

# Effectiveness of Alprostadil for Ductal Patency

Caitlin M. Gordon, PharmD; Jason T. Tan, PharmD; and Roxane R. Carr, PharmD

**OBJECTIVES** This study aims to describe the effectiveness of low initial alprostadil dosages to maintain a patent ductus arteriosus (PDA) in infants with ductal-dependent congenital heart disease (DDCHD). Secondary objectives were to describe any adverse drug events, describe prescribing trends, describe ductus arteriosus diameter changes, and compare the safety and efficacy of very low and low initial alprostadil dosage regimens.

**METHODS** This retrospective observational cohort study at the British Columbia's Women's and Children's Hospital neonatal intensive care unit and pediatric intensive care unit examined neonates admitted with DDCHD who received alprostadil to maintain ductal patency. Very low-dose alprostadil (less than 0.01 mcg/kg/min) versus low-dose alprostadil (equal to or greater than 0.01 mcg/kg/min) was examined. Effectiveness was defined as survival and infants not requiring a resuscitation event (cardiac arrest, cardiogenic shock, code blue, extracorporeal life support, requirement for emergent cardiac surgery, and respiratory acidosis). Adverse drug events with a Naranjo score of 3 or more were included.

**RESULTS** Alprostadil was effective for 88% of patients, with no difference between the very low-dose and low-dose groups. Of the 75 patients included, 25 received very low-dose alprostadil. Adverse drug events were common (51%) with neonates in the low-dose group experiencing more apnea and pyrexia than neonates in the very low-dose group.

**CONCLUSIONS** Alprostadil therapy was effective in maintaining the PDA in neonates with DDCHD with low-dosage regimens. Adverse drug events were common with both dosage regimens; however, the very low dosage appeared to have less apnea and pyrexia.

**ABBREVIATIONS** ADE, adverse drug event; BC, British Columbia; DA, ductus arteriosus; DDCHD, ductal-dependent congenital heart disease; PDA, patent ductus arteriosus

**KEYWORDS** alprostadil; congenital heart disease; ductus arteriosus; infant; intensive care units; pediatrics

J Pediatr Pharmacol Ther 2024;29(1):37–44

DOI: 10.5863/1551-6776-29.1.37

## Introduction

Congenital heart disease is one of the most common birth defects in newborns and accounts for significant morbidity and mortality.<sup>1–4</sup> The ductus arteriosus (DA) is a blood vessel between the aorta and pulmonary circulation that allows for blood flow from the right ventricle to bypass the fetus' lungs. After birth, the DA constricts and blood from the right ventricle enters the pulmonary circulation. However, in ductal-dependent congenital heart disease (DDCHD), a patent DA (PDA) is necessary to sustain life until surgical repair of the congenital heart defect can be performed.

Alprostadil is a prostaglandin analog administered as an intravenous or intra-arterial infusion to relax the DA in infants with DDCHD. Based on data from initial descriptive case series using alprostadil to maintain a PDA in fewer than 40 infants, the manufacturer recommends a standard alprostadil initial dose of 0.1 mcg/kg/min, which is subsequently decreased to a maintenance dose of 0.01 to 0.05 mcg/kg/min.<sup>5–9</sup> Surrogate markers, such

as oxygen saturation improvements, systemic blood pressure and pO<sub>2</sub>, are traditionally used to determine the response to alprostadil therapy.<sup>5–8</sup>

Published case reports and retrospective chart reviews with small numbers of patients reported that doses lower than the suggested manufacturer's dosing protocol could be used to effectively maintain a PDA.<sup>9–20</sup> These case reports described full-term infants with normal birth weights and reported, in general, initial alprostadil doses of 0.01 to 0.09 mcg/kg/min intravenously, which were then titrated to the lowest effective maintenance dose.<sup>9–20</sup> Three studies published in the 1980s and 1990s reported that a lower initial dose of alprostadil (mean dose, 0.005–0.01 mcg/kg/min) could be used successfully to maintain a PDA, with 1 study reporting mean maintenance doses of 0.009 to 0.028 mcg/kg/min.<sup>12,13,15</sup> Minimal recent data exist for describing the efficacy of initial alprostadil doses less than 0.01 mcg/kg/min to maintain a PDA.

