Hydroxyurea for Treatment of Polycythemia Secondary to Right-to-Left Shunting Patent Ductus Arteriosus in 4 Dogs

Kenneth W. Moore and Rebecca L. Stepien

Four adult dogs with polycythemia secondary to reversed patent ductus arteriosus (rPDA) were treated with hydroxyurea, a myelosuppressive agent, for 6–22 months. Regardless of initial hematocrit, clinical signs attributed to the presence of polycythemia improved with hydroxyurea treatment. Chronic hydroxyurea therapy (40–50 mg/kg PO q48h) was well tolerated in this group of animals; mild, clinically silent thrombocytopenia and leukopenia were detected in some animals but resolved with decreased dosage or dose frequency. Chronic hydroxyurea therapy may provide an alternative to repeated phlebotomy for therapy of polycythemia secondary to rPDA.

Key words: Case series; Chemotherapy; Cyanosis; Phlebotomy; Right-to-left shunt.

The right-to-left (“reversed”) form of patent ductus arteriosus (rPDA) is much less common than the left-to-right shunting form in dogs. Clinical signs associated with rPDA include hindlimb weakness, collapse, differential cyanosis and seizures, and are related to reduced oxygen delivery to tissues. Repeated phlebotomy has been used as a palliative measure to lessen the degree of polycythemia in affected dogs and thereby control clinical signs; however, this procedure may not be well tolerated by the patient. Hydroxyurea is a myelosuppressive agent that has been used to treat polycythemia due to noncardiovascular disease in dogs. This report documents successful use of chronic hydroxyurea therapy to alleviate clinical signs related to secondary polycythemia in 4 consecutive cases of canine rPDA.

Dog 1

A 9-month-old, 4-kg, spayed female Miniature Poodle was evaluated at the University of Wisconsin Veterinary Medical Teaching Hospital (UW-VMTH) for a possible portosystemic shunt. During diagnostic evaluation the dog was noted to have differential cyanosis and a rPDA was confirmed with contrast echoaortography. At the time of presentation, the dog’s PCV was 58% (reference range 38–55%). A portosystemic shunt was confirmed and ligated successfully.

Two months after shunt ligation, the dog’s PCV was 76% with total protein concentration within the reference range. Phlebotomy was performed every 3 weeks for a total of 7 treatments. After a volume of blood calculated to decrease the PCV to 60% (~15 mL/kg) was removed, lactated Ringer’s solution was administered intravenously. The dog consistently exhibited transient (approximately 1 hour) severe hindlimb weakness immediately after phlebotomy and the dog was lethargic for up to a week after phlebotomy. At each 3-week examination, the dog’s PCV had increased from a value after phlebotomy of 60% to 77–79%.

After the 7th phlebotomy treatment, hydroxyurea therapy was initiated (50 mg/kg PO q48h). No further phlebotomies were performed. The owners reported a marked improvement in the dog’s activity level and exercise tolerance with commencement of the hydroxyurea therapy. Improvements in the dog’s energy level were most noticeable when the PCV was 65% or less. No adverse effects were identified by the owners. The dog’s PCV ranged between 68% and 75% during the first 2 months of hydroxyurea therapy. White blood cell counts remained within the reference range; however, mild thrombocytopenia (128,000–147,000/L, reference range 200,000–500,000/L) was detected during the first 2 months of therapy. The hydroxyurea dosage was decreased (40 mg/kg PO q48h) for the next 4 months; platelet counts remained mildly decreased, the PCV remained between 67% and 71%, and the total white cell count remained within the reference range. The dog never developed clinical signs of thrombocytopenia, and the platelet count never fell below 100,000/L. In order to decrease the dog’s PCV further, the hydroxyurea dosage was increased (45 mg/kg PO q48h). One, 3, 6, and 9 months after this dosage increase the dog’s PCV was 62, 57, 60, and 66%, respectively. At 9 months, the hydroxyurea dosage was increased (50 mg/kg PO q48h). One, 2, 3, 4, and 6 months later, the dog’s PCV was 70, 65, 67, 64, and 54%, respectively. The dose frequency was decreased (50 mg/kg PO q72h) to prevent a further decrease in PCV. White blood cell counts remained within the reference range at all times. Mild asymptomatic thrombocytopenia (100,000–200,000/L) occurred intermittently. The dog continues to receive hydroxyurea (50 mg/kg PO q72h) 22 months after initiation of hydroxyurea therapy. The dog has a PCV of 60%, has no clinical signs, and is normally active.

