODUCTION**

One MAH submitted 29 completed paediatric studies for Milrinone, in accordance with Article 45 of the Regulation (EC) No 1901/2006, as amended on medicinal products for paediatric use.

A short critical expert overview has also been provided.

The MAH stated that the submitted paediatric studies influence the benefit risk for <name of the medicinal product> and that there is a consequential regulatory action.

The MAH proposed the following SmPC wording (*italic letters*):

#### **4. CLINICAL PARTICULARS**

##### **4.2. Posology and method of administration**

Paediatric population

- Intravenous

In published studies doses for children were:

- o Loading dose: 50 to 75 µg/kg administered over 30 to 60 minutes.
- o Infusion: 0.25 to 0.50 µg/kg/min for a period of 1 to 3 days.

##### **4.4. Special warnings and precautions for use**

Paediatric population

There have been reports of patent ductus arteriosus when milrinone was administered to premature infants.

## **5. PHARMACOLOGICAL PROPERTIES**

### **5.1. Pharmacodynamic properties**

*No controlled paediatric studies have been undertaken.*

*Literature review identified 11 efficacy studies in 219 paediatric patients. These patients were included after cardiac surgery, septic shock or pulmonary hypertension. The usual dosages were a loading dose of 50 to 75 µg/kg followed by an infusion of 0.25 to 0.50 µg/kg/min for a period of 1 to 3 days. In these studies, milrinone demonstrated an increase of cardiac output, a decrease in cardiac filling pressure, a decrease in systemic and pulmonary vascular resistance, with minimal changes in heart rate and in myocardial oxygen consumption.*

### **5.2. Pharmacokinetic properties**

*No controlled paediatric studies have been undertaken.*

*Published pharmacokinetic studies have demonstrated that the pharmacokinetic characteristics of milrinone were modified in infants and children, as compared in adults. Steady-state plasma concentrations of milrinone were lower in children than in adults, and milrinone clearance was faster in children. It was concluded that the optimal dose of milrinone in paediatric patients in order to obtain plasma levels above the threshold of pharmacodynamic efficacy appeared higher than in adults.*

### **5.3. Preclinical safety data**

*No preclinical studies have been performed in juvenile animals.*

*In published studies patent ductus arteriosus was observed in juvenile animals.*

In addition, the following documentation has been included as per the procedural guidance:

- A line listing
- An annex including SPC wording related to the paediatric use of the medicinal product (see above)

## **III.1 Background**

Heart failure occurs in children as a consequence of congenital or acquired disorders, either systemic or involving only the cardiovascular system. Heart failure due to congenital structural heart disease typically presents early in life, resulting from abnormal cardiac chamber morphology, valvular function, or circulatory connections. Disorders affecting the myocardium are diverse and may arise from genetic abnormalities or can be secondary to an acquired disease like myocarditis or septic shock induced by bacteria, viruses, or fungi or their biological products or toxic exposure like anthracycline toxicity. Genetically determined diseases of the myocardium (cardiomyopathies) may occasionally be apparent at birth but more frequently manifest later in infancy, childhood, or indeed during adult life.

Many paediatric patients undergoing cardiac surgery involving cardiopulmonary bypass have a predictable fall in cardiac index 6 to 18 hours after surgery. Low cardiac output syndrome,

affecting up to 25% of neonates and young children after cardiac surgery, associated with a marked decline in cardiac index, an elevation of systemic vascular resistance and of pulmonary vascular resistance, contributes to postoperative morbidity and mortality.<sup>6</sup> The distribution of proportions of decline in cardiac index and elevation of systemic vascular resistance and in pulmonary vascular resistance depends on type of cardiac surgery performed. In children who undergo corrective surgery for tetralogy of Fallot or Fontan procedure, postoperative pulmonary hypertension is a major challenge.

It is important to note that all known diagnoses account for only around 35% of patients in most paediatric series with the remainder being idiopathic. Moderate to severe congenital defects of the heart occur in less than 0.6% of live births. Heart failure associated with congenital defects of the heart occurs in approximately 20% of all patients. Cardiomyopathies occur in only eight per 100000 infants and even more infrequently in older children.<sup>1</sup> The incidence of symptomatic heart failure has declined compared to the past, with Massin et al.<sup>11</sup> now reporting that only 10% of their patients in tertiary-care paediatric cardiology care setting developed symptomatic heart failure. In the latter series, congenital abnormalities still account for over 50% of the cases, and most patients are under 12 months of age at diagnosis. The outcome of children with cardiomyopathy however remains poor, with a 5-year risk for death or cardiac transplantation of around 50% for patients with dilated cardiomyopathy commonly cited.<sup>2</sup> The incidence of heart failure is much lower in a paediatric population than in an adult population as the predominant cause of heart failure in a modern adult civilized society is coronary disease.<sup>4</sup>

*Heart failure has a tendency to manifest with one of two common stereotypical syndromes in infants and children:*

- 1) Increased systolic output with pulmonary overcirculation. The most common causes are large ventricular septal defects, moderate to large patent ductus arteriosus or persistent aortopulmonary connections. The typical age at presentation with hyperdynamic pulses, sweating, pallor and tachypnea is between 2 weeks and 6 months.<sup>1</sup>
- 2) Low cardiac output, especially following cardiac surgery or with septic shock. With mechanical obstruction to aortic outflow (hypoplastic left heart, critical aortic stenosis, severe coarctation of the aorta), the infant will present with decreased pulses, pallor, tachypnea and frank circulatory collapse between 2 and 14 days. This is distinguished from lack of compensatory overventilation which is seen in patients with hypoxemia from birth due to cyanotic heart disease. If infants with cardiomyopathy develop heart failure, they will present with low cardiac output symptoms as post cardiac surgery complications are characterised.<sup>1</sup>

Pulmonary hypertension (WHO Group I & II) following cardiopulmonary bypass in paediatric cardiac surgery is a well-known cause of a right ventricular failure, especially in children who undergo corrective surgery for tetralogy of Fallot or Fontan procedure. Elevation of pulmonary vascular resistance has been widely recognized as one of the most important risk factors contributing to haemodynamic compromise and early mortality after surgery.<sup>9, 10</sup>

Patients with septic shock initially present with severe hypovolemia, peripheral vasodilation, and absolute volume loss. The net result is diminished ventricular filling and depressed stroke volumes. Exacerbation of the ill effects of diminished preload is myocardial dysfunction. If septic shock progresses, the cardiac index becomes inappropriately low, systemic vascular resistance index becomes inappropriately high, and total body oxygen consumption falls (hypodynamic state). Progressive deterioration in oxygen consumption and oxygen extraction may lead to further deterioration in intracellular viability and death may ensue despite aggressive support.<sup>8</sup>

### *Pharmacological management of heart failure in infants and children:*

The goals of managing heart failure in infants and children are to alleviate symptoms of congestion and oedema, to improve the haemodynamic profile, without causing myocardial injury, and to preserve renal function.

Maximal anticongestive heart failure management, including diuretics, afterload-reducing agents (angiotensin-converting enzyme inhibitors), potassium-sparing agents (spironolactone), and  $\beta$ -blockers (metoprolol, carvedilol), may improve symptoms and cardiac function in selected patients. Candidates with elevated but reactive pulmonary vascular resistance may be treated with calcium channel blockers as well as prostanoids (prostacyclin), endothelin receptor antagonists (bosentan), and phosphodiesterase type 5 inhibitors (sildenafil). Most paediatric heart transplant candidates require higher levels of cardiac support before transplantation, including inotropic agents, intravenous diuretics, ventilatory support, and even mechanical circulatory support.<sup>5</sup>

The role of inotropic support including cardiac glycosides such as digoxin, catecholamines beta-agonists such as dopamine, epinephrine and norepinephrine, and phosphodiesterase inhibitors such as amrinone and milrinone for the failing heart is controversially discussed: While an increase in cardiac output is desirable, sustained use of inotropic agents is controversial. Several studies have found an increased hospital and medium-term mortality following their intermittent use in adult patients with heart failure.<sup>1</sup>

The use of catecholamines has several drawbacks, including increased myocardial oxygen consumption, heart rate, afterload, and risk of arrhythmia and  $\beta$ -adrenergic receptors may be down-regulated as well in patients with pre-existing heart failure. The pharmacological action of digoxin usually results in ECG changes, including ST depression or T wave inversion, which do not indicate toxicity. PR interval prolongation, however, may be a sign of digoxin toxicity. Additionally, increased intracellular  $Ca^{2+}$  may cause bigeminy, eventually ventricular tachycardia or fibrillation. The combination of increased (atrial) arrhythmogenesis and inhibited atrio-ventricular conduction is said to be pathognomonic of digoxin toxicity, which is dose-limiting. Because of these potential limitations of catecholamines and digoxin, phosphodiesterase inhibitors such as amrinone and milrinone are increasingly used for treatment of post-operative low cardiac output syndrome in infants and children.<sup>6</sup> Of note, it is important to integrate the use of inotropic, vasodilator, and diuretic therapy in a fashion that suits a patient's haemodynamic needs following a general categorical approach.<sup>1</sup>

In septic shock following volume resuscitation, inotropic and vasoactive agents are commonly utilized to increase cardiac output, maintain adequate blood pressure, and enhance oxygen delivery to the tissues. Myocardial hyporesponsiveness to catecholamine administration during septic shock has been documented by several investigators.<sup>8</sup> Because of this potential limitation, phosphodiesterase inhibitors such as amrinone and milrinone are increasingly off-label used for treatment of septic shock in infants and children.<sup>8</sup>

Although pathogenesis differs between WHO Groups I and II of the Venice 2003 Revised Classification system for pulmonary hypertension and conventional treatment depends on underlying pathogenesis, the independent inotropic and selective pulmonary vasodilatory effects of milrinone are increasingly off-label used for treatment of postoperative pulmonary hypertension (WHO Group I & II) in infants and children.<sup>9</sup>

Milrinone, a bipyridine derivative and a phosphodiesterase III inhibitor has moderate inotropic effects, moderate vasodilator properties and increases relaxation velocity. It results in a marked increase in cardiac index and a drop in pulmonary capillary wedge pressure and improved mixed

venous oxygen saturations, increased coronary venous flow, and minimal effects on mean arterial pressure. However milrinone has also been associated with arrhythmias and adverse haemodynamic effects.<sup>3</sup> Because of its potent vasodilatory effect and long half-life, milrinone should be initiated only if the patient is haemodynamically stable.<sup>5</sup> Milrinone has been shown to be efficacious in the management of low cardiac output in neonates, infants and children following cardiovascular surgery. Because it increases cardiac contractility and decreases afterload, milrinone could be first-line drug of choice over the more traditional catecholamines. Milrinone could be useful prior to surgery in neonates with poor myocardial function and increased afterload related to congenital heart defects. In cases of poor cardiac output caused by neonatal sepsis and for treatment of pulmonary hypertension following cardiac surgery which belongs to WHO Group I & II milrinone could be useful.<sup>9</sup> But more clinical research is needed to fully explore these potential indications.

Milrinone is currently registered and marketed in about 40 countries.

The currently approved indications are (for details please refer to Annex I):

- Short-term therapy (up to 48 h) of severe chronic heart failure that is refractory to cardiac glycosides, diuretics, vasodilators and/or ACE inhibitors (AT)
- Corotrope solution for infusion is intended for the short-lasting intravenous treatment of congestive cardiac decompensation (BE, LU)
- Short-term treatment of severe congestive heart failure in patients who do not adequately respond to common oral therapy; short-term treatment of patients with low output following cardiac surgery. The medicinal product is intended for adults (CZ)
- Short-term treatment of acute heart failure (FR)
- Short-term treatment of severe heart failure which is unresponsive to conventional maintenance therapy (cardiac glycosides, diuretics and vasodilators). During Corotrop infusion, continuous monitoring (ECG, blood pressure) must be guaranteed (DE)
- Congestive heart failure in patients not responding to therapy with digitalis, diuretics and vasodilators. Patients treated with Corotrope should be closely monitored during the intravenous infusion (GR)
- Corotrope is indicated for the short-term intravenous treatment of heart failure, including low output states following cardiac surgery (HU)
- Corotrope is indicated for chronic congestive heart failure when administered under continued monitoring in an intensive care unit for a maximum of 48 hours. Treatment of low output states following cardiac surgery (NL)
- Corotrope is indicated for a short-term intravenous therapy of circulatory failure, including low cardiac output syndrome after cardiosurgical procedures (PL)
- Milrinone is indicated for the short-term intravenous therapy of heart failure, including low output states following cardiac surgery (PT)
- Short-term intravenous treatment of heart failure and low output states following cardiac surgery (SK)
- Corotrope is indicated for short-term treatment of acute congestive heart failure (ES)
- Short-term treatment of pronounced left ventricular heart failure in which the usual therapy is either inadequately effective or unsuitable (SE)
- Primacor Injection is indicated for the short-term treatment of severe congestive heart failure unresponsive to conventional maintenance therapy, and for the treatment of patients with acute heart failure, including low output states following cardiac surgery (UK)

The currently approved dosage recommendations for paediatric population are:

- Sufficient experience in controlled clinical studies is not available with regard to the safety and effectiveness of Corotrop in children and adolescents up to the age of 18.

Therefore the administration of Corotrop to children and adolescents up to the age of 18 is not recommended (AT)

- Since safety and efficacy in children have not been established, the medication will be used in children under 18 years of age only if the anticipated potential benefits outweigh possible risks (BE, LU)
- Safety and effectiveness in children have not been established since milrinone is not recommended for children (CZ)
- The use of milrinone in children is not recommended as safety and efficacy in children have not been established (FR)
- Safety and effectiveness in children have not been established (GR)
- Safety and effectiveness in children and adolescents under 18 years of age have not been established. Therefore milrinone lactate should be used only if the potential benefits outweigh the potential risks (HU)
- As safety and efficacy in children have not been established, the use of Corotrope in children is not recommended (NL)
- Safety of use and efficacy in children have not been established. Therefore, milrinone can be used only, if expected benefits outweigh the potential risk (PL)
- Safety and effectiveness in children have not been established (< 18 years of age). Milrinone should only be used if potential benefits outweigh the potential risks (PT)
- Safety and effectiveness in children have not been established. Milrinone should be used only if potential benefits outweigh the potential risks (SK)
- Safety and effectiveness of the lactate of milrinone in children have not been established. Therefore, the lactate of milrinone will have to be used only if the potential benefits outweigh the potential risks (ES)
- Corotrop is not recommended for children, since the effect and safety of the substance have not been documented (SE)
- Safety and effectiveness in children and adolescents under 18 years of age have not been established. Primacor Injection should be used only if the potential benefits outweigh the potential risks (UK)
- Corotrop is contraindicated for use in children less than 12 years of age (see section 4.3). In adolescents (12–18 years of age) the safety and efficacy of Corotrop have not been established. Corotrop may only be used if the potential benefits outweigh the potential risks (DE)

## References

1. Kantor P.F., Mertens L.L. Clinical practice. Heart failure in children. Part I: clinical evaluation, diagnostic testing, and initial medical management. *Eur J Pediatr* 2010; 169: 269-279.
2. Massin M.M.M.A.I., Dessy H. Epidemiology of heart failure in tertiary paediatric centre. *Clin Cardiol* 2008; 31: 388-391.
3. Rettig W.J., Schieffer H.J. Acute effects of intravenous milrinone in heart failure. *Eur Heart J* 1989; 10 (Suppl C): 39-43.
4. Macicek S.M. et al. Acute heart failure syndromes in the paediatric emergency department. *Paediatrics* 2009; 124: 240-246.
5. Gazit A.Z. et al. Pharmaceutical management of decompensated heart failure syndrome in children. Current state of art and new approach. *Curr. Treat. Options cardiovasc. Med.* 2009; 12(1): 403-409.
6. Hoffman T.M. et al. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease. *Circulation* 2003; 107: 996-1002.
7. Bell S.G. Milrinone. *Neonatal Network* 2003; 22(4): 61-63.

8. Barton P. et al. Haemodynamic effect of IV milrinone lactate in paediatric patients with septic shock: a prospective, double-blinded, randomized, placebo-controlled, interventional study.  
Chest 1996, 109, 1032-12.
9. Chu CC. et al. Effect of milrinone on postbypass pulmonary hypertension in children after tetralogy of Fallot repair.  
Clin Med J 2000, 63, 294-300.
10. Cai J. et al. Nitric oxide and milrinone: combined effect on pulmonary circulation after Fontan-type procedure: a prospective, randomized study.  
Ann Thorac Surg 2008, 86, 882-8.
11. Massin M.M.M.A.I. et al. Epidemiology of heart failure in a tertiary paediatric centre.  
Clin Cardiol 2008, 31, 388-91.

## IV. SCIENTIFIC DISCUSSION

### IV.1 Information on the pharmaceutical formulation used in the clinical study(ies)

Pharmaceutical formulations used in the studies:  
Injectable solution for intravenous infusion  
Corotrope 10mg/20mg Amp.

### IV.2 Non-clinical aspects

#### 1. Introduction

The MAH submitted 1 report for:

- **Toyoshima LK et al.** In vivo dilatation of the foetal and postnatal ductus arteriosus by inhibition of phosphodiesterase 3 in rats.  
Biol Neonate 2006, 89, 251-56.

#### 2. Non clinical study(ies)

***Toyoshima LK et al. In vivo dilatation of the foetal and postnatal ductus arteriosus by inhibition of phosphodiesterase 3 in rats.  
Biol Neonate 2006, 89, 251-56.***

#### ➤ Description

**Abstract**

**Background:** Clinically, it appears that phosphodiesterase 3 (PDE 3) inhibitors, which are used for acute cardiac failure in premature infants, dilate the ductus arteriosus (DA). **Objectives:** To clarify the ductus-dilating effects of PDE 3 inhibitors in near-term rat pups and their differential effects in near-term and preterm fetal rats, in in vivo studies. **Methods:** The in vivo ductal diameter of rat pups and fetuses was measured using a rapid whole-body freezing method, by cutting on a freezing microtome and measuring with a microscope and micrometer. Eight to twenty pups and fetuses were studied in each group. Milrinone and amrinone (specific inhibitors of PDE 3) were injected into 1-hour-old pups and the DA was studied 0.5 and 1 h later. The differential effects of these PDE 3 inhibitors on the near-term and preterm ductus were studied by injecting indomethacin (10 mg/kg) and PDE 3 inhibitors into 21D (21st day of pregnancy: term-21.5 days) and 19D dams and studying the fetal ductus 4 and 8 h later. **Results:** Milrinone and amrinone dilated the postnatal ductus dose-dependently. Large doses of these drugs dilated it completely, and clinically equivalent doses dilated it minimally. Milrinone and amrinone prevent-

ed constriction of the fetal ductus by indomethacin. Their ductus-dilating effects were more potent in the preterm than in the near-term fetuses, and clinically equivalent doses of these PDE 3 inhibitors dilated preterm ductus completely. **Conclusion:** In rats, PDE 3 inhibitors reopen the constricted postnatal DA slightly. PDE 3 inhibitors dilate the fetal DA constricted with indomethacin effectively and more sensitively in preterm than in near-term fetuses.

**➤ Methods****• Study design**

The aim of this study was to clarify the ductus-dilating effects of PDE 3 inhibitors in near-term rat pups and their differential effects in near-term and preterm foetal rats, in in vivo studies.

**• Species/strain/age/dose**

The in vivo ductal diameter of rat pups and foetuses was measured using rapid whole-body freezing method, by cutting on a freezing microtome and measuring with a microscope and micrometer. Eight to fourteen pups and foetuses were studied for each drug, dose and time.

**Postnatal Studies:** Postnatal ductus arteriosus dilatation by milrinone was studied with three doses (10, 1 and 0.1mg/kg). Milrinone in 0.05ml physiological saline was injected intraperitoneally into the postnatal rat at 1 hour after birth. The ductal diameter was measured at 0.5 and 1 h after injection. In order to compare the prophylactic effect of postnatal ductus closure by reopening an already constricted ductus arteriosus, an additional study was performed by injecting milrinone to the rat pup within 2 min after birth, and studying the ductus at 1 h after birth.

**Foetal Studies:** The dilating effects of milrinone in the foetal ductus constricted by indomethacin were studied by simultaneous administration of milrinone and indomethacin to the mother rat, and examination 4 and 8 h later. Indomethacin (10 mg/kg) was administered through a nasogastric tube with 2 ml of water. Milrinone was injected intraperitoneally. The foetal ductus arteriosus dilating effects of milrinone were studied using 2 pregnant rats for each drug, dose and time. Foetuses with injection of a vehicle to the dams served as controls. Eight to twelve foetuses from each litter were studied.

***In Near-term (21D) foetes:***

Foetal ductal dilatation by milrinone was studied with 3 doses (10, 1 and 0.1mg/kg) of the drug at 4 and 8 h after administration.

*In Pre-term (19D) foetes:*

Foetal ductal dilatation by milrinone was studied with 3 doses (10, 1 and 0.1mg/kg) of the drug at 4 and 8 h after administration.

## ➤ Results

*Postnatal Studies:* With milrinone postnatal death was observed with the maximum dose in 2 of 10 pups. Milrinone dilated the postnatal ductus arteriosus both immediately and 1 h after birth, dose-dependently. The largest dose dilated the constricted postnatal ductus arteriosus completely. The smallest dose dilated the ductus arteriosus mildly, but significantly ( $p < 0.05$ ). The dilating effects were more potent with injection immediately after birth than at 1 h after birth. The difference was significant ( $p < 0.05$ ) with 1 mg/kg.

*Foetal Studies:* Orogastric administration of indomethacin to near-term rats induced severe foetal ductus arteriosus constriction. Milrinone dilated the 21D foetal ductus arteriosus dose-dependently. The largest dose prevented constriction of the foetal ductus arteriosus by indomethacin completely, but the smallest dose, did not prevent it. Orogastric administration of indomethacin to preterm rats induced only moderate ductus arteriosus constriction. Milrinone dilated the foetal indomethacin-constricted 19D preterm ductus arteriosus dose-dependently. Even the smallest clinical dose was effective in dilating the ductus at 4h ( $p < 0.05$ ).

### 3. Discussion on non clinical aspects

This in vivo study has shown that milrinone induces dose-dependent dilation of the foetal and the postnatal constricted ductus arteriosus. In addition, study showed that the premature ductus arteriosus is more sensitive than the mature ductus arteriosus to milrinone. A study limitation was that blood concentration of milrinone could not be measured as small rats were used. This study has to be mentioned in section 5.3 in the SmPC.

## IV.3 <Clinical aspects>

### 1. Introduction

The MAH submitted 28 reports for:

- **Rinder CS et al.** Platelet activation and aggregation during cardiopulmonary bypass. *Anesthesiology* 1991, 75, 388-393.
- **Kestin AS et al.** The platelet function defect of cardiopulmonary bypass. *Blood*, 1993, 82, 107-117.
- **Wernovsky G et al.** Postoperative course and haemodynamic profile after the arterial switch operation in neonates and infants: a comparison of low-flow cardiopulmonary bypass and circulatory arrest. *Circulation*, 1995, 92, 2226-2235.
- **Charpie JR et al.** Serial blood lactate measurements predict early mortality following neonatal repair or palliation for complex congenital heart disease. *Circulation suppl* 1, 1999, 100 (18), 1399.
- **Charpie JR et al.** Serial blood lactate measurements predict early outcome after neonatal repair or palliation for complex congenital heart disease. *J Thorac Cardiovasc Surg* 2000, 120, 73-80.
- **Evan Zucker, Sydney Heyman and Savas Ozdemir.** Reversed ventilation perfusion mismatch involving a paediatric patient in congestive heart failure. *The Journal of Nuclear Medicine* 1997 Nov, 38 (11).
- **Rosenzweig EB et al.** Intravenous arginin-vasopressin in children with vasodilatory shock after cardiac surgery. *Circulation* 1999, 100, II 182-6.

