



Nursing Practice Guidelines: Care of the Patient with Sickle Cell Disease Receiving Hydroxyurea

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Introduction

The International Association of Sickle Cell Nurses and Physician Assistants has developed this guideline with the intention of promoting interaction among disciplines to ensure consistency of practice for patients with sickle cell disease experiencing pain. This nursing practice guideline applies to inpatient or outpatient management of acute or chronic pain. This nursing practice guideline is not intended to limit or dictate pain management practices.

Background

Hydroxyurea (HU) is an oral agent that has been used for nearly three decades to treat myeloproliferative disorders such as chronic myelogenous leukemia and polycythemia vera. In 1998, HU received FDA approval as a treatment for adults with sickle cell anemia who had a history of frequent pain crises (at least 3 in 12 months). HU therapy in patients under 18 years of age remains an off-label use of the drug, although most sickle cell centers are comfortable treating pediatric patients with severe disease.

The principal rationale for treatment with HU is its ability to induce fetal hemoglobin (Hb F) production. Hb F is known to interfere with the polymerization of Hb S and therefore inhibit the sickling of red blood cells. People with sickle cell disease that have high levels of Hb F are known to have a milder disease course and a longer lifespan (1). However, the induction of Hb F cannot explain all the clinical effects of HU. Other important effects include: myelosuppressive effects on neutrophils, increased hydration of red cells, and decreased adhesion of red cells to endothelium (2).

Research

Many papers have been published in the last 10 years that describe the HU experience. In 1995, a report was published which presented the results of a national clinical trial which tested the effect of HU on the frequency of sickle cell pain crises (3). The trial involved 299 adult sickle cell anemia patients randomized to receive HU or placebo. All patients had a history of at least three documented pain crises in the year before the trial. Patients assigned to treatment with HU had a decreased incidence of pain crises (2.5 versus 4.5 crises per year), acute chest syndrome (25 versus 51) and blood transfusions (48 versus 73). These results were so compelling that the trial was stopped ahead of schedule. The most common toxicity noted was neutropenia and/or thrombocytopenia, which was dose dependent and resolved quickly upon temporary discontinuation of HU. In addition, a long-term follow-up study of patients who originally participated in the clinical trial demonstrated that taking HU was associated with a 40% reduction in mortality (4).

Several trials have evaluated the use of HU in children, though none have had the rigor and size of the adult clinical trial. (5); (6); (7); (8); (9); (10); (11); (12). These trials have reported



decreases in both the frequency of sickle cell pain crises and the number of hospital admissions. Importantly, no unexpected toxic effects have been reported.

Treatment Regimen

HU is available as 200, 300, 400 and 500mg capsules. A syrup (100mg/ml) can be made for pediatric use, although this is provided by compounding pharmacies typically, which are not readily available in many parts of the country. HU is best given as a once a day dose. General practice is to start patients at a dose of 15-20 mg/kg/day. Complete blood counts (including reticulocytes and manual differential), Hb F level, renal and liver function tests should be performed prior to starting treatment. Causes of anemia, other than sickle cell disease per se, should be excluded, including deficiencies of iron, folic acid, and vitamin B12.

HU may be increased by 5mg/kg per day every 8 to 12 weeks until a maximum dosage of 30 to 35 mg/kg daily is reached or unless toxicity is observed. Toxicity is defined as an absolute neutrophil count below 1,500 /mm³, a platelet count below 80,000/mm³, Hb below 5g/dl, 50% increase in creatinine, or ALT greater than twice upper limit of normal. The nurse should be aware that lab values considered toxic may vary according to the institution's treatment protocol. If toxicity occurs, HU should be discontinued until it resolves. After HU therapy resumes, if the same toxicity occurs, a dosage adjustment is recommended.

Complete blood counts and reticulocytes should be repeated at 2-4 week intervals during the initial phases of treatment. Renal and liver functions should be checked at least monthly. Once the patient is well established on a stable dose, monthly blood counts are sufficient. The interval between counts should not exceed 6-8 weeks.

Assessment/Documentation

Through assessment and documentation, the nurse can assure that the health care provider who is prescribing HU to the patient with sickle cell disease is well informed about the patient's status. Complete assessment, interventions and education provided to patients and families should be carefully documented and follow institutional guidelines. Assessment and documentation should include the following components: history of sickle cell related complications, treatment impediments, hematologic response to therapy, adverse events, and for pediatric patients, growth and development and splenic size.

