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Hydroxyurea in Pediatric Patients With Sickle Cell Disease: What Nurses Need to Know CE

Allison L. Rees, MSN, RN[1]

Abstract

Sickle cell disease (SCD) is an inherited disorder in which sickled red blood cells occlude the small vessels of the body, reducing oxygen delivery to tissues and ultimately negatively affecting many of the body's major organs. Hydroxyurea has proven beneficial in the treatment of SCD and prevention of disease-related complications. The 2014 guidelines put forth by the National Heart, Lung, and Blood Institute recommend hydroxyurea treatment in infants 9 months and older, children, and adolescents with SCD-SS or SCD-Sβ^0 thalassemia regardless of clinical severity. This is a change from the 2002 guidelines in which hydroxyurea was recommended for adolescents and children with SCD-SS or SCD-Sβ^0 thalassemia with frequent episodes of pain, a history of acute chest syndrome, severe and symptomatic anemia or other severe vaso-occlusive events. Nurses play a critical role in working with patients and families to provide education, guidance, and support to improve compliance to mitigate the long-term effects of SCD.

Keywords

hydroxyurea, sickle cell disease, compliance

Background

There are 70,000 to 100,000 Americans with sickle cell disease (SCD), the majority of affected individuals are of African descent (National Heart, Lung and Blood Institute [NHLBI], 2014). Affected children in the United States now survive into adulthood because of increased knowledge about SCD and advances in disease therapy, although the average lifespan remains 20 to 30 years less than those individuals without SCD (NHLBI, 2014). SCD continues to be associated with significant morbidity and mortality (Brandow, Jirovec, & Panepinto, 2010). The only known cure for SCD is hematopoietic stem cell transplantation, and this is rarely used because of cost, availability, and potentially life-threatening complications (Al-Anazi, 2015). Therefore, disease-modifying therapy through pharmacologic agents or chronic blood transfusions remains the primary treatment. Hydroxyurea, a pharmacologic agent, has been used for more than 20 years in adults with SCD to decrease complications associated with SCD (Hankins et al., 2014).

The 2014 guidelines issued by the National Heart, Lung and Blood Institute recommend expanded use of hydroxyurea among patients with SCD. As shown in Table 1, hydroxyurea is now indicated in treatment of infants as young as 9 months, children and adolescents with SCD-SS (homozygous SS) or SCD-Sβ^0 thalassemia regardless of clinical severity (NHLBI, 2014). Hydroxyurea was previously recommended for adults, adolescents, and children with SCD-SS or SCD-Sβ^0 thalassemia with frequent pain, history of acute chest syndrome, or symptomatic, severe anemia (NHLBI, 2002). The 2002 guidelines were problematic because they were open to interpretation regarding the frequency of pain episodes and, therefore, open to provider interpretation and inconsistent use of hydroxyurea (Brandow et al., 2010). The updated guidelines aim to reduce SCD-related complications. Education about the potential benefits of hydroxyurea should be provided to all patients and families with SCD (NHLBI, 2014). Hydroxyurea is an important drug in the treatment of SCD, and nurses play a critical role in working with patients and families to provide this education, guidance, and support to improve compliance that may mitigate the long-term effects of SCDs and damage to organ systems (Table 2).

[1]University of Pennsylvania School of Nursing, Philadelphia, PA, USA

Corresponding Author:
Allison L. Rees, 813 South 2nd Street, Philadelphia, PA 19147, USA.
Email: alrees86@gmail.com

Table 1. National Heart, Lung and Blood Institute Guidelines of 2002 and 2014.

	2002 Guidelines[a]	2014 Guidelines[b]
Treatment indication	▪ Adults, adolescents, or children with SCD-SS or SCD-Sβ^0 thalassemia and frequent episodes of pain, history of acute chest syndrome, other severe vaso-occlusive events or severe anemia that is symptomatic	▪ Infants 9 months and older, children and adolescents with SCD-SS or SCD-Sβ^0 regardless of clinical severity to reduce SCD-related complications
Starting dose	▪ 10-15 mg/kg/d (does not differentiate between children and adults)	▪ Infants and children: 20 mg/kg/d
Dose escalation	▪ Increase dose every 6-8 weeks if patient does not have major toxicity ▪ Monitor complete blood count (CBC) every 2 weeks while increasing dose	▪ Increase dose incrementally by 5 mg/kg/d every 8 weeks (maximum dose of 35 mg/kg/d) ▪ Monitor CBC every 4 weeks while increasing dose
Laboratory parameters	▪ Granulocytes ≥2500/μL ▪ Platelets ≥95 000/μL	▪ Goal neutrophil count ≥2500/μL; younger patients with lower baseline counts may tolerate neutrophil counts down to 1250/μL ▪ Platelets ≥80 000
Laboratory monitoring on the stable patient	▪ Monitor CBC every 4-8 weeks	▪ Monitor CBC with white blood cell differential and reticulocyte count every 2-3 months

[a] National Institutes of Health, National Heart, Lung and Blood Institute (2002).
[b] National Institutes of Health, National Heart, Lung and Blood Institute (2014).