- **Lindsay CA. et al.** Pharmacokinetics and pharmacodynamics of milrinone lactate in paediatric patients with septic shock.  
J Pediatr 1998; 132; 329-34.
- **Ramamoorthy C et al.** Pharmacokinetics and side effects of milrinone in infants and children after open heart surgery.  
Anesth Analg 1998, 86, 283-9.
- **Sanofi-Synthelabo Inc.** PRIMACORP: Prophylactic intravenous use of milrinone after cardiac operation in paediatrics.  
2001 Aug.
- **Bailey JM et al.** The pharmacokinetics of milrinone in paediatric patients after cardiac surgery.  
Anaesthesiology 1999, 90, 1012-18.
- **Bailey J.M. et al.** A population pharmacokinetic analysis of milrinone in paediatric patients after cardiac surgery.  
Journal of Pharmacokinetics and Pharmacodynamics 2004, 31(1)43-59.
- **Paradisis M. et al.** Population pharmacokinetics and dosing regimen design of milrinone in preterm infants.  
Arch Dis Child Foetal Neonatal Ed 2007, 92, 204-209.
- **Feneck RO. et al.** Intravenous milrinone following cardiac surgery: effect of bolus infusion followed by variable dose maintenance infusion.  
J Cardiothorac Anthes 1992, 6, 554-562.
- **Wright EM et al.** Milrinone in the treatment of low output states following cardiac surgery.  
Eur J Anaesthesiol 1992, 5 21-26.
- **Barton P. et al.** Haemodynamic effect of IV milrinone lactate in paediatric patients with septic shock: a prospective, double-blinded, randomized, placebo-controlled, interventional study.  
Chest 1996, 109, 1032-12.
- **Hoffman, TM et al.** Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease.  
Circulation 2003, 107, 996-1002
- **Chang AC et al.** Milrinone: systemic and pulmonary haemodynamic effects in neonates after cardiac surgery.  
Crit Care Med 1995, 23, 1907-14.
- **Chu CC. et al.** Effect of milrinone on postbypass pulmonary hypertension in children after tetralogy of Fallot repair.  
Clin Med J 2000, 63, 294-300.
- **Kikura M et al.** The effects of milrinone on platelets in patients undergoing cardiac surgery.  
Anesth Analg 1995, 81, 44 -48.
- **Cai J. et al.** Nitric oxide and milrinone: combined effect on pulmonary circulation after Fontan-type procedure: a prospective, randomized study.  
Ann Thorac Surg 2008, 86, 882-8.
- **McNamara P.J. et al.** Milrinone improves oxygenation in neonates with severe persistent pulmonary hypertension.  
Journal of Critical Care 2006, 21, 217-233.
- **Duggal B. et al.** Milrinone and low cardiac output following cardiac surgery in infants: is there a direct myocardial effect?  
Pediatr Cardiol 2005, 26, 642-45.
- **Paradisis M. et al.** Randomized trial of milrinone versus placebo for prevention of low systemic blood flow in very preterm infants.  
J Pediatr 2009, 154, 189-95.
- **Watson S. et al.** Use of milrinone in paediatric care unit.  
Paediatrics 1999, 104, 674-82.
- **Bassler D. et al.** Neonatal persistent pulmonary hypertension treated with milrinone: four case reports.  
Biol Neonate 2006, 89, 1-5.
- **Price J.F. et al.** Outpatient continuous parenteral inotropic therapy as bridge to transplantation in children with advanced heart failure.  
Journal of Cardiac Failure 2006, 12, 139-43.

- **Berg A.M. et al.** Home inotropic therapy in children. *J. Heart Lung Transplant.* 2007, 26(5), 453-57.

## 2. Clinical study(ies)

**Rinder CS et al.** Platelet activation and aggregation during cardiopulmonary bypass. *Anaesthesiology* 1991, 75, 388-393.

### ➤ Description

Increases in plasma concentrations of platelet granule products such as platelet factor 4 and  $\beta$ -thromboglobulin during cardiopulmonary bypass suggest that platelets are activated during extracorporeal circulation. Subsequent circulation of these activated platelets may be responsible for the ubiquitous platelet dysfunction associated with cardiopulmonary bypass. Using flow cytometry and a monoclonal antibody directed against an  $\alpha$ -granule membrane protein, granule membrane protein 140 (GMP-140), which is expressed on the platelet surface membrane after activation, we directly measured the percentage of circulating activated platelets in 41 patients before, during, and after cardiopulmonary bypass. In addition, we compared the GMP-140 expression with platelet aggregation in response to adenosine diphosphate (ADP). Cardiopulmonary bypass produced a significant increase in the percentage of GMP-140-positive platelets persisting in the circulation; the percentage peaked at a mean of 29% (range 10–58%) before separation from extracorporeal circulation. A significant percentage of these activated platelets continued to circulate in the early postoperative period. Simultaneous measurement of platelet aggregation in response to ADP demonstrated an aggregation defect that had a time course distinct from platelet activation and whose magnitude did not correlate with the degree of platelet activation in individual patients. We conclude that cardiopulmonary bypass causes a complex constellation of platelet defects, which include  $\alpha$ -granule release, prolonged circulation of activated, "spent" platelets, and impaired platelet aggregation. (Key words: Blood, coagulation; platelet activation; platelet aggregation; platelet glycoproteins. Measurement technique: flow cytometry. Surgery, cardiac: cardiopulmonary bypass.)

### ➤ Methods

- See description

### ➤ Results

- See description

#### Assessor's Comment

Since milrinone is not mentioned in the study, no conclusion on efficacy and safety of milrinone from this publication can be drawn.

**Kestin AS et al.** The platelet function defect of cardiopulmonary bypass. *Blood*, 1993, 82, 107-117.

### ➤ Description

The use of cardiopulmonary bypass (CPB) during cardiac surgery is associated with a hemostatic defect, the hallmark of which is a markedly prolonged bleeding time. However, the nature of the putative platelet function defect is controversial. In this study, blood was analyzed at 10 time points before, during, and after CPB. We used a whole-blood flow cytometric assay to study platelet surface glycoproteins in (1) peripheral blood, (2) peripheral blood activated in vitro by either phorbol myristate acetate, the thromboxane (TX)<sub>2</sub> analog U46619, or a combination of adenosine diphosphate and epinephrine, and (3) the blood emerging from a bleeding-time wound (shed blood). Activation-dependent changes were detected by monoclonal antibodies directed against the glycoprotein (GP)Ib-IX and GPIIb-IIIa complexes and P-selectin. In addition, we measured plasma glycofalicin (a proteolytic fragment of GPIb) and shed-blood TXB<sub>2</sub> (a stable breakdown product of TXA<sub>2</sub>). In shed blood emerging from a bleeding-time wound, the usual time-dependent increase in platelet surface P-selectin was absent during CPB, but returned to normal within 2 hours. This abnormality paralleled both the CPB-induced prolongation of the bleeding time and a CPB-induced marked reduction in shed-blood TXB<sub>2</sub> generation. In contrast, there was no loss of platelet reactivity in

vitro agonists during or after CPB. In peripheral blood, platelet surface P-selectin was negligible at every time point, demonstrating that CPB resulted in a minimal number of circulating degranulated platelets. CPB did not change the platelet surface expression of GPIb in peripheral blood, as determined by the platelet binding of a panel of monoclonal antibodies, ristocetin-induced binding of von Willebrand factor, and a lack of increase in plasma glycofalicin. CPB did not change the platelet surface expression of the GPIIb-IIIa complex in peripheral blood, as determined by the platelet binding of fibrinogen and a panel of monoclonal antibodies. In summary, CPB resulted in (1) markedly deficient platelet reactivity in response to an in vivo wound, (2) normal platelet reactivity in vitro, (3) no loss of the platelet surface GPIb-IX and GPIIb-IIIa complexes, and (4) a minimal number of circulating degranulated platelets. These data suggest that the "platelet function defect" of CPB is not a defect intrinsic to the platelet, but is an extrinsic defect such as an in vivo lack of availability of platelet agonists. The near universal use of heparin during CPB is likely to contribute substantially to this defect via its inhibition of thrombin, the preeminent platelet activator.

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## ➤ Methods

- See description

## ➤ Results

- See description

### Assessor's Comment

Since milrinone is not mentioned in the study, no conclusion on efficacy and safety of milrinone from this publication can be drawn.

### **Wernovsky G et al. Postoperative course and haemodynamic profile after the arterial switch operation in neonates and infants: a comparison of low-flow cardiopulmonary bypass and circulatory arrest.**

*Circulation, 1995, 92, 2226-2235.*

## ➤ Description

**Background** The neurological morbidity associated with prolonged periods of circulatory arrest has led some cardiac surgical teams to promote continuous low-flow cardiopulmonary bypass as an alternative strategy. The nonneurological postoperative effects of both techniques have been previously studied only in a limited fashion.

**Methods and Results** We compared the hemodynamic profile (cardiac index and systemic and pulmonary vascular resistances), intraoperative and postoperative fluid balance, and perioperative course after deep hypothermia and support consisting predominantly of total circulatory arrest or low-flow cardiopulmonary bypass in a randomized, single-center trial. Eligibility criteria included a diagnosis of transposition of the great arteries and a planned arterial switch operation before the age of 3 months. Of the 171 patients, 129 (66 assigned to circulatory arrest and 63 to low-flow bypass) had an intact ventricular septum and 42 (21 assigned to circulatory arrest and 21 to low-flow bypass) had an associated ventricular septal defect. There were 3 (1.8%) hospital deaths. Patients assigned to low-flow bypass had significantly greater weight gain and

positive fluid balance compared with patients assigned to circulatory arrest. Despite the increased weight gain in the infants assigned to low-flow bypass, the duration of mechanical ventilation, stay in the intensive care unit, and hospital stay were similar in both groups. Hemodynamic measurements were made in 122 patients. During the first postoperative night, the cardiac index decreased ( $32.1 \pm 15.4\%$ , mean  $\pm$  SD), while pulmonary and systemic vascular resistance increased. The measured cardiac index was  $<2.0 \text{ L} \cdot \text{min}^{-1} \cdot \text{m}^{-2}$  in 23.8% of the patients, with the lowest measurement typically occurring 9 to 12 hours after surgery. Perfusion strategy assignment was not associated with postoperative hemodynamics or other nonneurological postoperative events.

**Conclusions** After heart surgery in neonates and infants, both low-flow bypass and circulatory arrest perfusion strategies have comparable effects on the nonneurological postoperative course and hemodynamic profile. (*Circulation, 1995;92:2226-2235.*)

**Key Words** • cardiopulmonary bypass • circulatory arrest • transposition of great vessels • cardiac output • edema

## ➤ Methods

- See description

➤ **Results**

- See description

Assessor's Comment

Since milrinone is not mentioned in the study, no conclusion on efficacy and safety of milrinone from this publication can be drawn.

**Charpie JR et al. Serial blood lactate measurements predict early mortality following neonatal repair or palliation for complex congenital heart disease. *Circulation suppl 1, 1999, 100 (18) 1399.***

➤ **Description**

**Serial Blood Lactate Measurements Predict Early Mortality Following Neonatal Repair or Palliation for Complex Congenital Heart Disease**

John R Charpie, Mary K Dekeon, Caren S Goldberg, Ralph S Mosca, Edward L Bove, Thomas J Kulik, Univ of Michigan, Ann Arbor, MI

Postoperative neonates with congenital heart disease may appear hemodynamically stable, but then suddenly suffer catastrophic decompensation. An improved means of predicting which infants will suddenly die in the early postoperative period may lead to life-saving interventions. Studies in animals and adults indicate that blood lactate is proportional to tissue oxygen debt, but information linking lactate levels with outcome in postoperative infants is limited. Some studies suggest that an absolute lactate  $>6$  mmol/L is predictive of a poor outcome. To test this hypothesis, we prospectively studied 45 infants  $<1$  month old undergoing cardiac surgical palliation or repair. Additionally, we sought to determine if a change in lactate over time was predictive of a poor outcome defined as death or the need for extracorporeal membrane oxygenation (ECMO). Postoperative lactate levels were recorded on ICU admission and every 3-6 hours for the first 3 days. Four patients (8.9%) died and 5 patients (11%) required ECMO support for inadequate systemic perfusion, 4-72 hours following surgery. Initial mean lactate level was significantly greater in patients who died or required ECMO support ( $8.3 \pm 0.7$  mmol/L) than in patients who survived without ECMO ( $5.5 \pm 0.3$  mmol/L;  $p=0.0007$ ). However, an elevated initial lactate level ( $>6$  mmol/L) had a low positive predictive value (40%) for ECMO/death. In contrast, an increasing lactate [ $(\Delta \text{lactate}/\text{hour}) \geq 0.75$ ] predicted mortality or the requirement for ECMO support with 78% sensitivity, 100% specificity, 100% positive predictive value, and 95% negative predictive value. We conclude that serial blood lactate measurements may be a prognostic indicator of mortality or the requirement for ECMO support for patients undergoing complex neonatal cardiac surgery.

➤ **Methods**

- See description

➤ **Results**

- See description

Assessor's Comment

Since only the abstract is available, no conclusion on efficacy and safety of milrinone from this publication should be drawn.

**Charpie JR et al. Serial blood lactate measurements predict early outcome after neonatal repair or palliation for complex congenital heart disease. *J Thorac Cardiovasc Surg 2000, 120, 73-80.***

## ➤ Description

**Objectives:** Neonates with congenital heart disease may appear hemodynamically stable after operation and then suddenly experience catastrophic decompensation. An improved means of predicting which infants will suddenly die in the early postoperative period may lead to lifesaving interventions. Studies indicate that blood lactate level is proportional to tissue oxygen debt, but information linking lactate levels with outcome in infants after operation is limited. We sought to determine whether a change in lactate level over time was predictive of a poor outcome defined as death within the first 72 hours or the need for extracorporeal membrane oxygenation.

**Methods:** To test this hypothesis, we studied prospectively 46 infants who were less than 1 month old and were undergoing complex cardiac surgical palliation or repair. Postoperative arterial oxygen saturation, bicarbonate, and lactate levels were recorded on admission to the intensive care unit and every 3 to 12 hours for the first 3 days.

**Results:** Thirty-seven patients had a good outcome, and 9 patients had a poor outcome. Mean initial lactate level was significantly greater in patients with a poor outcome ( $9.4 \pm 3.8$  mmol/L) than in patients with a good outcome ( $5.6 \pm 2.1$  mmol/L;  $P = .03$ ). However, an elevated initial lactate level of more than 6 mmol/L had a low positive predictive value (38%) for poor outcome. In contrast, a change in lactate level of 0.75 mmol/L per hour or more was associated with a poor outcome ( $P < .0001$ ) and predicted a poor outcome with an 89% sensitivity value, a 100% specificity value, and a 100% positive predictive value.

**Conclusions:** Serial blood lactate level measurements may be an accurate predictor of death or the requirement for extracorporeal membrane oxygenator support for patients who undergo complex neonatal cardiac surgery. (J Thorac Cardiovasc Surg 2000;120:73-80)

## ➤ Methods

- See description

## ➤ Results

- See description

### Assessor's Comment

Since milrinone was only administered previous to the study drug, no conclusion on efficacy and safety of milrinone from this publication should be drawn.

***Evan Zucker, Sydney Heyman and Savas Ozdemir. Reversed Ventilation Perfusion Mismatch Involving a paediatric Patient in Congestive Heart Failure. The Journal of Nuclear Medicine 1997 Nov; 38 (11).***

## ➤ Description

Over the past 13 yr, at least 11 specific etiologies of reversed ventilation-perfusion mismatch have been reported in the literature. In this article, a case of reversed ventilation-perfusion mismatch involving a patient in congestive heart failure receiving dobutamine and milrinone therapy is presented. A brief review of the topic of reversed ventilation-perfusion mismatch is presented.

**J Nucl Med 1997; 38:1681-1683**

## ➤ Methods

- See description

➤ **Results**

- See description

Assessor's Comment

Since this is a case report, no conclusion on efficacy and safety of milrinone from this publication should be drawn.

**Rosenzweig EB et al. Intravenous arginin-vasopressin in children with vasodilatory shock after cardiac surgery.**  
*Circulation* 1999, 100, II 182-6.

➤ **Description**

**Background**—Recent investigations at our institution have studied a variety of vasodilatory shock states that are characterized by vasopressin deficiency and pressor hypersensitivity to the exogenous hormone. Our experience in adults prompted the use of arginine-vasopressin (AVP) in a similar group of critically ill children.

**Methods and Results**—This report describes our early experience (from February 1997 through April 1998) in 11 profoundly ill infants and children (5 male, 6 female) ages 3 days to 15 years (median, 35 days) treated with AVP for hypotension after cardiac surgery which was refractory to standard cardiopressors. Although underlying heart disease was present (congenital heart defects in 10 and dilated cardiomyopathy in 1), only 2 patients had severely depressed cardiac function as demonstrated by 2D echocardiogram before administration of AVP. All patients were intubated and receiving multiple catecholamine pressors and inotropes, including dobutamine (n=10), epinephrine (n=8), milrinone (n=7), and dopamine (n=4) before receiving AVP. Five patients received AVP intraoperatively immediately after cardiopulmonary bypass, 5 in the intensive care unit within 12 hours of surgery, and 1 on postoperative day 2 for hypotension associated with sepsis. The dose of AVP was adjusted for patient size and ranged from 0.0003 to 0.002 U · kg<sup>-1</sup> · min<sup>-1</sup>. During the first hour of treatment with AVP, systolic blood pressure rose from 65 ± 14 to 87 ± 17 mm Hg (P<0.0001; n=11), and epinephrine administration was decreased in 5 of 8 patients and increased in 1. Plasma AVP levels before treatment were available in 3 patients and demonstrated AVP depletion (median, 4.4 pg/mL; n=3). All 9 children with vasodilatory shock survived their intensive care unit stay. The 2 patients who received AVP in the setting of poor cardiac function died, despite transient improvement in blood pressure.

**Conclusions**—Infants and children with low blood pressure and adequate cardiac function after cardiac surgery respond to the pressor action of exogenous AVP. AVP deficiency may contribute to this hypotensive condition. (*Circulation*. 1999;100[suppl II]:II-182-II-186.)

➤ **Methods**

- See description

➤ **Results**

- See description

Assessor's Comment

Since milrinone was only administered previous to the study drug, no conclusion on efficacy and safety of milrinone from this publication should be drawn.

**Feneck RO. et al. Intravenous milrinone following cardiac surgery: effect of bolus infusion followed by variable dose maintenance infusion.**  
*J Cardiothorac Anthes* 1992, 6, 554-562.

➤ **Description**

The hemodynamic and adverse effects of intravenous milrinone were studied in 99 adult patients (66 men) following elective myocardial revascularization, mitral and/or aortic valve surgery. All patients had a low cardiac output (cardiac index [CI] mean 1.93, range, 1.11 to 2.5 L/min/m<sup>2</sup>) despite adequate cardiac filling pressure (mean pulmonary capillary wedge pressure [PCWP] 11.5 mmHg, range, 8 to 20 mmHg). Following a period of baseline stability (mean 17.8 minutes, range, 10 to 50 minutes), patients received a bolus infusion of 50 µg/kg over 10 minutes. A continuous maintenance infusion of 0.375 (low), 0.5 (mid) or 0.75 (high) µg/kg/min was administered for a minimum of 12 hours. Patients were allocated to each dosage group sequentially, not randomly. Hemodynamic measurements were made before the start of milrinone and 15 minutes after the bolus infusion. Further measurements were made at 30, 45, and 60 minutes, and at 3, 6, and 12 hours after the start of treatment. Measurements were also made at 2 and 4 hours after treatment was stopped. The bolus infusion caused significant increases in CI, heart rate (HR), and stroke index (SI), ( $P < 0.001$ ), and

significant falls in PCWP, right atrial pressure (RAP), mean pulmonary artery pressure (mPAP), pulmonary vascular resistance (PVR), mean arterial pressure (MAP), and systemic vascular resistance (SVR) ( $P < 0.001$ ). These effects were maintained to a significant degree by each of the three maintenance infusion regimens, although the pulmonary vasodilator effects appeared less predictable and more dose dependent. Eighteen patients (19%) had arrhythmias; 16 of these were judged not to be serious events. Two were deemed serious; these were both episodes of fast atrial fibrillation (AF). Recovery in these patients was otherwise uncomplicated. There were no other arrhythmias seen, and there were no other serious adverse effects related to the study drug. It is concluded that intravenous milrinone may be effective and safe treatment for low cardiac output states following cardiac surgery in this patient population.

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**KEY WORDS:** phosphodiesterase inhibitor, amrinone, cardiac surgery

## ➤ Methods

- See description

## ➤ Results

- See description

### Assessor's Comment

Since only adults have been studied, no conclusion on efficacy and safety of milrinone from this publication should be drawn.

**Wright EM et al. Milrinone in the treatment of low output states following cardiac surgery. Eur J Anaesthesiol 1992, 5 21-26.**

## ➤ Description

### Summary

Milrinone is known to have beneficial haemodynamic and clinical effects in patients with congestive heart failure. An investigation into the safety and efficacy of milrinone in patients following heart surgery was undertaken by the European Milrinone Multicentre Trial Group. This paper reports the efficacy, the effects on left heart function, and the adverse events in the study.

Ninety-nine adult patients, 61 coronary artery bypass grafting (CABG), 33 valve surgery (VS), and five CABG + VS were studied. Three dosage regimens were investigated sequentially. All patients received a loading dose of intravenous milrinone 50 µg kg<sup>-1</sup> over 10 min, followed by an infusion of either 0.375 µg kg<sup>-1</sup> min<sup>-1</sup>, 0.5 µg kg<sup>-1</sup> min<sup>-1</sup>, or 0.75 µg kg<sup>-1</sup> min<sup>-1</sup> over 12 h.

The groups were comparable for age, weight, and surface area; however, in the group receiving 0.5 µg kg<sup>-1</sup> min<sup>-1</sup> there were more females and

patients undergoing mitral valve surgery. Efficacy criteria of an increase in cardiac index of 30% and/or a decrease in mean pulmonary capillary wedge pressure of 25% were fulfilled by 77 patients at the 60-min measurement. Of the remaining 22 patients, 17 were clinically satisfactory and fulfilled efficacy criteria at some time during the study.

At 15 min and 60 min there was a dose-related decrease in systolic and diastolic arterial pressure; however, there was no significant difference in the mean arterial pressure measurements.

In all groups there was an improvement in cardiac index at 15 min following the start of milrinone, which was sustained during and up to 4 h after the infusion. This was closely associated with changes in stroke volume index and systemic vascular resistance, and not solely due to a change in heart rate.

**Keywords:** HEART; inotropism; cardiac index; PHARMACOLOGY; milrinone; SURGERY; cardiac.

➤ **Methods**

- See description

➤ **Results**

- See description

Assessor's Comment

Since only adults have been studied, no conclusion on efficacy and safety of milrinone from this publication should be drawn.

***Paradis M. et al. Population pharmacokinetics and dosing regimen design of milrinone in preterm infants.***

***Arch Dis Child Foetal Neonatal Ed 2007, 92, 204-209.***

➤ **Description**

**Aims:** To define the pharmacokinetics of milrinone in very preterm infants and determine an optimal dose regimen to prevent low systemic blood flow in the first 12 h after birth.

**Methods:** A prospective open-labelled, dose-escalation pharmacokinetic study was undertaken in two stages. In stage one, infants received milrinone at 0.25 µg/kg/min (n=8) and 0.5 µg/kg/min (n=11) infused from 3 to 24 h of age. Infants contributed 4–5 blood samples for concentration–time data which were analysed using a population modelling approach. A simulation study was used to explore the optimal dosing regimen to achieve target milrinone concentrations (180–300 ng/ml). This milrinone regimen was evaluated in stage two (n=10).

**Results:** Infants (n=29) born before 29 weeks gestation were enrolled. Milrinone pharmacokinetics were described using a one-compartment model with first-order elimination rate, with a population mean clearance (CV%) of 35 ml/h (24%) and volume of distribution of 512 ml (21%) and estimated half-life of 10 h. The 0.25 and 0.5 µg/kg/min dosage regimens did not achieve optimal milrinone concentration-time profiles to prevent early low systemic blood flow. Simulation studies predicted a loading infusion (0.75 µg/kg/min for 3 h) followed by maintenance infusion (0.2 µg/kg/min until 18 h of age) would provide an optimal milrinone concentration profile. This was confirmed in stage two of the study.

