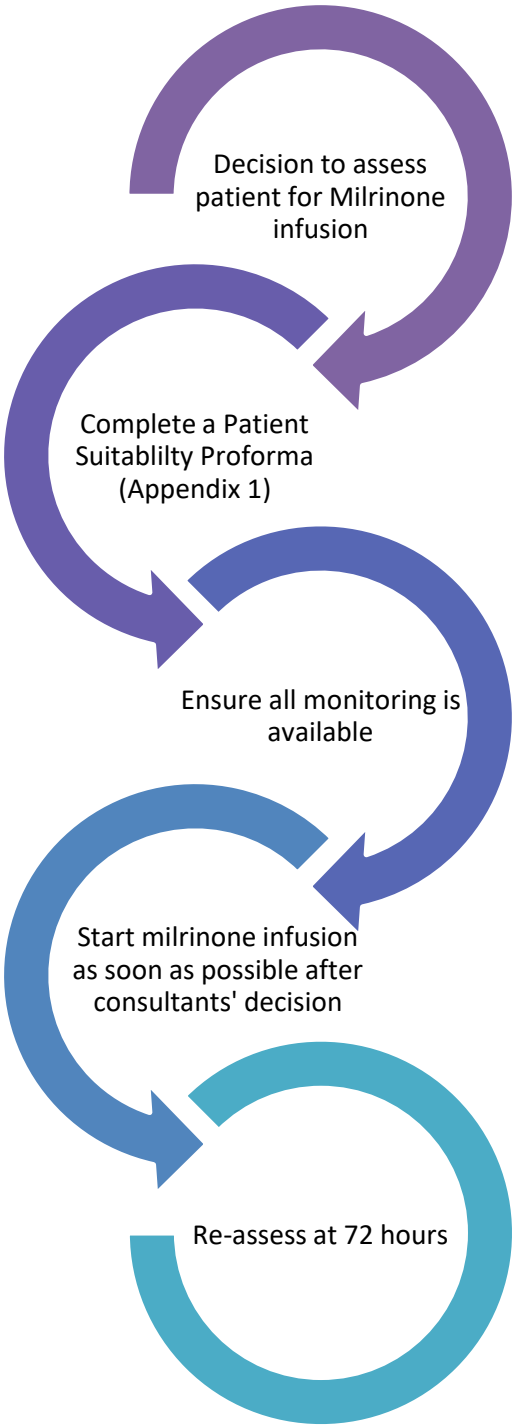
Use of Milrinone for the treatment of Delayed Cerebral Ischaemia (DCI) secondary to Aneurysmal Subarachnoid Haemorrhage [Unlicensed Indication]

Milrinone for DCI is at Consultant MDT Request Only



Patient displays clinical/radiological/neuromonitoring evidence of Delayed Cerebral Ischemia (DCI) unresponsive to tiered induced hypertension *(as per UHSussex Guidelines for the Management of SAH)*.
Decision to start milrinone infusion must be reached as part of an MDT discussion including a Consultant Intensivist, Consultant Neurosurgeon and Consultant Neuroradiologist.

Suitability proforma prompts consideration of primary and secondary measures for managing DCI.

Arterial BP monitoring
ECG
Serum K^+
PiCCO if noradrenaline greater than 0.2mcg/kg/min, or multiple inotropes/vasopressors

If there is a delay of more than 24 hours in initiating treatment the patient must be reassessed for suitability and the outcome agreed by the MDT including intensive care consultant, neurosurgery consultant and neuroradiology consultant.

Continue milrinone infusion for 72 hours up to a maximum of 7 days if signs of clinical improvement. If prolonged infusion required, suitability must be re-assed by the intensive care consultant, neurosurgery consultant and neuroradiology consultant.

