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Alprostadil (PGE_1) for Maintaining Ductal Patency

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Alprostadil, or prostaglandin E_1 (PGE_1), can be a lifesaving drug for infants born with ductus-dependent congenital heart disease. Therapy with PGE_1 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 PGE_1 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 PGE_1 at the local level, this issue of *Pediatric Pharmacotherapy* is provided as a staff resource. This article will review the role of PGE_1 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 PGE_2 and PGI_2, 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 PGE_1 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] PGE_1 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, PGE_1 is routinely used in infants with ductus-dependent cardiac lesions to improve circulation prior to balloon atrial septostomy or surgery.[2-5]

PGE_1 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).[2,3,9-14]

The recommended starting dose of PGE_1 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 PO_2, 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 PGE_1. With reopening of the ductus, PO_2 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 PGE_1 is continued until balloon atrial septostomy or cardiac surgery is performed. The infusion may be continued after surgery to provide afterload reduction, since

PGE_1 causes a generalized vasodilation. In some patients, long-term therapy is needed. PGE_1 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

PGE_1 must be administered as a continuous intravenous infusion because of its rapid extraction and metabolism by the lungs.[15-18] As much as 80% of a single dose may be metabolized in one pass through the lungs. The metabolites, 13,14-dihydro-PGE_1 and 15-keto-13,14-dihydro-PGE_1, are excreted renally. It is believed that 13,14-dihydro-PGE_1 is pharmacologically active. The elimination half-life of PGE_1 is approximately 42 seconds.[17]

The pulmonary extraction ratio of PGE_1 (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 PGE_1 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.[16]

Adverse Effects

Many of the adverse effects of PGE_1 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 PGE_1; it is not typically observed with doses < 0.01 mcg/kg/min.[3,14,19,20] Apnea is most likely to occur early in therapy, often within the first hour, and in infants weighing less than 2 kg.[19,20]

It has been recommended that, when possible, the PGE_1 dose be reduced to the lowest effective rate prior to transport to avoid having to initiate artificial ventilation during transport.[2] Even with the increased safety associated with lower doses, all hospitals considering the use of PGE_1 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 PGE_1. 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 PGE_1 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).[19,20]

Long-term administration of PGE_1 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.[19,21-23] More than two dozen cases of cortical proliferation in neonates receiving PGE_1 have been reported in the medical literature to date. Retrospective reviews have suggested an incidence as high as 50 to 60%.[24] 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 PGE_1 infusions as low as 0.008 mcg/kg/min.[22]

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 PGE_1; however, changes have persisted for up to 3 years in some case reports.[23]

Gastric outlet obstruction, resulting from mucosal hyperplasia in the antrum, has been also reported after long-term use of PGE_1.[19,25] After recognizing this adverse effect in several of their patients, Peled and colleagues performed a retrospective review of PGE_1-treated infants at their institution.[25] 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_1 for a significantly longer period than the normal infants (mean±SD 569±341hours versus 54±58 hours).

Another potential consequence of long-term PGE_1 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_1.[14,19] 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.[26]

Dose Calculations

PGE_1 may be diluted in either sodium chloride or dextrose solutions prior to infusion. There are two easy methods for calculating a PGE_1 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_1 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.

Add 500 mcg PGE_1 to:	***To get a final infusion rate of:***
25 ml	0.005 ml/kg/min
50 ml	0.01 ml/kg/min
100 ml	0.02 ml/kg/min
250 ml	0.05 ml/kg/min

Availability

PGE_1 is available in 1 ml ampules containing 500 mcg/ml (Prostin VR Pediatric; Pharmacia & UpJohn). The ampules must be refrigerated.[19] Prepared solutions should be discarded after 24 hours.

A new formulation of PGE_1, which incorporates the drug into lipid microspheres, is currently under investigation in Japan.[27] 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_1, for many it can be a lifesaving therapy. Early diagnosis and the initiation of PGE_1 to stabilize the patient can provide enough time to allow transfer to a tertiary care center for palliative or corrective surgery.

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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$\pm$2.3 hours and a volume of distribution of 7.21$\pm$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®) 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®) was added. Lansoprazole (Prevacid®) was removed from the Formulary and the request for addition of rabeprazole (Aciphex®) was rejected.
3. A request for levobupivacaine (Chirocaine®) was rejected. It was not determined to offer significant advantages over racemic bupivacaine.

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