**Conclusion:** Population pharmacokinetic modelling in the preterm infant has established an optimal dose regimen for milrinone that increases the likelihood of achieving therapeutic aims and highlights the importance of pharmacokinetic studies in neonatal clinical pharmacology.

➤ **Methods**

➤ **Objective(s)**

To define the pharmacokinetics of milrinone in very preterm infants and determine an optimal dose regimen to prevent low systemic outflow in the first 12 h after birth.

➤ **Study design**

Prospective, open-labelled, dose-escalation pharmacokinetic study.

➤ **Study population /Sample size**

Infants born before 29 weeks of gestation were eligible.

➤ **Treatments**

Study was undertaken in two stages. In stage one, infants received milrinone at 0.25 µg/kg/min (n = 8). A second cohort received milrinone infused at 0.5 µg/kg/min (n = 11). Infusions were commenced between 3 and 6 hours of age and ceased at 24 hours of age. A simulation study was used to explore the optimal dosing regimen to achieve target milrinone concentration (180 - 300 ng/ml). This milrinone regimen was evaluated in stage two: the dose regimen selected from the simulation study consisted of a milrinone

loading dose of 0.75 µg/kg/min for 3 hours followed by maintenance infusion of 0.2 µg/kg/min until 18 hours of age (n = 10).

In stage one of the study, samples were taken 6 hours after starting the infusion, at cessation of infusion and at 2 and 4 hours after ceasing the infusion. In stage two, blood samples were collected at 3 hours after loading dose, 3 hours after the infusion rate was decreased to 0.2 µg/kg/min, at 18 hours of age and at 2 and 4 hours after ceasing the infusion.

Further cardiovascular support with volume bolus and inotropes was provided as needed.

- Outcomes/endpoints/statistical methods  
Milrinone plasma concentration analysis. Population pharmacokinetic modelling using NONMEM (Version 5.1.1).

## ➤ Results

- Recruitment/ Number analysed  
29 infants were enrolled in the study.

### ➤ Baseline data

The mean gestational age was 26 weeks. The mean birth weight was 850 g.

**Table 3** Clinical characteristics of participants

|                          | Milrinone dose (µg/kg/min) |                |               |
|--------------------------|----------------------------|----------------|---------------|
|                          | 0.25                       | 0.5            | 0.75-0.2      |
| n                        | 8                          | 11             | 10            |
| Mean GA (weeks)          | 26 (25-28)                 | 25 (23-27)     | 26 (24-26)    |
| Mean BW (g)              | 947 (789-1258)             | 849 (562-1114) | 805 (520-960) |
| Any Antenatal steroids   |                            |                |               |
| Any                      | 3 (38%)                    | 4 (36%)        | 3 (30%)       |
| Complete                 | 5 (62%)                    | 7 (64%)        | 7 (70%)       |
| Gender : Male            | 4 (50%)                    | 7 (64%)        | 6 (60%)       |
| Apgar                    |                            |                |               |
| 1 min                    | 5                          | 5              | 6             |
| 5 min                    | 8                          | 7              | 8             |
| Cord pH/BE               | 7.31/-6.1                  | 7.23/-8.8      | 7.29/-4.5     |
| Singleton                | 8 (100%)                   | 7 (64%)        | 7 (70%)       |
| SVC flow (>45 ml/kg/min) | 5 (63%)                    | 7 (64%)        | 10 (100%)     |
| BP >24 mm Hg             | 6 (75%)                    | 6 (55%)        | 7 (70%)       |
| Inotropes                | 4 (50%)                    | 6 (55%)        | 4 (40%)       |
| Indomethacin             | 7 (87%)                    | 7 (63%)        | 5 (50%)       |
| Creatinine (mmol/l)      | 57 (50-80)                 | 68(55-88)      | 61 (50-76)    |
| 0-24 h:                  |                            |                |               |
| Creatinine (mmol/l)      | 76 (60-90)                 | 78 (66-104)    | 79 (54-105)   |
| 24-48 h:                 |                            |                |               |
| Exit criteria            | 0                          | 1              | 0             |

### ➤ Efficacy results

At both infusion rates, 35% of babies still developed low systemic blood flow. After the 0.25 µg/kg/min infusion, milrinone concentrations were below the target range at 6 hours of infusion. While the milrinone concentrations were within target range at 6 hours of infusion after the 0.5 µg/kg/min infusion rate, this may still have been too slow. For both milrinone dose regimens there was accumulation of the drug towards steady-state with concentration above the target range. These data suggest that both regimens may have increased milrinone concentrations too slowly to prevent low systemic blood flow (6 to 12 hours).

Milrinone pharmacokinetics were described using a one-compartment model with first-order elimination rate, with a population mean clearance of 35 ml/h (=0.64 ml/kg/min), a volume of distribution of 512 ml, and estimated half-life of 10 hours.

Simulation studies predicted a loading infusion of 0.75 µg/kg/min for 3 hours followed by maintenance infusion of 0.2 µg/kg/min until 18 hours of age would provide an optimal milrinone concentration profile. The milrinone concentration-time data demonstrates that optimal therapeutic concentrations have been achieved using this dose regimen. None of the 10 babies in this cohort developed low systemic blood flow.

- Safety results  
Not described.

#### Assessor's Comment

##### Interpretation and lacks of the study:

1. No adverse events were reported.

##### Conclusion:

Given the negative clinical outcome of the follow-on randomized, controlled, double-blind trial, the indication prevention of low systemic blood flow in preterm infants cannot be approved. Therefore, the dosing schedule used for the study is not likely to be adopted by practitioners for the indication.

But of substantial pharmacokinetic importance was the finding in this study that the model-derived estimate of milrinone half-life in this cohort of very preterm infants was more than 10 hours which is considerably longer than the estimated 2 to 4 hours in infants and children. The clearance of milrinone in the very preterm infant was substantially less than the published data of paediatric population. Therefore, for the same infusion rate, the steady-state concentration will be higher in preterm infants than in older patients. Use of a loading dose infusion reduces the time to approach steady-state significantly, underscoring the necessity of a loading dose for the rapid achievement of a therapeutic blood concentration. If the pharmacodynamics of milrinone is similar in the various age groups one can anticipate that the onset of effect will be similar in each group but the infusion rate may need reduction in younger patients. First of all, the selected dosage has to be adjusted to general condition, especially haemodynamical stability of the patient. Pharmacokinetic parameters defined should be mentioned in section 5.2 of the SmPC.

***Paradisis M. et al. Randomized trial of milrinone versus placebo for prevention of low systemic blood flow in very preterm infants. J Pediatr 2009, 154, 189-95.***

#### ➤ Description

**Objective** To assess the effectiveness of early prophylactic milrinone versus placebo for prevention of low systemic blood flow in high-risk preterm infants.

**Study design** Double-blind randomized placebo controlled trial of milrinone (loading dose 0.75 µg/kg/min for 3 hours then maintenance 0.2 µg/kg/min until 18 hours after birth) versus placebo. Infants born <30 weeks gestational age and <6 hours of age were eligible and were monitored with serial echocardiography, head ultrasound scanning, and continuous invasive blood pressure. Primary outcome was maintenance of superior vena cava (SVC) flow  $\geq 45$  mL/kg/min through the first 24 hours. The exit criterion was hypotension unresponsive to volume and inotropes.

**Results** Ninety infants were enrolled, equal proportions maintained SVC flow  $\geq 45$  mL/kg/min after treatment commenced. No significant difference was observed in SVC flow, right ventricular output, and blood pressure during the first 24 hours; or grades 3 to 4 periventricular/intraventricular hemorrhage and death. Heart rate was higher and constriction of the ductus was slower in the infants randomized to milrinone.

**Conclusions** Milrinone did not prevent low systemic blood flow during the first 24 hours in very preterm infants, and no adverse effects were attributable to milrinone. Use of a preventative treatment with rescue model allowed comparison of an inotrope with placebo in this high-risk group of infants. (*J Pediatr 2009;154:189-95*)

#### ➤ Methods

- Objective(s)

To assess the effectiveness of early prophylactic milrinone versus placebo for prevention of low systemic blood flow in high-risk preterm infants.

- Study design  
Double-blind, randomized, placebo-controlled study.
- Study population /Sample size  
Infants born < 30 weeks of gestational age and < 6 hours of age were eligible.
- Treatments  
Infants were randomized to milrinone (loading dose of 0.75 µg/kg/min for 3 hours followed by maintenance infusion of 0.2 µg/kg/min until 18 hours of age) or placebo (5% dextrose).

Indomethacin 0.1 mg/kg was administered if the ductus arteriosus diameter at first scan was > 2mm.

Further cardiovascular support with volume bolus (10 ml/kg) and dopamines was provided on the basis of hypotension.

- Outcomes/endpoints  
Maintenance of superior vena cava (SCV) flow  $\geq$  45 ml/kg/min through the first 24 hours.
- Statistical methods  
Data analyses were performed according to intention to treat. Categorical data were analyzed with  $\chi^2$  test or Fisher exact test where there were small expected frequencies. For continuous data, the means +/- SD were presented if the assumptions of normality were met. Differences between the treatment groups were assessed with the Student t test for normally distributed data or Mann Whitney U test for nonparametric data. Significance was set as p value less than 0.05.

## ➤ Results

- Recruitment/ Number analysed  
90 infants were enrolled in the study.



➤ Baseline data

**Table I. Baseline characteristics of infants at trial entry**

|   | Milrinone<br>(n = 42) | Placebo<br>(n = 48) |
|---|-----------------------|---------------------|
| Antenatal steroids                            |                       |                     |
| Any   | 41 (98%)              | 45 (94%)            |
| Complete (>24 h)                              | 23 (52%)              | 29 (60%)            |
| Vaginal delivery                              | 20 (48%)              | 18 (38%)            |
| Gestational age (weeks)                       | 26 ± 1.1              | 26 ± 1.3            |
| Birth weight (g)                              | 959 ± 185             | 853 ± 249           |
| Sex: Male                                     | 28 (67%)              | 23 (48%)            |
| Apgar score                                   |                       |                     |
| At 1 min                                      | 4 ± 2                 | 5 ± 2               |
| At 5 min                                      | 7 ± 1                 | 7 ± 2               |
| Umbilical arterial pH                         | 7.25 ± 1.1            | 7.29 ± 1.1          |
| Umbilical arterial base excess                | -6 ± 3.6              | -4 ± 4.1            |
| Age at first ultrasound (h)                   | 3.4 ± 1.1             | 3.4 ± 1             |
| Age at commencement of study drug (h)         | 4.4 ± 1.1             | 4.3 ± 1.1           |
| PDA <2 mm at first scan (before indomethacin) | 19 (45%)              | 22 (46%)            |

(Data presented as mean ± SD unless otherwise stated).

➤ Efficacy results

83% in the milrinone group and 81% in the placebo group maintained SVC flow after treatment was started, there is no significant difference between the milrinone-treated and the control group.

➤ Safety results

Infants randomized to milrinone had significantly higher heart rate after commencing the infusion ( $p < 0.0001$ ). No significant difference was seen in incidence of hypotension in infants randomized to milrinone. Infants randomized to milrinone had significantly larger patent ductus arteriosus (PDA) diameters after commencing the infusion. The overall rate

of PDA treated with indomethacin was 81% for milrinone and 69% for placebo group, not statistically significant. Of these, 44% of milrinone and 33% of the placebo group required "late" treatment with indomethacin after the study drug was commenced. Surgical ligation was performed in 4 infants from the milrinone group and 2 in the placebo group. There was no significant difference between the two groups in the rate of development of peri-/intraventricular haemorrhage, in major pulmonary haemorrhage, in necrotizing enterocolitis, or in chronic lung disease in survivors at 36 weeks postmenstrual age. No evidence of thrombocytopenia or tachyarrhythmia was seen in any infant during the first 24 hours of life. There was no significant difference between the groups in mortality rate before discharge from hospital. Causes of death in milrinone treated and control group were comparable.

#### Assessor's Comment

##### Interpretation and lacks of the study:

##### Conclusion:

Given the negative clinical outcome of the randomized, controlled, double-blind trial, the indication prevention of low systemic blood flow in preterm infants cannot be approved. Therefore, the dosing schedule used for the study is not likely to be adopted by practitioners for the indication. The mean start time of the infusion was 4 hours in both groups, which may have been too late as the nadir of SVC flow is between 3 and 12 hours of age. Additionally non-clinical trials suggest, milrinone has decreased effectiveness for the immature myocardium by way of diminished inotropic effect. Therefore, the used dose may have been too low. But safety results have to be taken into consideration. Milrinone appeared to slow the closure of the ductus arteriosus. Larger-diameter ductus are significantly related to low systemic blood flow. It is possible that any beneficial effects on systemic blood flow were balanced by increased left-to-right shunting through the ductus arteriosus from the systemic into the pulmonary circulation. Physiological dilators of the ductus muscle include prostaglandin E and nitric oxide, and both are augmented by inhibition of phosphodiesterase enzymes by milrinone. This effect is predictable and part of rationale for the use of early indomethacin in preterm or term infants with poor postnatal ductus constriction. The critical consequences of the patent ductus arteriosus in terms of mortality and morbidity in preterm and term infants are related to a combination of pulmonary overcirculation with consecutive pulmonary oedema and of reduced organ perfusion with consecutive intraventricular haemorrhage, periventricular leucomalacia and necrotizing enterocolitis. Almost all of these are mentioned in the study as adverse events. In addition, a higher incidence of bronchopulmonary dysplasia is found in infants with PDA. Therefore, a special warning and undesirable effects concerning preterm and term infants at risk of/with patent ductus arteriosus should be given in the SmPC.

**Lindsay CA. et al. Pharmacokinetics and pharmacodynamics of milrinone lactate in paediatric patients with septic shock. J Pediatr 1998; 132; 329-34.**

##### ➤ Description

**Objectives:** The objectives of this study were to determine the pharmacokinetics of milrinone lactate in pediatric patients with septic shock and to determine whether a relationship exists between steady-state plasma milrinone concentrations and changes in hemodynamic variables.

**Study design:** This was a randomized, double-blind, placebo-controlled, interventional study. In study phase 1 patients were randomized and underwent loading and infusion with milrinone lactate (50 µg/kg, then 0.5 µg/kg/min), and invasive hemodynamic values were determined. Steady-state was determined by obtaining plasma samples at 30, 15, and 0 minutes before the end of the milrinone infusion. Study phase 2 started when milrinone was discontinued by the patient care team. Steady-state was reaffirmed and plasma samples were obtained at 0.5, 1, 2, 4, 6, and 8 hours after the end of the infusion.

**Results:** The average plasma concentration at steady-state ( $C_{ss}$  avg) and total body clearance for phase 1 were  $81.3 \pm 38.6$  ng/ml (mean  $\pm$  SD) and  $0.0106 \pm 0.0053$  L/kg/min, respectively ( $n = 9$ ). All but two patients underwent reloading with milrinone. In phase 2  $C_{ss}$  avg and total body clearance were  $65.8 \pm 42.1$  ng/ml and  $0.0110 \pm 0.0096$  L/kg/min, respectively ( $n = 11$ ). The average time of infusion was  $51 \pm 21$  hours. Eight patients were evaluated for phase 2 elimination. The mean elimination rate constant was  $0.0091 \pm 0.0061$  min<sup>-1</sup> ( $n = 8$ ). The median half-life was 1.47 hours (range, 0.62 to 10.85 hours). All patients had creatinine clearances greater than 61 ml/min/1.73 m<sup>2</sup>. The volume of distribution at steady-state was  $1.47 \pm 1.03$  L/kg. No correlation existed between age and the elimination rate constant or the volume of distribution at steady-state. All patients achieved at least a 20% change in cardiac index and systemic vascular resistance index while maintaining a  $C_{ss}$  avg of 35 to 160 ng/ml. No adverse effects were noted. All patients achieved primary hemodynamic end points (cardiac index and systemic vascular resistance index) during the milrinone infusion.

**Conclusions:** Loading doses of 75 µg/kg milrinone lactate and starting infusion rates of 0.75 to 1.0 µg/kg/min for patients with normal renal function should be used; the infusion rate should then be titrated to effect. We recommend that for every increase of 0.25 µg/kg/min, a 25 µg/kg bolus dose be given. Because the median half-life is 1.47 hours, immediate hemodynamic effects may not be seen unless appropriate loading doses and infusion adjustments are made. (J Pediatr 1998;132:329-34)

## ➤ Methods

### ➤ Objective(s)

To characterize the pharmacokinetics of milrinone in paediatric patients with septic shock and to determine whether a relationship exists between steady-state plasma milrinone concentrations and changes in haemodynamic variables.

### ➤ Study design

Randomized, double-blind, placebo-controlled, interventional study.

### ➤ Study population /sample size

See Barton P. et al. 1996

### ➤ Treatments

See Barton P. et al. 1996

Steady-state was determined by obtaining plasma samples at 30, 15, and 0 minutes before the end of phase 1. In phase 2, plasma samples were obtained at 0.5, 1, 2, 4, 6, and 8 hours after the milrinone infusion was discontinued.

### ➤ Outcomes/endpoints/statistical methods

Milrinone plasma concentration analysis. For both phases total body clearance was determined from the following equation:  $Cl$  (L/kg/min) = Infusion rate (µg/kg/min) +  $C_{ss}$  (ng/ml). The elimination constant was calculated with Rstrip II version 2.02. Volume of distribution at steady-state was calculated by dividing the clearance at steady-state from phase 2 by the terminal elimination rate constant. Serum creatinine was obtained at the end of the infusion, and creatinine clearance was calculated by the Schwartz method. Descriptive statistics were used to analyze the patient aggregate data. Linear regression analysis of patient variables was performed by comparing the pharmacokinetic

parameters with the age of the patients and with creatinine clearance in an attempt to establish relationships among these parameters.

➤ **Results**

➤ Recruitment/ Number analysed  
See Barton P. et al. 1996

➤ Baseline data  
See Barton P. et al. 1996

➤ Efficacy results  
The best fit of data was to a one-compartment model. Steady-state plasma concentrations were obtained for nine patients in phase 1 and 11 patients in phase 2. Only eight patients of the latter group had plasma concentration above the detection limit of the assay and were analyzed for elimination rate constant and half-life. For both phases only patients who had at least two steady-state plasma concentrations within 10% of each other were analyzed for estimations of total body clearance. The median half-life was 1.47 hours. The average plasma concentration at steady-state and total body clearance were 81.3 +/- 38.6 ng/ml and 16 +/- 5.3 ml/kg/min. All but two patients underwent a reloading with milrinone. All patients achieved at least a 20% change in CI and SVRI while maintaining the plasma concentrations of 35 to 160 ng/ml. No relationship existed between plasma concentration and the change in CI and SVRI. No statistical relationship between the pharmacokinetic parameters and age or creatinine clearance was noted.

➤ Safety results  
One patient, not included to the analysis, had acute renal failure at the time of drug infusion. The mean plasma concentration in this patient receiving 0.5 µg/kg/min was 652 ng/ml in phase 1 and 1516 ng/ml in phase 2 after 13 hours at the same infusion rate. During the 2-hour study period the CI increased and the SVRI decreased. The mean arterial pressure dropped from 68 mmHg at baseline to 63 mmHg at 2 hours, which was treated by infusion of 10 ml/kg of isotonic crystalloid infusion. Continuous veno-venous haemofiltration was instituted 8 hours into the infusion, and therefore volume of distribution and elimination rate constant determinations were not calculated. 13 hours into the infusion the patient had an acute hypotensive episode with a sudden decrease in SVRI. This episode slowly responded to intravascular volume and an escalating norepinephrine infusion. Milrinone was discontinued.  
See Barton P. et al. 1996

Assessor's Comment

Interpretation and lacks of the study:

1. Number of subjects involved is relatively small.
2. Most of the patients (15 out of 18 patients) required reloading due to 20% or less increase in CI or lack of acceptable improvement in peripheral perfusion. A dosage recommendation for the studied population for loading dosage of 75 µg/kg and for continuous infusion of 0.75 µg/kg/min could be concluded.
3. The study was not designed to eliminate the possibility that a relationship between pharmacokinetic parameters and age and creatinine clearance might exist as cited by the author.
4. Some significant intersubject variability in half-life was found. Highlighting this variability is the fact that 3 of the 11 patients who were evaluated for elimination rate constants had

such rapid elimination of the drug that by one hour after the milrinone infusion was discontinued, the plasma concentrations were either undetectable or had fallen outside the linear curve. This result reflects the limitations of sampling strategy.

#### Conclusion:

In section 5.1 of SmPC the potential usage of milrinone for children with nonhyperdynamic septic shock with normal renal function referencing this study should be given. In order to prevent off label use, posology and further details are not given because this indication is not scientifically proven. In the one patient with impaired renal function, there was marked impairment of milrinone clearance and clinically significant side effects of hypotension, but the specific creatinine clearance at which doses must be adjusted in paediatric patients is still not clear. Therefore, a special warning concerning paediatric patients with impaired renal function should be given in the SmPC.

**Barton P. et al. Haemodynamic effect of IV milrinone lactate in paediatric patients with septic shock: a prospective, double-blinded, randomized, placebo-controlled, interventional study. Chest 1996, 109, 1032-12.**

#### ➤ Description

**Study objective:** To determine the hemodynamic effects of IV milrinone lactate in pediatric patients with nonhyperdynamic septic shock. Specifically we tested the hypothesis that IV milrinone would increase cardiac index by 20% and decrease systemic vascular resistance index by 20% during a 2-h study period.

**Design:** Prospective, double-blinded, randomized, placebo-controlled, descriptive, interventional study.

**Setting:** Twenty-six-bed pediatric ICU at Children's Medical Center of Dallas and a 10-bed pediatric trauma ICU at Parkland Memorial Hospital.

**Patients/participants:** Twelve patients (age range, 9 months to 15 years) with nonhyperdynamic septic shock despite administration of catecholamines (cardiac index [CI] normal [3.5 to 5.5 L/min/m<sup>2</sup>] or low [ $\leq 3.5$  L/min/m<sup>2</sup>]; systemic vascular resistance index [SVRI] normal [800 to 1,600 dyne·s·cm<sup>5</sup>/m<sup>2</sup>] or high [ $\geq 1,600$  dyne·s·cm<sup>5</sup>/m<sup>2</sup>]; and pulmonary capillary wedge pressure [PCWP] normal [8 to 12 mm Hg] or higher) with clinical signs of poor perfusion were enrolled, randomized, and treated in a blinded fashion with IV milrinone and placebo.

**Interventions:** Patients were randomized into two groups. Group A received a loading dose of 50 µg/kg IV of milrinone followed by a continuous IV infusion of 0.5 µg/kg/min while group B received an equal volume loading dose and continuous infusion of placebo. After 2 h, group A received an equal-volume loading dose followed by a continuous infusion of placebo while the milrinone infusion continued, while group B received a 50 µg/kg loading dose of milrinone followed by a continuous infusion of 0.5 µg/kg/min while the placebo infusion remained. Outcome variables were measured at baseline, 0.5, 1.0, 2.0, 2.5, 3.0, and 4.0 h. Echocardiographic measurements were taken at baseline, hour 2, and hour 4 in all subjects. No changes in other inotropic or mechanical ventilatory support were allowed during the study period.

**Measurements and main results:** Milrinone significantly increased CI, stroke volume index (SVI), right and left ventricular stroke work index, and oxygen delivery (DO<sub>2</sub>) at 0.5, 1.0, and 2.0 h post-loading dose ( $p < 0.05$ ) while significantly decreasing SVRI, pulmonary vascular resistance index, and mean pulmonary arterial pressure at 0.5, 1.0, and 2.0 h postloading dose ( $p < 0.05$ ). No clinically or statistically significant changes in heart rate, systolic and diastolic BP, mean systemic arterial pressure, or PCWP were observed during milrinone treatment compared to placebo.

**Conclusions:** CI, SVI, and DO<sub>2</sub> significantly increased while SVRI significantly decreased when compared to placebo after IV administration of milrinone to pediatric patients with nonhyperdynamic septic shock. No adverse effects were observed. In a volume-resuscitated pediatric patient with septic shock, when administered in addition to catecholamines, milrinone will improve cardiovascular function. (CHEST 1996; 109:1302-12)

#### ➤ Methods

##### ➤ Objective(s)

To investigate the haemodynamic effects of IV milrinone in paediatric patients with nonhyperdynamic septic shock.