Dog 2

A 14-month-old, 23-kg, neutered male Labrador Retriever with a 3-month history of episodic hindlimb weakness and collapse during exercise was evaluated at the UW-VMTH. Physical examination, electrocardiography, and survey thoracic radiographic findings suggested rPDA, and the diagnosis was confirmed with contrast echoaortography. The dog’s PCV was 76% with total protein concentrations within the reference range. Phlebotomy was performed once (~20 mL/kg); 1 week after phlebotomy, no change had occurred in the dog’s PCV. Hydroxyurea therapy (50 mg/kg PO q48h) was initiated. The owners reported improvement in the dog’s clinical signs soon after commencement of the hydroxyurea therapy, with complete resolution of clinical signs after 3 months. Thinning of the dog’s hair coat over the lateral thorax and abdomen was noted 9 months after initiation of hydroxyurea therapy but resolved spontaneously. No other adverse effects were noted. The dog’s PCV gradually decreased from 71 to 58% over 4 months. When the dog’s PCV was 58%, the dosing frequency was decreased (50 mg/kg PO q72h). One month later, the dog’s PCV had increased to 65% and despite an increase in dose frequency (50 mg/kg PO q48h), the dog’s PCV was 70% 2 months later. It was discovered at that time that the dog’s prescribed dosage had been gradually...
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decreasing over time because of substantial increases in body weight (actual dosage as administered: 32 mg/kg PO q48h). When the dosage was increased to intended levels (50 mg/kg PO q48h), the dog’s PCV decreased from 70 to 64% within 1 month. Total white cell and platelet counts remained within the reference range at all times. The dog continues to receive hydroxyurea (50 mg/kg PO q48h) 12 months after initiation of hydroxyurea therapy (PCV = 57%) and is asymptomatic with normal activity but shows occasional rear limb collapse with extreme exertion.

Dog 3

A 6-year-old, 6.2-kg, neutered male Miniature Poodle was evaluated at the UW-VMTH. Physical examination, electrocardiography, and survey thoracic radiographic findings were consistent with rPDA. This diagnosis was confirmed with contrast echocardiography.

The dog’s PCV was 72% with normal total protein concentrations. Initially, phlebotomy was performed at monthly intervals (~17 mL/kg). Mild transient improvement in the dog’s clinical signs with concomitant decreases in the dog’s PCV were noted, but the PCV remained at 70–72% when measured each month before phlebotomy. Phlebotomy was discontinued after 8 months and hydroxyurea therapy (50 mg/kg PO q48h) was commenced (PCV = 73%). After 4 weeks of therapy, the dog’s PCV had decreased from 73 to 63% and dramatic improvement in the dog’s clinical signs (greater than was noted after phlebotomy) was reported by the owners. Thrombocytopenia (87,000/μL) and leukopenia (5,800/μL, reference range 6,000–17,000/μL) were detected at the 2- and 4-week rechecks. The hydroxyurea dosing frequency was decreased (50 mg/kg PO q72h). Three and 7 weeks later, the platelet and white cell counts had returned to the reference range and the PCV was 61 and 55%, respectively. The owner reported a complete resolution of the dog’s clinical signs. However, at this time the owner elected to discontinue the hydroxyurea because of 2 episodes of vomiting after dosing. The owner also noted increased pigmentation in the nonhaired portions of the ears and on the pads. One month later, the dog’s PCV had increased from 55 to 63%. Hydroxyurea therapy was re instituted at a lower dosing frequency (50 mg/kg PO once weekly). No episodes of vomiting occurred at this dosage but the PCV increased from 63 to 67% after 1 month. The dosing frequency was increased (50 mg/kg PO every 5 days); however, no change in the PCV was observed after 2 months. Once the dosing frequency was increased to 3 times per week dosing (50 mg/kg PO) the dog’s PCV decreased from 66 to 58% within 1 month. White blood cell and platelet counts remained within the reference ranges. The dog continues to receive hydroxyurea (50 mg/kg PO q48h) 10 months after commencing therapy, and shows no clinical signs.

