Cochrane Library

Cochrane Database of Systematic Reviews

Milrinone for persistent pulmonary hypertension of the newborn (Review)

Bassler D, Kreutzer K, McNamara P, Kirpalani H

Bassler D, Kreutzer K, McNamara P, Kirpalani H.
Milrinone for persistent pulmonary hypertension of the newborn.
Cochrane Database of Systematic Reviews 2010, Issue 11. Art. No.: CD007802.
DOI: 10.1002/14651858.CD007802.pub2.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

HEADER 1
ABSTRACT 1
PLAIN LANGUAGE SUMMARY 2
BACKGROUND 3
OBJECTIVES 3
METHODS 3
RESULTS 6
DISCUSSION 6
AUTHORS' CONCLUSIONS 6
ACKNOWLEDGEMENTS 6
REFERENCES 7
CHARACTERISTICS OF STUDIES 8
CONTRIBUTIONS OF AUTHORS 9
DECLARATIONS OF INTEREST 9
SOURCES OF SUPPORT 9
INDEX TERMS 9

[Intervention Review]

Milrinone for persistent pulmonary hypertension of the newborn

Dirk Bassler[1], Karen Kreutzer[1], Patrick McNamara[2], Haresh Kirpalani[3]

[1]Department of Neonatology, University Children's Hospital, Tuebingen, Germany. [2]Division of Neonatology, Hospital for Sick Children, Toronto, Canada. [3]Department of Pediatrics, University of Pennsylvania School of Medicine and Dept of Clinical Epidemiology and Biostatistics, McMaster University, Philadelphia, Pennsylvania, USA

Contact address: Dirk Bassler, Department of Neonatology, University Children's Hospital, Tuebingen, Germany. dirk.bassler@med.uni-tuebingen.de.

Editorial group: Cochrane Neonatal Group
Publication status and date: New, published in Issue 11, 2010.

Citation: Bassler D, Kreutzer K, McNamara P, Kirpalani H. Milrinone for persistent pulmonary hypertension of the newborn. *Cochrane Database of Systematic Reviews* 2010, Issue 11. Art. No.: CD007802. DOI: 10.1002/14651858.CD007802.pub2.

ABSTRACT

Background

Persistent pulmonary hypertension of the newborn (PPHN) is a clinical syndrome characterized by suboptimal oxygenation as a result of sustained elevation in pulmonary vascular resistance after birth. Currently, the therapeutic mainstay for PPHN is optimal lung inflation and selective vasodilatation with inhaled nitric oxide (iNO). However, iNO is not available in all countries and not all infants will respond to iNO. Milrinone is a phosphodiesterase III inhibitor which induces pulmonary vasodilatation by its actions through a cyclic adenylate monophosphate mediated signaling pathway.

Objectives

To assess efficacy and safety in infants with PPHN either treated with: milrinone compared with placebo or no treatment; milrinone compared with iNO; milrinone as an adjunct to iNO compared with iNO alone; milrinone compared with potential treatments for PPHN other than iNO.

Search methods

We searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library*, Issue 2, 2010), MEDLINE and EMBASE databases from their inception until January 2010. We searched the reference lists of potentially relevant studies without any language restriction.

Selection criteria

Fully published randomized controlled trials (RCTs) and quasi-RCTs comparing milrinone with placebo, iNO or potential treatments other than iNO in neonates with PPHN were included if trials reported any clinical outcome.

Data collection and analysis

We found no studies meeting the criteria for inclusion in this review.

Main results

We found no studies meeting the criteria for inclusion in this review.

Authors' conclusions

The efficacy and safety of milrinone in the treatment of PPHN are not known and its use should be restricted within the context of RCTs. Such studies should address a comparison of milrinone with placebo (in clinical situations where iNO is not available) or, in well resourced countries, should compare milrinone with iNO or as an adjunct to iNO compared with iNO alone.