- **Study design**  
Prospective, double-blinded, randomized, placebo-controlled, descriptive, interventional study
- **Study population /Sample size**  
Paediatric patients between the ages of 6 months and 18 years admitted to the ICUs with a diagnosis of septic shock, with a pulmonary artery catheter, were eligible for enrolment.
- **Treatments**  
In this 4-hour study, group A patients received an IV loading dose of 50 µg/kg of milrinone, followed by a continuous IV infusion of 0.5 µg/kg/min in addition to catecholamines. Data were collected at 0.5, 1 and 2 hours after the milrinone loading dose was started. At the 2-hour time point, the patients received an equal-volume loading-dose of placebo while the milrinone infusion was continued. If the patients did not develop a 20% or greater increase in cardiac index (CI) or improvement in peripheral perfusion 1 hour after loading dose of milrinone or placebo, they were reloaded with 25 µg/kg of milrinone and the continuous infusion was increased to 0.75 µg/kg/min. In group B patients, the drug administration times were reversed with placebo being administered first followed by milrinone with the same measurements being taken as with group A in addition to catecholamines. Data were collected in 6 2-hour study periods in which patients (group B) received only placebo (control group, n = 6); and 12 2-hour study periods of milrinone administration (all patients, group A and group B – milrinone treatment group, n = 12).
- **Outcomes/endpoints**  
Primary endpoints: CI and systemic vascular resistance index (SVRI)
- **Statistical Methods**  
Statistical analysis was accomplished by analyzing each variable at each time point compared to base line with one-way, repeated measures analysis of variance (ANOVA). Treatment variables during the milrinone infusion were also compared with variables during the placebo infusion by unpaired t-test. Significance was set as p value less than 0.05.
- **Results**
  - **Recruitment/ Number analysed**  
Twelve consecutive, eligible patients (age range 9 months to 15 years) with a diagnosis of septic shock and a pulmonary artery catheter excluded for a hyperdynamic condition were enrolled and studied over a 10-month period.
  - **Baseline data**  
The mean duration of time patients received milrinone was 48 hours (range 13 to 76 hours).

Table 2—Clinical Data/Description of the Study Patients\*

| Patient/Secs/Age         | Admit-Enrollment Interval |       | Inotropic Support        |           | Underlying Disease  | Source        | Micro                       |
|--------------------------|---------------------------|-------|--------------------------|-----------|---------------------|---------------|-----------------------------|
|                          | hours                     | PRISM |                          | µg/kg/min |                     |               |                             |
| 1 <sup>1</sup> /M/14 mo  | 48                        | 23    | Dopa 3/Dobut 15          |           | Kerosene aspiration | Blood         | H flu                       |
| 2/M/2 yr                 | 60                        | 35    | Dobut 10/Epi 0.05        |           | Purpura fulminans   | Neg cults     | NA                          |
| 3 <sup>1</sup> /F/9 yr   | 24                        | 14    | Dopa 5/Dobut 10/Epi 0.1  |           | AML                 | Blood         | α-strep                     |
| 4/F/3 yr                 | 144                       | 18    | Dobut 15/Epi 0.4         |           | Trauma/pneumonia    | Sputum        | M cata                      |
| 5/M/9 mo                 | 30                        | 32    | Dopa 5/Epi 0.4           |           | Near drowning       | Sputum        | M cata<br>K pneu<br>E cloac |
| 6/F/15 yr                | 9                         | 29    | Dopa 3/Epi 0.05          |           | Purpura fulminans   | Neg cults     | NA                          |
| 7/M/10 mo                | 12                        | 31    | Dopa 3/Epi 0.5           |           | Pneumonia           | Pleural fluid | CAS                         |
| 8/M/11 yr                | 8                         | 32    | Epi 0.2                  |           | Meningococemia      | Blood         | N men                       |
|                          |                           |       |                          |           |                     | CSF           | N men                       |
| 9 <sup>1</sup> /M/2 yr   | 8                         | 41    | Dopa 10/Dobut 15/Epi 1.0 |           | Meningococemia      | CSF           | N men                       |
| 10/M/3 yr                | 60                        | 45    | Dopa 3/Dobut 12          |           | Trauma/aspiration   | Sputum        | Candida                     |
| 11/M/2 yr                | 36                        | 26    | Dobut 5/Epi 0.1/NE 0.05  |           | s/p Craniotomy      | Blood         | E coli                      |
|                          |                           |       |                          |           |                     | CSF           | E coli                      |
| 12 <sup>1</sup> /F/14 yr | 6                         | 36    | Dopa 5/Dobut 10/Epi 2.5  |           | Meningococemia      | Blood         | N men                       |

\*PRISM=pediatric risk of mortality score; Dopa=dopamine; Dobut=dobutamine; Epi=epinephrine; NE=norepinephrine; AML=acute myelogenous leukemia; neg cults=negative culture results; CSF=cerebrospinal fluid; H flu=*Haemophilus influenzae* (nontypable); α-strep=alpha-hemolytic streptococci; M cata=*Moraxella catarrhalis*; K pneu=*Klebsiella pneumoniae*; E cloac=*Enterobacter cloacae*; CAS=group A streptococci; N men=*Neisseria meningitidis*; E coli=*Escherichia coli*; NA=not applicable.

<sup>1</sup>Nonsurvivor.

➤ Efficacy results

All six placebo study periods and nine of the 12 milrinone study periods required reloading due to 20% or less increase in CI or lack of acceptable improvement in peripheral perfusion.

*Placebo-treated study period (n = 6)*

CI and SVRI did not significantly differ from baseline value during the placebo-treated time periods.

*Milrinone-treated study period*

CI significantly increased from baseline value at 0.5, 1 and 2 hours (p < 0.05). SVRI significantly decreased from baseline value at 0.5, 1 and 2 hours (p < 0.05).

*Milrinone-treated (n = 12) vs. placebo-treated (n = 6) comparison*

CI in the milrinone-treated group was significantly increased compared to the placebo-treated group at 0.5, 1 and 2 hours (p < 0.05). SVRI in the milrinone-treated group was significantly decreased at 0.5 and 2 hours (p < 0.05) compared to control.

➤ Safety results

The actual mortality rate for the study patients was 33%. The four deaths occurred after the study's completion: one death followed extracorporeal support for progressive acute respiratory distress syndrome while another was due to cerebral herniation secondary to leukemic brainstem infiltrates. Two other patients died secondary to developing multiple organ dysfunction syndrome. No acute adverse effects such as hypotension, increasing tachycardia, or supraventricular arrhythmias were observed during the 4-hour study period. During the duration of infusions, no progression of thrombocytopenia or new occurrence of thrombocytopenia was noted.

Assessor's Comment

Interpretation and lacks of the study:

1. Number of subjects involved is relatively small.
2. The validity of mentioned average paediatric risk of mortality score of 30 predicting a 75% mortality used as historical reference is not comprehensible.

3. Most of the patients (15 out of 18 patients) required reloading due to 20% or less increase in CI or lack of acceptable improvement in peripheral perfusion. A dosage recommendation for the studied population for loading dosage of 75 µg/kg and for continuous infusion of 0.75 µg/kg/min could be concluded.
4. Instead of absolute comparison of CI and SVRI between milrinone-treated group and placebo-treated group at specific time points, a statistical test on relative development of these endpoints between the milrinone-treated group and the placebo-treated group would be required.

**Conclusion:**

Data indicate efficacy concerning primary endpoints under examination, but due to lacks of the study statistical evidence is not proven. Therefore, the indication paediatric patients with nonhyperdynamic septic shock cannot be approved. In section 5.1 of SmPC the potential usage of milrinone for children with nonhyperdynamic septic shock with normal renal function referencing this study should be given. In order to prevent off label use, posology and further details are not given because this indication is not scientifically proven.

**Ramamoorthy C et al. Pharmacokinetics and side effects of milrinone in infants and children after open heart surgery. *Anesth Analg*1998, 86, 283-9.**

➤ **Description**

We investigated the pharmacokinetics and side effects of milrinone in infants and children (≤13 yr) after open heart surgery in this prospective, open-label study. Milrinone binding to cardiopulmonary bypass (CPB) circuitry was also examined in out two groups. Children in the small dose group (n = 11) received two 25-µg/kg boluses with a final infusion rate of 0.5 µg · kg<sup>-1</sup> · min<sup>-1</sup>; those in the large dose group (n = 8) received a 50-µg/kg bolus and a 25-µg/kg bolus with a final infusion rate of 0.75 µg · kg<sup>-1</sup> · min<sup>-1</sup>. Blood samples for milrinone concentration were drawn 30 min after each bolus, at steady state, and after discontinuing the milrinone infusion. Pharmacokinetics were evaluated using traditional and nonlinear mixed effects modeling analysis. Milrinone kinetics best fit a two-compartment model. Steady-state plasma levels in the small and large dose groups were within the adult therapeutic range (113 ± 39 and 206 ± 74 ng/mL, respectively). The volumes of

distribution (V<sub>β</sub>) in infants (0.9 L/kg) and children (0.7 L/kg) were not different, but infants had significantly lower milrinone clearance (3.8 vs 5.9 mL · kg<sup>-1</sup> · min<sup>-1</sup>). Thrombocytopenia (defined as platelet count ≤100,000 mm<sup>-3</sup>) occurred in 58%, and the risk increased significantly with duration of infusion. Tachyarrhythmias were noted in two patients. Milrinone did not bind to CPB circuitry. We conclude that milrinone is cleared more rapidly in children than in adults. The major complication was thrombocytopenia. **Implications:** Most pediatric dosing is based on data published for adults. Infants and children have kinetics that differ from adults. We studied the distribution of IV milrinone in infants and children after open heart surgery. Milrinone had a larger volume of distribution and a faster clearance in infants and children than in adults, and dosing should be adjusted accordingly.

(*Anesth Analg* 1998;86:283-9)

➤ **Methods**

- Objective(s)  
To investigate the pharmacokinetics and side effects of milrinone in infants and children (< 13 years) after open heart surgery.
- Study design  
Prospective, open-label study.
- Study population /Sample size  
19 infants and children after open heart surgery.
- Treatments

Children in the small dose group received a 25 µg/kg bolus over 5 min and a milrinone infusion of 0.25 µg/kg/min was started at the end of the first dose. Thirty minutes later, a second 25 µg/kg bolus over 5 min was given, and the infusion was increased to 0.5 µg/kg/min; those in the large dose group received a 50 µg/kg bolus over 10 minutes, and an infusion of 0.5 µg/kg/min was started at the end of the bolus. A 25 µg/kg bolus was given 30 minutes after the first bolus, and the final infusion rate was increased to 0.75 µg/kg/min. In addition, patients in both groups received a third 25 µg/kg milrinone bolus based on their clinical response, but their infusion rates were unchanged. Blood samples for milrinone plasma concentration were drawn 30 min after each bolus, at steady state (after 22 and 24 hours of continuous infusion), and after discontinuing the milrinone infusion (at 5, 10, 20, and 60 minutes, and 3, 5, and 7 hours).

➤ Outcomes/endpoints/statistical methods

Milrinone plasma concentration analysis. Population pharmacokinetic modelling using NONMEM (programme version IV level 1.0). Serial platelet counts. To test the effects of milrinone on serial platelet counts, data were analyzed by using a multivariate analysis of variance adjusted for dose and duration of milrinone infusion. Categorical data were analyzed by using the  $\chi^2$  and  $\chi^2$  for trend tests; significance was set as p value less than 0.05.

➤ Results

➤ Recruitment/ Number analysed

19 patients were entered in the study. There were 12 infants (aged < 1year) and 7 children (aged > 1year and < 13years).

➤ Baseline data

Table 1. Patient Demographics

| Patient   | Age (yr) | Weight (kg) | Cardiac surgical procedure | CPB duration (min) | ICU arrival to milrinone start (min) | Infusion duration (h) |
|-----------|----------|-------------|----------------------------|--------------------|--------------------------------------|-----------------------|
| 1         | 7.08     | 17.70       | MV & AV Rep                | 139                | 117                                  | 25                    |
| 2         | 6.35     | 40          | RV-PA conduit              | 140                | 120                                  | 65                    |
| 3         | 0.78     | 7.43        | RV-PA conduit              | 164                | 118                                  | 26                    |
| 4         | 0.44     | 5.3         | T of Fallot                | 123                | 83                                   | 26                    |
| 5         | 0.25     | 5.5         | AV Canal                   | 136                | 90                                   | 42                    |
| 6         | 0.28     | 5.6         | T of Fallot                | 114                | 85                                   | 19                    |
| 7         | 0.44     | 5.2         | AV Canal                   | 101                | 75                                   | 42                    |
| 8         | 0.62     | 5.31        | T of Fallot                | 118                | 145                                  | 67                    |
| 9         | 3.04     | 11          | ASD & VSD                  | 119                | 155                                  | 24                    |
| 10        | 0.36     | 5.87        | T of Fallot                | 130                | 70                                   | 43                    |
| 11        | 11.81    | 42          | RV-PA conduit              | 121                | 104                                  | 24                    |
| 12        | 10.55    | 30.2        | AV Canal                   | 52                 | 119                                  | 44                    |
| 13        | 0.28     | 4.43        | AV Canal                   | 98                 | 98                                   | 42                    |
| 14        | 0.10     | 3.45        | AV Canal                   | 108                | 85                                   | 16                    |
| 15        | 2.30     | 8.9         | RV-PA Conduit              | 131                | 55                                   | 91                    |
| 16        | 0.44     | 4.4         | AV Canal                   | 145                | 97                                   | 66                    |
| 17        | 3.15     | 13.2        | MV Rep                     | 97                 | 74                                   | 25                    |
| 18        | 0.36     | 4.9         | AV Canal                   | 134                | 192                                  | 40                    |
| 19        | 0.54     | 5.22        | AV Canal                   | 111                | 146                                  | 41                    |
| Mean ± SD | 3 ± 3.7  | 12 ± 12     |                            | 120 ± 24           | 107 ± 34                             | 40 ± 20               |

CPB = cardiopulmonary bypass, ICU = intensive care unit, MV = mitral valve, AV = aortic valve, Rep = replacement or repair, RV-PA = right ventricle to pulmonary artery, T of Fallot = tetralogy of Fallot, AV, atrioventricular, ASD & VSD = atrial and ventricular septal defect.

➤ Efficacy results

In all but one patient, the milrinone concentrations after discontinuing the infusion fit the two-compartment model best. A strong correlation between body weight and clearance and volume of distribution could be shown. Age alone was a significant factor, but because body weight correlated highly with age, deletion of age from the model did not alter the goodness of fit. Steady-state plasma levels in the small and the large dose groups were within the assumed adult therapeutic range (113 +/- 39 and 206 +/- 74

ng/ml). The volumes of distribution in infants (0,9 L/kg) and children (0,7 L/kg) were not different, but infants had significantly lower milrinone clearance (3.8 vs. 5.9 ml/kg/min).

**Table 3. Comparison of Milrinone Pharmacokinetics Among Infants, Children, and Adults**

| Parameter   | Infants<br>(<1 yr) <sup>a</sup><br>(n = 12) | Children<br>(>1 yr) <sup>a</sup><br>(n = 7) | Adults <sup>b</sup><br>(n = 6) |
|---|---|---|--------------------------------|
| V $\beta$ (L/kg)  | 0.9 $\pm$ 0.4*                              | 0.7 $\pm$ 0.2                               | 0.3 $\pm$ 0.1                  |
| CL (mL $\cdot$ kg <sup>-1</sup> $\cdot$ min <sup>-1</sup> ) | 3.8 $\pm$ 1*†                               | 5.9 $\pm$ 2*                                | 2 $\pm$ 0.7                    |
| T $_{1/2\beta}$ (h)   | 3.15 $\pm$ 2                                | 1.86 $\pm$ 2                                | 1.69 $\pm$ 0.18                |

$\beta$  = terminal elimination rate constant, V $\beta$  = volume of distribution, CL = milrinone clearance, T $_{1/2\beta}$  =  $\beta$  half-life.

\* P < 0.05, significantly different from adults.

† P < 0.05, significantly different from children.

\* Data derived using traditional washout kinetics.

\* Data from Das et al. (14).

### ➤ Safety results

Thrombocytopenia (defined as platelet count  $\leq$  100000/mm<sup>3</sup>) occurred in 58%, and the risk increased significantly (p  $\leq$  0,05) with duration of infusion. This was not different between dose groups. Two of those, both infants, required a platelet transfusion while receiving milrinone. Tachyarrhythmias were noted in two patients.

**Table 6. Changes in Platelet Counts During Milrinone Infusion**

| Time (h) | Small dose group<br>(n = 11) | Thrombocytopenia (%) <sup>a</sup> | Large dose group<br>(n = 8) | Thrombocytopenia (%) <sup>a</sup> |
|----------|------------------------------|-----------------------------------|-----------------------------|-----------------------------------|
| 0        | 184 $\pm$ 31                 | 0 / 11 (0)                        | 170 $\pm$ 53                | 0 / 8 (0)                         |
| 12       | 142 $\pm$ 41                 | 1 / 11 (9)                        | 135 $\pm$ 30                | 0 / 8 (0)                         |
| 24       | 126 $\pm$ 34                 | 2 / 11 (18)                       | 109 $\pm$ 29                | 3 / 8 (38)                        |
| 36       | 121 $\pm$ 33                 | 5 / 10 (50)                       | 98 $\pm$ 36                 | 3 / 7 (43)                        |
| 48       | 138 $\pm$ 38                 | 2 / 6 (33)                        | 99 $\pm$ 44                 | 3 / 6 (50)                        |
| 60       | 139 $\pm$ 20                 | 0 / 2 (0)                         | 152 $\pm$ 24                | 0 / 2 (0)                         |

The small dose group received a 0.5- $\mu$ g  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup> milrinone infusion; the large dose group received 0.75  $\mu$ g  $\cdot$  kg<sup>-1</sup>  $\cdot$  min<sup>-1</sup>.

\* Patients with thrombocytopenia/total number receiving a milrinone infusion for each time period.

### Assessor's Comment

#### Interpretation and lacks of the study:

1. The validity of mentioned therapeutic range in adults  $\geq$  100 ng/ml is not comprehensible and seems to be quite low taking recent publications into consideration.

#### Conclusion:

The most obvious difference between pharmacokinetics of paediatrics and adult patients is that milrinone is cleared more rapidly in children than in adults, indicating that paediatric patients require larger doses to achieve comparable plasma levels, but infants have significantly lower clearance than children. Pharmacokinetic parameters defined should be mentioned in section 5.2 of the SmPC.

**Bailey JM et al. The pharmacokinetics of milrinone in paediatric patients after cardiac surgery. Anaesthesiology 1999, 90, 1012-18.**

### ➤ Description

**Background:** Milrinone has been shown to increase cardiac output in children after cardiac surgery, but pharmacokinetic analysis has not been used to identify effective dose regimens. The purpose of this study was to characterize the pharmacokinetics of milrinone in infants and children and to apply the results to the issue of dosing.

**Methods:** Twenty children were studied after they underwent repair of congenital cardiac defects. Control hemodynamic measurement was made after the children were separated from cardiopulmonary bypass, and each patient was given a loading dose of 50 µg/kg progressively in 5 min. Hemodynamic measurements were recorded again at the end of the loading dose and when a blood sample was taken to determine milrinone plasma concentrations. Further blood samples were taken during the next 16 h for milrinone plasma concentration analysis.

¶ pharmacokinetics of milrinone were analyzed using the population pharmacokinetic program NONMEM.

**Results:** The loading dose of milrinone resulted in a mean decrease in mean blood pressure of 12% and a mean increase in cardiac index of 18% at a mean peak plasma concentration of 235 ng/ml. The pharmacokinetics of milrinone were best described by a three-compartment model. In the optimal model, all volumes and distribution clearances were proportional to weight, and weight-normalized elimination clearance was proportional to age; *i.e.*,  $Cl_1 = 2.5 \cdot \text{weight} \cdot (1 + 0.058 \cdot \text{age})$  where  $Cl_1$  is expressed as ml/min, and the units of weight and age are kg and months, respectively.

**Conclusions:** A loading dose of 50 µg/kg effectively increases cardiac index in children after cardiac surgery. Simulations indicate that the peak plasma concentration can be maintained

by following the loading dose of 50 µg/kg with an infusion of approximately  $3 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  for 30 min and then a maintenance infusion, which may require adjustment for age. (Key words: Congenital heart disease; pharmacokinetics; phosphodiesterase inhibitors.)

## ➤ **Methods**

### ➤ **Objective(s)**

To characterize the pharmacokinetics of milrinone in infants and children and to apply the results to the issue of dosing.

### ➤ **Study design**

Uncontrolled, pharmacokinetic study.

### ➤ **Study population /Sample size**

20 children after they underwent primary surgical repair of congenital heart defects.

### ➤ **Treatments**

Control hemodynamic measurement was made after the children were separated from cardiopulmonary bypass. The patients were weaned from cardiopulmonary bypass using inotropes chosen at the discretion of the attending anaesthesiologist. Each patient was given the loading dose of 50 µg/kg in 5 minutes. 12 patients were given the loading dose followed by continuous infusion of 0.5 µg/kg/min. The infusion rate was increased to 0.7 µg/kg/min before completion of the study for three patients at the request of the attending intensivist. Hemodynamic measurements were recorded again at the end of the loading dose and when a blood sample was taken to determine milrinone plasma concentrations. Further blood samples were taken during the next 16 hours for milrinone plasma concentration analysis.

### ➤ **Outcomes/endpoints/statistical methods**

Milrinone plasma concentration analysis. Population pharmacokinetic modelling using NONMEM.

Heart rate, mean blood pressure, central venous pressure, left atrial pressure, cardiac index.

## ➤ **Results**

- Recruitment/ Number analysed  
20 children after they underwent primary surgical repair of congenital heart defects.

- Baseline data

Table 1. Demographics

| Age (mo)  | Weight (kg) | Diagnosis | Dopamine<br>( $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ) |
|---|-------------|-----------|--|
| Patients receiving a single bolus dose of milrinone only                |             |           |  |
| 3   | 3.2         | VSD       | —  |
| 4   | 4.4         | VSD       | —  |
| 4   | 4.7         | VSD       | —  |
| 4   | 5.1         | VSD       | —  |
| 5   | 5.7         | VSD       | —  |
| 12  | 11.5        | ALCA      | 10   |
| 14  | 10.4        | VSD       | —  |
| 17  | 8.4         | VSD       | —  |
| Patients receiving a bolus dose of milrinone plus a continuous infusion |             |           |  |
| 3   | 3.3         | VSD       | 5  |
| 3   | 5.6         | TOF       | 10   |
| 4   | 4.6         | AVC       | 10   |
| 5   | 3.7         | VSD       | —  |
| 6   | 5.8         | AVC       | —  |
| 7   | 4.8         | VSD       | —  |
| 9   | 6           | AVC       | 10   |
| 11  | 9.5         | TOF       | —  |
| 12  | 9.7         | TOF       | 5  |
| 15  | 12          | TOF       | 3  |
| 16  | 9.2         | VSD, PS   | —  |
| 22  | 10.9        | VSD, PS   | —  |

VSD = ventricular septal defect; AVC = atrioventricular canal defect; TOF = tetralogy of Fallot; PS = pulmonary stenosis; ALCA = anomalous left coronary artery.

- Efficacy results

The loading dose of milrinone resulted in a significant decrease in mean blood pressure ( $p < 0,05$ ) and a significant increase in cardiac index ( $p < 0,05$ ) at a mean peak plasma concentration of 235 ng/ml. The pharmacokinetics were best described by a three-compartment model. The elimination clearance could be calculated with the following formula: Clearance (ml/min) =  $2.5 \times \text{weight (in kg)} \times (1 + 0.058 \times \text{age (in months)})$ . Volume of distribution at steady state found is 851ml/kg. Simulations indicate that a peak plasma concentration can be maintained by following the loading dose with an infusion of approximately 3  $\mu\text{g}/\text{kg}/\text{min}$  for 30 minutes and then a maintenance infusion of approximately 0.5  $\mu\text{g}/\text{kg}/\text{min}$  which may require adjustment for age.