Dog 4

A 6-year-old, 6.2-kg, neutered male Miniature Poodle was evaluated at the UW-VMTH for a 2-year history of exercise intolerance and exercise-induced weakness and disorientation, and a 2-month history of seizures. Differential cyanosis was identified on physical examination. A diagnosis of rPDA was confirmed by contrast echocardiography. Hyperviscosity was the suspected cause of the seizures (PCV = 84% at presentation).

Partial phlebotomy was performed once (~6 mL/kg); no change in the dog’s PCV was detected 24 and 72 hours after phlebotomy. Hydroxyurea therapy (50 mg/kg PO q48h) was initiated. The owners reported marked improvement in the dog’s clinical signs within 2 weeks of initiation of hydroxyurea therapy, at which time the dog’s PCV was 78%. No further seizures or syncopal episodes were observed but low exercise tolerance was still reported. The dog’s PCV declined progressively to 72% over 6 weeks and has remained relatively stable for the subsequent 5 months. Total white cell counts remained within the reference range. Platelet counts were frequently not possible because of platelet clumping but estimated counts from blood smears suggested thrombocytopenia. When a platelet count was possible (4 months after initiation of therapy) the count was 81,000/μL. Some transient hair thinning and skin pigment change on the dog’s flanks were noted by the owners but resolved spontaneously; no other adverse effects were noted. The dog continues to receive hydroxyurea (50 mg/kg PO q48h) 6 months after initiation of therapy, and is asymptomatic with a PCV of 67%.

Discussion

Functional closure of the ductus arteriosus occurs within hours after parturition when the sudden increased oxygen tension in the systemic vasculature leads to smooth muscle contraction within the vessel wall.1,3 Anatomical closure rapidly follows because of degeneration of the ductal smooth muscle, leaving only the elastic ligamentum arteriosum.3 When the ductus arteriosus fails to close at birth, the structure is termed a patent ductus arteriosus (PDA). In some animals, increased pulmonary blood flow and associated pulmonary hypertension lead to medial hypertrophy and intimal proliferation of the pulmonary vasculature. These changes may result in narrowing of the small and mid-sized pulmonary arteries and decreased vascular compliance. Other factors (eg, reduced number of intra-acinar arteries, decreased partial pressure of oxygen, and altitude) may contribute to pulmonary hypertension by increasing pulmonary vascular resistance.3,8–12 When pulmonary vascular resistance exceeds systemic vascular resistance, right-to-left shunting across the PDA occurs, carrying deoxygenated blood from the venous system into the descending aorta.3 Reversed patent ductus arteriosus is thought to occur in 1–6% of dogs with PDA.3,13

Ligation of the rPDA is contraindicated.10 Recommended therapy of clinical signs associated with rPDA is palliative with treatment aimed at reducing the polycythemia to reduce blood viscosity and improve tissue perfusion, especially of the heart and brain.5 At a PCV of 70%, viscosity is 2.5 times normal and results in obstruction of blood flow through small blood vessels.14 The therapeutic goal in treatment of polycythemia secondary to rPDA differs from that of primary polycythemia (polycythemia vera). In animals with polycythemia vera, therapy is undertaken to reduce the animal’s PCV to normal to high-normal ‘‘target’’ PCV values (50–55% for dogs). However, when polycythemia is secondary to right-to-left cardiac shunts, decreases in PCV may relieve clinical signs associated with polycythemia but the concomitant decrease in oxygen content of blood may result in clinical signs of decreased oxygen delivery to tissues.14 Some veterinary sources have suggested target PCV values of 58–65% for animals with cyanotic heart disease.15 In humans, 1 suggested clinical target is relief of clinical signs rather than a concrete range of PCV values.15 The results of therapy in these 4 dogs support the suggestion that therapy targeted at relief of clinical signs (eg, hindlimb collapse and seizures) without induction of hypoxia-related fatigue may be a reasonable clinical goal. In the dogs described here, clinical signs improved markedly with a 10–12% decrease in PCV, even if the PCV was initially as high as 84% (dog 4). Because marked variability exists in the PCV at which dogs with rPDA exhibit clinical signs, an
optimal PCV should be established for each patient based on close monitoring of the patient’s clinical signs. Reduction of degree of polycythemia can be achieved by phlebotomy, myelosuppressive drug therapy, or both.1,3–5