Background: Delayed cerebral ischaemia (DCI) following aneurysmal subarachnoid hemorrhage (aSAH) is associated with high levels of morbidity and mortality. There are limited treatment options recommended as standard of care for DCI highlighting a need for further research into potential therapies. Milrinone has been identified as a potential treatment option for DCI.
Milrinone is a phosphodiesterase-3 (PDE-3) inhibitor used as an unlicensed treatment for DCI secondary to cerebral vasospasm. The inhibition of PDE-3 present in cerebrovascular smooth muscle leads to vasodilation and thus increases cerebral perfusion[1]. Through its effect on interleukin 6, milrinone also exhibits some anti-inflammatory effects which may prevent abnormal proliferation of vascular smooth muscle and remodeling caused by DCI[2]. The exact mechanism of milrinone in treating DCI is unknown but there is evidence to show it may be an effective treatment in otherwise refractory cases.

Indication: Intravenous Milrinone is an unlicensed treatment for DCI secondary to cerebral vasospasm[3]. Treatment with milrinone should be considered if tiered induced hypertension management is unsuccessful, and other major causes of new neurological deficit have been excluded. UHSussex guidance on the management of subarachnoid haemorrhage should be followed.

Contra-indications: Severe hypovolaemia[4,5]

Cautions: Hypokalaemia, aortic, mitral or pulmonary stenosis, hypertrophic obstructive cardiomyopathy or other outlet obstruction[4].

Adverse effects: Supraventricular arrhythmia (increased risk in patients with pre-existing arrhythmias); ventricular tachycardia; hypotension, angina pectoris; hypokalemia; thrombocytopenia; tremor[4,5].

Interactions

- The effect of milrinone and diuretics may be mutually potentiated. Improvement in cardiac output and consequent diuresis may require a reduction in dose of diuretics[4,,5].
- Loss of potassium due to diuresis may increase the risk of arrhythmias in patients prescribed digoxin, therefore baseline potassium must be corrected prior to or during treatment with milrinone[4,5].
- If inotropic agents (e.g. dobutamine) are co-administered, the positive inotropic effects and vasodilator effects may be potentiated[4, 5].

Monitoring: Fluid and electrolyte status, invasive blood pressure, heart rate, ECG, central venous pressure, renal function, liver function, platelet count[4, 5].
Advanced cardiac monitoring (PiCCO) is recommended if the patient is also receiving Noradrenaline at greater than 0.2micrograms/kg/min.

Dose:

Calculate dose using actual body weight, unless BMI > 30, in which case use ideal body weight Round down to nearest 10kg for ease of dosing

Initiation: Bolus 100-200 micrograms/kg given slowly over 10 minutes, followed by a continuous maintenance infusion at 0.75 micrograms/kg/minute using an infusion pump[1, 3].

- If no improvement after 30 minutes refer to ITU consultant and neurosurgical consultant (see appendix 1 for escalation process) [1].
- Re-bolus 50-100 micrograms/kg and increase infusion rate to 1.25 micg/kg/min and titrate as required to maximum of 2.5 micrograms/kg/min if patient tolerates[1].
- If MAP <90 then start noradrenaline to maintain MAP >90 to the MAP target agreed and set by ITU consultant and neurosurgical consultant. See Appendix 2 for rescue therapy flowchart.
- Requirement for re-bolus or infusions ≥ 1.25 micg/kg/min should prompt consideration of intra-arterial therapy

Note that the Milrinone dose range for the treatment of DCI is much higher than the licensed dose

Preparation and Administration: Refer to the National Injectable Medicines Guide Milrinone monograph (access via UHSussex intranet) for detailed information regarding preparation, administration and example calculations.

Dose (micrograms/kg)	40kg	50kg	60kg	70kg	80kg	90kg
50	10 mL	12.5 mL	15 mL	17.5 mL	20 mL	22.5 mL
100	20 mL	25 mL	30 mL	35 mL	40 mL	45 mL
200	40 mL	50 mL	60 mL	60 mL	60 mL	60 mL

Table 2[5,6]: Using a 10mg in 50mL (200micrograms in 1 mL) milrinone solution the following specifies the maintenance infusion rate (mL/hour) required for different doses and patient weights