Standard doses of alprostadil have been associated with flushing, bradycardia, hypotension, tachycardia, edema, cardiac arrest, pyrexia, seizures, apnea, diarrhea, intravascular coagulation, and hypokalemia.<sup>5</sup> In 3 trials with alprostadil doses of less than 0.01 mcg/kg/min, 39% to 53% of patients experienced adverse effects.<sup>12,13,15</sup> Similar rates of adverse effects with alprostadil doses between 0.01 and 0.09 mcg/kg/min have also been reported.<sup>10,16,18,19</sup> A relationship between higher dosage and adverse effects rates has been reported in some studies, whereas others reported no correlation.<sup>10,16,18,19,21</sup> Currently, there are minimal safety data for initial alprostadil doses less than 0.01 mcg/kg/min in the setting of ductal patency in DDCHD.

The British Columbia (BC) Children's Hospital Drug Dosage Guidelines recommend an initial alprostadil dose of 0.02 mcg/kg/min, titrated down to 0.005 to 0.01 mcg/kg/min or to the lowest effective dose.<sup>22</sup> However, over time, clinical practice at BC Children's Hospital has adjusted to prescribe an initial alprostadil dose of 0.005 to 0.01 mcg/kg/min and titrate to the lowest effective dose once the patient is clinically stable. This change was implemented because prescribers noticed a trend toward maintaining a PDA with lower initial dosages. The purpose of this study was to describe the effectiveness of alprostadil dosages less than 0.01 mcg/kg/min for maintenance of PDA in neonates with DDCHD.

## Materials and Methods

A retrospective cohort study of patients receiving alprostadil was conducted at the BC Women's and Children's Hospital. Patients were identified by the BC Women's and Children's Hospital pharmacy department database. Infants were excluded from the study cohort if alprostadil was prescribed for other indications besides DDCHD, such as persistent pulmonary hypertension or congenital diaphragmatic hernias.

The primary outcome of this study was to describe the effectiveness of initial low-dose alprostadil in maintaining a PDA in infants with DDCHD. Effectiveness was defined as infants not requiring a resuscitation event (cardiac arrest, cardiogenic shock, code blue, extracorporeal life support, emergent cardiac surgery, respiratory acidosis pH <7.2) and survival at time of discharge or transfer. Cardiogenic shock was defined as an increase in oxygen requirements in infants with clinical manifestations of shock (cold extremities, tachycardia, metabolic acidosis, acrocyanosis) as diagnosed by the care team. Respiratory acidosis was defined as a pH less than 7.2 and an elevated serum bicarbonate greater than 40 with clinical worsening of respiratory status. The absence of resuscitation events and survival was used rather than traditionally studied efficacy metrics described in the literature, such as clinical condition of the infant, arterial blood gas analysis, improvements in oxygen saturations, acidosis, vital status, and PDA size, because the latter are often unrelated to alprostadil

therapy.<sup>6-8</sup> Secondary objectives were to describe prescribing trends over time at BC Children's Hospital, describe the types of adverse events observed, describe DA diameter (determined via echocardiogram) before initiation of and during alprostadil therapy, and compare the safety and effectiveness of very low-dose to low-dose alprostadil regimens. Apnea was defined as an infant experiencing cessation of breathing with an accompanied oxygen saturation drop less than 92% on room air or with an increase in ventilator requirements. Fever was defined as a temperature higher than 37.5°C.

