Yorkshire and Humber
Congenital Heart Disease
Operational Delivery Network

Regional guideline on use of Dinoprostone in duct dependent congenital heart conditions in neonates

Guideline Detail

Ownership: Dr Sam Wallis, Consultant Neonatologist Bradford Teaching Hospitals NHS Foundation Trust

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Contents

Summary of Guideline

Use of Dinoprostone in duct dependent congenital heart:

Antenatally diagnosed Transposition of Great Arteries (TGA) / duct dependent condition OR Cyanosed infant who is well and non-acidotic	Infants with absent femoral pulses but otherwise well and non-acidotic	Acidotic / Unwell infants with suspected duct dependent congenital heart condition

- **Manage Airway, Breathing, Circulation as per NLS / APLS guideline for sick infant**
- **Sepsis, respiratory (including PPHN) or metabolic conditions can mimic or can be associated with duct dependent heart conditions – treat these if any clinical suspicion.**
- **Acidotic / unwell infants usually need mechanical ventilation for severe hypoxaemia, acidosis or cardio-respiratory failure**
- **Do not delay in starting Dinoprostone, which can be given peripherally or centrally**

Start Dinoprostone 10 nanograms / Kg / min Discuss with Paediatric Cardiologist	Start Dinoprostone 25 nanograms / Kg / min Discuss with Paediatric Cardiologist	Start Dinoprostone 100 nanograms / Kg / min Discuss with Paediatric Cardiologist urgently via Embrace

Aim for oxygen saturations between 75-85% (in cyanosed) or palpable femoral pulses

Double the dose after every 20 min (to max 100 nanogramss/kg/min) if no improvement in oxygen saturations or femoral pulses and discuss with paediatric cardiologist via Embrace

Aim for maximum achievable oxygen saturations (unless a non-cardiac cause is reliably excluded) / palpable femorals

Consider correcting metabolic acidosis

Time Critical Emergency: Consider time critical emergency if oxygen saturations do not increase above 70% or no improvement in acidosis or lactate levels despite 100nanograms/Kg/min of Dinoprostone

Calling Embrace on 01143058200 at an early stage to allow discussion of transport options is strongly recommended.

Aims

To improve the management of duct dependent congenital heart conditions.

Objectives

1. To provide evidence-based recommendations for starting the appropriate dose of Dinoprostone depending upon the clinical presentation of duct dependent or suspected duct dependent congenital heart conditions.
2. To provide guidance on management of duct dependent or suspected duct dependent congenital heart conditions.
3. To enhance the uniformity of practice in management of duct dependent congenital heart conditions across the Yorkshire and Humber Neonatal ODN, Yorkshire and Humber Paediatric Critical Care ODN and Yorkshire and Humber Congenital Heart Disease ODN.

Background

Infants with suspected duct dependent congenital heart disease (CHD) require Dinoprostone infusion to promote patency of the ductus arteriosus.

Dinoprostone is a Prostaglandin E2 and paediatric preparation is marketed as: *Prostin VR.*

Duct dependent conditions include:

1. Left ventricular outflow obstruction: Coarctation of aorta, critical aortic stenosis, severe hypoplastic / interrupted aortic arch
2. Right ventricular outflow tract obstruction: Pulmonary atresia, critical pulmonary stenosis, tricuspid atresia
3. Transposition of great arteries (TGA). May require urgent transfer for atrial septostomy

Sepsis, respiratory or metabolic conditions are far more common than duct dependent CHD in the neonatal period and these can mimic similar clinical presentation or can be associated with duct dependent CHD - Treat these conditions if any clinical suspicion.

Indications for the use of Dinoprostone

Dinoprostone is a potent vasodilator which is effective in maintaining the patency of the ductus arteriosus in duct dependent congenital heart conditions. The common indications for starting Dinoprostone are:

1. Antenatally diagnosed left ventricular (LV) or right ventricular (RV) outflow tract obstruction or TGA
2. High suspicion of CHD with poor pulses or significant cyanosis
3. Confirmed or suspected duct dependent congenital heart condition on echocardiogram

Dosing regimen

The dose of Dinoprostone ranges from 5 to 100 nanograms/Kg/min.