- Safety results

No adverse events were reported.

### Assessor's Comment

#### Interpretation and lacks of the study:

1. The endpoints had no adjustment of the probability value for multiple comparisons.
2. Statistical methods are insufficiently described.
3. The age range is relatively small.
4. No adverse events were reported.

#### Conclusion:

The most obvious difference between pharmacokinetics of paediatrics and adult patients is the increase in elimination clearance with increasing age in the paediatric model. Therefore, weight-

normalized elimination clearance is expressed as a linear function of age. An extrapolation of the result beyond the range of ages (3 - 22 months) and weights (3.2 – 12 kg) is not possible.

**Bailey J.M. et al. A population pharmacokinetic analysis of milrinone in paediatric patients after cardiac surgery.**  
*Journal of Pharmacokinetics and Pharmacodynamics* 2004, 31(1)43-59.

### ➤ Description

*The purpose of this study was to ascertain the optimal pharmacokinetic model for milrinone in pediatric patients after cardiac surgery when milrinone was administered as a slow loading dose followed by a constant-rate infusion. The data used for pharmacokinetic analysis were collected in a prospective, randomized, placebo-controlled multi-center trial of milrinone as prophylaxis for the development of low cardiac output syndrome after surgery for repair of complex congenital cardiac defects. Two blood samples were randomly collected from each patient for determination of plasma milrinone concentrations with subsequent population pharmacokinetic modeling. The pharmacokinetics of milrinone in pediatric patients under 6 year's age were best described by a weight-normalized one compartment model after a slow loading dose followed by a constant-rate infusion. The volume of distribution was  $482 \text{ ml kg}^{-1}$ , and was independent of age. Clearance was a linear function of age given by  $Cl = 2.42 \text{ ml kg}^{-1} \text{ min}^{-1} [1 + 0.0396 * \text{age}]$ .*

### ➤ Methods

#### ➤ Objective(s)

To ascertain the optimal pharmacokinetic model for milrinone in paediatric patients after cardiac surgery when milrinone was administered as a slow loading dose followed by a constant rate infusion.

#### ➤ Study design

The data used for pharmacokinetic analysis were collected in a prospective, randomized, placebo-controlled trial of milrinone as prophylaxis for the development low cardiac output syndrome after surgery for repair of complex congenital cardiac defects. (PRIMACORP trial, Hoffman et al. 2003).

#### ➤ Study population /Sample size

Eligible patients were 6 years of age or younger without preoperative LCOS who were undergoing biventricular repair of certain cardiac lesions involving cardiopulmonary bypass.

#### ➤ Treatments

Patients were randomly assigned, in a 1:1:1 ratio within 90 minutes after arriving in the intensive care unit, to receive either low-dose intravenous milrinone (25 µg/kg over 60 minutes followed by a 0.25 µg/kg/min infusion for 35 hours), high-dose intravenous milrinone (75 µg/kg over 60 minutes followed by a 0.75 µg/kg/min infusion for 35 hours), or placebo. The physicians were given the option to discontinue study drug between 24 and 36 hours for patients who appeared clinically well. Baseline catecholamines were administered at the discretion of the physician; a combined inotropic drug score was calculated for each patient to account for differences in baseline medications among treatment groups. Two blood samples were drawn from each patient for determination of milrinone plasma concentrations. The sampling times were randomly selected.

#### ➤ Outcomes/endpoints/statistical methods

Milrinone plasma concentration analysis. Population pharmacokinetic modelling using NONMEM (Version 5).

➤ **Results**

➤ Recruitment/ Number analysed

There were 78 patients in the placebo and high dose groups and 79 patients in the low dose group. There were 46 neonates (0 - 1 month), 93 infants (1 - 24months), and 18 children (> 24months) who received either the high or the low dose.

➤ Baseline data

The per-protocol population (n = 227) ranged in age from 2 days to 6.9 years. There were no statistically significant differences among the 3 treatment groups with respect to demographic variables, surgical procedures, intraoperative support times, and baseline inotropic support.

➤ Efficacy results

In contrast to previous studies of milrinone using two and three compartment models, the pharmacokinetics of milrinone in paediatric patients under 6 year's age were best described by a weight-normalized one-compartment model after a slow loading dose followed by a constant rate infusion. The volume of distribution was 482 ml/kg and independent of age. Clearance was a linear function of age given by following formula: Clearance (ml/min) = 2.42 ml/kg/min x (1 + 0.0396 x age (in months)).

**ESTIMATES OF PHARMACOKINETIC PARAMETERS FOR THE ONE COMPARTMENT WEIGHT-CORRECTED MODEL**

| GROUP                            | PARAMETER  |  |
|----------------------------------|--|--|
|                                  | Volume of distribution<br>(mL·kg <sup>-1</sup> ) | Clearance<br>(mL·kg <sup>-1</sup> ·min <sup>-1</sup> ) |
| Total<br>(n=152)                 | 482 (39.3)                                       | 2.42 (0.228)*[1+age*0.0396(0.0139)]                    |
| High<br>(n=75)                   | 466 (17.1)                                       | 2.21 (0.184)*[1+age*0.0379(0.0166)]                    |
| Low<br>(n=77)                    | 505 (57)   | 2.55 (0.396)*[1+age*0.0491(0.032)]                     |
| Neonates<br>(0-1 mo)<br>(n=46)   | 523 (28.5)                                       | 1.64 (0.373)   |
| Infants<br>(1-24 mo)<br>(n=93)   | 461 (40.2)                                       | 3.38 (0.2)   |
| Children<br>(24-72 mo)<br>(n=13) | 353  | 6.68   |

**Note:** Parameter estimates with standard errors in parentheses are shown. The covariance step was unsuccessful for children so standard errors are not shown for this group. Use of age as a covariate on Cl was not used for age-stratified groups (neonates, infants, children).

➤ Safety results

The incidence of serious adverse events overall and by organ system was not significantly different among treatment groups. Serial measurements showed no statistical difference in platelet count over time by treatment arm, and there was no difference in the incidence of thrombocytopenia during the study infusion. Ventricular arrhythmia (n = 1) and supraventricular tachycardia (n = 1) were rare. Hypotension was reported in 1 patient in the placebo and low-dose arms and in 2 patients in the high-dose arm. Two patients who underwent surgery for complete atrioventricular canal died after completion of study drug administration; both deaths were deemed by their physicians to

be unrelated to study drug (aspiration pneumonia on postoperative day 5 and multiorgan failure on postoperative day 13).

#### Assessor's Comment

##### Interpretation and lacks of the study:

1. As described in the protocol study population should be younger than 6 years of age. The per-protocol population ranged in age from 2 days to 6,9 years.
2. The pharmacokinetic component of the PRIMACORP trail was an "add-on" study.
3. Because of safety concerns in this prophylaxis trial, it was deemed essential for patient enrolment and successful completion of the study to give the loading dose over 1 hour. In contrast, in the prior pharmacokinetic studies of milrinone the loading doses were given much more quickly.
4. Furthermore, and most significantly for model development, only two samples were taken from each patient.

##### Conclusion:

Given the positive clinical outcome of the PRIMACORP trial, the dosing schedule used for the study is likely to be adopted by practioners and should be given in section 4.2 of the SmPC including the maximal treatment duration of 35 hours, and the pharmacokinetic model reported in the study will be relevant to how the drug is likely to be given. The most notable finding from this analysis of the influence of covariates is that clearance, but not volume of distribution, increases linearly with patient age. The clearance of milrinone in neonates was less than 25% of that of children, when analyzed by age stratification. Therefore, for the same infusion rate, the steady-state concentration will be higher in preterm infants than in older patients. Use of a loading dose infusion reduces the time to approach steady-state significantly, underscoring the necessity of a loading dose for the rapid achievement of a therapeutic blood concentration. If the pharmacodynamics of milrinone is similar in the various age groups one can anticipate that the onset of effect will be similar in each group but the infusion rate may need reduction in younger patients. But first of all, the selected dosage has to be adjusted to general condition, especially hemodynamic stability of the patient. Pharmacokinetic parameters defined should be mentioned in section 5.2 of the SmPC.

**Sanofi-Synthelabo Inc. PRIMACORP: Prophylactic Intravenous use of milrinone after cardiac operation in Paediatrics.**  
**2001 Aug.**

See Bailey J.M. et al. A population pharmacokinetic analysis of milrinone in paediatric patients after cardiac surgery.

Journal of Pharmacokinetics and Pharmacodynamics 2004, 31(1)43-59.

**Hoffman, TM et al. Efficacy and safety of milrinone in preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease.**  
**Circulation 2003; 107: 996-1002**

#### ➤ Description

**Background**—Low cardiac output syndrome (LCOS), affecting up to 25% of neonates and young children after cardiac surgery, contributes to postoperative morbidity and mortality. This study evaluated the efficacy and safety of prophylactic milrinone in pediatric patients at high risk for developing LCOS.

**Methods and Results**—The study was a double-blind, placebo-controlled trial with 3 parallel groups (low dose, 25- $\mu\text{g}/\text{kg}$  bolus over 60 minutes followed by a 0.25- $\mu\text{g}/\text{kg}$  per min infusion for 35 hours; high dose, 75- $\mu\text{g}/\text{kg}$  bolus followed by a 0.75- $\mu\text{g}/\text{kg}$  per min infusion for 35 hours; or placebo). The composite end point of death or the development of LCOS was evaluated at 36 hours and up to 30 days after randomization. Among 238 treated patients, 25.9%, 17.5%, and 11.7% in the placebo, low-dose milrinone, and high-dose milrinone groups, respectively, developed LCOS in the first 36 hours after surgery. High-dose milrinone significantly reduced the risk the development of LCOS compared with placebo, with a relative risk reduction of 55% ( $P=0.023$ ) in 238 treated patients and 64% ( $P=0.007$ ) in 227 patients without major protocol violations. There were 2 deaths, both after infusion of study drug. The use of high-dose milrinone reduced the risk of the LCOS through the final visit by 48% ( $P=0.049$ ).

**Conclusions**—The use of high-dose milrinone after pediatric congenital heart surgery reduces the risk of LCOS. (*Circulation*. 2003;107:996-1002.)

## ➤ **Methods**

### ➤ **Objective(s)**

To evaluate the efficacy and safety of the prophylactic use of milrinone in paediatric patients at high risk of developing low cardiac output syndrome (LCOS) after cardiac surgery.

### ➤ **Study design**

Multicenter, double-blinded, randomized, placebo-controlled, parallel-treatment study.

### ➤ **Study population /Sample size**

Eligible patients were 6 years of age or younger without preoperative LCOS who were undergoing biventricular repair of certain cardiac lesions involving cardiopulmonary bypass.

### ➤ **Treatments**

Patients were randomly assigned, in a 1:1:1 ratio within 90 minutes after arriving in the intensive care unit, to receive either low-dose intravenous milrinone (25  $\mu\text{g}/\text{kg}$  over 60 minutes followed by a 0.25  $\mu\text{g}/\text{kg}/\text{min}$  infusion for 35 hours), high-dose intravenous milrinone (75  $\mu\text{g}/\text{kg}$  over 60 minutes followed by a 0.75  $\mu\text{g}/\text{kg}/\text{min}$  infusion for 35 hours), or placebo. The physicians were given the option to discontinue study drug between 24 and 36 hours for patients who appeared clinically well. Baseline catecholamines were administered at the discretion of the physician; a combined inotropic drug score was calculated for each patient to account for differences in baseline medications among treatment groups.

### ➤ **Outcomes/endpoints**

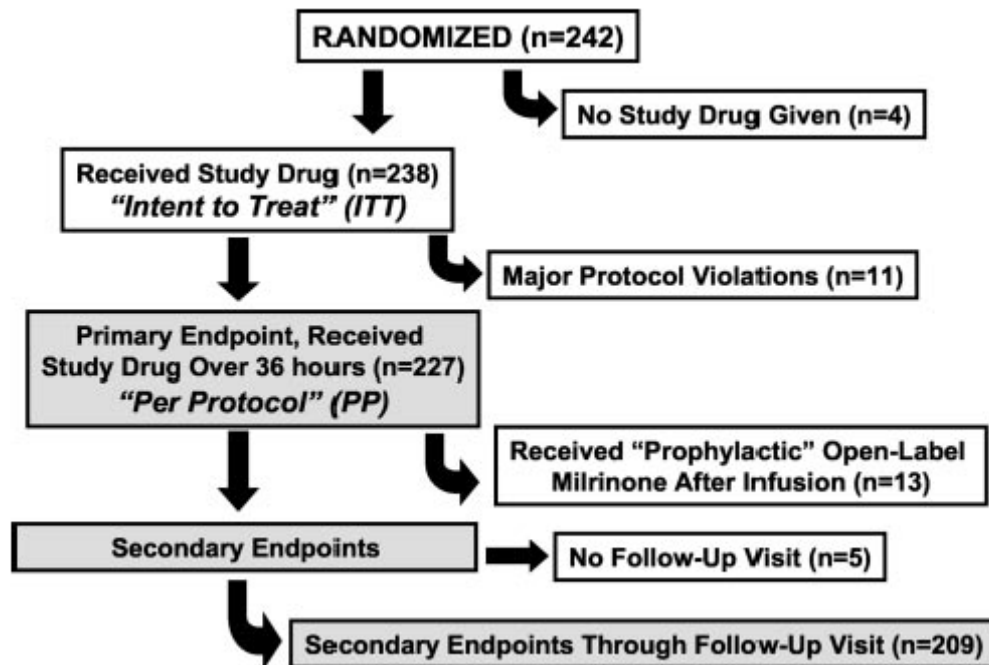
Primary endpoint: composite variable consisting of death or development of LCOS requiring additional pharmacological or other support administered within the first 36 hours after receiving study drug.

### ➤ **Statistical Methods**

The primary and secondary endpoints were analyzed using a pairwise comparison test (t test) at the 0.025 and 0.05 levels. Categorical variables were analyzed using a  $\chi^2$  test, and continuous variables were analyzed using ANOVA t tests with treatment and physicians as main effects in the model. Geometric means were used for analysis of variables with extreme outliers. Log-rank and Kaplan-Meier curves were used to compare the time to development of LCOS or death between low- and high-dose milrinone.

➤ **Results**

➤ Recruitment/ Number analysed



➤ Baseline data

The per-protocol population (n = 227) ranged in age from 2 days to 6.9 years. There were no statistically significant differences among the 3 treatment groups with respect to demographic variables, surgical procedures, intraoperative support times, and baseline inotropic support.

➤ Efficacy results

No patients died during administration of study drug; therefore, the primary endpoint was based solely on the occurrence of LCOS requiring treatment. The use of high-dose milrinone significantly reduced risk of the development of LCOS compared to that of placebo in all treated patients (p = 0.023, relative risk reduction 55%) and in the per-protocol population (p = 0.007, relative risk reduction 64%). There is a statistically insignificant trend toward a lower incidence of primary endpoint with low-dose milrinone.

➤ Safety results

The incidence of serious adverse events overall and by organ system was not significantly different among treatment groups. Serial measurements showed no statistical difference in platelet count over time by treatment arm, and there was no difference in the incidence of thrombocytopenia during the study infusion. Ventricular arrhythmia (n = 1) and supraventricular tachycardia (n = 1) were rare. Hypotension was reported in 1 patient in the placebo and low-dose arms and in 2 patients in the high-dose arm. Two patients who underwent surgery for complete atrioventricular canal died after completion of study drug administration; both deaths were deemed by their physicians to be unrelated to study drug (aspiration pneumonia on postoperative day 5 and multiorgan failure on postoperative day 13).

Assessor's Comment

### Interpretation and lacks of the study:

1. The secondary endpoints had no adjustment of the probability value for multiple comparisons.
2. As described in the protocol study population should be younger than 6 years of age. The per-protocol population ranged in age from 2 days to 6.9 years.
3. A statistical significant risk reduction of the development of LCOS was shown in high-dose milrinone arm compared to that of placebo. A dosage recommendation for the studied population for loading dosage of 75 µg/kg and for continuous infusion of 0.75 µg/kg/min could be concluded.

### Conclusion:

Data prove milrinone to be efficacious and safe in the management of low cardiac output in the study population following cardiovascular surgery. A dosage recommendation for the studied population for loading dosage of 75 µg/kg and for continuous infusion of 0.75 µg/kg/min could be concluded and should be mentioned in section 4.2 of the SmPC.

**Duggal B. et al. Milrinone and low cardiac output following cardiac surgery in infants: is there a direct myocardial effect?**  
*Pediatr Cardiol* 2005, 26, 642-45.

### ➤ Description

**Abstract.** We assessed the effect of milrinone on myocardial function in pediatric patients with post-operative low cardiac output syndrome by index of myocardial performance in a prospective, open-label, nonrandomized, consecutive study. Fifteen patients with low cardiac output syndrome following cardiac surgical treatment were studied in the tertiary cardiothoracic pediatric intensive care unit between April 2001 and November 2003 (age range, 0.2–16 months; median, 7; weight, 2.7–11.8 kg; median, 5). Echocardiographic, Doppler-derived, time interval-based index of myocardial performance (Tei index) was used to study cardiac function prior to and while on intravenous milrinone treatment for 18–24 hours. Treatment with milrinone led to improvement in bi-ventricular myocardial function [mean right ventricular index from 0.521 (SD-0.213) to 0.385 (SD-0.215),  $p = 0.003$ ; mean left ventricular index from 0.636 (SD-0.209) to 0.5 (SD-0.171),  $p = 0.012$ ]. No difference was found in the values of heart rate corrected right or left ventricular ejection time prior to and while on treatment with milrinone (right ventricle: mean, 1.23 (SD-0.42) and 1.14 (SD-0.48),  $p = 0.29$ ; left ventricles: mean, 1.17 (SD-0.51) and 1.13 (SD-0.48),  $p = 0.66$ ) Our data support the direct myocardial effect of milrinone as part of the mechanism behind its already proven benefit in children with low cardiac output syndrome following cardiac surgery.

**Key words:** Low cardiac output — Cardiac surgery — Myocardial function — Milrinone — Infants

### ➤ Methods

#### ➤ Objective(s)

complications. The incidence of low cardiac output syndrome (LCOS) as one of these complications at a single institution remained approximately 25% despite change in the spectrum of treated defects and patients' age throughout the years [17, 25]. The multicenter PRIMACORP study not only found a similar incidence of LCOS in its placebo arm but also showed that prophylactic use of milrinone, a phosphodiesterase-3 inhibitor and inodilator, reduced the risk of LCOS by 55% in pediatric patients undergoing cardiac surgical treatment [9]. Moreover, milrinone has proven beneficial hemodynamic effect in neonates with established LCOS following cardiac surgery [4], lowering systemic and pulmonary vascular resistance with a concomitant increase in cardiac output. Despite its experimental inotropic and lusitropic effects [12], there is no evidence of a direct effect of phosphodiesterase-3 inhibitors on myocardial function in the pediatric postoperative clinical setting.

We used Doppler interval-derived index of myocardial performance [22] to study the effect of milrinone on myocardial function in infants with LCOS following cardiac surgery.

### Materials and Methods

We studied 15 patients with LCOS following cardiac surgical treatment between April 2001 and November 2003. Their age range was 0.2–16 months (median, 7) and weight was 2.7–11.8 kg (median, 5). The underlying cardiac diagnoses are listed in Table 1.

To evaluate the effect of milrinone on myocardial function in paediatric patients with postoperative low cardiac output syndrome by index of myocardial performance.

- Study design  
Prospective, open-label, nonrandomized, consecutive study.
- Study population /Sample size  
15 patients with low cardiac output syndrome following cardiac surgery treatment were studied in the tertiary cardiothoracic paediatric intensive care unit.
- Treatments  
All patients received catecholamines as standard inotropic support throughout the study period. All patients were started on infusion of milrinone (0.3-0.6 µg/kg/min without bolus loading dose) following their first perioperative echocardiogram.
- Outcomes/endpoints  
Echocardiographic, Doppler-derived, time interval-based index of myocardial performance (Tei index) was used to study cardiac function prior to and while on intravenous milrinone treatment for 18 - 24 hours.  
Previously 60 children with normal cardiovascular anatomy and function to establish normal values of myocardial performance index were studied.
- Statistical Methods  
Two-sided, paired Student's t-test was used to analyze the results and a value of  $p < 0.05$  was considered significant.
- **Results**
  - Recruitment/ Number analysed  
15 patients with low cardiac output syndrome following cardiac surgery treatment were studied in the tertiary cardiothoracic paediatric intensive care unit.
  - Baseline data  
Their age range was 0.2 – 16 months and weight was 2.7 – 11.8 kg.

Table 1. Cardiac diagnoses of infants with postoperative low cardiac output state

| Diagnosis                               | n |
|---|---|
| Tetralogy of Fallot                     | 4 |
| Transposition of the great arteries     | 3 |
| Ventricular septal defect               | 3 |
| Atrioventricular septal defect          | 3 |
| Total anomalous pulmonary venous return | 1 |
| Aortic stenosis                         | 1 |

- Efficacy results  
Postoperative values of right and left ventricular myocardial performance index (RMPI and LMPI) were above the normal upper limit of 95% confidence interval in all patients subsequently treated with milrinone. Treatment with milrinone led to improvement in biventricular myocardial function ( $p = 0.003$  and  $p = 0.012$ ). No significant difference was found in the values of heart rate corrected right or left ventricular ejection time in these patients prior to and while treatment with milrinone ( $p = 0.29$  and  $p = 0.66$ ).

- Safety results  
Not described.

Assessor's Comment

Interpretation and lacks of the study:

1. Number of subjects involved is relatively small.
2. There is no control group.
3. The validity of established normal values of myocardial performance index used as reference is not comprehensible.
4. The endpoints had no adjustment of the probability value for multiple comparisons.
5. Statistical methods are insufficiently described.
6. Adverse events are not reported.

Conclusion:

Data indicate efficacy concerning primary endpoints under examination, but due to lacks of the study statistical evidence is not proven by this study.

**Chang AC et al. Milrinone: systemic and pulmonary haemodynamic effects in neonates after cardiac surgery.**  
*Crit Care Med* 1995, 23, 1907-14.

➤ **Description**

**Objective:** To evaluate the hemodynamic effects of intravenous milrinone in neonates with low cardiac output after cardiac surgery.

**Design:** Prospective cohort study.

**Setting:** Pediatric cardiac intensive care unit.

**Patients:** Ten neonates with low cardiac output (cardiac index of  $\leq 3.0$  L/min/m<sup>2</sup>) after corrective cardiac surgery were enrolled in the study. The neonates' ages ranged from 3 to 27 days (median 5) and their weights ranged from 2.0 to 4.8 kg (median 3.7). The diagnoses were: transposition of the great arteries (n = 6, including two with ventricular septal defect), tetralogy of Fallot (n = 2), truncus arteriosus (n = 1), and total anomalous pulmonary venous connection (n = 1).

**Interventions:** Milrinone was intravenously administered in three stages: a) baseline stage, in which patients had a stable hemodynamic status, ventilation and gas exchange, hemostasis, and body temperature; b) loading stage, in which a 50 µg/kg intravenous loading dose of milrinone was administered over 15 mins; and c) infusion stage, in which milrinone was continuously infused at 0.50 µg/kg/min for 30 mins.

**Measurements and Main Results:** The mean heart rate increased after the loading stage (149 ± 13 to 163 ± 12 beats/min,  $p < .01$ ) but slowed during the infusion stage (154 ± 11 beats/min,  $p < .01$  vs. loading stage). Both right

and left atrial pressures were lowered in all ten neonates. Compared with baseline, mean arterial pressure decreased after the loading stage (66 ± 12 to 57 ± 10 mm Hg,  $p < .01$ ) but did not decrease further at the infusion stage (59 ± 12 mm Hg); changes in mean pulmonary arterial pressure were comparable. Cardiac index increased from a baseline mean of 2.1 ± 0.5 to 3.0 ± 0.8 L/min/m<sup>2</sup> ( $p < .01$ ) with the loading stage, and was maintained at 3.1 ± 0.6 L/min/m<sup>2</sup> during the infusion stage. Systemic vascular resistance index decreased below baseline values with loading, from 2136 ± 432 to 1336 ± 400 dyne·sec/cm<sup>5</sup>·m<sup>2</sup> ( $p < .01$ ), and pulmonary vascular resistance index also decreased with loading dose of milrinone, from 488 ± 160 to 360 ± 120 dyne·sec/cm<sup>5</sup>·m<sup>2</sup> ( $p < .01$ ). There was no change in the rate pressure index, an indirect measurement of myocardial oxygen consumption, throughout the study.