Pathophysiology of SCD

Sickle cell disease is an inherited disorder transmitted in an autosomal recessive pattern that results from a mutation in the beta globin chain of hemoglobin (Hgb). The mutation is caused by one amino acid, valine, being replaced by glutamic acid, which results in Hgb S (NHLBI, 2014). When homozygous for the sickle cell mutation, Hgb SS disease results (McCavit, 2012). A beta thalassemia mutation may be inherited along with the sickle cell mutation resulting in Sβ^0 thalassemia in which no beta globin is produced, or Sβ^+ thalassemia where a decreased amount of beta globin is produced (McCavit, 2012). Hgb SS and Hgb Sβ^0 thalassemia are clinically similar and the most severe manifestations of SCD (NHLBI, 2014). The discussion in this article will be limited to these 2 genotypes.

Under deoxygenation, polymerization of Hgb S causes a change in the shape of a red blood cell, which results in the characteristic sickled shape of red blood cells seen in SCD (McCavit, 2012). Sickled red blood cells are stiff and unable to change shape causing occlusion of the microvasculature and ultimately decreased oxygen delivery to tissues (McCavit, 2012). The complexity of SCD is partially because of the ability of the disease to affect multiple organs. Organ damage occurs because of the sickling of red blood cells and chronic hemolysis and increases throughout an individual's life (Ware, 2010). Chronic hemolysis of erythrocytes results in a decreased lifespan, 10-20 days compared with the normal 120-day survival of an erythrocyte, ultimately causing anemia (McCavit, 2012). Among other SCD-related complications, splenic sequestration is common. Splenic sequestration occurs because of hemolysis of erythrocytes in the spleen that results in pooling of blood and infarction of splenic vessels (Kline, 2010). Both acute and chronic disease–related complications can occur. Acute clinical manifestations of SCD include thrombosis or hemorrhage in the brain, lung infarction, splenic sequestration, gallstones, swelling of hands and feet, and hematuria. Chronic complications include retinopathy, pulmonary hypertension, congestive heart failure, atrophy of the spleen, skin ulcers, and glomerular disease (McCance & Huether, 2010).

Pain is the leading cause of emergency department visits and hospitalizations in patients with SCD (Ballas, Gupta, & Adams-Graves, 2012). Dactylitis, experienced in infants as young as 6 months, may be the first pain crisis for an individual with SCD (NHLBI, 2014). Vaso-occlusive crises occur as the acute onset of severe pain generally arising from the bone or bone marrow. Diagnosis of a vaso-occlusive crisis in a patient with SCD is often a diagnosis of exclusion when other causes of pain are ruled out as there is no definitive test. Occlusion of the microvasculature caused by sickled cells leads to hypoxia, ischemia, and ultimately tissue damage (Ballas et al., 2012). Inflammation occurs during the acute sickle cell pain crisis as inflammatory mediators are released from damaged cells. Over time, the cumulative effect of inflammation can cause organ damage; therefore, early intervention to treat a pain crisis is optimal (Ballas et al., 2012). In addition to the physical challenges of dealing

Table 2. Myth versus Fact-Hydroxyurea Treatment in Sickle Cell Disease.

	Myth	Fact	Key Teaching Points
Age to start hydroxyurea	▪ Hydroxyurea is only for adults with SCD	▪ Hydroxyurea is indicated in treatment of infants as young as 9 months, children and adolescents	▪ Recommendation for hydroxyurea use in infants 9 months and older, children, and adolescents is for all patients with SCD-SS or SCD-Sβ^0 regardless of severity of disease.
Side effects	▪ Hydroxyurea started as chemotherapy drug, won't it cause cancer? ▪ I don't want hydroxyurea to affect my growth and development.	▪ Available evidence does not demonstrate an increased risk of leukemia with the use of hydroxyurea. ▪ Studies have demonstrated similar growth and development in individuals taking hydroxyurea since infancy compared with the general population.	▪ Listen to the concerns of the individual and family and provide factual information regarding available research. ▪ Validate concerns expressed by the individual or family that growth and development are extremely important, and they will continue to be monitored while taking hydroxyurea.
Treatment efficacy	▪ I took hydroxyurea for a couple of weeks and didn't notice a difference and my labs didn't change, so I stopped taking it.	▪ Although the effects of hydroxyurea may be noted within the first few weeks, it can take 4-6 months for hydroxyurea to reach maximal effect.	▪ Hydroxyurea compliance is important to assess the effect that hydroxyurea has on an individual patient with SCD. ▪ Hydroxyurea should be continued for a full 6 months to evaluate effect, along with appropriate laboratory monitoring.
Feasibility	▪ I'm never going to be able to get my child to swallow a pill!	▪ Hydroxyurea is available both as a capsule and as a liquid formulation and is administered once daily.	▪ Discuss the availability of different formulations and ways to make the medication more palatable.
Monitoring	▪ Labs have to be checked way too often.	▪ A complete blood count (CBC) is monitored every 4 weeks while the dose is being increased. ▪ Once an individual is stable on a specified dose, labs are only required every 2-3 months.	▪ Labs are checked more frequently initially to monitor the effect of hydroxyurea, however, once stable, these labs are less frequent. ▪ Potential benefits of hydroxyurea include less acute sickle cell–related problems including pain crises and hospitalizations.

