Alprostadil (PGE₁) for Maintaining Ductal Patency
Marcia L. Buck, Pharm.D., FCCP

Alprostadil, or prostaglandin E₁ (PGE₁), can be a lifesaving drug for infants born with ductus-dependent congenital heart disease. Therapy with PGE₁ can effectively maintain an infant's cardiovascular function until palliative or corrective cardiac surgery can be performed. In many cases, this allows transport of the patient from the local institution to a tertiary care center capable of performing neonatal cardiac surgery.

It has been recommended that early medical stabilization of these infants with PGE₁ be initiated at the local hospital immediately after establishing a preliminary diagnosis and continued during transport.¹⁻⁶ For this to be accomplished, it is necessary to have the drug available at most hospitals offering obstetric services. Because of the infrequent need for PGE₁ at the local level, this issue of Pediatric Pharmacotherapy is provided as a staff resource. This article will review the role of PGE₁ in maintaining systemic oxygenation, describe commonly encountered adverse effects, and provide dosing recommendations.

The Ductus Arteriosus
In the fetus, the ductus arteriosus connects the pulmonary artery to the descending aorta. Endogenous prostaglandins, primarily PGE₂ and PGI₂, are produced within the vessel lumen during gestation to keep the ductus patent. As a result of this difference in anatomy, the majority of the blood flow in the fetus passes from the pulmonary artery through the ductus, bypassing the lungs and going directly to the aorta, where it is transported to the placenta for oxygenation. At the time of birth, an increase in arterial oxygen saturation and a decrease in the amount of endogenous prostaglandin produced stimulate an alteration of vascular integrity promoting closure of the ductus, with resultant separation of blood going to the lungs from blood going to the periphery.⁵,⁷

Use of PGE₁ to Maintain Patency
Exogenous prostaglandins can be used to artificially extend the patency of the ductus in neonates where bypassing the defective vessel or continued mixing of oxygenated and unoxygenated blood is needed to provide adequate systemic circulation.⁷ PGE₁ was first used in 1975 to dilate the ductus arteriosus and improve pulmonary blood flow in infants with obstructive right heart malformations.⁸ In the past 25 years, our knowledge of this drug's usefulness has grown considerably. Now, PGE₁ is routinely used in infants with ductus-dependent cardiac lesions to improve circulation prior to balloon atrial septostomy or surgery.²⁻⁵

PGE₁ is currently recommended as initial therapy for infants with isolated defects that restrict pulmonary blood flow (eg, pulmonary stenosis, pulmonary atresia), poor arterial-venous mixing (eg, transposition of the great arteries), and conditions that interfere with systemic circulation (eg, interruption or coarctation of the aorta).²,¹⁻⁹⁻¹⁴

The recommended starting dose of PGE₁ is 0.05-0.1 mcg/kg/min. The dose may be titrated to maintain an open ductus with the use of clinical signs of adequate perfusion, in addition to arterial blood pH and PO₂, arterial blood pressure, pulse oximetry, urine output, and echocardiography. Doses up to 0.4 mcg/kg/min have been required in some patients. In most infants, the ductus will reopen within 30 minutes to 2 hours after starting PGE₁. With reopening of the ductus, PO₂ values typically rise 20-30 mm Hg.⁵ Once the ductus has opened, the dose can usually be reduced to 0.002-0.05 mcg/kg/min.¹⁻⁵,⁷,¹⁴

In most patients, therapy with PGE₁ is continued until balloon atrial septostomy or cardiac surgery is performed. The infusion may be continued after surgery to provide afterload reduction, since...
PGE₁ causes a generalized vasodilation. In some patients, long-term therapy is needed. PGE₁ has proven to be useful in maintaining adequate blood flow for prolonged periods in infants born with hypoplastic left heart syndrome who are awaiting cardiac transplantation and in infants for whom a longer period of growth and maturation is desired to reduce the risk of complications during surgery.

**Pharmacokinetics**

PGE₁ must be administered as a continuous intravenous infusion because of its rapid extraction and metabolism by the lungs. As much as 80% of a single dose may be metabolized in one pass through the lungs. The metabolites, 13,14-dihydro-PGE₁ and 15-keto-13,14-dihydro-PGE₁, are excreted renally. It is believed that 13,14-dihydro-PGE₁ is pharmacologically active. The elimination half-life of PGE₁ is approximately 42 seconds.