**Conclusions:** Administration of milrinone in neonates with low cardiac output after cardiac surgery lowers filling pressures, systemic and pulmonary arterial pressures, and systemic and pulmonary vascular resistances, while improving cardiac index. Milrinone increases heart rate without altering myocardial oxygen consumption. While milrinone appears to be effective and safe during short-term use, the relative distribution of inotropic and vasodilatory properties of milrinone remains to be elucidated. (*Crit Care Med* 1995; 23:1907-1914)

➤ **Methods**

➤ Objective(s)

To assess the hemodynamic effects of intravenous milrinone in neonates with low cardiac output after cardiac surgery.

➤ Study design

Prospective, cohort study

➤ Study population /Sample size

Neonates with low cardiac output (defined as cardiac index of  $\leq 3,0$  L/min/m<sup>2</sup>), despite adequate filling pressures (defined as a left atrial filling pressure of  $> 8$  mmHg), were enrolled in the study.

➤ Treatments

Haemodynamic assessments were made at the completion of each of the following three stages:

*Baseline*

In which patients were stable with regards to haemodynamic status, ventilation and gas exchange, haemostasis, and body temperature.

*Loading stage*

In which a 50 µg/kg intravenous loading dose of milrinone was administered over 15 minutes.

*Infusion stage*

In which milrinone was continuously infused at 0.50 µg/kg/min for 30 minutes.

In addition all patients were receiving a dopamine infusion at 3.0 to 7.5 µg/kg/min and received 5 to 10 ml/kg of 5% albumin to maintain a left atrial pressure of  $> 8$  mmHg before the study begun. All drug infusions were held constant during the study.

➤ Outcomes/endpoints

Haemodynamic parameters: heart rate & rhythm, systemic arterial pressure, right & left atrial pressures, pulmonary arterial pressure, thermodilution cardiac output, systemic & pulmonary vascular resistance indices, right & left ventricular stroke indices, rate pressure index.

➤ Statistical Methods

Two-tailed analyses of variance for paired samples with post hoc comparison were performed for detecting changes in haemodynamic parameters between stages of milrinone protocol. A  $p < 0.05$  was considered statistically significant.

➤ **Results**

➤ Recruitment/ Number analysed

Ten neonates were enrolled in the study.

➤ Baseline data

They ranged in age from 3 to 27 days and in weight from 2.0 to 4.8kg. The diagnoses were: transposition of the great arteries, tetralogy of Fallot, truncus arteriosus, and total anomalous pulmonary venous return.

➤ Efficacy results

Compared with baseline values, the mean heart rate significantly increased after the loading stage ( $p < 0.01$ ), and remained increased compared with baseline ( $p < 0.01$ ).

Compared with baseline values, the right & left atrial pressures significantly decreased after the loading stage ( $p < 0.01$ ) but did not decrease further after the infusion.

Compared with baseline values, the mean systemic ( $p < 0.01$ ) & pulmonary ( $p < 0.05$ ) arterial pressure significantly decreased after the loading stage.

Compared with baseline values, the cardiac index significantly increased with loading dose ( $p < 0.01$ ), and remained increased compared with baseline during the infusion stage ( $p < 0.01$ ).

Compared with baseline values, the systemic & pulmonary vascular resistance index significantly decreased with the loading stage ( $p < 0.01$ ), and remained decreased compared with baseline during the infusion stage.

Compared with baseline values, the right ( $p < 0.05$ ) & left ( $p < 0.01$ ) ventricular stroke work index significantly increased during the loading and infusion stages.

There was no significant change in the rate pressure index, an indirect measurement of myocardial oxygen consumption, throughout the study.

➤ **Safety results**

One patient had occasional premature atrial beats after initiation of intravenous milrinone, no patient had sustained supraventricular tachyarrhythmias, and no patient had ventricular ectopy. Two patients had a decrease in mean systemic arterial pressure of  $> 20\%$  by infusion stage. No patient required additional administration of volume.

Assessor's Comment

Interpretation and lacks of the study:

1. Number of subjects involved is relatively small.
2. The protocol design focused only on the immediate haemodynamic effects of intravenous milrinone without a control group and did not include haemodynamic measurements with either cessation of milrinone or with sustained use of milrinone. As there is no control group, criteria of study design of a cohort study are not fulfilled.
3. The endpoints had no adjustment of the probability value for multiple comparisons.
4. Rate pressure index as an indirect measurement of myocardial oxygen consumption is controversially discussed in literature. In addition, there is no appropriate statistical tool used to prove equivalence of myocardial oxygen consumption in the three stages.
5. Measurements of serum concentrations of milrinone were not accomplished, and therefore concentration-response relationship was not investigated. Therefore, the dosage recommendation of a loading dose of  $50 \mu\text{g}/\text{kg}$  and maintenance infusion of  $0.50 \mu\text{g}/\text{kg}/\text{min}$  is not based on pharmacokinetic data.
6. Statistical methods performed in the study are described insufficiently.

Conclusion:

Data indicate efficacy concerning primary endpoints under examination, but due to lacks of the study statistical evidence is not proven by this study.

**Chu CC. et al. Effect of milrinone on postbypass pulmonary hypertension in children after tetralogy of Fallot repair.**

**Clin Med J 2000, 63, 294-300.**

➤ **Description**

**Background.** Postbypass pulmonary hypertension in surgical correction of tetralogy of Fallot (TOF) is a risk for right ventricular failure. Effective management remains a major challenge. Milrinone is a new drug with a unique mechanism of "inodilation", which offers both inotropic and vasodilatory effects. We attempted to determine if application of milrinone could improve cardiopulmonary dysfunction in children after TOF repair.

**Methods.** We studied 10 children with postbypass pulmonary hypertension after TOF repair within six months. Heart rate, systolic pulmonary arterial pressure (PAP), systolic arterial blood pressure (SBP), pulmonary capillary wedge pressure and PAP/SBP ratio were recorded. Standard cardiopulmonary bypass (CPB) was performed. After CPB, if PAP/SBP was more than 0.5, pulmonary hypertension was suspected and milrinone was administered with a loading dose of 20 µg/kg followed by continuous infusion of 0.2 µg/kg/minute. Hemodynamics were compared before and after administration of milrinone to evaluate its effect.

**Results.** A significant reduction in PAP/SBP ratio within 15 minutes was found after administration of milrinone. The effect persisted for 24 hours during continuous infusion of milrinone. No remarkable adverse effect was noted in the study.

**Conclusions.** We conclude that milrinone is effective in the management of pulmonary hypertension following CPB in children who underwent TOF repair.

## ➤ **Methods**

### ➤ **Objective(s)**

To evaluate the effect of milrinone in children with postbypass pulmonary hypertension after surgical correction of tetralogy of Fallot (TOF).

### ➤ **Study design**

Uncontrolled clinical trial.

### ➤ **Study population /Sample size**

Children who had undergone total correction of TOF from February 1996 to July 1996 were prospectively screened and those with postbypass pulmonary hypertension were recruited for the trial.

### ➤ **Treatments**

If the PAP/SBP ratio increased to greater than 0.5 despite adequate filling pressure after the first attempt of weaning from CPB, postbypass pulmonary hypertension was suspected and intravenous milrinone was administered.

Haemodynamic assessments were made at the completion of each of the following five stages:

#### *Baseline stage*

Stable condition before bypass.

#### *Stage II*

Weaning from bypass was done and loading dose of 20 µg/kg was administered.

#### *Stage III*

15 minutes after the loading dose of milrinone, continuous infusion of 0.2 µg/kg/min for 24 hours was started.

#### *Stage IV*

One hour after the loading dose of milrinone.

#### *Stage V*

24 hours after milrinone administration.

Other vasoactive agents were forbidden in the study period except dopamine.

- **Outcomes/endpoints**  
Heart rate & rhythm, systolic blood pressure (SBP), pulmonary arterial pressure (PAP), pulmonary capillary wedge pressure (PCWP) and PAP/SBP ratio were recorded at five different stages.
- **Statistical Methods**  
Repeated measures ANOVA with Dunnett's multiple comparisons were used. A  $p < 0.05$  was considered statistically significant.
- **Results**
  - **Recruitment/ Number analysed**  
Ten TOF patients with postbypass pulmonary hypertension after successful TOF repair were enrolled in the study.
  - **Baseline data**  
They ranged in age from 1 to 19 years and in weight from 8.6 to 46.7kg.
  - **Efficacy results**  
No difference in heart rate and PCWP was noted.  
A significant decreased PAP/SBP ratio was noted within 15 minutes after milrinone 20 µg/kg administration, that persisted up to 24 hours, given an infusion rate at 0.2 µg/kg/min. Although the early therapeutic effect of milrinone on PAP/SBP ratio was clearly evident, the increase in PAP/SBP ratio induced by CBP or surgery persisted until one hour after treatment with milrinone.
  - **Safety results**  
No arrhythmias or tachycardia was found during observation. No remarkable adverse effects from milrinone were noted in the study period.

#### Assessor's Comment

##### Interpretation and lacks of the study:

1. Number of subjects involved is relatively small.
2. The endpoints had no adjustment of the probability value for multiple comparisons.
3. There is no control group.

##### Conclusion:

Data indicate efficacy concerning primary endpoints in study population, but due to lacks of the study statistical evidence is not proven in this study. Therefore, the indication postbypass pulmonary hypertension after surgical correction of tetralogy of Fallot cannot be approved. In section 5.1 of SmPC the potential usage of milrinone for children undergoing total correction of TOF with postbypass pulmonary hypertension referencing this study should be given. In order to prevent off label use, posology and further details are not given because this indication is not scientifically proven.

***Cai J. et al. Nitric oxide and milrinone: combined effect on pulmonary circulation after Fontan-type procedure: a prospective, randomized study. Ann Thorac Surg 2008, 86, 882-8.***

#### ➤ **Description**

**Background.** Early morbidity and mortality after Fontan operations are related to the elevation of postoperative pulmonary vascular resistance. Inhalation of nitric oxide (iNO) and intravenous milrinone are two options capable of reducing pulmonary vascular resistance. We hypothesized that their combined use could maximally stabilize the pulmonary circulation after Fontan operation.

**Methods.** Forty-six patients with high pulmonary vascular resistance (transpulmonary pressure gradient >10 mm Hg or central venous pressure >15 mm Hg) and impaired oxygenation after Fontan operation were prospectively randomized into three groups: group Mil (n = 15, milrinone at 0.5  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ ), group iNO (n = 15, iNO at <20 ppm), and group iNO + Mil (n = 16, iNO plus Mil). Pulmonary hemodynamic and oxygenation changes were compared among the three groups.

**Results.** Inhalation of nitric oxide with milrinone led to (1) the most significant reduction of pulmonary vascular

resistance (transpulmonary pressure gradient from  $11.26 \pm 1.40$  mm Hg [baseline] to  $7.93 \pm 0.90$  mm Hg [24-hour use] in group iNO + Mil versus from  $11.10 \pm 1.38$  to  $8.69 \pm 0.86$  mm Hg;  $p = 0.048$  in group iNO and from  $11.17 \pm 1.41$  mm Hg to  $9.72 \pm 1.32$  mm Hg;  $p < 0.001$  in group Mil); (2) the most significant improvement of arterial blood oxygenation (ratio of arterial oxygen partial pressure to inspired fraction of oxygen from  $68.88 \pm 14.09$  to  $131.25 \pm 15.92$  in group iNO + Mil versus from  $70.07 \pm 14.24$  to  $120.20 \pm 15.92$ ;  $p = 0.047$  in group iNO and from  $72.60 \pm 12.92$  to  $95.20 \pm 13.49$ ;  $p < 0.001$  in group Mil). Time on mechanical ventilation was shortest in group iNO + Mil ( $p = 0.043$ ).

**Conclusions.** Combined use of iNO and milrinone optimally stabilized pulmonary hemodynamics after Fontan operation.

(Ann Thorac Surg 2008;86:882–8)

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## ➤ **Methods**

### ➤ Objective(s)

To determine the early haemodynamic and oxygenation responses to iNO, milrinone, or both in patients with marked elevation of pulmonary vascular resistance (PVR) after a Fontan operation.

### ➤ Study design

Prospective, randomized study.

### ➤ Study population /Sample size

Paediatric patients, who underwent modified fenestrated Fontan operation and suffered marked elevation of PVR with no explainable causes and without response to conventional managements, were enrolled in this study.

### ➤ Treatments

Group milrinone alone (n = 15) at the dose of 0.5  $\mu\text{g}/\text{kg}/\text{min}$ .

Group iNO alone (n = 15): inhalation began from 10 ppm with subsequent adjustment aiming at achieving greater than 20% improvement in transpulmonary pressure gradient or greater than 10%  $\text{SaO}_2$  with the lowest possible dose of iNO (1 to 20 ppm) within 2 hours after initiation.

Group iNO + milrinone (n = 16): dosages see above.

To prevent confounding results, normal ventilation, stable oxygen inspiration fraction (60%), and one intravenous positive inotropic agent, i.e., dopamine (5  $\mu\text{g}/\text{kg}/\text{min}$ ) were continued throughout the study.

### ➤ Outcomes/endpoints

Pulmonary (transpulmonary pressure gradient and central venous pressure) and systemic haemodynamics and arterial blood oxygenation (oxygenation index, i.e., ratio of arterial oxygen partial pressure to inspiratory oxygen fraction, and  $\text{SaO}_2$ ).

### ➤ Statistical Methods

Two-way analysis of variance for repeated measures was used to test null hypotheses regarding the effects of between-subject factor (medication group), the within-subject factor (time), and the interaction between them. If a statistically significant interaction between group and time was found, subsequent comparison among the groups at

respective time points was performed by one-way analysis of variance followed by Duncan's multiple range test. Nominal variables were analyzed by nonparametric test. A  $p < 0.05$  was considered statistically significant.

➤ **Results**

➤ Recruitment/ Number analysed

46 patients with high PVR defined by transpulmonary pressure gradient  $< 10$  mmHg or central venous pressure  $> 15$  mmHg, and impaired oxygenation were prospectively randomized in three groups.

➤ Baseline data

Table 1. Preoperative and Operative Data of Patients Undergoing Modified Fontan Procedure

| Variable   | Milrinone (n = 15) | iNO (n = 15) | iNO + Milrinone (n = 16) | p Value |
|--|--------------------|--------------|--------------------------|---------|
| Demographic characteristics                      |                    |              |                          |         |
| Age (y)  | 5.8 ± 2.1          | 5.5 ± 2.6    | 5.7 ± 2.8                | 0.97    |
| Weight (kg)                                      | 19.1 ± 5.9         | 18.4 ± 6.5   | 20.0 ± 7.7               | 0.86    |
| Sex (male/female)                                | 8/7                | 6/9          | 9/7                      | 0.63    |
| Preoperative oxygen saturation (%)               | 77.2 ± 5.4         | 80.5 ± 5.2   | 78.5 ± 4.6               | 0.229   |
| Preoperative diagnosis                           |                    |              |                          |         |
| Tricuspid atresia                                | 3/15               | 4/15         | 1/16                     |         |
| Heterotaxy syndrome (asplenia or polysplenia)    | 5/15               | 6/15         | 8/16                     |         |
| Double-outlet right ventricle                    | 3/15               | 4/15         | 4/16                     |         |
| Pulmonary atresia with intact ventricular septum | 4/15               | 1/15         | 3/16                     |         |
| Prior staging with Glenn                         | 4/15               | 6/15         | 6/16                     |         |
| Preoperative mPAP (mm Hg)                        | 13.8 ± 2.9         | 14.4 ± 2.1   | 13.5 ± 4.1               | 0.786   |
| Operative feature                                |                    |              |                          |         |
| Lateral tunnel/extracardiac conduit              | 10/5               | 7/8          | 6/10                     |         |
| Cardiopulmonary bypass time (min)                | 143 ± 69           | 138 ± 44     | 134 ± 55                 | 0.929   |
| Aortic cross-clamp time (min)                    | 67.9 ± 36.1        | 61.1 ± 32.8  | 63.1 ± 29.6              | 0.871   |

iNO = inhalational nitric oxide; mPAP = mean pulmonary arterial pressure.

The duration of treatment was 24 hours.

➤ Efficacy results

Three patients in group milrinone, who had to be shifted to combined therapy of iNO and milrinone because of severe hypoxemia and abnormally high TPG within 6 hours of the use of milrinone, were excluded during the study period.

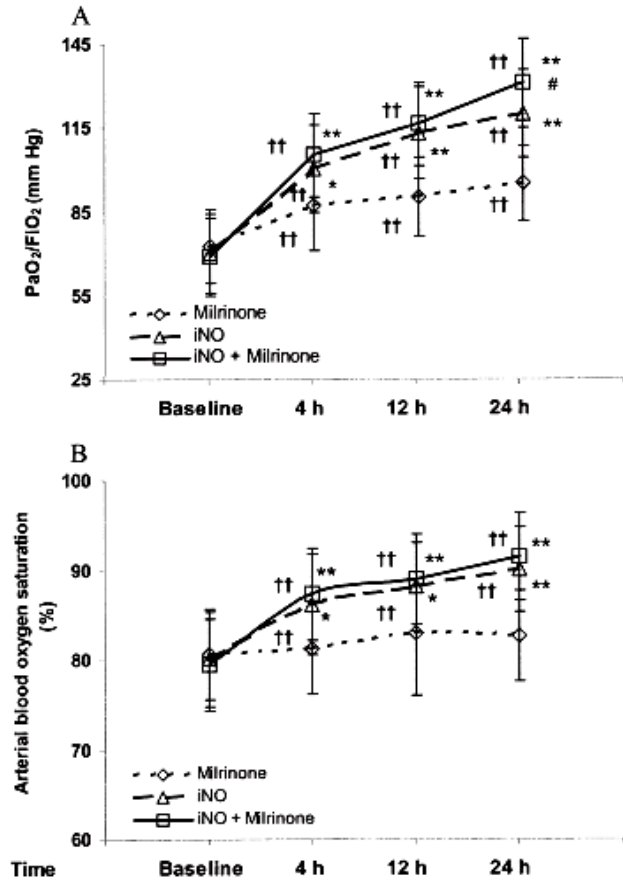
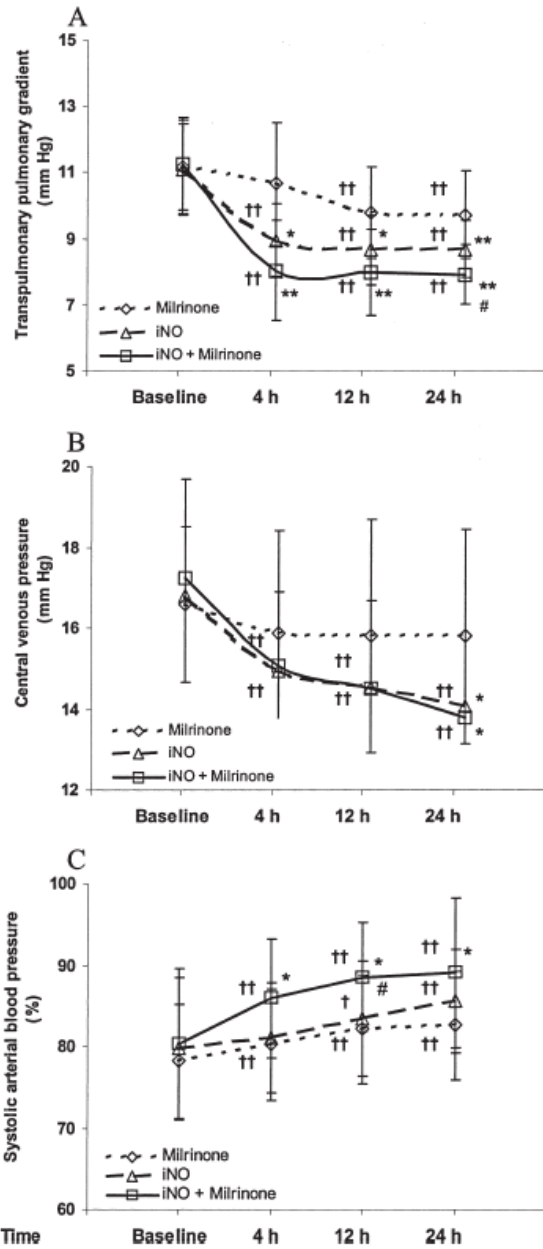


Fig 2. Change of oxygenation index ( $\text{PaO}_2/\text{FiO}_2$ , A) and arterial blood oxygen saturation (B) after the use of intravenous milrinone ( $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , group Mil), inhalational nitric oxide ( $<20 \text{ ppm}$ , group iNO), or both (group iNO + Mil). Data are expressed as mean  $\pm$  standard deviation. Significant interactions existed between group and time in each variable ( $p < 0.001$  in both variables; two-way analysis of variance for repeated measurements). Subsequent comparison was carried out with Duncan's multiple range test. Baseline is before administration of milrinone, inhalation of nitric oxide, or both, 4 h is 4 hours after medication, 12 h is 12 hours after medication, 24 h is 24 hours after medication. \* $p < 0.05$ ; \*\* $p < 0.01$  as compared with group Mil at respective time points. # $p < 0.05$  as compared with group iNO at respective time points. † $p < 0.05$ ; †† $p < 0.01$  as compared with respective baseline value in each group.

Fig 1. Absolute change of transpulmonary pressure gradient (A) and central venous pressure (B) and percent change of systolic arterial blood pressure (C) after the use of intravenous milrinone ( $0.5 \mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$ , group Mil), inhalational nitric oxide ( $<20 \text{ ppm}$ , group iNO), or both (group iNO + Mil). Data are expressed as mean  $\pm$  standard deviation. Significant interactions existed between group and time in every variable ( $p < 0.001$  for transpulmonary pressure gradient,  $p = 0.021$  for central venous pressure and  $0.008$  for systolic arterial blood pressure; two-way analysis of variance for repeated measurements). Subsequent comparison was carried out with Duncan's multiple range test. Baseline is before administration of milrinone, inhalation of nitric oxide, or both, 4 h is 4 hours after medication, 12 h is 12 hours after medication, 24 h is 24 hours after medication. \* $p < 0.05$ ; \*\* $p < 0.01$  as compared with group Mil at respective time points. # $p < 0.05$  as compared with group iNO at respective time points. † $p < 0.05$ ; †† $p < 0.01$  as compared with respective baseline value in each group.

As described with “#  $p < 0.05$  as compared with group iNO at respective time points” statistical significance could only be shown in TPG at time point 24 hours, in systolic arterial blood pressure at time point 12 hours and in  $\text{PsO}_2/\text{FiO}_2$  at time point 24 hours between group iNO and group iNO + milrinone.

Patients receiving both iNO and milrinone had least time on mechanical ventilation ( $p = 0.043$ ).

➤ Safety results

1 patient each in group milrinone and group iNO+milrinone was excluded because of severe thrombocytopenia. One patient in group iNO+milrinone and 3 patients in group iNO suffered CVP and TPG rebound during the process of iNO withdrawal. In addition, 1 patient in each group iNO+milrinone and iNO and 2 patients in group milrinone had to be intubated after weaning from the ventilator because of compromised blood oxygenation.

Assessor's Comment

Interpretation and lacks of the study:

1. The endpoints had no adjustment of the probability value for multiple comparisons.
2. There is no placebo-control.
3. iNO as gold standard therapy for postoperative pulmonary hypertension is controversially discussed in literature taking recent publications into consideration.
4. Statistical significant superiority of iNO+milrinone vs. iNO could only be shown in TPG at time point 24 hours, in systolic arterial blood pressure at time point 12 hours and in  $\text{PsO}_2/\text{FiO}_2$  at time point 24 hours.
5. A comparison of frequency and severity of adverse events between iNO+milrinone and iNO was not listed.