Sickle Cell History

An accurate detailed history of all sickle cell related complications is vital prior to starting HU and throughout the treatment course. The nurse should obtain and document a detailed history of pain episodes, including episodes treated at home and those requiring emergency room or hospital admission. Location and duration of pain and any precipitating events should be noted. A complete history of all other sickle cell related complications should be included and one should obtain summaries of hospital and emergency room visits when possible.

Treatment Impediments

Any impediments to adherence with the prescribed treatment regime should be determined. A common impediment is the expense of HU. Patients without insurance coverage most often need a social work referral.

Hematologic Response

The nurse should monitor laboratory values during each clinic visit or hospitalization to detect both response to therapy and toxicity. Laboratory values indicating a response to therapy may include an increase in Hb, Hb F percentage, and MCV, and a decrease in the total white blood cell count. Laboratory values indicating toxicity include an absolute neutrophil count < 1500/mm³, a platelet count < 80,000/mm³, a Hb < 5 g/dl, an ALT > 2x normal, or a 50% increase in creatinine. HU leads to predictable changes in the peripheral blood film. Reviewing the peripheral blood film is helpful in monitoring compliance with HU. The film will demonstrate non-reticulated macrocytes and only rare sickled forms.

Adverse Events

The nurse should assess for nail and skin hyperpigmentation, a common, but clinically insignificant side effect of treatment. Patients should be informed of the likelihood of this occurrence since it can be distressing. Assess for GI problems, skin rashes, and hair loss. The nurse should note that although hair loss, nausea, rash and other GI upsets have been described with HU treatment, these problems are just as common among patients taking placebo (13).

Growth and Development

For pediatric patients, height, weight and, if under 3 years of age, head circumference, should be obtained at each HU surveillance clinic visit. In all studies to date, growth and development appear to be unaffected in children; however, this is still a concern and should be accurately assessed at every visit (14). Because adult patients often gain weight with treatment, a weight check should be obtained at each visit.

Splenic Size

Also for pediatric patients, splenic size should be assessed. Wang et al (2001) reported that HU given to very young children with sickle cell anemia lowers the frequency of functional asplenia, but may prolong the period of risk for acute splenic sequestration (11). Therefore, splenic size should be carefully assessed and documented at each clinic visit and hospitalization.

Interventions

Education

The nurse should review the patient's treatment regimen and carefully explain the plan for increasing dosage and the need to monitor the physical examination and lab values. The importance of keeping follow-up appointments should be stressed. Since patients rarely have overt symptoms with toxicity, patients and families need to understand that the only way to detect adverse side effects is by physical examination and blood tests. The nurse should make patients aware that lack of adherence to the treatment regimen and follow-up surveillance visits may result in discontinuation of therapy. For patients on liquid HU, instruction should be given on the use of the syringe to measure dosage (15).

The nurse must be knowledgeable concerning important HU safety issues. The patient should be informed that HU can theoretically cause fetal harm. Both male and female patients wishing to conceive should stop treatment 3-6 months prior to discontinuing birth control. There have been a small number of reported cases of malignancy in sickle cell patients on HU; however,

the relationship to treatment is uncertain (16). Although the risk appears small, and there is no certainty that the risk is real, caution is needed and patients should be informed of this theoretical possibility.

In addition, patients should be informed of current research involving HU and referred to appropriate web sites for further information. Educational literature should be provided and the content reviewed with the patient. Because of the complicated nature of sickle cell disease and the HU treatment regimen, the nurse needs to allow appropriate time to adequately address the patient's concerns and questions.

Support

The fact that all patients do not respond to therapy in the same way should be stressed. Although lack of adherence to the treatment regimen is the most common cause of poor response, some patients appear to be resistant to HU (17). For the vast majority of patients, both a hematological and clinical response should be noted 3-6 months after treatment initiation.

Emotional support and, if needed, referral to counseling should be provided to patients who fail to respond. Patients with a positive response may also need nursing support. For example, those who have lived with chronic pain and become nearly pain-free may need assistance in adjusting to a less encumbered lifestyle. Adults may be able to consider employment yet may have few job skills; therefore, a referral to vocational counseling is needed. Children may have special needs when returning to school full time and appropriate referrals to social work and counseling should be made.

