Hydroxyurea in the Treatment of Sickle Cell Anemia

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Approximately 90,000 Americans have sickle cell disease, making it the most common genetic disease in the U.S. Its occurrence is most common in people who are descendants of residents in regions of the world where the parasitic-borne disease malaria is prevalent. The ethnic groups most affected are African-Americans, Arabs, Turks, Greeks, Italians, Iranians, and Asiatic Indians.1,2

Sickle cell anemia is an inherited, chronic disease in which the red blood cells assume a crescent (sickled) shape instead of the normal disc shape. As a result, the cells function abnormally and cause small blood clots. These clots give rise to recurrent painful episodes called “sickle cell pain crises.”3 Patients with sickle cell disease need treatment and follow-up even when they are not experiencing a painful crisis. Leg ulcers, blindness, kidney damage, lung damage, strokes, and acute chest syndrome are a few complications that sometimes result secondary to sickle cell anemia.1,2,3

In this article, we attempt to create an awareness of sickle cell anemia and its symptoms and to help readers identify treatment options, with an emphasis on prevention of complications in sickle cell disease and decreases the need for blood transfusions; it also reduces pain events and hospital admissions by 50%.

EPIDEMIOLOGY

Although many ethnic groups are affected by sickle cell anemia, the African-American population seems to have the greatest predilection for the disease; one of every 500 African-Americans have sickle cell disease, and 8% of them have sickle cell trait. As a result of the ability to identify the disease through neonatal screening, the early initiation of penicillin therapy, close medical monitoring, and early intervention to relieve symptoms, the life expectancy for patients with sickle cell anemia has improved despite the absence of effective treatment modalities.2,3

Some patients have one episode every few years; others may have multiple episodes each year. Approximately 10% to 15% of patients have three or more painful crises per year. Rates of early mortality are highest among those with severe disease. The more crises experienced, the greater the probability of premature death.

Half of all patients with sickle cell anemia survive into their 40s. Patients with a more severe form of the disease sometimes die 10 to 15 years earlier than patients with milder cases. Because of a lack of blood oxygen transport, their organs become more damaged.

Studies have shown that hydroxyurea improves the survival of the most severely affected patients with sickle cell disease. Among sickle cell anemia patients who took hydroxyurea over nine years, there was a 40% reduction in mortality. Hydroxyurea reduced the number of painful crises and episodes of acute chest syndrome by 50%, and patients taking hydroxyurea also required almost 50% fewer transfusions and hospitalizations.2,3,5

ETIOLOGY AND PATHOPHYSIOLOGY

An abnormal type of hemoglobin—hemoglobin S—causes sickle cell anemia. In tropical regions of the world where malaria is prevalent, individuals with a single copy of this particular genetic mutation have a survival advantage. In areas where malaria is prevalent, inheriting one copy of the mutation is beneficial because it aids in combating the disease. Inheriting two copies of the mutation, however, portends tragedy (Figure 1).2,3,5 People from these regions migrated over time, married one another, and had children, and some of these children inherited two copies of the mutation.

Normal hemoglobin consists of two alpha and two beta chains to form a four-chain tetramer (Figure 2). In sickle cell anemia, valine is substituted for glutamic acid in both beta chains (hemoglobin SS). This substitution alters the beta chain and its interaction with other beta chains. The altered beta chains bind with other beta chains in deoxygenated red blood cells (RBCs). Polymerization occurs, and hemoglobin polymers distort the RBCs into sickled shapes; these changes ultimately cause vaso-occlusion (Figure 3). Polymerization leads to abnormal permeability, red blood cell dehydration, endothelial adhesion, and irreversible sickling. The lack of blood flow results in anemia, pain crises, and, eventually, infarction.7,8

CLINICAL PRESENTATION

Individuals who inherit hemoglobin S from one parent and normal hemoglobin (hemoglobin A) from the other parent will have sickle cell trait, which usually causes only mild symptoms or none at all. Most people do not even know that...
they have the trait until they are tested. In patients with sickle cell anemia, the hemoglobin molecules stick together in long, rigid rods after they release oxygen. These rods cause the RBCs to become hard and sickle-shaped, making them unable to squeeze through tiny blood vessels. The misshapen cells can become stuck in the small blood vessels, causing a blockage that deprives the body's cells and tissues of blood and oxygen (Figure 4).

Duane A. Bonds, MD, leader of the sickle cell disease scientific research group at the National Heart, Lung, and Blood Institute (NHLBI), states that when the misshapen cells get stuck in the small blood vessels, “it’s like having mini heart attacks throughout the entire body.”