The tradition therapy for reduction of PCV in polycythemic animals has involved periodic phlebotomy. Textbook sources17,18 have recommended removal of 10–20 mL/kg of blood per phlebotomy with or without concurrent replacement with crystalloid fluids (1–2 times the amount of blood removed), with some sources suggesting serial phlebotomies rather than 1 single withdrawal.3,17 The amount of blood to be removed to achieve a desired PCV can also be calculated.5 In a report of a single case of canine rPDA with polycythemia and seizures, the dog experienced a gradual decrease in PCV when serially phlebotomized (~2.6–10 mL/kg at 2- to 3-day intervals) over a 21-day period before diagnosis of the cardiac abnormality.11

In a case series reported by Côté et al.,4 long-term control of clinical signs associated with secondary polycythemia was achieved in 4 dogs by periodic phlebotomy. Adverse effects were seen in some but not all patients. Although a PCV around 70% is associated with a marked increase in blood viscosity,14 clinical signs in the 4 patients reported by Côté et al seemed to have been relieved with a mean PCV of 69%.5 Risks of frequent phlebotomy include iron deficiency; introduction of air, thrombi, or bacteria to vital organs; and detrimental hemodynamic or oxygenation effects associated with acute blood volume reduction.5,19 Even with fluid replacement, 1 dog in our study repeatedly exhibited profound hindlimb weakness for approximately 1 hour after phlebotomy.

Hydroxyurea is an antineoplastic agent that causes reversible bone marrow suppression by inhibiting DNA synthesis, and has been recommended for treatment of polycythemia and other blood dyscrasias in dogs, cats, and humans.5,6,20–24 Potential advantages of hydroxyurea over phlebotomy in polycythemic dogs with rPDA include avoidance of clinical adverse effects of phlebotomy, such as weakness, and decreased risk of thrombosis. In addition, use of hydroxyurea to control PCV avoids the development of iron deficiency, which, when accompanied by hypochromia and microcytosis, may increase blood viscosity.15 Adverse effects of hydroxyurea in dogs are reported to include anorexia, vomiting, bone marrow hypoplasia, sloughing of toe nails, alopecia, and spermatogenic arrest.5,6 Most clinical reports cite cytopenias as the most frequent cause of dosage change or discontinuation of this drug when used to treat myeloproliferative disorders in dogs and cats.10,22,23 In 1 report, reversible alopecia was reported as an adverse effect of chronic hydroxyurea therapy in a dog with chronic granulocytic leukemia at a dosage rate similar to that used in the present study (50 mg/kg administered 2 days out of 3).23 Two of the dogs in this series had mild alopecia noted; the hair regrew without adjustments to medication. In humans, pigmented changes in skin and nails are reported as an adverse effect of chronic hydroxyurea therapy; darkening of some areas of the skin was noted in 2 of the dogs in this series. Although sloughing of the toenail or claw has been mentioned as an adverse effect in textbooks,27 no clinical reports of this effect could be located.