PLAIN LANGUAGE SUMMARY

Milrinone for persistent pulmonary hypertension of the newborn

Persistent pulmonary hypertension of the newborn (PPHN) is a condition caused by a failure in the systemic and pulmonary circulation to convert from the antenatal circulation pattern to the normal postnatal pattern. Due to persistent high pressure in the pulmonary vessels, less than normal blood flows to the lungs and thus less oxygen reaches the organs of the body. Milrinone may cause the pulmonary vessels to relax and allow for an increased oxygen supply for the body. However, the review found no trials of the use of milrinone for babies with persistent pulmonary hypertension. Research is needed into the effects of milrinone on PPHN.

BACKGROUND

Description of the condition

Persistent pulmonary hypertension of the newborn (PPHN) is a clinical syndrome characterized by suboptimal oxygenation as a result of sustained elevation in pulmonary vascular resistance after birth. In PPHN, there is vasoconstriction of the pulmonary vessels that may occur secondary to one of several reasons (e.g. prolonged hypoxemia, perinatal ischemic injury or an underlying lung parenchymal disease process). When the pulmonary vascular resistance exceeds the systemic vascular resistance, a right to left shunt of deoxygenated blood occurs through the persistent foramen ovale (PFO) or ductus arteriosus (PDA) resulting in hypoxemia.

The incidence of PPHN of the newborn ranges between 0.4 and 6.8 per 1000 live births (Walsh-Sukys 2000). Extracorporeal membrane oxygenation (ECMO) has been used in term and near term infants with hypoxic respiratory failure, including infants with PPHN (UK Collaborative ECMO Trial Group 1995; Mugford 2008). Although expensive and highly invasive, ECMO has proven to be life saving in many of these infants. PPHN can also be treated with inhaled nitric oxide (iNO). iNO reduces the need for ECMO in term and near term infants with hypoxic respiratory failure (Finer 2001). It remains controversial as to whether iNO may confer benefit to preterm infants with hypoxic respiratory failure (Barrington 2001). Furthermore, between 30% and 40% of the term and near term infants treated with iNO still require ECMO or die (NINOS 1997).

Other interventions that have been used for the treatment of PPHN include alkalization, hyperventilation, and vasodilators, such as tolazoline. The use of alkalinizing agents and hyperventilation is controversial. The short-term beneficial physiologic change that has been seen in some observational studies following these interventions has not been systematically studied in controlled trials (Walsh-Sukys 2000; Farrow 2005). There are a number of adverse outcomes related to these interventions that also seem to apply when vasodilators such as tolazoline are used for the treatment of PPHN (Stevens 1980; Farrow 2005). More recently, phosphodiesterase inhibitors, such as sildenafil (PDE V inhibitor) and milrinone (PDE III inhibitor) have been used for the treatment of PPHN (Bassler 2006; McNamara 2006; Shah 2007).

Description of the intervention

Milrinone is a selective inhibitor of type III cAMP phosphodiesterase isoenzyme in cardiac and vascular muscle. It has both positive inotrope and vasodilator effects (Levy 2000). Milrinone has been compared to placebo in randomized controlled trials (RCTs) in children with septic shock (Barton 1996), to improve low cardiac output in children and infants after heart surgery (Hoffman 2003) and to prevent low systemic blood flow in very preterm infants (Paradisis 2009). In two recent uncontrolled case series including a total of 13 neonates, infants with severe PPHN showed improvements in their cardiovascular and respiratory status after being treated with a combination of iNO and milrinone (Bassler 2006; McNamara 2006). However, in one case series including four patients, two developed serious intraventricular hemorrhage (IVH), and one had a small IVH (Bassler 2006).