With sickle cell anemia, the blood flow can be interrupted in any major organ, causing severe pain and organ damage where the flow has been blocked. Individuals who experience painful crises may complain of bone pain, difficulty in breathing, fever, and extreme fatigue. Recognizing that sickled cells are abnormal, the body destroys them at a faster rate than it can replenish them, causing anemia and predisposing these patients to infections.

PREVENTION

Genetic counseling is recommended for all known carriers of the sickle cell trait. Prenatal diagnosis of sickle cell anemia is also available. Prompt treatment of infections, adequate oxygenation, avoidance of extreme temperatures, and prevention of dehydration may prevent sickling of the RBCs in these patients.

Children of carriers should receive prophylactic penicillin from birth until they are six years of age. The Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices (ACIP) recommends the 7-valent pneumococcal polysaccharide-protein conjugate vaccine for children with sickle cell disease from 24 to 59 months of age.

General health visits with a physician are recommended to ensure that patients are getting adequate nutrition, receiving scheduled vaccinations, and maintaining proper activity levels.

TREATMENT

Treatment of sickle cell disease usually focuses on alleviating the symptoms. Although bone marrow transplantation can be curative, it is indicated for only a minority of patients because of the difficulty in finding suitable donors and the high risk of the procedure. Folic acid supplementation is required for all patients because of the rapid RBC turnover, and antibiotics and vaccines are given to children to prevent common bacterial infections. Acute painful crises are treated with analgesics and adequate liquid intake. Non-narcotic medications may be effective, but narcotics are sometimes required.

Hydroxyurea therapy has been effec-
Hydroxyurea is an orally administered, tasteless, white crystalline powder. It is approved for use in patients 18 years of age and over who have had at least three painful crises in the previous year.

The main side effect is a decrease in blood counts, particularly of the white blood cells (neutropenia) and platelets (thrombocytopenia). The precise mechanism by which hydroxyurea produces its cytotoxic and cytoreductive effects is not known, although several studies suggest that it causes an immediate inhibition of DNA synthesis by acting as a ribonucleotide reductase inhibitor without interfering with the synthesis of ribonucleic acid or of protein.

Some of the known pharmacological effects of hydroxyurea that might contribute to its beneficial effects in sickle cell disease include:

- increasing fetal hemoglobin (hemoglobin F) levels in RBCs (thus preventing the formation of hemoglobin S polymers)
- decreasing the number of neutrophils
- increasing the water content of RBCs
- increasing the deformability of sickled cells
- altering the adhesion of RBCs to the endothelium

The product is available in 200-, 300-, and 400-mg capsules.

**Pharmacokinetics**

Hydroxyurea is readily absorbed after oral administration, and peak plasma levels are reached in one to four hours. With increasing doses, disproportionately greater mean peak plasma concentrations and area-under-the-curve (AUC)
concentrations are observed. Hydroxyurea is distributed rapidly in the body, with an estimated volume of distribution approximating total body water and concentrates in leukocytes and RBCs.

Conversion through metabolic pathways that are not fully characterized occurs in up to 50% of an oral dose. In one minor pathway, urease found in intestinal bacteria may degrade hydroxyurea.

Excretion of hydroxyurea occurs through two pathways in a nonlinear process. One pathway is saturable, through hepatic metabolism; the other is first-order renal excretion.

**Efficacy**

A large-scale, double-blind, randomized, placebo-controlled clinical trial, the Multicenter Study of Hydroxyurea in Sickle Cell Anemia (MSH), assessed the efficacy of hydroxyurea in 299 adults with moderate to severe disease. The investigators evaluated the severity of disease according to the number of painful crises experienced by patients in a year (all patients experienced three or more painful crises per year). A painful crisis was defined as acute sickling-related aching that resulted in a visit to a medical facility, lasted more than four hours, and required treatment with a parenteral narcotic or a nonsteroidal anti-inflammatory drug (NSAID). Priapism, acute chest syndrome, and hepatic sequestration were also included in this definition.

Compared with patients receiving placebo, patients taking hydroxyurea showed (1) a significant decrease in the yearly rate of painful crises, including those requiring hospitalization; (2) a reduced incidence of acute chest syndrome; and (3) a decrease in the number of units needed for blood transfusions.

Hydroxyurea treatment significantly increased the average time between the first and second painful crises. Most of the benefits in crisis reduction were seen in the patients with six or more painful crises during the preceding 12 months, although patients with three or more painful crises during the preceding year were eligible for the study (Table 1).

In the MSH Patient Follow-up Study, conducted from 1996 to 2001, the objective was to determine whether hydroxyurea reduced mortality in patients with sickle cell anemia. During the follow-up, patients could continue, stop, or start hydroxyurea. Complete data were available for 233 of 299 patients from the original MSH study.