The most effective dose regimen for chronic control of polycythemia in dogs is unknown. Multiple hydroxyurea dosage regimens have been suggested in the veterinary literature, but occur either as case reports of chemotherapy of polycythemia vera,6,22 or other myeloproliferative diseases,5,26,29 or as general recommendations regarding chemotherapy of myeloproliferative disease.18,22 No primary reports of hydroxyurea treatment regimens for polycythemia secondary to cyanotic heart disease could be located. An un referenced dosage recommended for use for treatment of polycythemia secondary to rPDA in dogs was 30 mg/kg/d for 7–10 days followed by 15 mg/kg/d.13 Similarly, regimens for the therapy of primary myeloproliferative diseases usually consist of a higher loading dosage followed by a lower maintenance dosage (eg, 25 mg/kg PO q12h until desired blood values are achieved, then 25 mg/kg q48h).27 Higher dosages given twice daily (50 mg/kg PO q12h) have been associated with acute cytopenias that respond to discontinuation of the drug.25 Intermittent dosing with hydroxyurea (eg, 80 mg/kg q72h) has been proposed as a useful regimen for treatment of solid tumors in humans and may be associated with reduction in toxicity.30 Although clinical information regarding the pharmacology of hydroxyurea in polycythemic dogs was not available, every-other-day dosing regimens have proved effective in management of myeloproliferative diseases in dogs.23,27 We empirically chose to use an every-other-day regimen (50 mg/kg PO q48h)4 in an attempt to induce gradual reduction of PCV while minimizing the occurrence of adverse effects. Efficacy of the daily dosage regimens in treatment of polycythemia secondary to rPDA above was not investigated.

Adverse effects of hydroxyurea in the 4 dogs in this series consisted of apparent mild thrombocytopenia (3 dogs), neutropenia (2 dogs), transient hair loss (2 dogs), and mild skin pigment changes (2 dogs). Abnormal blood count findings were not associated with clinical signs and responded variably to decreased hydroxyurea doses. Platelet clumping associated with polycythemia limited accurate platelet counts on many occasions; the true prevalence and severity of thrombocytopenia in these dogs remains unknown. In all dogs, no clinical evidence of severe thrombocytopenia was observed. The relationship between the medication and the 2 episodes of vomiting observed in 1 dog (dog 3) is unclear. Although the vomiting ceased when the dosing interval was increased, the dog had received the drug for 8 weeks before the vomiting episodes with no occurrence of gastrointestinal upset reported. The long-term effects of chronic hydroxyurea in dogs with rPDA are unknown.

This case series has limitations typical of retrospective clinical reports: limited patient numbers, patient variability, and reliance on owners for clinical evaluations and consistent drug administration. No control group of unmedicated dogs was used in this study, but all dogs had previous histories of persistent elevations in PCV before initiation of therapy and 1 dog (dog 3) exhibited a marked and rapid rise in PCV with discontinuation of hydroxyurea therapy. Manipulation of dosing regimens (changes in dosing frequency versus changes in the dose itself) were uncontrolled and based on clinician preference. Although both methods seemed to effect the desired directional changes in blood values, no clear indication of which method of dose manipulation is preferable was found based on this small num-
number of dogs. As seen in dogs in this study, PCV values can fluctuate markedly despite a constant hydroxyurea dosage, but PCV values seem to respond predictably to changes in dosage or frequency. Therefore, changes in dosage (dose, frequency, or both) should be based on PCV trends over time, clinical signs, adverse effects, and detection of marked myelosuppression (thrombocytopenia, leukopenia, or both). In this study, dogs generally had PCV evaluations monthly, but evaluation frequency varied based on owner compliance. Frequent monitoring of cell counts by CBC during hydroxyurea therapy allows detection of iatrogenic leukopenia, thrombocytopenia, or anemia before the appearance of clinical signs.

This clinical case series documents successful treatment of clinical signs associated with rPDA with hydroxyurea treatment alone in 4 consecutive cases. All dogs experienced complete resolution or marked improvement of their clinical signs coincident with reductions in PCV. All owners expressed a strong preference for hydroxyurea therapy versus phlebotomy based on inability of phlebotomy to provide sustained relief of clinical signs and because of the negative physical effects of phlebotomy in some patients. Some owners also expressed a preference for frequent “short” blood sampling (PCV evaluation) to what they perceived as a more complicated and time-consuming procedure (phlebotomy). The results of this case series suggest that hydroxyurea is an effective treatment option to control clinical signs associated with polycythemia in dogs with rPDA and may provide an alternative to frequent phlebotomy. Loading doses of hydroxyurea were not required in these dogs and adverse effects were mild and responsive to changes in dosage. Controlled clinical trials are needed to determine the most effective and safe dosage regimen in dogs with polycythemia secondary to rPDA.

**Footnote**

*Hydroxyurea, Hydrea, Bristol Laboratories, Princeton, NJ*

**References**