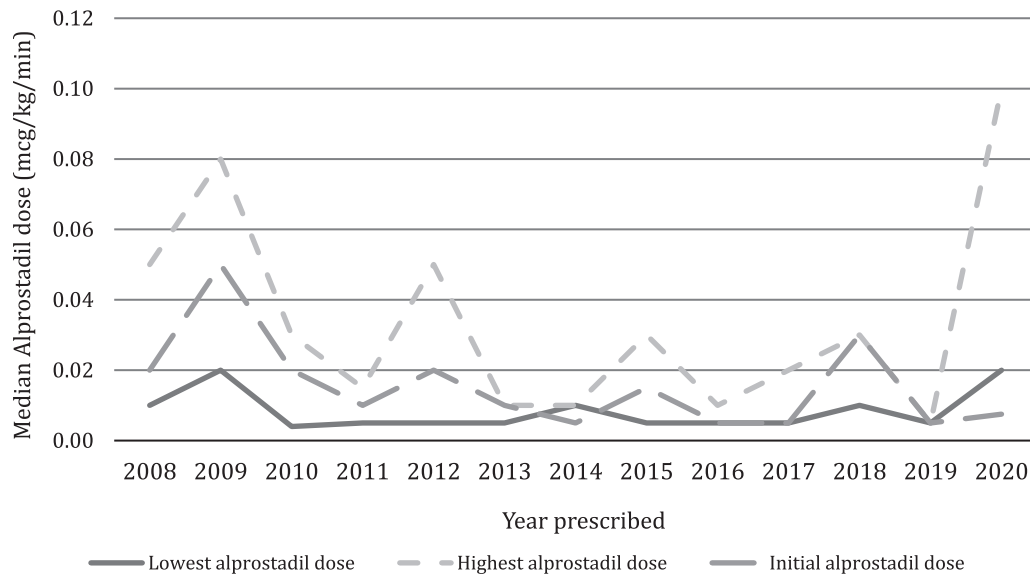
Infants were included in the very low-dose alprostadil regimen group if they received an initial alprostadil dose less than 0.01 mcg/kg/min. Infants who received initial alprostadil doses greater or equal to 0.01 mcg/kg/min were included in the low-dose group. Once separated into these groups, the highest and lowest maintenance doses were recorded for each infant (Figure 1). The study included initial alprostadil doses because this dosage remains important for stabilizing the infant clinically if DDCHD is diagnosed after birth or for maintaining stability if diagnosed *in utero*.

The study included neonates who had received alprostadil for DDCHD between January 1, 2008, and August 31, 2020. This time frame was determined based on the number of charts reviewed sequentially in chronological order to meet the sample size goal (see below). Infants who had initially received alprostadil but were subsequently deemed palliative because of inoperable cardiac lesions or non-survivable comorbidities were excluded from the secondary effectiveness outcome.

Adverse events were assigned a Naranjo Score by 2 independent investigators to determine the likelihood of the event being a result of alprostadil.<sup>23</sup> Events with a Naranjo score of 3 or more (possible to definite likelihood) were included.<sup>23</sup> Because alprostadil is a lifesaving therapy until corrective surgery is performed, several of the scoring questions could not be answered, including stopping alprostadil, administering a placebo, and readministering alprostadil after it was stopped. Because of these limitations of using the Naranjo score to assess adverse events with alprostadil therapy, a Naranjo score of 3 or more was included to avoid underreporting of adverse events when they may in fact be commonly observed.

One investigator, using a standardized data collection form, obtained the following information from patients' medical records: demographic characteristics, medical problems and diagnoses, initial and maintenance doses of alprostadil therapy, number of dose changes required, time between birth and alprostadil initiation, duration of alprostadil infusion, number of infants requiring a resuscitation event, number of mortalities, mean PDA diameter at baseline and during alprostadil therapy, and any adverse events related to alprostadil. Data were entered into REDCap.<sup>24</sup>

**Figure 1.** Alprostadil dose in year prescribed. The n for year prescribed: 2008, n = 1; 2009, n = 9; 2010, n = 6; 2011, n = 10; 2012, n = 9; 2013, n = 3; 2014, n = 5; 2015, n = 8; 2016, n = 5; 2017, n = 5; 2018, n = 2; 2019, n = 10; and 2020, n = 2.



Reports of survival or absence of resuscitation events for standard and low-dose alprostadil are sparse throughout the literature and are often associated with other patient factors, such as age beyond the neonatal period, and surrogate markers for effectiveness, such as change in vital signs or oxygen saturations.<sup>6–8</sup> Treatment effectiveness of alprostadil has not been explicitly studied as an outcome in the available literature. Clinical judgment from expert opinion was used to generate a true proportion value of a single cohort because no other studies have performed a sample size calculation or explicitly reported this as a primary outcome. The proportion of failures on alprostadil therapy was estimated to be close to zero. However, a conservative proportion of 5% with a confidence level of 95% was selected. A true proportion test was used for the sample size calculation to estimate the effectiveness of low-dose alprostadil therapy in a single cohort of patients.<sup>25</sup> A sample size of 73 patients was determined using this test.