with pain, psychological well-being is often affected as well.

Hydroxyurea

Hydroxyurea was originally developed and used as a chemotherapeutic agent in the 1980s. It was found to cause an increase in fetal hemoglobin, Hgb F, which inhibits the polymerization of Hgb S; therefore, hydroxyurea was trialed in adults with SCD (McCavit, 2012). The trials demonstrated benefits of hydroxyurea in adults with SCD, ultimately leading to Food and Drug Administration (FDA) approval for use in this population in 1998 (Strouse & Heeney, 2012). After proving beneficial in adults, hydroxyurea was tested in children and adolescents and showed similar effects. Despite the increased use of hydroxyurea in the pediatric population, FDA approval remains limited to use in adults. In addition to increased Hgb F and subsequent reduction in Hgb S, hydroxyurea also reduces white blood cell count, platelet count, and reticulocyte count and causes an increase in mean corpuscular volume (Ware, 2010). This is important as high white blood cell count has been associated with increased morbidity in SCD (Ware, 2010). Hydroxyurea is administered orally, once daily, and is available in both a capsule and liquid formulation, making it feasible for both adults and children (Ware, 2010).

Hydroxyurea was initially studied only in adults with SCD but after demonstrated efficacy trials in children and infants were conducted (Ware, 2010). Results from these studies have shown that the benefits of hydroxyurea are seen in children and adolescents as well. Effects of hydroxyurea may be noted within the first few weeks after initiation of therapy, although it may take 4-6 months to reach maximal effect (Strouse & Heeney, 2012). Higher concentrations of Hgb F are associated with a decrease in frequency of pain crises (Wang et al., 2011). In the BABY HUG trial, patients with SCD, aged 9 to 18 months treated with daily hydroxyurea for 2 years experienced significantly less acute sickle cell–related problems including pain events, episodes of acute chest syndrome, hospitalizations, and transfusions, when compared with those in the placebo group (Thornburg, Calatroni, & Panepinto, 2011). Increases in transcranial Doppler velocity, an indicator to evaluate the risk of stroke, was also assessed, and the average increase in transcranial Doppler velocity in those receiving hydroxyurea was significantly less than that of the placebo group (Wang et al., 2011).

Since hyrdoxyurea was initially developed for use as a chemotherapeutic agent, there were concerns about effects on the growth and development of infants and children. In the BABY HUG trial, hydroxyurea was not found to have an adverse effect on growth or neurological development (Wang et al., 2011). There have been concerns about long-term effect of hydroxyurea on the growth and sexual development of children. However, a 15-year follow-up study by Hankins et al. (2014) of 7 patients who have been on hydroxyurea since infancy, now 15 years out, found there were no differences in growth or sexual development when compared with the general population. Furthermore, sustained hematologic benefits were seen in this same small sample of patients taking hydroxyurea (Hankins et al., 2014). Additionally, there was concern that hydroxyurea would have a negative impact on the immune system's ability to mount a response to vaccinations. Lederman et al. (2014) found that children demonstrated no severe detrimental effects on the immune system, mounted an appropriate response to vaccinations, and should follow the recommended immunization schedule.

Side effects of hydroxyurea include mild to moderate neutropenia (Thornburg et al., 2012). The occurrence of severe neutropenia is rare and resolves with temporary discontinuation of hydroxyurea (Strouse & Heeney, 2012). Of note, those on hydroxyurea did not have an increased rate of infection or incidence of bacteremia compared with the placebo group (Thornburg et al., 2012). Hydroxyurea has not been found to cause hepatic or renal toxicity (Strouse & Heeney, 2012).

Sickle cell disease–related complications can have a considerable impact on an individual's life, physically, psychologically, and emotionally. A study by Thornburg et al. (2011) looked at the health-related quality of life in children with SCD receiving hydroxyurea compared with those not receiving hydroxyurea. Children treated with hydroxyurea reported better physical functioning as well as better quality of life compared with those not receiving hydroxyurea (Thornburg et al., 2011). Oyeku et al. (2013) surveyed parents of children on hydroxyurea, and more than two-thirds of parents reported a decrease in the number of pain crises, emergency department visits, hospitalizations, and missed school days since starting hydroxyurea.