Higher doses, up to 200 nanograms/Kg/min, can be used on advice of the Paediatric Cardiologist, Neonatologist or Intensivist.

An open duct (e.g. shortly after birth, in antenatally diagnosed duct dependent cases) requires a small dose to keep it patent. A closing or closed duct requires higher dose to open and maintain it. However, echocardiogram facilities may not be available in emergency situations or out of hours.

Clinical presentation and dose regimen

Antenatally diagnosed TGA or duct dependent circulation (LV or RV obstruction): Start on 10 nanograms/Kg/min and monitor for the response.

- **Cyanotic infant who is non-acidotic and well with suspected duct dependent CHD:**
  Start on 10 nanograms/Kg/min. If there is poor response (no improvement in oxygen saturation), increase the dose stepwise (double the dose up to a maximum of 100 nanograms/Kg/min) every 20 minutes aiming to achieve a clinical improvement of oxygen saturation levels (to between 75-85% providing infant remains well). Remember to consider alternative non-cardiac diagnoses.

- **Infant with poorly palpable femoral pulses who is non-acidotic and otherwise well:**
  Start on 25 nanograms/Kg/min. These infants may take longer to respond. Increase dose every 20 minutes (double the dose up to a maximum of 100 nanograms/Kg/min) to achieve a clinical improvement of palpable pulses with lactate maintained below 2 mmol/L.

- **Acidotic / unwell infants and suspected duct dependent CHD:**
  Start on 100 nanograms/Kg/min and consider mechanical ventilation. These infants usually need mechanical ventilation for severe hypoxaemia, acidosis or cardio-respiratory failure.

If not ventilated there is clearly a higher risk of apnoea in non-ventilated infants on high doses of Dinoprostone (>25nanograms/Kg/min).

Rarely some of these infants may need a much higher dose (up to 200 nanograms/Kg/min) which should be used after urgent discussion with the paediatric cardiologist or intensivist. The infusion rate can be reduced to 50 nanograms/Kg/min if there is rapid improvement but this is usually done after cardiology assessment.

General management of acidotic / unwell infants with suspected duct dependent CHD:
DO NOT FORGET common differential diagnosis like Sepsis, Respiratory / PPHN and Metabolic conditions. These conditions are far more common than duct dependent CHD and can mimic similar clinical presentation.
Manage as per newborn life support (NLS) or advanced paediatric life support (APLS) guideline for sick infant
Correcting severe acidosis may help in improving cardiac function.
Discuss with Neonatologist or PICU Intensivist via Embrace for further support.

Important notes on starting Dinoprostone

1. **DO NOT DELAY IN STARTING Dinoprostone if there is clinical suspicion of duct dependent CHD** while waiting for Paediatric Cardiology opinion or echocardiogram, even when in-house echo facilities are present.
2. **Dinoprostone infusion can be given via peripheral or central line.**
3. Infusion rates, particularly for small babies can be low. This may cause a delay between starting Dinoprostone and it reaching the patient. In these instances, giving Dinoprostone alongside a continuous maintenance dextrose infusion can improve flow rate and allow quicker recognition if the line tissues. Other drugs such as antibiotics or fluid boluses need to be given through a separate line and a second line should be available so that Dinoprostone can be quickly switched if the first line fails.
4. Remember to **prime the giving set** to minimise delay in Dinoprostone reaching the patient. Ideally the infusion should be connected via a Y connector close to the cannula with an anti-syphon valve to prevent backtracking up the line.
5. All cases suspected to have duct dependent congenital heart condition should be discussed with the on-call Paediatric Cardiologist at the first opportunity but collapsed or sick infants will need immediate stabilisation, including starting Dinoprostone.
6. If likely transfer to Leeds, use of the Embrace (01143058200) number when calling the Paediatric Cardiologist will allow discussion of transport options at an early stage.