Descriptive statistics were used to report patients' demographic information, adverse drug events (ADEs), PDA diameter before and during alprostadil therapy, and prescribing trends over time. The  $\chi^2$  test was used to compare categorical variables, such as effectiveness and adverse events of alprostadil between the low-dose and very low-dose groups. A 2-sample *t* test was used to compare continuous variables such as initial and maintenance alprostadil dosing between the low-dose and very low-dose groups as well as gestational age and weights of infants. A *p* value <0.05 was considered to be statistically significant.

## Results

A total of 75 patients were included from the 246 charts screened (see Supplemental Figure). Twenty-five (33%) of these patients received a very low initial alprostadil dose, whereas the remaining 50 patients (66%) received a low initial alprostadil dose. Gestational age, birth weight, and concomitant medical conditions were similar between the groups given the lack of statistical significance (Table 1). Median time from birth to initiation of alprostadil was 3.75 hours (IQR, 2.3–7.4) for patients receiving very low-dose alprostadil and 6.3 hours (IQR, 2.6–21.4) for patients receiving low-dose alprostadil (*p* = 0.174).

The median initial dose of alprostadil for all patients was 0.01 mcg/kg/min (IQR, 0.005–0.045; Table 2). Median initial dosages were significantly lower in the very low-dose group compared with the low-dose group, 0.005 vs. 0.02 mcg/kg/min (*p* < 0.001). Infants in the very low-dose group received lower minimum maintenance doses than infants in the low-dose group, 0.005 vs. 0.01 mcg/kg/min (*p* < 0.001), as well as lower highest maintenance doses, 0.005 vs. 0.05 mcg/kg/min (*p* < 0.001). The median duration of alprostadil therapy was similar between the groups, 2.6 vs. 2.42 days (*p* = 0.305). A temporal relationship between dose prescribed and year of therapy was observed (Figure 1). Although it appears that higher maintenance doses are being prescribed in 2020, it is important to note that only 2 patients comprised this cohort, one of which had a closed DA at birth.

Twenty-four patients (32%) had a reported DA size before and after alprostadil initiation (Table 3). Six

**Table 1.** Patient Baseline Characteristics

Characteristics	All N = 75	Very Low Initial Dose n = 25	Low Initial Dose n = 50	p value
Median (IQR) gestational age, wk	38.7 (37.5–39.9)	38.9 (38–40.4)	38.7 (36.7–39.8)	0.190
Male sex, n (%)	35 (47)	8 (32)	27 (54)	0.264
Median (IQR) birth weight, kg	3.1 (2.8–3.5)	3.1 (2.9–3.5)	3.0 (2.8–3.4)	0.289
Median (IQR) time from birth to alprostadil start, hr	5.2 (2.6–19)	3.75 (2.3–7.4)	6.3 (2.6–21.4)	0.174
Medical conditions, n (%)	36 (48)	15 (60)	21 (42)	0.392
Concomitant cardiovascular anomalies	23 (31)	9 (36)	14 (28)	0.609
Chromosomal disorder	7 (9)	3 (12)	4 (8)	0.611
ICH/IVH	2 (3)	1 (4)	1 (2)	0.623
Other*	13 (17)	8 (32)	5 (10)	0.052

ICH, intracranial hemorrhage; IVH, intraventricular hemorrhage

\* Other medical conditions observed (n) were: hyperbilirubinemia (2), neonatal abstinence (2), necrotizing enterocolitis (1), lung hypoplasia (1), seizures (1), microcephaly (1), asplenia (1), heterotaxy (1), intrauterine growth restriction (1), sacrocygeal teratoma (1), renal fusion (1), and apnea of prematurity (1).

**Table 2.** Alprostadil Dosage

Group	All N = 75	Very Low Initial Dose n = 25	Low Initial Dose n = 50	p value
Median (IQR) initial alprostadil dose, mcg/kg/min	0.01 (0.005–0.045)	0.005 (0.005–0.005)	0.02 (0.01–0.05)	<0.001
Median (IQR) lowest maintenance alprostadil dose, mcg/kg/min	0.01 (0.005–0.01)	0.005 (0.003–0.005)	0.01 (0.005–0.014)	<0.001
Median (IQR) highest maintenance alprostadil dose, mcg/kg/min	0.02 (0.01–0.05)	0.005 (0.005–0.006)	0.05 (0.02–0.05)	<0.001

**Table 3.** Ductal Diameter Before and During Alprostadil Infusion\*

Study Population Group (N = 75)	n (%)
Patients with a reported PDA size before AND during alprostadil therapy	24 (32)
Patients who maintained their DA size	15 (63)
Patients with a larger DA after starting alprostadil	9 (38)
Patients with a smaller DA after starting alprostadil	0 (0)

DA, ductus arteriosus; PDA, patent ductus arteriosus

\* The DA diameter was determined by echocardiogram.