A dosage regimen for milrinone in preterm infants has been established (Paradisis 2007) and population pharmacokinetics of milrinone in neonates with hypoplastic left heart syndrome undergoing stage I reconstruction have been performed (Zuppa 2006). Currently, a pharmacokinetic study of milrinone in infants with PPHN is ongoing (Kirpalani). In this study, infants already receiving iNO are randomized to one of two dosing regimens of milrinone (high dose: 50 mcg/kg IV load followed by 0.5 mcg/kg/min infusion IV for 24 hours; low dose: 20 mcg/kg IV load followed by 0.2 mcg/kg/min infusion IV for 24 hours).

How the intervention might work

Since the pulmonary vasodilation following inhalation of NO is mediated by increased cyclic guanosine monophosphate (cGMP) in vascular smooth muscle, specific phosphodiesterase inhibitors (by preventing/delaying cGMP or cAMP breakdown) can cause acute pulmonary vasodilation, and enhance the pulmonary vasodilator response to iNO (Clarke 1994). Milrinone may be an attractive adjunctive therapy in the treatment of PPHN, to enhance pulmonary vasodilator response to iNO, and attenuate the rebound effect observed in some infants with PPHN upon withdrawal of iNO.

Why it is important to do this review

Since iNO is not a panacea for pulmonary hypertension and since there are concerns regarding escalating costs of iNO therapy, other options for therapy are being actively explored.

OBJECTIVES

To assess mortality and neurodevelopment in infants with PPHN either treated with:

- milrinone compared with placebo or no treatment;
- milrinone compared with iNO;
- milrinone as an adjunct to iNO compared with iNO alone;
- milrinone compared with potential treatments for PPHN other than iNO.

To estimate the effect on primary outcome measures in the following subgroups: preterm (less than 37 weeks' gestation) versus term infants; infants with underlying conditions such as congenital diaphragmatic hernia versus infants with no such conditions; severity of PPHN (oxygenation index more or less than 20); dose of milrinone (more or less than 0.5 µg/kg/min); duration of treatment with milrinone (more or less than three days); methodological quality of studies [studies with at least four methodological criteria (adequate randomization, allocation concealment, blinding of parents, blinding of caregivers, blinding of assessors of outcome, completeness of follow-up (over and under 90%) in randomized subjects for the primary outcome defined as "yes" versus studies that meet fewer than four methodological criteria].

METHODS

Criteria for considering studies for this review

Types of studies

We considered fully published RCTs and quasi-RCTs for this review if they assessed any clinical outcome.

Types of participants

Any term and preterm infants (less than 37 weeks' gestation) with PPHN (either diagnosed clinically and/or by at least one of the following echocardiographic findings (high right ventricular systolic

pressure, right to left or bidirectional shunt at PFO or PDA, severe tricuspid regurgitation).

Types of interventions

We considered studies comparing the following interventions: milrinone as an adjunct to iNO compared with iNO alone; milrinone compared with iNO; milrinone compared with potential treatments for PPHN other than iNO (such as hyperventilation, alkalinization, tolazoline and ECMO); milrinone compared with placebo or no treatment. We considered any dose and any duration of milrinone therapy for this review.

Types of outcome measures

Primary outcomes

- Mortality (measured in the first week of life, in the first 28 days of life, up to the time of discharge from hospital).
- Neurodevelopment (assessed by the presence of cerebral palsy, cognitive delay, blindness or deafness, and the Bayley Scales of Infant Development-II) assessed after 18 months of life.

Secondary outcomes

- Intraventricular hemorrhages (IVH) on ultrasounds (any grade by Papille classification) assessed at any point in time.
- Severe IVH on ultrasounds (grades 3 and 4 by Papille classification and periventricular echodensity (PVED)) at any point in time.
- ECMO therapy.
- Duration of mechanical ventilation (days).
- Duration of iNO therapy (days)*.
- Infants receiving iNO as rescue therapy**.
- Duration of therapy with inotropes (days).
- Systemic hypotension (defined as any hypotension requiring treatment) within six hours following initiation of milrinone therapy.
- Bronchopulmonary dysplasia (defined as oxygen requirements at 36 weeks postmenstrual age).
- Any adverse events reported in the primary studies.

