Use of prostaglandins in duct-dependent congenital heart conditions

Yogen Singh, Paraskevi Mikrou

ABSTRACT
Congenital heart disease (CHD) remains a leading cause of infant mortality, which is even higher in infants with undiagnosed duct-dependent CHDs. Up to 39%–50% of infants with critical CHD are being discharged undiagnosed from the hospital. Infants with duct-dependent critical CHD remain well during the fetal period and may deteriorate when the ductus arteriosus (commonly called ‘duct’) closes after birth. It is critical to open or maintain ductus arteriosus patent in infants with duct-dependent CHDs. Prostaglandin E1 (alprostadil marketed as ‘Prostin VR’) and prostaglandin E2 (dinoprostone) are used to maintain a patent ductus arteriosus and the dose of medication depends on the clinical presentation. Delay in starting prostaglandin infusion can have deleterious effects on infants and can even lead to death. These infants often present as an emergency, and professionals caring for these infants need to have a good understanding of these conditions and medications used for ductal patency.

BACKGROUND
The incidence of congenital heart disease (CHD) in the general population is around 6–10 per 1000 live births, and the incidence of critical CHD (needing intervention or operation within 1 month after birth) is 1.6–2 per 1000 live births.1,2 Infants with critical or serious CHD remain well during fetal period and may deteriorate when the ductus arteriosus (commonly called ‘duct’) closes after birth.3 It is critical to maintain a patent ductus arteriosus in these infants with duct-dependent CHDs. There should be high index of suspicion to recognise critical CHD in a sick neonate.2,4 Ductus arteriosus is a normal anatomic connection between the aorta and pulmonary artery, and it helps in maintaining fetal circulation while infant is in utero. Soon after birth, the ductus arteriosus constricts and functionally closes within 24–72 hours in most term infants. Exposure to oxygenated blood (after left to right shunt) and drop in prostaglandin levels play a significant role in the closure of patent ductus arteriosus. Anatomical closure of ductus arteriosus may take up to 10–14 days. In preterm infants, it may remain persistent and its incidence is directly related to lower gestational age. The duct-dependent congenital heart defects can be primarily divided into the following three categories:

2. Right-sided duct-dependent lesions: pulmonary atresia, critical pulmonary stenosis, tricuspid atresia.
3. Transposition of great arteries (TGAs).
Medications for ductal patency in children with congenital heart defects

Prostaglandin therapy is a known effective way to maintain the patency of the ductus arteriosus in neonates and infants with known or suspected duct-dependent congenital heart defects. Two different preparations of prostaglandins exist in the UK:

- Prostaglandin E1 (PGE1) or Prostin VR, also known as alprostadil.
- Prostaglandin E2 (PGE2) or Prostin E2, also known as dinoprostone.

Both drugs are often referred as ‘prostin’ in clinical practice. They should not be confused with other prostaglandins (such as prostacyclin) which are used for other indications.

Both PGE1 and PGE2 are produced by the placenta and equally potent. They act by dilating the vascular smooth muscle of the ductus arteriosus. PGE1 (alprostadil) is licensed for maintaining the ductus arteriosus patent in infants while use of PGE2 (dinoprostone) is not licensed in infants. Both drugs remain stable in infusion after dilution for 24 hours and infusion has to be changed after 24 hours. Knowing both, alprostadil and dinoprostone, have similar efficacy to maintain ductus arteriosus patent and they have similar adverse effects profile; dinoprostone is more often used in clinical practice.

Both alprostadil and dinoprostone are usually administered via intravenous infusion, and both can be effectively delivered via central or peripheral line. In emergency situations, they even can be delivered via an intraosseous route in a collapsed infant.

Oral dosing of dinoprostone is being used in some cardiac centres for chronic use in stable infants. However, oral administration of dinoprostone is not licensed to maintain ductal patency in infants. The efficacy and absorption of dinoprostone via enteral route is unreliable. When used, injectable preparation can be given orally (20–40 μg/kg)—initially given 1 hourly; reduce the frequency of the dose to 4 hourly over several days after 1 week. This route should not be used in emergency or acute situations. It has been recommended that the decision to use oral dinoprostone should be taken by a paediatric cardiologist after a thorough assessment of risks and benefits.

The indications to commence prostaglandin infusion are broadly divided into four categories:

1. Antenatal diagnosis of duct-dependent congenital heart disease.
2. Cyanotic infant who is well and non-acidotic.
   - Consider right-sided duct-dependent lesions or TGA.
3. Infant with absent femoral pulses who is well and non-acidotic.
   - Consider left-sided duct-dependent lesions.
4. Unwell or acidotic infant.

Clinical presentation and dosage of alprostadil and dinoprostone (prostaglandin infusion)

The dosing of prostaglandin infusion depends on the clinical presentation. An open duct, (eg, 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.