Resources

- International Association of Sickle Cell Nurses and Physician Assistants: <http://www.iascnapa.org>
- Management and Therapy for Sickle Cell Disease; NIH; 301-496-4236: <http://www.nhlbi.nih.gov>
- The Sickle Cell Information Center, Grady Memorial Hospital; 404-616-3572. <http://www.emory.edu/PEDS/Sickle>
- Sickle Cell Disease Association of America. *Who is affected by sickle cell disease?* [online]. <http://sicklecelldisease.org/affected.htm>.
- Food and Drug Administration (U.S.). Summary of safety-related drug labeling changes approved by FDA [online]. *MedWatch: the FDA Medical Products Reporting Program*. <http://www.fda.gov/medwatch/safety>

References

1. [Platt OS et al.](#) Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N.Engl.J.Med.* 1994; 330: pp. 1639-1644.
2. [Halsey C, Roberts IA.](#) The role of hydroxyurea in sickle cell disease. *Br.J.Haematol.* 2003; 120: pp. 177-186.
3. [Charache S et al.](#) Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. *N.Engl.J.Med.* 1995; 332: pp. 1317-1322.
4. [Steinberg MH et al.](#) Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. *JAMA* 2003; 289: pp. 1645-1651.
5. [Scott JP, Hillery CA, Brown ER, Misiewicz V, Labotka RJ.](#) Hydroxyurea therapy in children severely affected with sickle cell disease. *J.Pediatr.* 1996; 128: pp. 820-828.

6. [Jayabose S et al.](#) Clinical and hematologic effects of hydroxyurea in children with sickle cell anemia. *J.Pediatr.* 1996; 129: pp. 559-565.
7. [Ferster A et al.](#) Hydroxyurea for treatment of severe sickle cell anemia: a pediatric clinical trial. *Blood* 1996; 88: pp. 1960-1964.
8. [de Montalembert M et al.](#) Three-year follow-up of hydroxyurea treatment in severely ill children with sickle cell disease. The French Study Group on Sickle Cell Disease. *J.Pediatr.Hematol.Oncol.* 1997; 19: pp. 313-318.
9. [Olivieri NF, Vichinsky EP.](#) Hydroxyurea in children with sickle cell disease: impact on splenic function and compliance with therapy. *J.Pediatr.Hematol.Oncol.* 1998; 20: pp. 26-31.
10. [Kinney TR et al.](#) Safety of hydroxyurea in children with sickle cell anemia: Results of the HUG-KIDS study, aPhase I/II trial. *Blood*, Vol. 94 No. 5 (September 1), 1999: pp. 1550-1554.
11. [Wang WC, Wynn LW, Rogers ZR, et al.](#) A two-year pilot trial of hydroxyurea in very young children with sickle cell anemia.*J Peds* 2001, 139, 790-796.
12. [Ferster A et al.](#) Five years of experience with hydroxyurea in children and young adults with sickle cell disease. *Blood* 1996; 88: pp. 1960-1964.
13. [O'Branski EE, Ware RE, Prose NS, Kinney TR.](#) Skin and nail changes in children with sickle cell anemia receiving hydroxyurea therapy. *J.Am.Acad.Dermatol.* 2001; 44: pp. 859-861.
14. [Wang WC et al.](#) Effect of hydroxyurea on growth in children with sickle cell anemia: results of the HUG-KIDS Study. *J.Pediatr.* 2002; 140: pp. 225-229.
15. [Day SW, Wynn LW.](#) Sickle cell pain & hydroxyurea. *Am.J.Nurs.* 2000; 100: pp. 34-38.
16. [Schultz WH and Ware RE](#) for the International Association of Sickle Cell Nurses and Physician Assistants.Malignancy in patients with sickle cell disease.*Am J Hematol.* 2003; 74: pp.249-253.
17. [Yang YM, Pace B, Kitchens D, Shah A, Baliga BS.](#) BFU-E colony growth in response to hydroxyurea: correlation between in vitro and in vivo fetal hemoglobin induction. *Am.J.Hematol.* 1997; 56: pp. 252-258.