*we will assess only for the following comparison: milrinone as an adjunct to iNO compared with iNO alone.

**we will assess only for the following comparisons: milrinone compared with potential treatments for PPHN other than iNO; milrinone compared with placebo or no treatment.

Post hoc analyses

- We considered all other clinical outcomes reported in the studies for this review.

Search methods for identification of studies

See: Collaborative Review Group search strategy. We used the standard search method of the Cochrane Neonatal Review Group.

Electronic searches

We used the following terms to search the electronic databases (Milrinone OR phosphodiesterase inhibitor OR phosphodiesterase-III inhibitor OR PDE inhibitor OR PDE-III inhibitor). We used the standard search strategy of the Cochrane Neonatal Review Group; this includes electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL, *The Cochrane Library*, Issue 2, 2010). A MEDLINE search (1966 to January 2010) was limited to clinical trials and by age to newborn (birth to one month). We performed further searches in EMBASE. We applied no language restriction. We cross checked references from identified studies for possible additional studies. In this review, we considered only fully published studies for inclusion.

Searching other resources

We also searched clinical trials registries for ongoing or recently completed trials (clinicaltrials.gov; controlled-trials.com; and who.int/ictrp)

Data collection and analysis

Selection of studies

We considered studies comparing four different interventions for this review (see Types of interventions above). These comparisons constitute four separate groups, and we considered separate analysis. Two review authors examined the abstract of each reference generated by the literature search for inclusion criteria; where relevant, we obtained a full article.

Data extraction and management

We planned to have two review authors independently extract data from included studies on data collection forms. We planned to request additional information from the authors of each trial to clarify methodology and results as necessary.

Assessment of risk of bias in included studies

Two authors (DB, KK) reviewed the relevant studies for methodological quality. If necessary, we discussed areas of disagreement with a third author; we required that consensus be reached before analysis of the results. Criteria for assessing methodological quality were: adequate randomization, allocation concealment, blinding of parents, blinding of caregivers, blinding of assessors of outcome, completeness of follow-up (over and under 90%) in randomized subjects for the primary outcome. We defined all criteria as "yes", "no" or "unsure". If available, we added this information to the Characteristics of included studies table.

In addition, we planned to evaluate the following issues and enter this information into the Risk of Bias table:

(1) Sequence generation (checking for possible selection bias). Was the allocation sequence adequately generated?

For each included study, we planned to categorize the method used to generate the allocation sequence as:

- adequate (any truly random process e.g. random number table; computer random number generator);

- inadequate (any non-random process e.g. odd or even date of birth; hospital or clinic record number);

- unclear.

(2) Allocation concealment (checking for possible selection bias). Was allocation adequately concealed?

For each included study, we planned to categorize the method used to conceal the allocation sequence as:

- adequate (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes);

- inadequate (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);

- unclear.

(3) Blinding (checking for possible performance bias). Was knowledge of the allocated intervention adequately prevented during the study? At study entry? At the time of outcome assessment?

For each included study, we planned to categorize the methods used to blind study participants and personnel from knowledge of which intervention a participant received. Blinding was assessed separately for different outcomes or classes of outcomes. We planned to categorize the methods as:

- adequate, inadequate or unclear for participants;

- adequate, inadequate or unclear for personnel;

- adequate, inadequate or unclear for outcome assessors.

In some situations there may be partial blinding e.g. where outcomes are self-reported by unblinded participants but they are recorded by blinded personnel without knowledge of group assignment. Where needed, “partial” was added to the list of options for assessing quality of blinding.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations). Were incomplete outcome data adequately addressed?

For each included study and for each outcome, we planned to describe the completeness of data including attrition and exclusions from the analysis. We planned to note whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we re-included missing data in the analyses. We planned to categorize the methods as:

- adequate (less than 20% missing data);

- inadequate (more than 20% missing data):

- unclear.

(5) Selective reporting bias. Are reports of the study free of suggestion of selective outcome reporting?