The pulmonary extraction ratio of PGE₁ (i.e. the fractional efficiency of removal of drug from the pulmonary plasma flow on a single pass), also demonstrates its nearly complete elimination by the lungs. The extraction ratio of PGE₁ appears to be independent of dose, but dependent on cardiac output and respiratory status. In a study of 14 adult patients, the 10 subjects with normal lung function had pulmonary extraction ratios consistently > 0.7. In the four patients with severe respiratory failure, pulmonary extraction ratios were significantly reduced.

**Adverse Effects**

Many of the adverse effects of PGE₁ are dose-related. Apnea, flushing, fever, bradycardia, and/or hypotension may indicate excessive prostaglandin effect and the need for dose reduction. Apnea occurs in approximately 12% of neonates receiving PGE₁; it is not typically observed with doses < 0.01 mcg/kg/min. Apnea is most likely to occur early in therapy, often within the first hour, and in infants weighing less than 2 kg.

It has been recommended that, when possible, the PGE₁ dose be reduced to the lowest effective rate prior to transport to avoid having to initiate artificial ventilation during transport. Even with the increased safety associated with lower doses, all hospitals considering the use of PGE₁ should be capable of providing adequate ventilatory support in the event that severe apnea does occur, including possible emergency intubation. In cases where a reduction in dose is not tolerated, elective intubation prior to transport should be considered.

Hyperthermia occurs in 10-14% of patients treated with PGE₁. Cutaneous vasodilation (resulting in flushing and edema) occurs in approximately 10% of infants, with bradycardia in 7%, and hypotension in up to 4%. Other adverse effects associated with PGE₁ administration include seizures (4%), tachycardia (3%), diarrhea (2%), and sepsis (2%), as well as respiratory depression, arrhythmias, congestive heart failure, wheezing, gastric regurgitation, bleeding, anuria, hematuria, thrombocytopenia, peritonitis, hypokalemia or hyperkalemia, hypoglycemia, and jitteriness (all occurring in 1% or less).

Long-term administration of PGE₁ in infants with hypoplastic left heart syndrome awaiting heart transplantation has revealed other adverse effects. Cortical proliferation, or hyperostosis, of the long bones has been reported after prolonged use ranging from 9 to over 200 days. More than two dozen cases of cortical proliferation in neonates receiving PGE₁ have been reported in the medical literature to date. Retrospective reviews have suggested an incidence as high as 50 to 60%. The reaction appears to involve hyperostosis in the diaphyses of the long tubular bones and, less commonly, in the ribs, scapulae, and clavicles. Widening of the cranial sutures has also been observed. The mechanism of this effect is not known. Cortical proliferation does not appear to be dose-related; it has occurred in patients receiving PGE₁ infusions as low as 0.008 mcg/kg/min.

The diagnosis of hyperostosis may be made by clinical examination revealing joint swelling or loss of motion, or radiographically. Cortical proliferation begins to regress after discontinuing therapy. In most patients, bone changes have disappeared within 6 to 12 weeks after stopping PGE₁; however, changes have persisted for up to 3 years in some case reports.

Gastric outlet obstruction, resulting from mucosal hyperplasia in the antrum, has been also reported after long-term use of PGE₁. After recognizing this adverse effect in several of their patients, Peled and colleagues performed a retrospective review of PGE₁-treated infants at their institution. Among the 74 patients evaluated, five had both clinical and radiologic or pathological evidence of gastric obstruction, another four had clinical signs only, and the
remaining 65 were considered normal. The infants with gastric outlet obstruction had received PGE<sub>1</sub> for a significantly longer period than the normal infants (mean±SD 569±341hours versus 54±58 hours).

Another potential consequence of long-term PGE<sub>1</sub> exposure is the development of intimal tears within the pulmonary arteries and changes in vessel muscularity. Aneurysmal dilatation and vessel wall edema have recently been reported in infants who have received PGE<sub>1</sub>.<sup>14,19</sup> It has been suggested that these changes may be dose-related, occurring more frequently when higher infusion rates are used to maximize pulmonary blood flow.<sup>26</sup>

**Dose Calculations**

PGE<sub>1</sub> may be diluted in either sodium chloride or dextrose solutions prior to infusion. There are two easy methods for calculating a PGE<sub>1</sub> infusion. The first method is a derivation of the standard "Rule of 15" calculation used for pediatric drips. In this method, the fluid volume and rate are constants, with the amount of drug as the variable.

0.15 x wt (in kg) = ___ mg of PGE<sub>1</sub> added to 50 ml fluid to run at 1 ml/hr = 0.05 mcg/kg/min

In the second method, the entire 500 mcg ampule is used, with the volume and rate as the variables. For example, if the desired dose is 0.1 mcg/kg/min, dilute the contents of one ampule according to the chart below and infuse at the rate multiplied by the patient's weight.