Barriers

Despite proven benefits, multiple barriers to the use of hydroxyurea remain. The use of hydroxyurea varies greatly between institutions (Oyeku et al., 2013). Both patients and providers lack accurate information about the toxicities of hydroxyurea (Thornburg et al., 2012). Parental demographics including age, gender, race/ethnicity, level of education, and income were not found to be independent predictors of hydroxyurea use (Oyeku et al., 2013). Patient and parental concerns about safety and effectiveness remain barriers and decrease medication adherence (Walsh et al., 2014). Increased parental knowledge about hydroxyurea was associated with increased use among children (Oyeku et al., 2013). Specific concerns reported by parents that affect medication adherence among pediatric patients with SCD are that hydroxyurea would not work for their children, worry about potential adverse effects, and the lack of FDA approval for the use of hydroxyurea in children (Oyeku et al., 2013). Patients and families who refused hydroxyurea reported doing so for a variety of reasons including worry about the potential of hydroxyurea to cause cancer, increased medication burden, required laboratory monitoring, and lack of belief that hydroxyurea would be beneficial (Brandow et al., 2010). Oyeku et al. (2013) found that 89% of parents with children taking hydroxyurea had concern about the potential of hydroxyurea to cause cancer. Because of the widespread worry about the association of hydroxyurea with cancer, nurses should understand that current available evidence does not demonstrate an increased risk of leukemia with the use of hydroxyurea (Brandow et al., 2010).

Poor compliance is the biggest reason hydroxyurea therapy is ineffective in children (Strouse & Heeney, 2012). Provider concerns about patient compliance, ability to adhere to the required laboratory monitoring, and female contraception affect prescribing practices (Brandow et al., 2010). Forgetting to take medication and being too busy are among patient-reported reasons for poor compliance (Walsh et al., 2014). Medication compliance appears higher in self-reported versus objective measures;

therefore, the combination of report and objective monitoring is necessary to ascertain more accurate compliance (Walsh et al., 2014).

Nursing Implications

Nurses are pivotal in the care of pediatric patients with SCD. Knowledge of hydroxyurea indication, risks and benefits, and an understanding of appropriate nursing interventions must be addressed.

The trusting partnership formed between the nurse and a patient and family provides an opportunity for an open discussion about compliance and identification of individual barriers. Identifying the reason for poor compliance is important to address the obstacles. Access to care and concern about perceived side effects are among the barriers (Brandow et al., 2010). Compliance may be improved by the use of a pillbox, alarm reminders, or placement of medication by the child's toothbrush or something used on a daily basis. The utilization of school nurses to assist with medication compliance should also be considered (Ware, 2010). Estepp and colleagues (2014) found that text message reminders improved hydroxyurea compliance in children and adolescents. A study by Creary, Gladwin, Byrne, Hildesheim, and Krishnamurti (2014) demonstrated improved hydroxyurea compliance with electronic directly observed therapy. Participants received daily alert messages via email or text to remind them to take their medication and then participants submitted a video record documenting their administration of hydroxyurea (Creary et al., 2014). As the role of technology in society continues to grow, it is important to consider the use of electronic communication to improve hydroxyurea compliance. Nurses are integral in the assessment and monitoring of medication compliance and laboratory testing.

Education is crucial as the use of hydroxyurea is expanded in children and adolescents. Nurses are in the position to provide patients and families with accurate information about the risks and benefits of hydroxyurea, and engage in a discussion with families to address individual concerns. Lack of knowledge about the risks and benefits of hydroxyurea is associated with decreased use (Oyeku et al., 2013). In addition to discussions, parents of pediatric patients were receptive to handouts about the use of hydroxyurea as well as reliable Internet resources (Oyeku et al., 2013). Nurses frequently spend more time interacting with a patient and family than other members of the health care team, presenting an opportunity to not only educate but engage and empower patients to assume active roles in their care. An individual's laboratory results and trends in laboratory values should be reviewed to educate about the benefits of hydroxyurea on a personal level (Strouse & Heeney, 2012).

Conclusion

Sickle cell disease continues to affect a large number of individuals and remains associated with a high morbidity and mortality. The NHLBI guidelines recommend expanded use of hydroxyurea. Knowledge of these changes and the impact on patients and families allows nurses to provide timely and evidence-based care as well as necessary education to increase adherence. It is important for nurses to have a foundational knowledge of SCD, sickle cell–related complications, the use of hydroxyurea, and understand the recommendations of the most recent published guidelines.

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Author Biography

Allison L. Rees recently completed the the Acute Care Pediatric Nurse Practitioner Program at the University of Pennsylvania. Allison continues to work as a registered nurse in oncology and bone marrow transplant at the Children's Hospital of Philadelphia.

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