For each included study, we planned to describe how we investigated the possibility of selective outcome reporting bias and what we found. We planned to assess the methods as:

- adequate (where it is clear that all of the study’s pre-specified outcomes and all expected outcomes of interest to the review have been reported);

- inadequate (where not all the study’s pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);

- unclear.

(6) Other sources of bias. Was the study apparently free of other problems that could put it at a high risk of bias?

For each included study, we planned to describe any important concerns we had about other possible sources of bias (for example, whether there was a potential source of bias related to the specific study design or whether the trial was stopped early due to some data-dependent process). We planned to assess whether each study was free of other problems that could put it at risk of bias as:

- yes; no; or unclear.

If needed, we planned to explore the impact of the level of bias through undertaking sensitivity analyses.

Measures of treatment effect

For dichotomous outcomes, we planned to express treatment effects as relative risk (RR), for continuous outcomes as a mean difference (MD), both with a 95% confidence interval (CI) as a measure of uncertainty.

Assessment of heterogeneity

We planned to estimate the treatment effects of individual trials and examine heterogeneity between trials by inspecting the forest plots and quantifying the impact of heterogeneity using the I^2 statistic. If we detected statistical heterogeneity, we planned to explore the possible causes (for example, differences in study quality, participants, intervention regimens, or outcome assessments) using post hoc subgroup analyses. We planned to use a fixed-effect model for meta-analysis.

Data synthesis

If appropriate, we planned to perform meta-analyses of pooled data from all contributing trials using a random-effects model. We planned to assess heterogeneity in the results of the trials by calculating a test of heterogeneity and an I^2 test. We intended to use the results of these tests as a trigger to explore sources of heterogeneity. We planned to do data entry by two review authors independently and to analyze the data using Review Manager 5 (RevMan 2008).

Subgroup analysis and investigation of heterogeneity

We planned to carry out analyses for the following subgroups: preterm (less than 37 weeks' gestation) versus term infants; infants with underlying conditions such as congenital diaphragmatic hernia versus infants with no such conditions; severity of PPHN (Oxygenation Index less than 20); dose of milrinone (more or less than 0.5 µg/kg/min); duration of treatment with milrinone (more or less than three days); methodological quality of studies (studies with at least four methodological criteria defined as "yes" versus studies that meet less than four methodological criteria).

RESULTS

Description of studies

We found no randomized studies meeting the inclusion criteria for this review. A pharmacokinetic study of milrinone in infants with PPHN is ongoing (Kirpalani). Its results will be useful to enable a randomized trial of the intervention in infants with PPHN. Most randomized studies identified, either included children after cardiac surgery (Hoffman 2003), children with septic shock (Barton 1996) or preterm infants at risk for low systemic blood flow (Paradisis 2009).

We identified two case series of neonates with severe PPHN that received treatment with milrinone by the search strategy. Bassler 2006 retrospectively examined data for four infants with PPHN (three term, one preterm) who received a combination of iNO and milrinone. Primary causes of PPHN included oligohydramnios, pneumothoraces and meconium aspiration syndrome. All four cases were unresponsive to therapy including iNO, with a mean oxygenation index (OI) of 40 (standard deviation (SD) 12) before milrinone. The dosing of milrinone was based on data from the randomized PRIMACORP study that aimed at preventing low cardiac output syndrome in infants and children after corrective surgery for congenital heart disease (Hoffman 2003). Infants were loaded with 50 µg/kg over 20 minutes, followed by a continuous infusion of 0.33 µg/kg/min. The OI of all four cases improved after milrinone (mean OI 28, SD 16) and all infants could be extubated and survived. However, of four patients, two developed serious intraventricular hemorrhages (IVHs) and one had a small IVH. None of the four infants had systemic hypotension following milrinone.