Desired response to Dinoprostone

In absence of echocardiographic diagnosis aim for palpable pulses, resolving acidosis and improving oxygen saturation.

If PPHN remains a differential diagnosis then appropriate respiratory support should be provided with an aim to maximise oxygenation.

After confirming diagnosis monitor for response as:

1. Suspected LV obstruction with acidosis: aim for palpable pulses and resolving acidosis.
2. Cyanotic heart disease with restricted pulmonary blood flow (PBF): aim for saturations 75-85%.Accept saturations down to 70% if lactate is maintained below 2mmol/L.

Time critical emergency:

Some infants with TGA will have restrictive mixing despite opening of the duct. These infants constitute a time critical emergency and are at significant risk of death without a balloon septostomy. Arrange for urgent transfer (Embrace) and discuss with the Paediatric Cardiologist.

Consider this diagnosis in any infant whose saturations do not increase above 70% or do not show improvement in their acidosis or lactate levels despite 100 nanograms/Kg/min of Dinoprostone for at least 20 minutes duration.

Antenatally diagnosed or suspected TGA:

Infants known to have a TGA antenatally should be delivered wherever possible in a centre able to carry out a septostomy (Leeds General Infirmary for Yorkshire).

Acute in-utero transfers can be organised by calling Embrace 01143058200.

Side effects and monitoring

Side effects:

The common side effects are apnoea, hypotension, fever, tachycardia and looking flushed. Other known side effects include hypothermia, cardiac arrest; bradycardia, convulsions, diarrhoea and disseminated intravascular coagulation.

Side effects after prolonged Dinoprostone infusion therapy include gastric outlet obstruction secondary to antral hyperplasia and hypertrophic osteoarthropathy

In practice the major complication on starting therapy is apnoea requiring ventilator support. Apnoea after starting Dinoprostone:

- Apnoea after starting Dinoprostone is the most common side effect.
- Apnoea is a less likely a complication on a dose of <15 nanogramss/kg/min of Dinoprostone [1-2].
- Apnoea as a side effect normally occurs within 1 hour after starting Dinoprostone unless dose is being increased.

In acidotic or collapsed infants the recommended dose of Dinoprostone is much higher and likely to cause apnoea needing mechanical ventilation.

Side effects:

During the infusion the newborn requires the normal close physiological monitoring of heart rate, oxygen saturation, blood pressure, respiratory rate, and core body temperature.

a) Stable infants on Dinoprostone**:** Side effects like apnoea, profound bradycardia, or severe hypotension may warrant more intensive care support. Recurrent or prolonged apnoea may require ventilatory support in order for the infusion to be continued.

b) Critically sick infants: Dinoprostone infusion MUST NOT be stopped and complications should be dealt with by providing intensive care support.

Fever after starting Dinoprostone infusion

Dinoprostone, Prostaglandin E2 is known to stimulate the hypothalamus to induce fever. Fever may of course also be a sign of infection and many patients on Dinoprostone infusions will be newly born with a higher risk of perinatal infection or have a central line with a higher risk of line related sepsis. It is therefore important to consider the cause of the fever when assessing how to respond. *In a recent audit 73% of neonates, receiving a Prostaglandin infusion, had a fever >37.5* ^{o}C *in the 7 days after starting treatment and 27% had an infection screen and antibiotics. All had normal CRP and negative blood cultures.*

In all cases of fever >37.5 ^{o}C the baby should be carefully examined and assessed by an experienced clinician. If the following criteria are met then there may be a role, in discussion with a senior decision maker, to consider withholding antibiotics, whilst continuing careful regular observations.

- No additional perinatal risk factors or red flags for infection (see NICE guideline)
- Clinically well baby, normal HR, BP and CRT
- Central line insertion site, (if present), looks normal
- Clinically otherwise well baby

If antibiotics are withheld then there may still be a role for starting a septic screen including FBC, CRP/Procalcitonin +/- blood culture and CXR depending on senior review and local policy. Babies must be kept under regular observation and frequent review. Do not administer Paracetamol which may mask the fever and counteract the effect of the prostaglandin.