(25%) of these patients were prescribed very low initial alprostadil dosages. None experienced narrowing or closure of the DA after alprostadil initiation, regardless of alprostadil dosage.

Fifteen patients (20%) were deemed palliative after alprostadil initiation because of inoperable cardiac

lesions or non-survivable comorbidities. Alprostadil was electively stopped in these infants, and therefore they were excluded from the effectiveness outcomes. Fifty-three of the remaining 60 patients (88%) had effective alprostadil therapy (Table 4). There was no difference in effectiveness between the very low-dose and the low-dose groups, 87% vs. 89% ( $p = 0.954$ ). Six neonates (10%) required resuscitation, with 4 requiring resuscitations more than once. Respiratory acidosis was the most common reason for resuscitation (8 of 16). Four patients (7%) died while receiving alprostadil therapy. Of these neonates, 1 had a closed DA at birth, 1 had a thrombosed DA, and 2 died postoperatively after having a cardiac arrest in the OR.

Adverse drug events were common, with infants frequently experiencing more than 1 event (Table 5). More than half of the patients who experienced an adverse event required medical intervention; however, all recovered from the adverse event. Depending on the adverse event, these interventions included stimulating the infant, changing ventilator settings, replacing electrolytes, or administering antipyretics. The low-dose group had a higher overall incidence

**Table 4. Effectiveness of Alprostadil Therapy**

Parameter	All n = 60*	Very Low Initial Dose n = 15	Low Initial Dose n = 45	p value
Patients with effective alprostadil therapy, n (%)	53 (88)	13 (87)	40 (89)	0.954
Patients requiring a resuscitation event, n (%)	6 (10)	1 (7)	5 (11)	0.650
Death, n (%)	4 (7)	2 (13)	2 (4)	0.273

\* Excluding palliative patients n = 15.

of ADEs than the very low-dose group, 52% vs. 48%, although this difference was not statistically significant ( $p = 0.851$ ). Because of our small sample size, however, the presence of a type 2 error is possible. Several specific adverse events, such as tachypnea, hypokalemia, and tachycardia, were more frequent in the very-low dose group (Figure 2). Infants who experienced adverse events had weights similar to those who did not experience adverse events, 3.10 vs. 3.13 kg ( $p = 0.242$ ). The median gestational age of infants with adverse events and those without adverse events were similar, 38.7 vs. 38.7 weeks ( $p = 0.78$ ).

Apnea and pyrexia were more common in the low-dose group compared with the very low-dose group (Figure 2). Infants with apneic episodes appeared to be younger at birth than infants without apnea, 37.7 vs. 38.9 weeks' gestational age ( $p = 0.046$ ). Weight was not different between infants with apneas and those without, 2.96 vs. 3.15 kg ( $p = 0.142$ ).

The Naranjo score was 3 for 68% of the patients who experienced an ADE, and 32% had Naranjo scores of 4 or more. This indicates the reaction followed a temporal relationship with alprostadil administration and could be explained by characteristics of the patient's disease state. A small number of adverse events (21%) achieved higher Naranjo scores (Naranjo score = 5) as a dose response relationship was observed.

## Discussion

Traditionally, definitions of alprostadil effectiveness have been based on the clinical condition of the infant, arterial blood gas analysis, improvements in oxygen saturations, acidosis, vital signs, and PDA size.<sup>12,13</sup> Reports of alprostadil failure leading to a resuscitation event or mortality are sparse in the literature. However, we chose to use absence of resuscitation events and survival to define alprostadil effectiveness because the aforementioned surrogate markers are often reliant on