McNamara 2006 retrospectively examined data for nine term infants with PPHN and echocardiographic confirmation with a mean baseline OI of 28.1 (SD 5.9) who received milrinone after a poor initial response to iNO treatment. The etiology of PPHN was meconium aspiration syndrome, birth asphyxia, transient tachypnea of the newborn and sepsis. Intravenous milrinone was started at a dose of 0.33 µg/kg/min without a loading dose. The dose was titrated according to the clinical response and increased in increments of 0.33 to a maximum of 0.99 µg/kg/min. Oxygenation index was significantly reduced after milrinone, particularly in the immediate 24 hours of treatment (mean 8.0; SD 6.6). Eight of nine infants survived. Intensive care support was withdrawn on the infant who died on the grounds of severe asphyxia and poor neurodevelopmental prognosis. As in the other case series, infants who received milrinone did not develop systemic hypotension. None of the infants developed an IVH.

Risk of bias in included studies

We found no studies meeting the inclusion criteria for this review.

Effects of interventions

We found no studies meeting the inclusion criteria for this review.

DISCUSSION

Given that we found no randomized controlled trials which address the use of milrinone in infants with PPHN, this systematic review does not establish if such a treatment reduces mortality and neurodevelopmental impairment in affected neonates. The search strategy used for this review did identify two small case series, but no controlled clinical trial data. These retrospective studies, while highlighting some possible benefits and dangers associated with the use of milrinone, cannot be used to establish firm practice recommendations, and future RCTs are needed.

Such trials could be challenging and likely require a multicenter collaboration due to the relatively low incidence of PPHN. Initial randomized studies should include term infants with severe PPHN (OI > 25) and an optimal dosing regimen of milrinone in such infants needs to be established prior to the start of the study. Pharmacokinetic data of milrinone in neonates with hypoplastic left heart syndrome undergoing reconstruction (Zuppa 2006) and in preterm infants born before 29 weeks' gestation (Paradisis 2007) are already reported, and pharmacokinetic data of milrinone in infants with PPHN are currently collected (Kirpalani). In regards to the appropriate comparison, studies in wealthy countries would require that milrinone be compared to other established therapies for PPHN, such as inhaled NO or as an adjunct to iNO compared with iNO alone. Settings with limited resources in which iNO therapy is not available could provide a platform for studies comparing milrinone with best alternative therapy or with placebo, provided that ethical issues are considered. A reduction in the rate of death and/or need for ECMO could be used as a primary short-term outcome in initial studies but long-term data will be needed to ensure safety.

AUTHORS' CONCLUSIONS

Implications for practice

The efficacy and safety of milrinone are not known and its use should be restricted within the context of RCTs.

Implications for research

RCTs are needed to support or refute the administration of milrinone to infants with PPHN. In wealthy countries, future studies should compare milrinone with iNO or as an adjunct to iNO compared with iNO alone. In countries in which inhaled NO is not available, studies could address a comparison of milrinone with placebo, provided that ethical issues are considered or with best alternative therapy. A reduction in the rate of death and/or need for ECMO could be used as a primary short-term outcome in initial studies, but long-term data will be needed to ensure safety.

ACKNOWLEDGEMENTS

The Cochrane Neonatal Review Group has been funded in part with Federal funds from the Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA, under Contract No. HHSN267200603418C.

REFERENCES

References to studies excluded from this review

Bassler 2006 *{published data only}*

Bassler D, Choong K, McNamara P, Kirpalani H. Neonatal persistent pulmonary hypertension treated with milrinone: four case reports. *Biology of the Neonate* 2006;**89**(1):1-5.

McNamara 2006 {*published and unpublished data}*

McNamara PJ, Laique F, Muang-In S, Whyte HE. Milrinone improves oxygenation in neonates with severe persistent pulmonary hypertension of the newborn. *Journal of Critical Care* 2006;**21**(2):217-22.

References to ongoing studies

Kirpalani {*unpublished data only***}**

Kirpalani H. Pharmacokinetic Study of Milrinone in Babies With Persistent Pulmonary Hypertension of the Newborn. ClinicalTrials.gov.