Dose (micrograms/kg/minute	Patient dosing weight					
	40kg	50kg	60kg	70kg	80kg	90kg
0.25	3.0 mL/hour	3.8 mL/hour	4.5 mL/hour	5.3 mL/hour	6.0 mL/hour	6.75 mL/hour
0.50	6.0 mL/hour	7.5 mL/hour	9.0 mL/hour	10.5 mL/hour	12.0 mL/hour	13.5 mL/hour
0.75	**9.0mL/hour**	**11.3 mL/hour**	**13.5 mL/hour**	**15.8 mL/hour**	**18.0 mL/hour**	**20.3 mL/hour**
0.80	9.6mL/hour	12.0mL/hour	14.4mL/hour	16.8mL/hour	19.2mL/hour	21.6mL/hour
0.90	10.8 mL/hour	13.8 mL/hour	16.2 mL/hour	19.2 mL/hour	21.6 mL/hour	24.6 mL/hour
1.00	12.0 mL/hour	15.0 mL/hour	18.0 mL/hour	21.0 mL/hour	24.0mL/hour	27.0 mL/hour
1.25	**15.0 mL/hour**	**18.8 mL/hour**	**22.5 mL/hour**	**26.3 mL/hour**	**30.0 mL/hour**	**33.8 mL/hour**
1.50	18.0 mL/hour	22.5 mL/hour	27.0 mL/hour	31.5 mL/hour	36.0 mL/hour	40.5 mL/hour
1.75	21.0 mL/hour	26.3 mL/hour	31.5 mL/hour	36.8 mL/hour	42.0 mL/hour	47.3 mL/hour
2.00	24.0 mL/hour	30.0 mL/hour	36.0 mL/hour	42.0 mL/hour	48.0 mL/hour	54.0 mL/hour
2.25	27.0 mL/hour	33.8 mL/hour	40.5 mL/hour	47.3 mL/hour	54.0 mL/hour	60.8 mL/hour
2.50	30.0 mL/hour	37.5 mL/hour	45 mL/hour	52.5 mL/hour	60.0 mL/hour	67.5 mL/hour

Duration of treatment: 72 hours, if required maximum 7 days[2] treatment, Consultant Intensivist, Consultant Neurosurgeon and Consultant Neuroradiologist decision only if a longer duration is considered.

Discontinuation: Wean milrinone infusion after maximum 7 day[2] treatment by 0.25 micrograms/kg/minute every 24-48 hours until discontinuation[1].
If clinical deterioration occurs during weaning, increase infusion rate to the previous effective dose, and discuss a more cautious weaning plan with the Consultant Intensivist, and Consultant Neurosurgeon and Consultant Neuroradiologist.
Pharmacokinetics: 70-90% protein bound. Renal excretion with 90% in urine unchanged[4].

References

1. Lannes, M., Zeiler, F., Guichon, C. and Teitelbaum, J., 2017. The use of milrinone in patients with delayed cerebral ischemia following subarachnoid hemorrhage: a systematic review. *Canadian Journal of Neurological Sciences*, *44*(2), pp.152-160.
2. Crespy T, MD * et al. Which Protocol for Milrinone to treat cerebral vasospasm associated with subarachnoid hemorrhage? J Neurosurg Anasthesiol 2018;00;00
3. Lannes, M., Teitelbaum, J., del Pilar Cortés, M., Cardoso, M. and Angle, M., 2012. Milrinone and homeostasis to treat cerebral vasospasm associated with subarachnoid hemorrhage: the Montreal Neurological Hospital protocol. *Neurocritical care*, *16*(3), pp.354-362.
4. British National Formulary 80 Milrinone monograph, accessed 21/12/2020 via https://medicinescomplete.com
5. Summary of product characteristics, Milrinone, Wockhardt Ltd, last updated 18/6/2018, accessed on 26/11/2020 via https://www.medicines.org.uk/emc/product/2625/smpc
6. Injectable Medicines Guide, Milrinone monograph, accessed on 23/12/2020 via https://medusa.wales.nhs.uk

Name.....
DOB .....
Hospital No.....
Weight (kg) .....