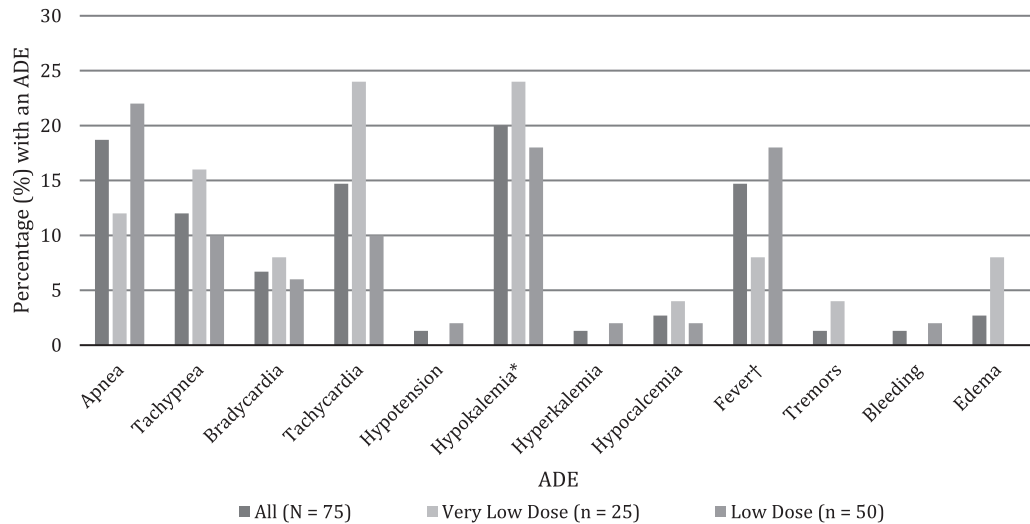
**Table 5. Adverse Drug Events (ADEs)**

Parameter	All N = 75	Very Low Initial Dose n = 25	Low Initial Dose n = 50	p value
Patients experiencing ADEs, n (%)	38 (51)	12 (48)	26 (52)	0.851
ADEs requiring medical intervention, n (%)	24 (63)	7 (58)	17 (65)	0.841
Patients with complete resolution of ADE after medical intervention, n (%)	36 (100)	12 (100)	26 (100)	1
Median ADEs per patient (IQR)	2 (1)	2 (2)	2 (1)	0.457

factors unrelated to alprostadil. For example, a drop in oxygen saturation in a ventilated infant receiving alprostadil was often corrected with a change to the ventilator settings and not a change in the alprostadil dose. Similarly, changes in vital sign status in critically ill infants were often unrelated to the alprostadil dose. Although resuscitation events and death are inherently more common in infants with DDCHD, using the absence of these events as markers for effectiveness is a salient outcome that a clinician would consider when deciding if alprostadil is efficacious.

The PDA diameter was not included in our effectiveness outcome because infants infrequently received more than 1 echocardiogram, and many doses were changed without information about the PDA diameter. However, because of the frequent reporting of DA diameter throughout older literature, it was examined as a secondary outcome in this study. Although only 32% of patients had a reported DA diameter before and during alprostadil therapy, none of these patients experienced a narrowing of the DA, regardless of whether they received a low or very low initial alprostadil dose.

Absence of resuscitation events and survival were not statistically different between the very low-dose and the low-dose alprostadil group. To date, there is no published literature characterizing the number of resuscitation events following alprostadil therapy. Mortality has been described in 2 previous studies, with 1 reporting a mortality rate of 7.4% with a mean intravenous alprostadil dose of 0.005 mcg/kg/min.<sup>12</sup> Similarly to our

**Figure 2.** Percentage with an adverse drug event (ADE).

\* Five cases of hypokalemia with concomitant furosemide (3 in the low-dose group, 2 in the very low-dose group).

† Three cases where fever subsided after mattress warmer turned off (2 in the low-dose group, 1 in the very-low dose group).

study, deaths were largely due to complications unrelated to alprostadil therapy, such as congestive heart failure, cardiac tamponade, intravascular coagulopathy, or non-operable cardiac lesions.<sup>12</sup> A higher mortality rate of 31% was described in 1 study conducted in the early 1980s; however, no dosing regimen was reported. This higher mortality rate may be explained by a longer time between birth and alprostadil initiation (59% of infants starting therapy within 48 hours), higher rates of apnea, and dated medical management practices for critically ill infants.<sup>22</sup> Our study had a shorter time to initiation of alprostadil from birth (5.2 hours) than reported elsewhere in the literature (2 days to 9 weeks).<sup>10,14,17,21,26</sup>