Conclusion:

Data indicate efficacy concerning primary endpoints in study population, but due to lacks of the study statistical evidence is not proven and a positive benefit/risk ratio for the study population with pulmonary hypertension after Fontan procedure cannot be concluded. Therefore, the indication pulmonary hypertension after Fontan procedure cannot be approved. In section 5.1 of SmPC the potential usage of milrinone for children undergoing Fontan procedure with pulmonary hypertension referencing this study should be given. In order to prevent off label use, posology and further details are not given because this indication is not scientifically proven.

**McNamara et al., 2006. Milrinone improves oxygenation in neonates with severe persistent pulmonary hypertension.**  
*Journal of Critical Care* 2006, 21, 217-233.

## ➤ Description

### Abstract

**Background:** Many neonates with severe persistent pulmonary hypertension of the newborn (PPHN) are nonresponders to inhaled nitric oxide (iNO). Milrinone is a promising adjunctive therapy because of its pulmonary vasodilator properties and cardiotropic effects.

**Design:** Case series of neonates with severe PPHN (defined as oxygenation index [OI] >20, failure of iNO therapy, and echocardiographic confirmation of PPHN).

**Setting:** Tertiary neonatal intensive care unit.

**Subjects:** Full-term ( $\geq 37$  weeks) neonates with severe PPHN who received intravenous milrinone.

**Measurements:** The primary end point was the effect of intravenous milrinone on OI and hemodynamic stability over a 72-hour study period. Secondary end points examined included duration of iNO and degree of cardiorespiratory support.

**Results:** Nine neonates at a mean gestation of  $39.25 \pm 2.76$  weeks, birth weight of  $3668 \pm 649.1$  g, and baseline OI of  $28.1 \pm 5.9$  received milrinone treatment after a poor initial response to iNO treatment. Intravenous milrinone was commenced at a median age of 21 hours (range, 18-49 hours), and patients were treated for median of 70 hours (range, 23-136). Oxygenation index was significantly reduced after milrinone treatment, particularly in the immediate 24 hours of treatment ( $8.0 \pm 6.6$ ,  $P < .001$ ). There was a significant improvement in heart rate ( $179 \pm 15.2$  vs  $149.6 \pm 22.4$ ,  $P < .001$ ) over the same period. Infants who received milrinone did not develop systemic hypotension; in fact, there was a nonsignificant trend toward improved blood pressure.

**Conclusions:** Intravenous milrinone produces early improvements in oxygenation without compromising systemic blood pressure.

## ➤ Methods

### ➤ Objective(s)

To evaluate the effect of milrinone in neonates with oxygenation failure secondary to pulmonary hypertension.

### ➤ Study design

Case series.

### ➤ Study population /Sample size

Between January 2002 and April 2004, neonates with severe persistent pulmonary hypertension (PPHN) who responded poorly to inhaled nitric oxide were treated with intravenous milrinone.

### ➤ Treatments

Milrinone was started at a dose of  $0.33 \mu\text{g}/\text{kg}/\text{min}$  if inclusion criteria were met. A loading dose was not administered. The dose was titrated according to the clinical response and increased in increments of  $0.33$  to a maximum of  $0.99 \mu\text{g}/\text{kg}/\text{min}$ .

Decisions to commence or adjust alternative inotropes or vasopressors were left to the discretion of the attending neonatologist.

### ➤ Outcomes/endpoints

Effect of milrinone on oxygenation and blood pressure over a 72-hour period after commencement of treatment.

### ➤ Statistical Methods

Continuous data were analyzed using Student t test and Mann-Whitney U test for respective parametric and nonparametric data sets. Categorical data were analyzed using  $\chi^2$  or Fisher exact test. Analysis of variance testing was used to investigate the effects of milrinone (post hoc Tukey or Dunnett method) on each endpoint. A  $p < 0.05$  was considered statistically significant.

➤ **Results**

➤ Recruitment/ Number analysed

Nine full-term newborns, who received intravenous milrinone combination therapy in severe PPHN, were identified after a poor initial response to iNO.

➤ Baseline data

Their mean gestational age was 39.2 +/- 2.8 weeks and birth weight, 3668 +/- 649.1g. The aetiologies of the PPHN were meconium aspiration syndrome, birth asphyxia, diabetic cardiomyopathy and birth asphyxia, transient tachypnea of the newborn and sepsis.

Intravenous milrinone treatment was initiated at a median time of 21 hours (range 18 to 49 hours), median milrinone dose was 0.66  $\mu\text{g}/\text{kg}/\text{min}$  (range 0.33 to 0.99  $\mu\text{g}/\text{kg}/\text{min}$ ), and patients were treated for a median of 70 hours (range 23 to 136 hours).

➤ Efficacy results

There was a significant improvement in oxygenation after commencement of milrinone ( $p < 0.001$ ), particularly in the immediate 24 hours of treatment.

There was a significant improvement in heart rate ( $p < 0.001$ ) over the same period. Infants who received milrinone did not become hypotensive or receive additional inotropic support; they demonstrated a nonsignificant trend toward improved blood pressure.

➤ Safety results

Adverse events are not reported.

Assessor's Comment

Interpretation and lacks of the study:

1. Number of subjects involved is relatively small.
2. The endpoints had no adjustment of the probability value for multiple comparisons.
3. There is no control group.
4. Adverse events are not reported.

Conclusion:

Data indicate efficacy concerning primary endpoints in study population, but due to lacks of the study statistical evidence is not proven. Therefore, the indication neonates with oxygenation failure secondary to pulmonary hypertension cannot be approved.

**Kikura M et al. The effects of milrinone on platelets in patients undergoing cardiac surgery. Anest Analg 1995, 81, 44 -48.**

➤ **Description**

Although amrinone produces thrombocytopenia, no information is available regarding the acute effects of milrinone on platelets. Therefore, we evaluated the effects of milrinone on platelet number and function in cardiac surgical patients. Twenty-seven patients were studied during cardiac surgery requiring cardiopulmonary bypass (CPB). Patients were randomized to receive no milrinone (n = 10), or milrinone (n = 17) at a loading dose of 50–75  $\mu\text{g}/\text{kg}$  in the CPB circuit followed by 0.5–0.75  $\mu\text{g} \cdot \text{kg}^{-1} \cdot \text{min}^{-1}$  for 12–24 h. Bleeding times and blood samples for coagulation studies were obtained prior to induction, and at 2 and 24 h after

CPB. In both groups, platelet counts decreased significantly from the baseline at 2 and 24 h after CPB, and bleeding time increased significantly from the baseline at 2 and 24 h after CPB. No significant thromboelastoplasty (TEG) changes were observed in either group, and there were no significant differences in platelet aggregation or chest tube drainage between the groups. Acute milrinone administration did not cause significant changes in platelet number or function in patients undergoing cardiac operations requiring CPB, beyond the usual adverse effects of cardiac surgery and CPB.

(Anesth Analg 1995;81:44–8)

## ➤ **Methods**

### ➤ Objective(s)

To evaluate the effects of milrinone on platelet number and function in cardiac surgical patients.

### ➤ Study design

Randomized, placebo-controlled study.

### ➤ Study population /Sample size

Adult patients electively scheduled for cardiac operations requiring cardiopulmonary bypass.

### ➤ Treatments

Patients were randomized to receive no milrinone (n = 10), or milrinone (n = 17) at a loading dose of 50 to 75  $\mu\text{g}/\text{kg}$  immediately prior to separation from cardiopulmonary bypass followed by 0.5 – 0.75  $\mu\text{g}/\text{kg}/\text{min}$  continuous infusion for 12 – 24 hours. Any patients who received blood products throughout the study period were excluded.

### ➤ Outcomes/endpoints

Hematocrit, platelet count, prothrombin time, partial thromboplastin time, bleeding time,  $\text{ED}_{50}$  of platelet aggregation to adenosine diphosphat and collagen-induced platelet aggregation, and TEG (thromboelastograph) measurements.

### ➤ Statistical Methods

Statistical analysis of variance, followed by the Bonferroni multiple comparison test. A  $p < 0.05$  was considered statistically significant.

## ➤ **Results**

### ➤ Recruitment/ Number analysed

27 adult patients electively scheduled for cardiac operations requiring cardiopulmonary bypass.

### ➤ Baseline data

|                        | Control<br>group<br>(n = 10) | Milrinone<br>group<br>(n = 14) |
|------------------------|------------------------------|--------------------------------|
| Age (yr)               | 62 ± 12                      | 60 ± 13                        |
| Gender (M/F)           | 9/1                          | 10/4                           |
| Weight (kg)            | 81 ± 11                      | 76 ± 16                        |
| Height (cm)            | 178 ± 9                      | 172 ± 10                       |
| Cross-clamp time (min) | 49 ± 18                      | 56 ± 22                        |
| CPB time (min)         | 103 ± 27                     | 112 ± 35                       |

CPB = cardiopulmonary bypass.

➤ **Efficacy results**

In the milrinone group 3 patients who received blood products including platelets were excluded from the study. No abnormal bleeding was observed in any patients after cardiac surgery in this study. Plasma milrinone levels at 2 h were 152 +/- 42 ng/ml in the milrinone-treated patients. There were no significant differences in hematocrit, platelet count, prothrombin time, partial thromboplastin time, bleeding time, ED<sub>50</sub> of platelet aggregation to adenosine diphosphat and collagen-induced platelet aggregation, and TEG measurements between milrinone-treated and control group. There were no significant differences in the 24-h chest tube drainage in the control group compared to the milrinone-treated group. In both groups, platelet counts decreased significantly from the baseline at 2 h and 24 h after cardiopulmonary bypass, and bleeding time increased significantly from the baseline at 2 h and 24 h after cardiopulmonary bypass.

➤ **Safety results**

Milrinone administration did not cause significant changes in platelet number or function in patients undergoing cardiac surgery requiring cardiopulmonary bypass, beyond the usual adverse effects of cardiac surgery and cardiopulmonary bypass.

Assessor's Comment

Interpretation and lacks of the study:

1. There are only adults included to the study.
2. Number of subjects involved is relatively small.

Conclusion:

Since only adults are included to the study, no conclusion on safety of milrinone in paediatric population from this publication should be drawn.

**Watson S. et al. Use of milrinone in paediatric care unit. Paediatrics 1999, 104, 674-82.**

➤ **Description**

No abstract is available.

➤ **Methods**

➤ **Objective(s)**

To describe the incidence of milrinone-related cardiac arrhythmias and thrombocytopenia described in adults to that observed in a population of children who received this agent after cardiac surgery.

➤ **Study design**

Retrospective, uncontrolled, clinical study.

- Study population /Sample size  
Children who received milrinone for inotropy and afterload reduction after cardiac surgery.
- Treatments  
Patient received an average milrinone dose of 0.63 µg/kg/min.
- Outcomes/endpoints  
Data recorded were age, diagnosis, milrinone hours and average dosage per patient, presence of thrombocytopenia (< 100000/µl), and occurrence of cardiac arrhythmias requiring medical or electrical therapy.
- Statistical Methods  
Incidences of thrombocytopenia and arrhythmia were determined as a percent of total patients receiving milrinone. Data from patients with other likely sources of thrombocytopenia and arrhythmias were then excluded, and the remaining patient data were re-analyzed in the above fashion. Average milrinone dose and duration were determined for the population.
- **Results**
  - Recruitment/ Number analysed  
Data from 30 children from newborn to 36 months of age were included.
  - Baseline data  
Most common cardiac diagnosis for which patients received milrinone after operative repair included atrioventricular septal defect (6), tetralogy of Fallot (3), D-TGA (3) and pulmonary atresia with VSD (3). Beyond the first 48 post-operative hours, patients received milrinone for an average of 4.7 days.
  - Efficacy results  
None.
  - Safety results  
Two (6.6%) of children receiving milrinone exhibited arrhythmias (sinus bradycardia and supraventricular tachycardia) that could not otherwise be explained. Thrombocytopenia occurred in 8 (26.7%) patients. Five of these had other compelling reasons for low platelets including CNS anoxia, disseminated intravascular coagulation, infection, and concurrent heparin infusions. When these patients were excluded, the remaining three patients represented 10% of children receiving milrinone.

Assessor's Comment

Interpretation and lacks of the study:

1. Number of subjects involved is relatively small.
2. Efficacy results were not recorded.

Conclusion:

These preliminary data suggest that milrinone-related arrhythmias are less common in children than in adults (6.6 vs. 16.2%), whereas milrinone-related thrombocytopenia is more common in children than in adults (10 vs. 0.4%). Larger patient numbers are needed to more clearly detect and define an accurate milrinone paediatric side effect profile. These preliminary data have to be

**Bassler D. et al. Neonatal persistent pulmonary hypertension treated with milrinone: four case reports.**

***Biol Neonate 2006, 89, 1-5.***

➤ **Description**

Current standard therapy for persistent pulmonary hypertension of the newborn (PPHN) consists of optimal lung inflation, hemodynamic support and selective vasodilation with inhaled nitric oxide (iNO). However, not all infants will respond. Milrinone, a phosphodiesterase (PDE) III inhibitor, is routinely used in pediatric cardiac intensive care units to improve inotropy and reduce afterload. Although its use in post-operative cardiac failure has been proven in a randomized trial, it has not been reported to be beneficial in PPHN. We report four cases with severe PPHN treated with a combination of iNO and Milrinone. All four cases were unresponsive to therapy including iNO, with a mean oxygenation index (OI) of 40 (standard deviation (SD) 12)) before Milrinone. Substantial improvement in OI (mean of 28; SD 16) was followed by extubation and survival. However, of 4 patients, 2 developed serious intraventricular hemorrhages (IVHs), and 1 had a small IVH. To clarify the risk benefit ratio, of death versus survival with impairment, a randomized controlled trial is needed.

➤ **Methods**

➤ Objective(s)

Case description.

➤ Study design

Case series.

➤ Study population /Sample size

4 cases with severe persistent pulmonary hypertension of the newborn (PPHN) treated with a combination of inhaled nitric oxide (iNO) and milrinone. All cases were unresponsive to therapy including iNO, with a mean oxygenation index(OI) of 40 before milrinone.

➤ Treatments

Case 1: loading dose of 50µg/kg/min over 20 min followed by a continuous infusion of 0.33 µg/kg/min.

Case 2: no information on loading dose and continuous infusion until day 6 when milrinone was weaned to 0.2 mg/kg/min.

Case 3: no information on loading dose and continuous infusion.

Case 4: no information on loading dose and continuous infusion.

Further information see table below.

➤ Outcomes/endpoints

Oxygenation index before starting milrinone and 12 – 24 h after.

- Statistical Methods  
Not described.

- **Results**

- Recruitment/ Number analysed  
4 cases with severe persistent pulmonary hypertension of the newborn (PPHN) treated with a combination of inhaled nitric oxide (iNO) and milrinone.
- Baseline data/efficacy results/safety results

| Case                              | 1   | 2   | 3  | 4                                     |
|-----------------------------------|---|---|--|---------------------------------------|
| Gestational age, weeks            | 26  | 40  | 41   | 39                                    |
| Birth weight, g                   | 1,020   | 2,820                                     | 4,091  | 2,926                                 |
| APGAR scores (1/5 min)            | 1/6   | 8/9                                       | 9/9  | 6/8                                   |
| Primary cause of PPHN             | oligohydramnios   | pneumothoraces/<br>unrecognized hypoxemia | meconium aspiration<br>syndrome                              | meconium aspiration<br>syndrome       |
| Number of surfactant doses (BLES) | 1   | 0   | 2  | 5                                     |
| Sedation (max. dose)              | morphine<br>(20 µg/kg/h)                                | morphine<br>(20 µg/kg/h)                  | morphine<br>(10 µg/kg/h)                                     | morphine<br>(20 µg/kg/h)              |
| Paralysis (max. dose)             | vecuronium<br>(0.1 mg/kg/h)                             | vecuronium<br>(0.1 mg/kg/h)               | vecuronium<br>(0.12 mg/kg/h)                                 | vecuronium<br>(0.1 mg/kg/h)           |
| Inotropes (max. dose)             | dopamine<br>(20 µg/kg/min)                              | dopamine<br>(20 µg/kg/min)                | dopamine<br>(30 µg/kg/min)<br>epinephrine<br>(0.5 µg/kg/min) | dopamine<br>(22 µg/kg/min)            |
| Steroids                          | hydrocortisone<br>(2.5 mg/kg) × 4                       |   |  |                                       |
| iNO (max. dose)                   | 10 ppm  | 20 ppm                                    | 20 ppm   | 20 ppm                                |
| iNO started/stopped               | start day 1<br>end day 4                                | start day 3<br>end day 7                  | start day 2<br>end day 12                                    | start day 2<br>end day 9              |
| Milrinone started/stopped         | start day 2<br>end day 5                                | start day 4<br>end day 7                  | start day 7<br>end day 12                                    | start day 2<br>end day 9              |
| Extubation                        | day 9   | day 7                                     | day 21   | day 10                                |
| HUS (days 7–14)                   | bilateral IVH, moderate<br>dilatation of all ventricles | left IVH                                  | normal   | small left subependymal<br>hemorrhage |

HUS = Head ultrasound; IVH = intraventricular hemorrhage; iNO = inhaled nitric oxide; BLES = bovine lipid extract surfactant; PPHN = persistent pulmonary hypertension of the newborn.

|   | Case 1  | Case 2  | Case 3   | Case 4  |
|---|---|---|--|---|
| <i>Values immediately before starting Milrinone</i>           |   |   |  |   |
| Ventilator mode and settings                                  | pressure control<br>PIP 20 cm H <sub>2</sub> O<br>PEEP 8 cm H <sub>2</sub> O<br>rate 60/s<br>I-Time 0.25 s<br>FiO <sub>2</sub> 0.99 | pressure control<br>PIP 25 cm H <sub>2</sub> O<br>PEEP 9 cm H <sub>2</sub> O<br>rate 40/s<br>I-Time 0.35 s<br>FiO <sub>2</sub> 0.99 | high frequency<br>MAP 23 cm H <sub>2</sub> O<br>ΔP 59<br>frequency 8 Hz<br>FiO <sub>2</sub> 0.99<br>I/E ratio 0.33 | high frequency<br>MAP 20 cm H <sub>2</sub> O<br>ΔP 60<br>frequency 10 Hz<br>FiO <sub>2</sub> 0.99<br>I/E ratio 0.33 |
| OI  | 35  | 28  | 55   | 43  |
| ECHO  | RV hypertension,<br>decreased forward flow<br>across pulmonary valve  | RV systolic pressure<br>estimated at<br>53 mm Hg  | ECHO day 2 of life:<br>mild-moderate<br>pulmonary hypertension   | no ECHO done  |
| MBP, mm Hg  | 24  | 47  | 58   | 55  |
| <i>Maximal values in the 12–24 h after starting Milrinone</i> |   |   |  |   |
| OI (maximum)  | 16  | 15  | 49   | 32  |
| ECHO  | improved flow across<br>pulmonary valve   | no ECHO done  | RV pressure at least<br>50% systemic   | mildly elevated<br>pulmonary pressures  |
| MBP (minimum), mm Hg  | 22  | 45  | 51   | 52  |
| Changes in co-interventions                                   |   |   |  |   |
| Morphine  | unchanged   | ↑by 10 μg/kg/h  | unchanged  | unchanged   |
| Vecuronium  | unchanged   | unchanged   | unchanged  | unchanged   |
| Dopamine  | ↓by 6 μg/kg/min   | unchanged   | unchanged  | ↑by 10 μg/kg/min  |
| Epinephrine   | –   | –   | ↓by 0.2 μg/kg/min  | –   |
| NS/albumin 5%   | × 2   |   | × 5  | × 3   |
| Sodium bicarbonate  | × 1   |   | × 2  |   |

ECHO = Echocardiogram; OI = oxygenation index; MBP = mean blood pressure; NS = normal saline.

### Assessor's Comment

#### Interpretation and lacks of the study:

1. Number of subjects involved is relatively small.
2. Statistical methods are not described.
3. Milrinone loading dose and continuous infusion rates are with exception of case 1 not described.

#### Conclusion:

Of 4 patients, 2 developed serious intraventricular haemorrhages, and 1 had a small intraventricular haemorrhage. Other risk factors like low birth weight, pneumothoraces, meconium aspiration syndrome or previous iNO administration could be identified. The adverse event intraventricular haemorrhages should be added to the section 4.8 of the SmPC.

**Price J.F. et al. Outpatient continuous parenteral inotropic therapy as bridge to transplantation in children with advanced heart failure. *Journal of Cardiac Failure* 2006, 12, 139-43.**

### ➤ Description

**Background:** Advanced heart failure in children is associated with high morbidity and mortality and is often refractory to standard medical therapy. The purpose of this study was to review our institutional experience with the use of outpatient parenteral inotropic therapy (PIT) for advanced chronic heart failure in children.

**Methods and Results:** We reviewed the medical records of all patients treated with PIT as outpatients. Seven patients received outpatient PIT from 2/99 to 1/05 (mean age was 14.6 years  $\pm$  3.7). Median duration of therapy was 10 weeks (range 4–84 weeks). The mean number of emergency department visits per patient was greater before starting PIT than after starting PIT ( $2.3 \pm 1.8$  versus  $1.1 \pm 2.2$ ,  $P < .05$ ). The mean number of hospital admissions from exacerbation of heart failure symptoms decreased after starting PIT ( $2.1 \pm 1.3$  versus  $0.6 \pm 0.8$ ,  $P < .05$ ). Mean EF% in patients with systolic dysfunction improved while on therapy ( $30 \pm 14\%$  before versus  $39 \pm 16\%$  after,  $P < .05$ ). There was 1 death and 5 complications in 2 patients. Six patients were successfully bridged to transplantation.

**Conclusion:** Outpatient continuous parenteral inotropic therapy may serve as a successful bridge to cardiac transplantation in selected pediatric outpatients.

**Key Words:** Pediatric, heart failure, inotrope, transplant.

## ➤ **Methods**

### ➤ Objective(s)

To review the medical records of all patients treated with the use of parenteral inotropic therapy as outpatients.

### ➤ Study design

Case series.

### ➤ Study population /Sample size

All patients younger than 21 years of age treated with the use of parenteral inotropic therapy as outpatients.

### ➤ Treatments

The mean dose of milrinone used was  $0.25 \pm 0.03 \mu\text{g}/\text{kg}/\text{min}$ .

The mean dose of dopamine used was  $2.8 \pm 0.3 \mu\text{g}/\text{kg}/\text{min}$ .

### ➤ Outcomes/endpoints

Number of emergency department visits, hospital admissions, and ejection fractions before and after starting outpatient therapy.

### ➤ Statistical Methods

The Wilcoxon signed-rank test was used to compare the number of emergency department visits, hospital admissions, and ejection fractions before and after starting outpatient therapy. A  $p < 0.05$  was considered statistically significant.

## ➤ **Results**

### ➤ Recruitment/ Number analysed

Seven patients received outpatient parenteral inotropic therapy.

### ➤ Baseline data

Median duration of therapy was 10 weeks (range 4 – 84 weeks).

Inotropic medications used for parenteral inotropic therapy included dopamine alone ( $n = 1$ ), milrinone alone ( $n = 4$ ), and dopamine + milrinone ( $n = 2$ ).

**Table 1.** Patient Characteristics at Initiation of Inotropic Therapy

| Patient | Age (years) | NYHA Class | Sex | Etiology of HF                 | Other Therapies                               |
|---------|-------------|------------|-----|--------------------------------|---|
| 1       | 11.7        | IV         | M   | TCAD                           | β-blocker, ACEI, diuretic                     |
| 2       | 15.8        | IV         | M   | Tricuspid atresia, s/p Fontan  | digoxin, ACEI, diuretic, amio                 |
| 3       | 15.8        | IV         | F   | Complex heterotaxy, s/p Fontan | digoxin, ACEI, diuretic                       |
| 4       | 16.0        | IV         | F   | TCAD                           | digoxin, ACEI, diuretic                       |
| 5       | 20.2        | III        | M   | CCTGA                          | β-blocker, digoxin, ACEI, diuretic, amio, ICD |
| 6       | 13.7        | III        | M   | Aortic stenosis                | β-blocker, ACEI, diuretic                     |
| 7       | 8.5         | IV         | M   | Idiopathic DCM                 | β-blocker, digoxin, ACEI, diuretic, amio, ICD |

HF, heart failure; M, male; F, female; TCAD, transplant coronary artery disease; ACEI, angiotensin-converting enzyme inhibitor; s/p, status post; amio, amiodarone; ICD, implantable cardio defibrillator; CCTGA, congenitally corrected transposition of the great arteries; DCM, dilated cardiomyopathy.