Transfer of infants on Dinoprostone and indications for mechanical ventilation

Transfer of infants on Dinoprostone:

Infants with severe hypoxaemia, acidosis and cardiorespiratory failure will need mechanical ventilation.

- Collapsed babies / those on higher doses of Dinoprostone (e.g. 100nanograms/Kg/min) will need intubation and ventilation. However at lower doses, if the infant is not suffering apnoea after 1 hour of fixed dose infusion then ventilation is not necessary. However, it is recommended that these infants are transferred by a person who is competent to manage the airway if it becomes necessary.
- Elective intubation and ventilation may be required if the infant is to be transferred immediately after starting Dinoprostone infusion. This will be agreed with the Embrace team.
- An infant on Dinoprostone should have 2 routes of intravenous access.

Indications for mechanical ventilation:

- Severe hypoxemia, acidosis or cardio respiratory failure
- Apnoea following the introduction of Dinoprostone
- Elective ventilation may be required for transfer, especially if dose > 25 nanograms/Kg/min or has recently been increased.

Audit and monitoring compliance

This guideline will be audited yearly. Audit criteria will include dosing of Dinoprostone in different conditions, time taken to start the infusion and apnoea following starting infusion.

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Clinical condition	Duct dependent congenital heart lesions
Target patient group	Neonates across the Yorkshire and Humber Neonatal ODN, Yorkshire and Humber Paediatric Critical Care ODN and Yorkshire and Humber Congenital Heart Disease ODN
Target group	Doctors, nurses and pharmacists involved in the care of neonates across the Yorkshire and Humber Neonatal ODN, Yorkshire and Humber Paediatric Critical Care ODN and Yorkshire and Humber Congenital Heart Disease ODN

Evidence Base:

Evidence: B Robust experimental and observational studies

References and evidence levels:

A. Meta-analyses, randomised controlled trials/systematic reviews of RCTs

B. Robust experimental or observational studies

C. Expert consensus.

D. Leeds consensus. (where no national guidance exists or there is wide disagreement with a level C recommendation or where national guidance documents contradict each other)

References:

1. Carmo KAB, Barr P, West M, Hopper NW, White JP, Badawi N. Transporting newborn infants with suspected duct dependent congenital heart disease on low- dose prostaglandin E1 without routine mechanical ventilation. Arch Dis Child Fetal Neonatal Ed 2007; 92; F117-9
2. Y Singh, C Watt, S Clark. Need of mechanical ventilation of infants on prostaglandin E1 during transport. Acta Paediatrica 2009; 98 (S): 235.
3. Kramer HH, Sommer M, Rammos et al. Evaluation of low dose prostaglandin E1 treatment of ductus dependent congenital heart disease. Eur J Paediatr 1995; 154: 700-7.
4. Lewis AB, Takahashi M, Lurie PR. Administration of prostaglandin E1 in neonates with critical congenital cardiac defects. J Pediatr 1978; 93(3):481-5.
5. Moulaert A, Senders R, VanErtbruggen I, Huysmans H, Harinck E. Effect of E1 type Prostaglandin on hypoxemia in the cyanotic congenital cardiac malformation. Eur J Cardiol 1978;5 (4):321-5.
6. Peled N, Dagan O, Babyn P. Gastric-outlet obstruction induced by prostaglandin therapy in neonates. N Engl J Med 1992; 327: 505-10.
7. Mills PJ. Gastric-outlet obstruction in children. N Engl J Med 1992; 327: 558-60.
8. Olley PM, Coceani F, Rowe RD. Role of prostaglandin E1 and E2 in the management of neonatal heart disease. Adv Prostaglandin Thromboxane Res 1978;4: 345-53.
9. Noah ML. Use of prostaglandin E1 for maintaining the patency of the ductus arteriosus. Adv Prostaglandin Thromboxane Res 1978;4:355 -62.
10. Penny DJ, Shekerdemian LS. Management of the neonate with symptomatic congenital heart disease. Arch Dis Child Fetal Neonatal Ed 2001; 84: 141-5.
11. Heymann MA, Rudolph AM. Ductus arteriosus dilatation by prostaglandin E1 in infants with pulmonary atresia. Pediatrics 1977; 59: 325-9.
12. Fariello R, Olley PM, Coceani F. Neurological and electroencephalographic changes in newborns treated with prostaglandins E1 and E2. Prostaglandins1977;13 (5): 901-7.
13. Sone K, Tashiro M, Fujinaga T, Tomomasa T, Tokuyama K, Kuroume T. Long- term low dose prostaglandin E1 administration. Pediatr 1980; 97:86-7.
14. Ueda K, Saito A, Nakano H, Aoshima M, Yokata M, Muruoha R, Iwaya T. Cortical hyperostosis following long-term administration of prostaglandin E1 in infants with cyanotic congenital heart disease. J Pediatr 1980; 97: 834-6.
15. Hellstram-Westas L, Hanseus K, Jogi P et al. Long distance transports of newborn infants with congenital heart disease. Pediatr Cadiol 2001; 22: 380-4.
16. Singh GK, Fong LV, Salmon AP, et al. Study of low dosage prostaglandin usages and complications. Eur Heart J 1994; 15: 377-81.
17. Drugs database and US national library of medicine
18. BNF for children 2017 (and see neonatal e-formulary http://www.leedsformulary.nhs.uk/chaptersSubDetails.asp?FormularySectionID=24&SubSectionRef=24.16&SubSectionID=A100)

Dinoprostone	
Indication	To maintain or restore patency of the ductus arteriosus *Only to be used in infants who are ventilated or where ventilation is immediately available* Vasodilator with specific action on the tissues of the ductus arteriosus Inhibitor of platelet aggregation
Dose	Varying initial doses depending on diagnosis – please see regional guideline – between 10 and 100nanogram/kg/min *(Doses of up to 200nanogram/kg/min may be required to re-open the ductus arteriosus in certain circumstances as guided based on patient presentation and medical advice and a dose of 5nanogram/kg/min may be required at the discretion of the paediatric cardiologists)*
Route of administration	Intravenous infusion (central or peripheral)
To prepare the infusion	1mg/mL ampoules Preferred diluent: glucose 5% Other diluent: sodium chloride 0.9% 300micrograms in 50mL: draw up 0.3mL of 1mg/mL dinoprostone (300 micrograms) and add to 49.7mL of diluent Note: 50 nanograms/kg/minute = 0.5mL/kg/hour
Compatibilities	No compatibility information is known. Do not infuse with any other medicines
Notes	Always use a separate line for infusion. Always prescribe as DINOPROSTONE. Never prescribe as prostaglandin E2 or prostin. Patients should have 2 routes of intravenous access to allow other infusions to be given. Do not stop the infusion suddenly. Prime the giving set prior to administration to minimise the delay in delivery of dinoprostone to the patient. At low infusion rates it may take time for dinoprostone to reach the patient. For example- priming volume for 4Fr UVC = 0.26mL for each lumen. Running dinoprostone alongside a continuous glucose 5% infusion allows quicker delivery to the patient. Use diluted solution within 24 hours. Dinoprostone use can potentially cause line degradation over time (weeks). Discard and draw up a new solution if the solution looks hazy. For side-effects see the BNFc.
References	Medusa (paediatric) accessed online 28/01/2020 v. 7, , BNFc accessed online 28/01/2020, Guy's and St. Thomas', King's college and university Lewisham hospital's Paediatric Formulary 9th edition, Lexicomp accessed online 28/01/2020, Paediatrics with Expertise in Cardiology Specialist Interest Group 'Prostaglandin Guideline' accessed online 28/01/2020