There should not be any delay in starting alprostadil or dinoprostone infusion when there is clinical suspicion of duct-dependent CHD and do not wait for a paediatric cardiology review or an echocardiogram to confirm the diagnosis. These infants should be discussed with the paediatric cardiologist as soon as possible.

The clinical presentation and dosing can be divided primarily into four categories:

1. Antenatally diagnosed TGA or duct-dependent circulation (left ventricle or right ventricle RV obstruction): Start on 5–10 ng/kg/min and monitor for the response (see below).
2. Cyanotic infant who is non-acidotic and well with suspected duct-dependent CHD: Start on 5–10 ng/kg/min. If there is poor response (no improvement in oxygen saturation and/or acidosis), increase the dose stepwise (double the dose up to a maximum of 100 ng/kg/min) every 20 min aiming to achieve a clinical improvement of oxygen saturation levels to between 75% and 85%. Accept saturations >70% if lactate remains <2 mmol/L.
3. Infant with poorly palpable femoral pulses who is non-acidotic and otherwise well: Start on 10–15 ng/kg/min. These infants may take longer to clinically respond. Increase the dose every 20 min (double the dose up to a maximum of 100 ng/kg/min) to achieve a clinical improvement of palpable pulses with lactate maintained <2 mmol/L.
4. Acidotic/unwell infants and suspected duct-dependent CHD: Start on 50 ng/kg/min and optimise general care (see box 1). These infants usually need mechanical ventilation for severe hypoxaemia, acidosis or cardiorespiratory failure. If not ventilated, there is clearly a higher risk of apnoeas in non-ventilated infants. These infants may need a much higher dose (up to 100–200 ng/kg/min) which should be used after urgent discussion with the paediatric cardiologist or intensivist. The infusion rate may be reduced to 25–50 ng/kg/min if there is rapid improvement, but this is usually done after a cardiology assessment.

Desired response to alprostadil or dinoprostone

In the absence of echocardiographic diagnosis, aim for palpable pulses, resolving acidosis and improving oxygen saturation (75%–85%). It is important that infants/neonates who have been commenced on a prostaglandin infusion are continuously monitored and clinically assessed closely by experienced clinical staff. After confirming diagnosis, monitor for response as

1. Suspected left ventricle obstruction with acidosis: Aim for palpable pulses and resolving acidosis/normalising serum lactate.
Box 1  General management of acidotic/unwell infants with suspected duct-dependent congenital heart disease (CHD)\(^9\)\(^{10}\)

- Manage as per newborn life support or advanced paediatric life support guideline for sick infant: follow airway, breathing and circulation protocol while managing sick infants.
- Do not forget common differential diagnosis like sepsis, respiratory and metabolic conditions. These conditions are far more common than duct-dependent CHD and can mimic similar clinical presentation.
- When hypovolaemia is suspected, consider small aliquots of fluid boluses (5–10 mL/kg) in children with suspected congenital heart defects.
- Correcting severe acidosis may help in improving cardiac function.
- Monitor for commonly occurring side effects such as apnoea and be prepared to provide ventilatory support if needed.
- Paediatricians or neonatologists with cardiology expertise, where available, can help to establish a cardiac diagnosis, but this should not delay initiation of prostaglandin infusion where indicated clinically.
- All cases need to be discussed with the on-call paediatric cardiologist at the nearest Cardiac Tertiary Centre to plan further management and/or transfer.

2. Cyanotic heart disease with restricted pulmonary blood flow: Aim for saturations 75%–85%. Consider accepting saturations down to 70% if lactate is maintained <2 mmol/L.
3. TGA: Aim for oxygen saturations >75% with normal lactate <2 mmol/L.

Monitoring of infants on prostaglandin infusion
While on prostaglandin infusion, infants need to be monitored for heart rate, blood pressure, oxygen saturations, respiratory rate and core temperature. Frequent clinical assessment of systemic perfusion (skin perfusion, skin temperature, peripheral and femoral pulses, urine output) with monitoring of blood gases (pH, glucose, lactate levels) is essential.

Monitoring in stable infants on alprostadil/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.

Monitoring in critically sick infants
Alprostadil or dinoprostone infusion must not be stopped if there are apnoeas or other adverse effects of medication—complications should be dealt with by providing intensive care support.

Side effects of alprostadil and dinoprostone
Apnoea is the most common side effect after starting prostaglandin infusion, especially in infants requiring high dose of alprostadil or dinoprostone. It is less likely a complication in infants needing a dose of <15 ng/kg/min and often occurs within 1 hour after starting prostaglandin infusion unless dose is being increased. In acidotic or collapsed infants, the recommended dose of alprostadil or dinoprostone is much higher and risk of apnoea is higher needing mechanical ventilation. The other side effects are listed in table 1.\(^8\)

Indications for intubation and mechanical ventilation
- Severe hypoxaemia, acidosis and cardiorespiratory failure.\(^5\)\(^9\)\(^{13}\)
- Apnoea after starting prostaglandin infusion.
- Elective intubation if preferred by paediatric cardiologist, intensivist or retrieval doctor.