➤ Efficacy results

**Table 2.** Inotropic Therapy and Complications

| Patient | Inotrope and Dose (mcg · kg · min) | Length of Therapy | Complications                    | Outcome      |
|---------|------------------------------------|-------------------|----------------------------------|--------------|
| 1       | Milrinone 0.3                      | 27 days           | None                             | Transplant   |
| 2       | Milrinone 0.2                      | 50 days           | Died at home                     | Sudden death |
| 3       | DA 3.0 and milrinone 0.25          | 588 days          | Occlusion; extravasation (twice) | Transplant   |
| 4       | Milrinone 0.2                      | 111 days          | None                             | Transplant   |
| 5       | DA 3.0                             | 392 days          | Leaking catheter; infection      | Transplant   |
| 6       | Milrinone 0.3                      | 98 days           | None                             | Transplant   |
| 7       | DA 2.5 and milrinone 0.25          | 56 days           | None                             | Transplant   |

DA, dopamine.

**Table 3.** Mean Emergency Department Visits, All-Cause, and Cardiac Admissions

|                               | Before Infusion | During Infusion | P Value |
|-------------------------------|-----------------|-----------------|---------|
| Emergency department visits   | 2.3 ± 1.8       | 1.1 ± 2.2       | <.05    |
| All-cause hospital admissions | 2.1 ± 1.3       | 1.2 ± 1.8       | .06     |
| Cardiac admissions            | 2.1 ± 1.3       | 0.6 ± 0.6       | <.05    |

The mean number of hospital admissions for exacerbation of heart failure symptoms significantly decreased after starting parenteral inotropic therapy ( $p < 0.05$ ). The ejection fraction significantly improved while on therapy ( $p < 0.05$ ). Six patients were successfully bridged to transplantation.

➤ Safety results

Five catheter complications occurred in 2 patients. One of these patients developed a central line infection. One patient died suddenly at home during parenteral inotropic infusion. That patient had undergone a Fontan procedure and had a history of nonsustained ventricular tachycardia for which he was being treated with oral amiodarone. He did not receive an implantable cardioverter defibrillator (ICD) due to risk

associated with surgical placement of an epicardial system which he would have needed because of not being a candidate for a transvenous system. Two other patients with a history of nonsustained ventricular tachycardia received an ICD and were successfully bridged to transplantation.

#### Assessor's Comment

##### Interpretation and lacks of the study:

1. Number of subjects involved is relatively small.
2. The endpoints had no adjustment of the probability value for multiple comparisons.
3. Adverse event monitoring system at home is not reported.

##### Conclusion:

Data indicate efficacy concerning primary endpoints in study population, but due to small number of patients, no outpatient adverse event monitoring system, and one sudden death out of seven patients reported, a positive risk/benefit ratio for long-term use of milrinone cannot be drawn. Therefore, the long-term use of milrinone in paediatric patients waiting for heart transplantation cannot be approved.

**Berg A.M. et al. Home inotropic therapy in children. J. Heart Lung Transplant. 2007, 26(5), 453-57.**

#### ➤ Description

**Background:** Inotropic therapy is a well-established practice for children with advanced congestive heart failure (CHF). Traditionally, children have been maintained on inotropic therapy in the hospital under close, monitored supervision. Changes to UNOS listing criteria now allow patients awaiting heart transplantation to be discharged to home yet maintain 1B status. In adults, home inotropic therapy has been shown to be a safe and cost-effective bridge to transplantation. To date, there are limited data on the use of home inotropic therapy in children.

**Methods:** We reviewed the safety and efficacy of continuous ambulatory home inotropic therapy in children. Data were obtained from a single institution from January 2000 to January 2007.

**Results:** There were 14 pediatric patients with end-stage CHF, who received home intravenous inotropic therapy. The indications for home inotropic therapy included palliative care ( $n = 8$ ) and awaiting heart transplantation ( $n = 6$ ). Patients ranged in age from 6 to 18 years (median 14.5 years). The majority of subjects ( $n = 11$ ) received milrinone at a dose of 0.5 to 1.0  $\mu\text{g}/\text{kg}/\text{min}$ , 2 received dobutamine at 5  $\mu\text{g}/\text{kg}/\text{min}$ , and 1 received both agents. Duration of therapy ranged from 14 to 476 days (median 68 days). There were 26 hospital re-admissions and 4 suspected catheter infections. No unexpected deaths or pump failures occurred.

**Conclusions:** Based on this initial review, continuous home inotropic therapy in children with CHF is safe with few complications. Home inotropic therapy may result in substantial cost-savings and improve family dynamics by avoiding prolonged hospitalization. J Heart Lung Transplant 2007;26:453-7. Copyright © 2007 by the International Society for Heart and Lung Transplantation.

#### ➤ Methods

- Objective(s)  
To review the safety and efficacy of continuous ambulatory inotropic therapy in children.
- Study design  
Retrospective uncontrolled study.
- Study population /Sample size  
All children who were maintained at home on continuous inotropic agents.
- Treatments  
The dose of milrinone ranged from 0.5 to 1.0  $\mu\text{g}/\text{kg}/\text{min}$ .

- The mean dose of dobutamine was 5 µg/kg/min.
- Outcomes/endpoints  
Survival.
- Statistical Methods  
None.
- **Results**
  - Recruitment/ Number analysed  
Fourteen patients received outpatient parenteral inotropic therapy.
  - Baseline data  
Patients ranged in age from 6 to 18 years (median 14.5), with end-stage heart failure who received home intravenous inotropic therapy: milrinone (n = 11), dobutamine (n = 2), and both agents (n = 1). Duration of therapy ranged from 14 to 476 days (median 68).

**Table 1. Patients' Data**

| Patient       | Diagnosis              | Age (years) | Gender | Inotropic agent(s)                 | Indication for inotropic use | Ejection fraction <sup>a</sup> | Therapy (days) | Number of hospital re-admissions | Outcome             |
|---------------|------------------------|-------------|--------|------------------------------------|------------------------------|--------------------------------|----------------|----------------------------------|---------------------|
| 1             | Graft failure          | 10.0        | F      | Dobutamine                         | Awaiting transplant          | 0.58                           | 37             | 0                                | Transplanted        |
| 2             | Graft failure          | 17.0        | M      | Dobutamine                         | Palliative care              | 0.10                           | 84             | 3                                | Death               |
| 3             | Dilated cardiomyopathy | 6.1         | M      | Milrinone                          | Awaiting transplant          | 0.32                           | 51             | 0                                | Transplanted        |
| 4             | Graft failure          | 11.8        | F      | Dobutamine, milrinone <sup>b</sup> | Palliative care              | 0.45                           | 20             | 1                                | Death               |
| 5             | Graft failure          | 13.0        | F      | Milrinone                          | Awaiting transplant          | 0.55                           | 34             | 0                                | Transplanted        |
| 6             | Graft failure          | 12.9        | M      | Milrinone                          | Awaiting transplant          | 0.53                           | 23             | 0                                | Transplanted        |
| 7             | Dilated cardiomyopathy | 18.2        | M      | Milrinone                          | Palliative care              | 0.29                           | 38             | 3                                | Death               |
| 8             | Graft failure          | 14.6        | M      | Milrinone                          | Palliative care              | NA                             | 91             | 0                                | Death               |
| 9             | Graft failure          | 14.4        | F      | Milrinone                          | Awaiting transplant          | 0.30                           | 476            | 8                                | Awaiting transplant |
| 10            | Muscular dystrophy     | 17.7        | M      | Milrinone                          | Palliative care              | 0.12                           | 319            | 2                                | Alive               |
| 11            | Muscular dystrophy     | 16.1        | M      | Milrinone                          | Palliative care              | 0.21                           | 467            | 4                                | Alive               |
| 12            | Graft failure          | 17.8        | M      | Milrinone                          | Palliative care              | 0.40                           | 153            | 3                                | Death               |
| 13            | Pulmonary atresia/VSD  | 14.9        | F      | Milrinone                          | Palliative care              | 0.24                           | 201            | 2                                | Alive               |
| 14            | Dilated cardiomyopathy | 13.6        | M      | Milrinone                          | Awaiting transplant          | 0.18                           | 14             | 0                                | Transplanted        |
| <b>Median</b> |                        | 14.5        |        |                                    |                              | 0.225                          | 68             | 1.5                              |                     |

VSD, ventricular septal defect.

<sup>a</sup>Left ventricular ejection fraction determined by echocardiography.

<sup>b</sup>Nesiritide was also administered at home.

- Efficacy results  
Six of patients receiving palliative care died, 2 while hospitalized and 4 while at home under hospice care. Two patients were alive at the end of the study and continued to receive palliative care. Five of six patients listed for cardiac transplantation have been successfully bridged to transplantation. One patient continued to wait for cardiac transplantation at the end of the study.
- Safety results  
There were 26 hospital-readmissions: 4 suspected catheter infections, 15 episodes of heart failure decompensation requiring additional inpatient management, 6 infections not specifically related to indwelling catheter, and 1 admission for hyperglycemia.

### Assessor's Comment

#### Interpretation and lacks of the study:

1. Number of subjects involved is relatively small.
2. Adverse event monitoring system at home is not reported.

Conclusion:

Due to small number of patients, no outpatient adverse event monitoring system, and six deaths out of fourteen patients reported, a positive risk/benefit ratio for long-term use of milrinone cannot be drawn. Therefore, the long-term use of milrinone in paediatric patients cannot be approved.

### 3. Discussion on clinical aspects

*Please see Assessor's Comments.*

After evaluating the presented data we conclude that the administration of milrinone in children in Europe in the following indication can be recommended:

- Short-term treatment (up to 35 hours) of severe congestive heart failure unresponsive to conventional maintenance therapy (glycosides, diuretics, vasodilators and/or ACE-inhibitors), and for the short-term treatment (up to 35 hours) of patients with acute heart failure, including low output states following cardiac surgery.

Dosage recommendations (incl. maximal treatment duration of 35 hours), special warnings (esp. paediatric patients with renal impairment, with patent ductus arteriosus.), adverse events (esp. patent ductus arteriosus, intraventricular haemorrhage) and pharmacological properties concerning paediatric population have to be added to the specific sections of SmPC and PIL.

## V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION

### ➤ Overall conclusion

After evaluating the presented data we conclude that the administration of milrinone in children in Europe in the following indication can be recommended:

- *In paediatric population <National approved name> is indicated for the short-term treatment (up to 35 hours) of severe congestive heart failure unresponsive to conventional maintenance therapy (glycosides, diuretics, vasodilators and/or angiotensin converting enzyme (ACE) inhibitors), and for the short-term treatment (up to 35 hours) of paediatric patients with acute heart failure, including low output states following cardiac surgery.*

Dosage recommendations (incl. maximal treatment duration of 35 hours), special warnings (esp. paediatric patients with renal impairment, with patent ductus arteriosus), adverse events (esp. patent ductus arteriosus, intraventricular haemorrhage) and pharmacological properties concerning paediatric population have to be added to the specific sections of SmPC and PIL.

### ➤ Recommendation

After consideration of the MAH's response document and CMS' comments our recommendation is to implement to following concised SmPC wording (*italic letters*):

Final proposed SmPC changes

4.1 Therapeutic indications

*In paediatric population <National approved name> is indicated for the short-term treatment (up to 35 hours) of severe congestive heart failure unresponsive to conventional maintenance therapy (glycosides, diuretics, vasodilators and/or angiotensin converting enzyme (ACE) inhibitors), and for the short-term treatment (up to 35 hours) of paediatric patients with acute heart failure, including low output states following cardiac surgery.*

4.3 Posology and method of administration

Paediatric population:

*In published studies selected doses for infants and children were:*

- *Intravenous loading dose: 50 to 75 µg/kg administered over 30 to 60 minutes.*
- *Intravenous continuous infusion: To be initiated on the basis of hemodynamic response and the possible onset of undesirable effects between 0.25 to 0.75 µg/kg/min for a period up to 35 hours.*

*In clinical studies on low cardiac output syndrome in infants and children under 6 years of age after corrective surgery for congenital heart disease 75 µg/kg loading dose over 60 minutes followed by a 0.75 µg/kg/min infusion for 35 hours significantly reduced the risk of development of low cardiac output syndrome.*

*Results of pharmacokinetic studies (see section 5.2) have to be taken into consideration.*

Renal impairment:

*Due to lack of data the use of milrinone is not recommended in paediatric population with renal impairment (for further information please see section 4.4).*

Patent ductus arteriosus:

*If the use of milrinone is desirable in preterm or term infants at risk of/with patent ductus arteriosus, the therapeutic need must be weighed against potential risks (see section 4.4, 4.8, 5.2, and 5.3).*

4.4 Special warnings and precautions for use

Paediatric population:

*The following should be considered in addition to the warnings and precautions described for adults:*

*In neonates, following open heart surgery during <National approved name> therapy, monitoring should include heart rate and rhythm, systemic arterial blood pressure via umbilical artery catheter or peripheral catheter, central venous pressure, cardiac index, cardiac output, systemic vascular resistance, pulmonary artery pressure, and atrial pressure. Laboratory values that should be followed are platelet count, serum potassium, liver function, and renal function. Frequency of assessment is determined by baseline values, and it is necessary to evaluate the neonate's response to changes in therapy.*

*Literature revealed that in paediatric patients with impaired renal function, there were marked impairment of milrinone clearance and clinically significant side effects, but the specific*

creatinine clearance at which doses must be adjusted in paediatric patients is still not clear, therefore the use of milrinone is not recommended in this population (see section 4.2).

In paediatric patients milrinone should be initiated only if the patient is hemodynamically stable.

Caution should be exercised in neonates with risk factors of intraventricular haemorrhage (i.e. preterm infant, low birth weight) since milrinone may induce thrombocytopenia. In clinical studies in paediatric patients, risk of thrombocytopenia increased significantly with duration of infusion. Clinical data suggest that milrinone-related thrombocytopenia is more common in children than in adults (see section 4.8).

In clinical studies milrinone appeared to slow the closure of the ductus arteriosus in paediatric population. Therefore, if the use of milrinone is desirable in preterm or term infants at risk of/with patent ductus arteriosus, the therapeutic need must be weighed against potential risks (see section 4.2, 4.8, 5.2, and 5.3).

#### 4.9 Undesirable effects

##### Blood and lymphatic system disorders

Uncommon: thrombocytopenia\*

Not known: reduction of red blood count and/or haemoglobin concentration

\*In infants and children, risk of thrombocytopenia increased significantly with duration of infusion. Clinical data suggest that milrinone-related thrombocytopenia is more common in children than in adults (see section 4.4).

##### Cardiac disorders

Common: ventricular ectopic activity, non-sustained and sustained ventricular tachycardia (see section 4.4), supraventricular arrhythmias

Uncommon: ventricular fibrillation, angina pectoris, chest pain

Very rare: torsades de pointes

The incidence of both supraventricular and ventricular arrhythmias has not been related to the dose or plasma level of milrinone. Life-threatening arrhythmias have commonly been linked to underlying factors such as existing arrhythmias, metabolic abnormalities (e.g. hypokalaemia), abnormal digoxin levels and catheterisation. Clinical data suggest that milrinone-related arrhythmias are less common in children than in adults.

##### Paediatric population:

##### Nervous system disorders

Not known: intraventricular haemorrhage (see section 4.4)

##### Congenital, familial, and genetic disorders

Not known: patent ductus arteriosus\*\*\* (see section 4.2, 4.4, 5.2, and 5.3)

\*\*\*The critical consequences of the patent ductus arteriosus are related to a combination of pulmonary overcirculation with consecutive pulmonary oedema and haemorrhage and of reduced organ perfusion with consecutive intraventricular haemorrhage and necrotizing enterocolitis with possible fatal outcome as described in literature.

Long-term safety data for paediatric population are not yet available.

## 5.1 Pharmacodynamic properties

### Paediatric population:

Literature review identified clinical studies with patients treated for low cardiac output syndrome following cardiac surgery, septic shock or pulmonary hypertension. The usual dosages were a loading dose of 50 to 75 µg/kg administered over 30 to 60 minutes followed by an intravenous continuous infusion of 0.25 to 0.75 µg/kg/min for a period up to 35 hours. In these studies, milrinone demonstrated an increase of cardiac output, a decrease in cardiac filling pressure, and decrease in systemic and pulmonary vascular resistance, with minimal changes in heart rate and in myocardial oxygen consumption.

Studies of a longer use of milrinone are not sufficient to recommend an administration of milrinone during a period of more than 35 hours.

Some studies explored the paediatric use of milrinone in patients with nonhyperdynamic septic shock (Barton et al., 1996; Lindsay et al., 1998); the effect of milrinone on postbypass pulmonary hypertension after tetralogy of Fallot repair (Chu et al., 2000); the combined effect of nitric oxide and milrinone on pulmonary circulation after Fontan-type procedure (Cai et al., 2008).

The results of these studies were inconclusive. Therefore, the use of milrinone in these indications cannot be recommended.

## 5.4. Pharmacokinetic properties

### Paediatric population:

Milrinone is cleared more rapidly in children than in adults, but infants have significantly lower clearance than children, and preterm infants have even lower clearance. As a consequence of this more rapid clearance compared to adults, steady-state plasma concentrations of milrinone were lower in children than in adults. In paediatric population with normal renal function steady-state milrinone plasma concentrations after 6 to 12 hours continuous infusion of 0.5 to 0.75 µg/kg/min were about of 100 to 300 ng/ml.

Following intravenous infusion of 0.5 to 0.75 µg/kg/min to neonates, infants and children after open heart surgery, milrinone has a volume of distribution ranging from 0.35 to 0.9 litres/kg with no significant difference across age groups. Following intravenous infusion of 0.5 µg/kg/min to very preterm infants to prevent systemic outflow after birth, milrinone has a volume of distribution of about 0.5 litres/kg.

Several pharmacokinetic studies showed that, in paediatric population, clearance increases with increasing age. Infants have significantly lower clearance than children (3.4 to 3.8 ml/kg/min versus 5.9 to 6.7 ml/kg/min). In neonates milrinone clearance was about 1.64 ml/kg/min and preterm infants have even lower clearance (0.64 ml/kg/min).

Milrinone has a mean terminal half-life of 2 to 4 hours in infants and children and a mean terminal elimination half-life of 10 hours in preterm infants.

It was concluded that the optimal dose of milrinone in paediatric patients in order to obtain plasma levels above the threshold of pharmacodynamic efficacy appeared higher than in adults, but that optimal dose in preterms in order to obtain plasma levels above the threshold of pharmacodynamic efficacy appeared lower than in children.

### Patent ductus arteriosus:

Milrinone is cleared by renal excretion and has a volume of distribution that is restricted to extracellular space which suggests that the fluid overload and hemodynamic changes associated with patent ductus arteriosus may have an effect on distribution and excretion of milrinone (see section 4.2, 4.4, 4.8, and 5.3).

#### 5.5. Preclinical safety data

##### *Juvenile animals:*

A preclinical study was performed to clarify the ductus-dilating effects of PDE 3 inhibitors in near-term rat pups and their differential effects in near-term and preterm foetal rats. Postnatal ductus arteriosus dilatation by milrinone was studied with three doses (10, 1 and 0.1mg/kg). The dilating effects of milrinone in the foetal ductus constricted by indomethacin were studied by simultaneous administration of milrinone (10, 1 and 0.1mg/kg) and indomethacin (10 mg/kg) to the mother rat at D21 (near-term) and D19 (preterm). This in vivo study has shown that milrinone induces dose-dependent dilation of the foetal and the postnatal constricted ductus arteriosus. Dilating effects were more potent with injection immediately after birth than at 1 hour after birth. In addition, study showed that the premature ductus arteriosus is more sensitive to milrinone than the mature ductus arteriosus (see section 4.2, 4.4, 4.8, and 5.2).

After consideration of the MAH's response document and CMS' comments our recommendation is to implement to following concised PIL wording (*italic letters*):

### **1. WHAT TM IS AND WHAT IT IS USED FOR**

*TM can be used in children for:*

- Short term treatment (up to 35 hours) of severe congestive heart failure (where the heart cannot pump enough blood to the rest of the body) when other medicines have not worked
- Short term treatment (up to 35 hours) of acute heart failure after a heart operation i.e. when your heart is having difficulty pumping blood around your body.

### **2. BEFORE YOU TAKE TM**

*The following should be considered in addition to warnings and precautions described for adults:*

**Take special care with TM:**

**Using TM in children:**

*Before giving TM infusion, your doctor will check a lot of parameters such as heart rhythm and blood pressure. He/she will order blood tests as well.*

*The infusion will not start if your child's heart rhythm and blood pressure is not stable.*

*Please tell your doctor if:*

- your child has kidney problems
- your child is a preterm infant or has a low birth weight
- your child has a certain heart problem named Patent Ductus Arteriosus: a connection between 2 major blood vessels (aorta and pulmonary artery) which persists though it should be closed.

*In these cases, your doctor will decide if your child will be treated with TM.*

### **3. HOW TO TAKE TM**

**Use in children:**

- Your doctor should give your child a first dose ranging between 50 and 75 micrograms for every kilogram of his weight, over a period of 30 to 60 minutes.

- This is then followed by a dose ranging from 0.25 to 0.75 micrograms for every kilogram of his/her weight per minute according to your child's response to the treatment and occurrence of side effects. TM can be given for up to 35 hours.

During infusion, your child will be closely monitored: your doctor will check a lot of parameters such as heart rhythm and blood pressure and blood will be taken to evaluate the response to therapy and occurrence of side effects.

#### **4. POSSIBLE SIDE EFFECTS**

In addition to side effects observed in adults, the following were reported in children:

Frequency not known:

- bleeding into the fluid-filled areas (ventricles) surrounded by the brain (intraventricular haemorrhage)

- a heart problem known as Patent Ductus Arteriosus: a connection between 2 major blood vessels (aorta and pulmonary artery) which persists though it should be closed. This can cause excess fluid in the lungs, bleedings, destruction of the bowel or part of the bowel and possibly be fatal.

Moreover, compared to adults, decrease in the number of platelets in the blood seems to occur more often in children and the risk of this side effect is increased with the duration of the TM infusion. Heart rhythm troubles seem to occur less often in children than in adults.

#### **Final outcome:**

All concerned members of states endorsed the Rapporteur's final proposed SmPC changes as above.

Therefore the EU worksharing procedure of paediatric data for Milrinon is considered finalised on the 09 April 2011.

## **VI. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED**

Sanofi Aventis GmbH Österreich  
Sanofi Aventis Produtos Farmace  
Sanofi Aventis Produtos Farmace  
SANOFI-AVENTIS AEBE, GREECE  
SANOFI-AVENTIS BELGIUM  
SANOFI-AVENTIS BELGIUM  
SANOFI-AVENTIS DEUTSCHLAND GMBH  
SANOFI-AVENTIS DEUTSCHLAND GMBH  
SANOFI-AVENTIS FRANCE  
SANOFI-AVENTIS FRANCE

SANOFI-AVENTIS FRANCE

SANOFI-AVENTIS NETHERLANDS BV

Corotrop 10 mg solution for injection  
Corotrope 10 mg solution for injection  
Corotrope 20 mg solution for injection  
Corotrope 10 mg solution for injection  
Corotrope 10 mg solution for injection  
Corotrope 10 mg solution for injection  
Corotrop 10 mg solution for injection  
Corotrop 10 mg solution for injection  
Corotrope 10 mg solution for injection  
COROTROPE 10 MG/10 ML, SOLUTION  
INJECTABLE (IV)  
COROTROPE 20 MG/20 ML, SOLUTION  
INJECTABLE (IV)  
Corotrope 10 mg solution for injection