Additional references

Barrington 2001

Barrington KJ, Finer NN. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database of Systematic Reviews* 2007, Issue 3. [DOI: 10.1002/14651858.CD000509.pub3]

Barton 1996

Barton P, Garcia J, Kouatli A, Kitchen L, Zorka A, Lindsay C, et al. Hemodynamic effects of i.v. milrinone lactate in pediatric patients with septic shock. A prospective, double-blinded, randomized, placebo-controlled, interventional study. *Chest* 1996;**109**(5):1302-12.

Clarke 1994

Clarke WR, Uezono S, Chambers A, Doepfner P. The type III phosphodiesterase inhibitor milrinone and type V PDE inhibitor dipyridamole individually and synergistically reduce elevated pulmonary vascular resistance. *Pulmonary Pharmacology* 1994;**7**(2):81-9.

Farrow 2005

Farrow KN, Fliman P, Steinhorn RH. The disease treated with ECMO: focus on PPHN. *Seminars in Perinatology* 2005;**29**(1):8-14.

Finer 2001

Finer NN, Barrington KJ. Nitric oxide for respiratory failure in infants born at or near term. *Cochrane Database of Systematic Reviews* 2006, Issue 4. [DOI: 10.1002/14651858.CD000399.pub2]

Hoffman 2003

Hoffman TM, Wernovsky G, Atz AM, Kulik TJ, Nelson DP, Chang AC, 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**(7):996-1002.

Levy 2000

Levy JH, Bailey JM. Phosphodiesterase inhibitors: the inotropes of choice for the new millennium?. *Journal of Cardiothoracic and Vascular Anesthesia* 2000;**14**(4):365-6.

Mugford 2008

Mugford M, Elbourne D, Field D. Extracorporeal membrane oxygenation for severe respiratory failure in newborn infants. *Cochrane Database of Systematic Reviews* 2008, Issue 3. [DOI: 10.1002/14651858.CD001340.pub2]

NINOS 1997

The Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. *New England Journal of Medicine* 1997;**336**(9):597-604.

Paradisis 2007

Paradisis M, Jiang X, McLachlan AJ, Evans N, Kluckow M, Osborn D. Population pharmacokinetics and dosing regimen design of milrinone in preterm infants. *Archives of Disease in Childhood. Fetal and Neonatal Edition* 2007;**92**(3):F204-9.

Paradisis 2009

Paradisis M, Evans N, Kluckow M, Osborn D. Randomized trial of milrinone versus placebo for prevention of low systemic blood flow in very preterm infants. *Journal of Pediatrics* 2009;**154**(2):189-95.

RevMan 2008 [Computer program]

The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.0. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008.

Shah 2007

Shah PS, Ohlsson A. Sildenafil for pulmonary hypertension in neonates. *Cochrane Database of Systematic Reviews* 2007, Issue 3. [DOI: 10.1002/14651858.CD005494.pub2]

Stevens 1980

Stevens DC, Schreiner RL, Bull MJ, Bryson CQ, Lemons JA, Gresham EL, et al. An analysis of tolazoline therapy in the critically-ill neonate. *Journal of Pediatric Surgery* 1980;**15**(6):964-70.

UK Collaborative ECMO Trial Group 1995

UK Collaborative ECMO Trial Group. UK collaborative randomised trial of neonatal extracorporeal membrane oxygenation. *Lancet* 1996;**348**(9020):75-82.

Walsh-Sukys 2000

Walsh-Sukys MC, Tyson JE, Wright LL, Bauer CR, Korones SB, Stevenson DK, et al. Persistent pulmonary hypertension of the newborn in the era before nitric oxide: practice variation and outcomes. *Pediatrics* 2000;**105**(1 Pt 1):14-20.