Overall, ADEs were common (51%) with no difference in rates between the very low dose and low dose alprostadil groups. This is consistent with the literature reporting similar rates of overall adverse events. Types of adverse events observed were also consistent with that in the literature including apnea, pyrexia and hypokalemia being very common.<sup>10,12–16,18,21,26</sup> While some adverse events such as tachypnea, tachycardia and edema appear to be more frequent in the very low dose group, this distribution is likely a chance finding due to the small number of each event observed within our sample. Apnea and pyrexia were observed more frequently in the low dose group compared to the very low dose group. While some studies have shown no correlation between dose and adverse events, other studies have found a dose relationship between apnea and pyrexia with dose reductions correlating with a resolution of the ADE.<sup>16,18,21</sup> Unlike some other published reports, no seizures were reported in our study.<sup>16,21</sup>

Most adverse events (79%) included had a possible association with alprostadil therapy. Because

alprostadil is a lifesaving infusion and as a result several of the answers to the questionnaire would default to 0, the Naranjo scoring tool was unlikely to be able to detect adverse events that were probably or definitely associated with alprostadil therapy. A conservative score of 3 was chosen to be able to report more adverse events as being associated with alprostadil therapy. The remainder of adverse events (21%) scored higher as a relationship between the alprostadil dose and the adverse event was observed. This occurred when either the infusion rate was decreased and the adverse event resolved or the adverse event was seen only when the infusion rate was increased.

Limitations of our study include a smaller overall proportion of infants who received very low-dose alprostadil therapy from our sample. Given the study's retrospective nature, it is unclear if prescriber preference or clinical reasons accounted for this, given the similar baseline characteristics between the groups. Given our power calculation was based on a single cohort and the number of patients treated with very low-dose alprostadil after excluding palliative patients, our study was not powered to detect differences between the groups. Our analysis of DA diameter was limited because of the underreporting of echocardiogram results. We may have overreported the incidence of adverse events as well, given our conservative threshold of a Naranjo score of 3.

## Conclusions

Low initial alprostadil dosages effectively maintained ductal patency in infants with DDCHD. Adverse drug events were common, and apnea and pyrexia occurred

more frequently as doses increased (e.g., in the low-dose group compared with the very low-dose group). Very low-dose alprostadil infusion may be considered in infants with DDCHD to maintain the PDA and to potentially minimize the risk of some ADEs, such as apnea and pyrexia.

## Article Information

**Affiliations.** Pharmacy Department (JTT, RRC), BC Women's and Children's Hospital, Vancouver, BC, Canada; Lower Mainland Pharmacy Services (CMG), Vancouver General Hospital, Vancouver, BC, Canada.

**Correspondence.** Roxane R. Carr, ACPR, PharmD, BCPS, FCSHP; rcarr2@cw.bc.ca

**Disclosure.** The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria. The authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

**Ethical Approval and Informed Consent.** This study was approved by the BC Women's and Children's Research Ethics Board (study ID: H20-03022) with a waiver of parental or patient consent.

**Acknowledgments.** We thank Dr. Michael Castaldo and Dr. Joseph Ting for their expertise, advise, and contributions to this study.

**Submitted.** January 10, 2023

**Accepted.** April 18, 2023

**Copyright.** Pediatric Pharmacy Association. All rights reserved. For permissions, email: membership@pediatricpharmacy.org