<table>
<thead>
<tr>
<th>Add 500 mcg PGE&lt;sub&gt;1&lt;/sub&gt; to:</th>
<th>To get a final infusion rate of:</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 ml</td>
<td>0.005 ml/kg/min</td>
</tr>
<tr>
<td>50 ml</td>
<td>0.01 ml/kg/min</td>
</tr>
<tr>
<td>100 ml</td>
<td>0.02 ml/kg/min</td>
</tr>
<tr>
<td>250 ml</td>
<td>0.05 ml/kg/min</td>
</tr>
</tbody>
</table>

**Availability**

PGE<sub>1</sub> is available in 1 ml ampules containing 500 mcg/ml (Prostin VR Pediatric; Pharmacia & UpJohn). The ampules must be refrigerated.<sup>19</sup> Prepared solutions should be discarded after 24 hours.

A new formulation of PGE<sub>1</sub>, which incorporates the drug into lipid microspheres, is currently under investigation in Japan.<sup>27</sup> This product has been designed to provide a greater concentration of drug directly at the ductus arteriosus. It appears to maintain patency of the ductus with fewer systemic adverse effects.

**Cost**

A package of five ampules costs approximately $500 to $600, making this product relatively expensive to stock in order to treat a modest number of infants each year. Several hospitals have developed methods for cooperative purchasing within communities or with referral centers to help defray the initial expense.

**Summary**

While not all infants with congenital heart disease will benefit from the use of PGE<sub>1</sub>, for many it can be a lifesaving therapy. Early diagnosis and the initiation of PGE<sub>1</sub> to stabilize the patient can provide enough time to allow transfer to a tertiary care center for palliative or corrective surgery.

**References**


Pharmacology Literature Review

Nalmefene safety and pharmacokinetics

Like other opioid antagonists, nalmefene, has been used successfully in combination with opioid infusions to reduce their adverse effects. The tolerability and pharmacokinetics of nalmefene in children were evaluated in this randomized, double-blind placebo-controlled trial. Thirty-four children between the ages of 2 and 12 years received either a placebo or 1 mcg/kg intravenous bolus of nalmefene. All of the children had just undergone cardiac or thoracic surgery and were receiving epidural opioid infusions. Nalmefene pharmacokinetic parameters were similar to values previously reported in adults, including an elimination half-life of 8.7±2.3 hours and a volume of distribution of 7.21±2.49 L/kg. All patients tolerated the single dose without symptoms of opioid withdrawal. Opioid-induced adverse effects were not significantly different between the groups, which may reflect the need for higher nalmefene doses. Rosen DA, Morris JL, Rosen KR, et al. Nalmefene to prevent epidural narcotic side effects in pediatric patients: a pharmacokinetic and safety study. Pharmacotherapy 2000;20:745-9.

Phenytoin interaction with enteral feedings

In this concise review, the authors weigh the evidence supporting or refuting the significance of decreased serum phenytoin concentrations when the drug is given with enteral feedings. Twenty-nine articles are evaluated, including the only randomized, controlled trial published to date. Despite the lack of overwhelming scientific evidence, the authors acknowledge the likelihood of a significant interaction based on clinical experience and recommend separation of phenytoin from feedings. Au Yeung SCS, Ensom MHH. Phenytoin and enteral feedings: does evidence support an interaction? Ann Pharmacother 2000;34:896-905.

Formulary Update

The following actions were taken by the Pharmacy and Therapeutics Committee during their meeting on 8/25/00:

1. Alosetron (Lotronex$^\text{®}$) was added to the Formulary for use in patients with irritable bowel syndrome whose predominant symptom is diarrhea. Its use is restricted to the Gastroenterology Division.
2. Several changes were made in the proton pump inhibitors carried on our Formulary. The oral form of pantoprazole (Protonix$^\text{®}$) was added. Lansoprazole (Prevacid$^\text{®}$) was removed from the Formulary and the request for addition of rabeprazole (AcipHex$^\text{®}$) was rejected.
3. A request for levobupivacaine (Chirocaine$^\text{®}$) was rejected. It was not determined to offer significant advantages over racemic bupivacaine.

Contributing Editor: Marcia L. Buck, Pharm.D.
Editorial Board: Anne E. Hendrick, Pharm.D.
Michelle W. McCarthy, Pharm.D.
Douglas S. Paige, R.Ph.

If you have any comments or suggestions for future issues, please contact us at Box 274-11, UVA Medical Center, Charlottesville, VA 22908 or by phone (804) 982-0921, fax (804) 982-1682, or e-mail to mib3u@virginia.edu.