Of the original 299 patients, 75 died. Pulmonary disease accounted for 28% of the deaths. In patients with reticulocyte counts below 250,000/mm³ and hemoglobin levels lower than 9 g/dl, mortality rates were increased (P = .002). The cumulative mortality rate, at nine years, was 28% when hemoglobin F levels were lower than 0.5 g/dl, and 15% when hemoglobin F levels were 0.5 g/dl or higher (P = .03).

During the trial, the mortality rate for patients with acute chest syndrome was 32%; for patients without the syndrome, it was 18% (P = .02). For patients with three or more painful episodes per year, the mortality rate was 27%; for patients with fewer episodes, the rate was 17% (P = .06).

Hydroxyurea therapy was associated with an overall 40% reduction in mortality (P = .04) in this observational follow-up with self-selected treatment. Three patients had cancer, and one of them died.

The main contributing factors to the survival of the sickle cell patients in the follow-up study were increased hemoglobin F levels and a reduction in the number of painful crises. It is believed that hydroxyurea works, at least in part, by restarting the production of hemoglobin F in adults with sickle cell anemia. In these affected individuals, having more hemoglobin F is very beneficial because that version of the hemoglobin molecule is not affected by the problematic mutation. Hemoglobin F can function as the protein in the RBCs that enables them to carry oxygen throughout the body.

**Adverse Reactions**

In the study, the most commonly occurring adverse reactions were hematologic, including neutropenia, and low reticulocyte and platelet levels, which necessitated temporary cessation of therapy in almost all patients. Hematologic recovery usually occurred within two weeks. Other nonhematologic effects included skin rash, hair loss, fever, weight gain, gastrointestinal disturbances, bleeding, and parvovirus B-19 infection.

The nonhematologic events occurred with similar frequencies in the hydroxyurea and placebo treatment groups. Melanonychia has also been reported in patients receiving hydroxyurea for sickle cell anemia.

**Contraindications and Precautions**

Hydroxyurea is contraindicated in patients with a previous hypersensitivity to it or to any other components of its formulation. Hydroxyurea therapy should be closely supervised, because some patients who received the recommended dose—15 mg/kg/day—have experi-
enced severe myelosuppression, requiring interruption of treatment and dose reduction. Kidney and liver function, as well as hematological status, should be assessed before treatment is begun, and these tests should be repeated during treatment. Interruptions of therapy are recommended when:12,17

- neutrophil levels are below 2,000/mm³.
- platelet counts are below 80,000/mm³.
- hemoglobin levels fall below 4.5 g/dl.
- reticulocyte counts are below 320,000/mm³.
- reticulocyte counts fall below 80,000/mm³ and hemoglobin concentrations are below 9 g/dl.

Although hydroxyurea has not been indicated for patients with human immunodeficiency virus (HIV) infection, if HIV-infected patients are receiving this agent and, in particular, didanosine (Videx®, Bristol-Myers Squibb Immunology) and/or stavudine (Zerit®, Bristol-Myers Squibb Immunology), close monitoring for signs and symptoms of pancreatitis and hepatotoxicity is recommended. If signs and symptoms of pancreatitis or hepatotoxicity develop, patients should permanently discontinue hydroxyurea therapy.12

Studies are now under way to test the safety and effectiveness of hydroxyurea in children.12,18,19

**Pregnancy and Lactation**

Hydroxyurea is a potent teratogen in a wide variety of animal models, and it may cause fetal harm when administered to pregnant women. It is embryotoxic and causes fetal malformations at a dosage of 180 mg/kg per day (about 0.8 times the maximum recommended human daily dose on a milligram-per-squared-meter [mg/m²] basis) in rats and at 30 mg/kg per day (about 0.3 times the maximum recommended human daily dose on an mg/m² basis) in rabbits. Decreased fetal viability, reduced live litter sizes, and developmental delays were characteristic of embryotoxicity.

Because hydroxyurea is excreted in human milk, nursing mothers need to decide whether to discontinue nursing or to discontinue the drug because of the potential for serious adverse reactions.12,20

**CONCLUSION**

Sickle cell disease is the most common genetic disease in the U.S. As a result of increasing educational efforts being made in public health, the number of new cases in the U.S. should decline in the years ahead.

Unfortunately, no cure is yet available; treatment usually focuses on alleviating symptoms. Hydroxyurea can significantly prevent associated complications, but it is approved only for patients over age 18 who have had at least three painful crises in the previous year. Patients should be carefully monitored for hematologic adverse reactions.

Because of the teratogenic effects of hydroxyurea, mothers who are breastfeeding should either discontinue nursing or discontinue the drug therapy. Studies are being conducted to gain approval for hydroxyurea to be used in patients younger than age 18. As our understanding of sickle cell disease and various treatments used to combat painful crises increases, it is hoped that better pain management and a possible cure might be realized.

**REFERENCES**