**Supplemental Material.** DOI: 10.5863/1551-6776-29.1.37.S1

## References

- McCance KL, Huether SE. *Pathophysiology: The Biologic Basis for Disease in Adults and Children*. Elsevier Health Sciences; 2014.
- Lopes SA, Guimarães IC, Costa SF, et al. Mortality for critical congenital heart diseases and associated risk factors in newborns: a cohort study. *Arq Bras Cardiol*. 2018;111(5):666–673.
- Oster ME, Lee KA, Honein MA, et al. Temporal trends in survival among infants with critical congenital heart defects. *Pediatrics*. 2013;131(5):e1502–e1508.
- Samanek M, Slavik Z, Zborilova B, et al. Prevalence, treatment, and outcome of heart disease in live-born children: a prospective analysis of 91,823 live-born children. *Pediatr Cardiol*. 1989;10(4):205–211.
- Prostin VR Sterile Solution [package insert]. Quebec, Canada: Pfizer Canada; 2020.
- Heymann MA, Rudolph AM. Ductus arteriosus dilatation by prostaglandin E1 in infants with pulmonary atresia. *Pediatrics*. 1977;59(3):325–329.
- Graham Jr TP, Atwood GF, Boucek Jr RJ. Pharmacologic dilatation of the ductus arteriosus with prostaglandin E1 in infants with congenital heart disease. *South Med J*. 1978;71(10):1238–1241.
- Heymann MA, Berman Jr WI, Rudolph AM, Whitman VI. Dilatation of the ductus arteriosus by prostaglandin E1 in aortic arch abnormalities. *Circulation*. 1979;59(1):169–173.
- Brodie M, Chaudhari M, Hasan A. Prostaglandin therapy for ductal patency: how long is too long? *Acta Paediatr*. 2008;97(9):1303–1304.
- Cucerea M, Simon M, Moldovan E, et al. Congenital heart disease requiring maintenance of ductus arteriosus in critically ill newborns admitted at a tertiary neonatal intensive care unit. *Crit Care Med*. 2016;24(4):185–191.
- Shivananda S, Kirsh J, Whyte HE, et al. Accuracy of clinical diagnosis and decision to commence intravenous prostaglandin E1 in neonates presenting with hypoxemia in a transport setting. *J Crit Care*. 2010;25(1):174–e1.
- Silove ED, Roberts DG, De Giovanni JV. Evaluation of oral and low dose intravenous prostaglandin E2 in management of ductus dependent congenital heart disease. *Arch Dis Child*. 1985;60(11):1025–1030.
- Singh GK, Fong LV, Salmon AP, Keeton BR. Chrome congestive heart failure: study of low dosage prostaglandin-usages and complications. *Eur Heart J*. 1994;15(3):377–381.
- Abidin AZ, Khalid F, MSaid R. Evaluation of infusion prostaglandin (PGE2) versus infusion prostaglandin e1 (PGE1) in management of duct-dependent pulmonary circulation congenital heart disease. *Pediatr Crit Care Med*. 2014;15(4 suppl):131.
- Kramer HH, Sommer M, Rammos S, Krogmann O. Evaluation of low dose prostaglandin E1 treatment for ductus dependent congenital heart disease. *Eur J Pediatr*. 1995;154(9):700–707.
- Carmo KA, Barr P, West M, et al. 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(2):F117–F119.
- Yucel IK, Cevik A, Bulut MO, et al. Efficacy of very low-dose prostaglandin E1 in duct-dependent congenital heart disease. *Cardiol Young*. 2015;25(1):56.
- Buck M, Lim S, Attridge J. Effectiveness of alprostadil dose titration in neonates with congenital heart disease. *Pharmacotherapy*. 2012;32(10):e227.
- Huang FK, Lin CC, Huang TC, et al. Reappraisal of the prostaglandin E1 dose for early newborns with patent ductus arteriosus-dependent pulmonary circulation. *Pediatr Neonatol*. 2013;54(2):102–106.
- Badheka A, Prakash PB, Allareddy V. Prostaglandin E1-induced periostitis and reversibility with discontinuation. *J Pediatr*. 2017;189:237.
- Lewis AB, Freed MD, Heymann MA, et al. Side effects of therapy with prostaglandin E1 in infants with critical congenital heart disease. *Circulation*. 1981;64(5):893–898.
- Alprostadil. In: Esau R, ed. *BC Children's Hospital Pediatric Drug Dosage Guidelines*. 7th ed. Vancouver, Canada: Children's and Women's Health Centre Department of Pharmacy. 2019:14. <http://www.pedmed.org/DrugApp/index.html>

23. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *J Clin Pharm Ther.* 1981;30(2):239–245.
24. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support. *J Biomed Inform.* 2009;42(2): 377–381.
25. Epitools. Sample size to estimate a proportion or apparent prevalence with specified precision. 2020. Accessed September 4, 2020. <https://epitools.ausvet.com.au/oneproportion>
26. Lewis AB, Takahashi M, Lurie PR. Administration of prostaglandin E1 in neonates with critical congenital cardiac defects. *J Pediatr.* 1978;93(3):481–485.