Transfer of infants on alprostadil or dinoprostone
Liaise with tertiary paediatric cardiologist and local transport team for transferring infants with suspected duct-dependent CHDs to the nearest tertiary cardiac centre. Please see box 2 for indications needing time-critical transfers.\(^5\)\(^9\)\(^{10}\)\(^{13}\)\(^{14}\)
- If the prostaglandin infusion has been started for >1 hour at a low dose (5–20 ng/kg/min) and the infant is clinically stable with no evidence of apnoeas, transfer can take place without a definite airway. It is prudent that these transfers should be done by professionals competent in airway management.

Box 2  Indications for time-critical transfers

- Infants with transposition of great arteries or hypoplastic left heart syndrome or hypoplastic right heart syndrome with oxygen saturations persistently <70% and worsening lactates require urgent discussion with the tertiary cardiology centre—rapid assessment and emergency balloon atrial septostomy may be necessary.
- Infants with suspected duct-dependent heart disease who remain persistently acidic or cyanotic (oxygen saturations <70%) despite maximum dose of prostaglandin infusion require time-critical transfer to the tertiary paediatric cardiology centre.

**Table 1** Side effects of alprostadil and dinoprostone (prostaglandin infusion therapy)\(^8\)\(^{11}\)

<table>
<thead>
<tr>
<th>Very common adverse effects</th>
<th>Common adverse effects</th>
<th>Uncommon adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apnoea (usually occurs within first hour and with increasing dosing)</td>
<td>Hypotension (due to vasodilatation consider fluid bolus)</td>
<td>Hypothermia</td>
</tr>
<tr>
<td>Fever</td>
<td>Tachycardia or bradycardia</td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td></td>
<td>Flushing</td>
<td>Disseminated intravascular coagulation</td>
</tr>
<tr>
<td></td>
<td>Convulsions</td>
<td>Vascular fragility</td>
</tr>
<tr>
<td></td>
<td>Diarrhoea</td>
<td></td>
</tr>
</tbody>
</table>

Adverse effects on prolonged use:
- Cortical hyperostosis
- Gastric outlet obstruction syndrome.
If the infant has just been started on prostaglandin infusion, then elective intubation and ventilation may be required for transfer.

Indications for intubation and mechanical ventilation (as above).

Need for a national guideline

Infants with suspected duct-dependent CHDs often need transfer to a specialist paediatric cardiology centres for assessment and further management. They often present in non-specialist cardiology centres, and given the lower incidence, the professionals providing care in district general hospitals may have less experience in managing these infants. Clear network guidance on suspecting duct-dependent congenital heart defects and initiating prostaglandin infusion therapy (alprostadil/dinoprostone) has shown to decrease the delay in starting the infusion and drug errors. Many networks across the UK have developed network guidelines. These infants often need transferring long distances across the networks, and hence we recommend adopting a national guideline to improve the care for sick infants with suspected duct-dependent congenital heart conditions. A national guideline on the use of prostaglandin infusion has been proposed, and it has been endorsed by the Paediatricians with Expertise in Cardiology Specialist Interest Group (PECSIG). This can be found on the PECSIG website: www.pecsig.co.uk

CONCLUSIONS

A large number of duct-dependent congenital heart defects are being diagnosed after birth, and they often present after closure or constriction of the ductus arteriosus. Maintaining patency of ductus arteriosus is critical to improve the outcomes in these infants. A high index of suspicion is needed to diagnose a duct-dependent congenital heart defect in sick infants. There should not be any delay in starting prostaglandin infusion (alprostadil or dinoprostone) to maintain ductal patency after suspicion of a duct-dependent condition. The dose of medication depends on clinical presentation. Infants requiring prostaglandin infusion need close monitoring for the desired response and side effects. There is an urgent need of a national guideline on use of prostaglandins in duct dependent conditions which may further improve the care of infants with critical congenital heart defects.

Competing interests None declared.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

Use of prostaglandins in duct-dependent congenital heart conditions

Yogen Singh and Paraskevi Mikrou

Arch Dis Child Educ Pract Ed published online November 21, 2017

Updated information and services can be found at:
http://ep.bmj.com/content/early/2017/11/21/archdischild-2017-313654

These include:

References
This article cites 11 articles, 2 of which you can access for free at:
http://ep.bmj.com/content/early/2017/11/21/archdischild-2017-313654
#BBL

Email alerting service
Receive free email alerts when new articles cite this article. Sign up in the box at the top right corner of the online article.

Notes

To request permissions go to:
http://group.bmj.com/group/rights-licensing/permissions

To order reprints go to:
http://journals.bmj.com/cgi/reprintform

To subscribe to BMJ go to:
http://group.bmj.com/subscribe/