Zuppa 2006

Zuppa AF, Nicolson SC, Adamson PC, Wernovsky G, Mondick JT, Burnham N, et al. Population pharmacokinetics

of milrinone in neonates with hypoplastic left heart syndrome undergoing stage I reconstruction. *Anesthesia and Analgesia* 2006;**102**(4):1062-9.

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Bassler 2006	Retrospective case series; not a randomized controlled trial
McNamara 2006	Retrospective case series; not a randomized controlled trial

Characteristics of ongoing studies *[ordered by study ID]*

Kirpalani

Trial name or title	Milrinone Pharmacokinetics and Pharmacodynamics in Newborns With Persistent Pulmonary Hypertension of the Newborn - a Pilot Study to Enable a Randomized Trial of Intervention
Methods	Allocation: randomized Endpoint classification: pharmacokinetics/dynamics study Intervention model: parallel assignment Masking: single blind (outcomes assessor)
Participants	Inclusion criteria: • Gestational age > 34 weeks • Birth weight of > 2500g • Post-natal age < 10 days • Hypoxemia defined by: Oxygenation Index (OI) >20 (mean airway pressure x fraction of inspired oxygen x 100 /PaO2) as drawn from two post-ductal arterial blood gas samples (in-dwelling arterial catheter) taken at least 15 minutes apart OR mechanically ventilated and with > 90% FiO2 for > 6 hours while on iNO • Absence of congenital heart disease based on a two-dimensional echocardiogram and/or clinical assessment • An in-dwelling arterial catheter to facilitate painless sampling • Currently on iNO or plan to start iNO before enrollment Exclusion criteria: • Lethal non-cardiac congenital anomalies including diaphragmatic hernia • Clinically apparent bleeding; thrombocytopenia < 30,000 or other laboratory evidence of coagulopathy • Currently on ECMO or plan to initiate ECMO within 2 hours of enrollment
Interventions	Milrinone lactate High dose: experimental 50 mcg/kg load followed by 0.5 mcg/kg/min infusion Low dose: experimental 20 mcg/kg load followed by 0.2 mcg/kg/min infusion
Outcomes	Primary: • pharmacokinetic profile of milrinone in newborns with PPHN Secondary:

Kirpalani *(Continued)*	• oxygenation index • echocardiographic signs of pulmonary hypertension (parameters measured will be: myocardial performance index (MPI) of LV and RV, cardiac output of LV, tricuspid regurgitation (trivial, mild, moderate, severe), RV systolic pressure, mitral regurgitation (trivial, mild, moderate, severe), presence or absence of patent foramen ovale (PFO) with peak and mean pressure gradient, and presence or absence of patent ductus arteriosus (PDA) with peak and mean pressure gradient) • safety profile: safety analysis will be performed as follows: blood pressure will be monitored hourly for 48 hours, platelet count will be measured daily, cardiac rhythm will be monitored continuously for 48 hours, renal function will be monitored daily, and liver transaminases will be monitored within a week. All adverse events will be included in the safety analysis
Starting date	April 2010
Contact information	ClinicalTrials.gov identifier: NCT01088997
Notes	The Children's Hospital of Philadelphia; Pennsylvania Hospital

CONTRIBUTIONS OF AUTHORS

Dirk Bassler searched for studies, planned and wrote a first draft of the review. Karen Kreutzer also searched for studies and all reviewers contributed to the final version of the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Department of Neonatology, University Children's Hospital, Tuebingen, Germany.
- Division of Neonatology, Hospital for Sick Children, Toronto, Canada.
- Department of Pediatrics, University of Pennsylvania School of Medicine and Dept of Clinical Epidemiology and Biostatistics, McMaster University, Philadelphia, Pennsylvania, USA.

External sources

- No sources of support supplied

INDEX TERMS

Medical Subject Headings (MeSH)

Milrinone [*therapeutic use]; Persistent Fetal Circulation Syndrome [*drug therapy]; Vasodilator Agents [*therapeutic use]

MeSH check words

Humans; Infant, Newborn