Appendix 1

Patient Suitability Proforma for initial Unlicensed Milrinone infusion for the treatment of Delayed Cerebral Ischaemia (DCI) Secondary to aneurysmal subarachnoid hemorrhage (SAH)

Before starting the unlicensed milrinone infusion please ensure you are familiar with the attached guidelines. Complete this form to indicate that all management measures detailed in the guidelines to control ICP are in place or have been considered.

		Variance
Are there symptoms of DCI present: New focal deficit and/or change in GCS?	Yes ☐ No ☐	
Is there radiological / neuromonitoring evidence of DCI?	Yes ☐ No ☐	
Does the patient have a secured aneurysm?	Yes ☐ No ☐	
Is the patient receiving optimal sedation, analgesia and neuromuscular blockade?	Yes ☐ No ☐	
Ensure optimal position to allow cerebral venous drainage	Yes ☐ No ☐	
Is PaO_2 > 13kPa, O_2 Sat > 97% and $PaCO_2$ 4.7 – 5.3kPa	Yes ☐ No ☐	
Is the MAP at a level to achieve CPP>60-70mmHg with euvolaemia?	Yes ☐ No ☐	
Exclude other causes of hypotension (e.g. poor cardiac output) if euvolaemia does not achieve adequate MAP	Yes ☐ No ☐	
Has vasopressor therapy been initiated if euvolaemia has not achieved target MAP?	Yes ☐ No ☐	
Has vasopressor therapy been increased, within the prescribed limits, to achieve a CPP >60-70mmHg *and* target MAP?	Yes ☐ No ☐	
Ensure normothermia; consider Temperature management	Yes ☐ No ☐	
Is the blood glucose controlled?	Yes ☐ No ☐	
Consider repeat CT, including need for CSF drainage	Yes ☐ No ☐	
Having reviewed the above has the Consultant Neurosurgeon in consultation with the Consultant Intensivist made the decision to start MILRINONE infusion?	Yes ☐ No ☐	Name of Consultant Neurosurgeon Name of Consultant Intensivist Name of Consultant Neuroradiologist

Completed by:			
Name:	Signature:	Date	Time

Did patient respond to Milrinone bolus dose and infusion of 0.75mcg/kg/min over 30 minutes? Yes ☐ No ☐
(if No, refer back to Consultant Neurosurgeon, Consultant Intensivist and Consultant Neuroradiologist)

Date and time Milrinone started		Date and time Milrinone stopped	

Comments

Appendix 2

Proposed Milrinone Protocol for Delayed Cerebral Ischaemia (DCI)
Use in conjunction with UHSussex guidelines on management of DCI

Patient details
Patients name:
Hospital number:
DOB:
ICU Consultant on call:
Neurosurgeon on call:

Is there clinical / radiological / neuromonitoring evidence of DCI?

And other aetiological factors are ruled out or corrected ?

TIERED / ESCALATED HYPERTENSIVE THERAPY
(MAP 100 → 120)

If no improvement

If DCI is refractory to hypertensive therapy:
Inform Neurosurgical SpR ☐
Inform ICU Consultant ☐
Consider CT head ☐
Consider if the patient needs intubating (GCS <8 or airway concerns) ☐

CONSIDER RESCUE THERAPY WITH MILRINONE

Start Milrinone
100-200 micg/kg bolus IV
0.75 micg/kg/min infusion
If MAP < 100, start noradrenaline to maintain MAP

If no improvement after 30 minutes
Re-bolus with 50-100 micg/kg IV
Increase infusion up to 1.25mcg/kg/min
Titrate up noradrenaline to maintain MAP>90

If no improvement after 30 minutes
Emergency angiogram
Repeat IV milrinone bolus vs intra-arterial milrinone vs angioplasty

Calculations
Patient's weight: KG
IV bolus dose (100-200 micg/kg)
Initial infusion (0.75 micg/kg/min)
Max IV infusion (2.5 micg/kg/min)

Does the patient need a PiCCO?
Discuss with consultant covering the unit (if on >0.2 micg/kg/min noradrenaline or rapidly rising requirements)