Hydroxyurea Treatment for Pediatric Patients with Sickle Cell Disease

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Abstract
The significant causes of morbidity and mortality in sickle cell disease are the acute and long-term consequences of vaso-occlusion and hemolysis, many of which cannot be reversed (e.g., tissue infarction, vasculopathy). This review discusses hydroxyurea therapy in sickle cell disease, including the mechanism of action and adverse effects.

INTRODUCTION

Genetic hemoglobin disorders are a growing global health concern, with more than 300,000 children born each year with severe hereditary hemoglobinopathies. One of these disorders is sickle cell disease (SCD), an autosomal recessive condition characterized by the production of abnormal hemoglobin (Hb) S. It is predicted that the global number of newborns with SCD will increase by one-third by 2050 (1-3).

In the eastern region, SCD is a significant public health problem with the highest prevalence. Patients with SCD experience various health issues that adversely affect their quality of life and lead to morbidity. The abnormal Hb production in SCD causes red blood cells to assume a sickle-like shape in low-oxygen conditions, resulting in a wide range of complications, including vaso-occlusive crises, hemolytic episodes, stroke, acute chest syndrome, and susceptibility to infections (1, 2).

In 1998, the US Food and Drug Administration (FDA) approved hydroxyurea as a therapeutic agent for SCD treatment. Before this approval, most treatments for SCD were supportive in nature, including episodic red blood cell transfusions, pain medications, antibiotics, and intravenous fluids. Hydroxyurea marked a significant milestone as the first FDA-approved therapeutic drug for SCD. While hydroxyurea may have potential side effects like anorexia, nausea, vomiting, and infertility, it also offers several benefits for SCD treatment, primarily through the increased production of fetal hemoglobin (HbF). Additionally, it may impact SCD treatment by increasing nitric oxide levels, improving red blood cell rheology, and reducing white blood cell counts (1-4). Although the efficacy of hydroxyurea in reducing the frequency of painful crises and hospitalizations has been studied extensively, there is a gap in knowledge concerning its effectiveness in eastern Saudi Arabia. Hence, the study aims to assess the impact of hydroxyurea

therapy on reducing pain crises, hospital admissions, and length of hospital stays for SCD patients in the eastern region of Saudi Arabia. The study also seeks to identify any barriers that might prevent SCD patients from considering hydroxyurea as a treatment option (1-4).

MECHANISM OF ACTION:

The mechanism of action of Hydroxyurea, a drug with a long history of use in various medical conditions, including the treatment of multiple cancers and sickle cell disease (SCD), remains incompletely understood. It was initially approved by the US Food and Drug Administration (FDA) in 1967 for its antineoplastic properties and later for treating SCD in adults in 1998, with a specific pediatric formulation approved in 2017 (4-6). One of the primary mechanisms of action of Hydroxyurea is its inhibition of ribonucleotide reductase enzymes, which are iron-containing enzymes responsible for converting ribonucleoside diphosphates into deoxyribonucleotide triphosphates (dNTPs). These dNTPs are essential for DNA synthesis and repair. Hydroxyurea appears to interfere with the function of ribonucleotide reductases by binding to iron molecules and scavenging free radicals. As a result, cells experience a deficiency in dNTPs, causing them to arrest in the S-phase of the cell cycle. Over time, these cells will either delay the S-phase until DNA synthesis can proceed or undergo cell death. Additionally, Hydroxyurea affects other enzymes, such as iron-sulfur cluster-containing enzymes, and leads to global myelosuppression, including conditions like neutropenia, anemia, and thrombocytopenia (4-6).

Another crucial effect of Hydroxyurea is its ability to increase the production of fetal hemoglobin (Hb F) while decreasing the production of adult hemoglobin (Hb A) in individuals with SCD. This shift in gene expression results in a relative decrease in hemoglobin S (Hb S), which is responsible for the sickling of red blood cells. Hb F, produced during fetal development and early infancy, exhibits properties that differ slightly from Hb A but are well-tolerated and do not cause clinical issues. Hydroxyurea can increase Hb F production significantly, affecting the concentration of Hb F per cell, the proportion of Hb F-containing cells, and the overall percentage of Hb F. This reduction in intracellular Hb S concentration leads to decreased hemoglobin polymerization and precipitation, ultimately reducing the formation of sickled red blood cells. Consequently, RBC lifespan is extended, hydration is improved, hemolysis is reduced, and adhesion to vascular endothelium is lessened. This cascade of effects leads to improved blood flow through the microcirculation and a decreased likelihood of vaso-occlusive events, characteristic of SCD (6-8). The precise mechanisms by which Hydroxyurea increases Hb F production are not fully understood but may involve epigenetic modifications, gene transcription, and cell signaling pathways. Additionally, increased levels of nitric oxide (NO) and cyclic nucleotides like guanylyl cyclase may induce Hb F transcription by influencing genes that regulate globin gene transcription and translation, including BCL11A. Hydroxyurea may also induce the expression of SAR1 (secretion-associated and ras-related signaling protein), which activates gamma-globin expression through c-Jun N-terminal kinase (JNK/Jun). These effects primarily occur in reticulocytes, with a delay before they become evident in mature red blood cells and potentially up to six months before clinical symptom improvement is observed. It is important to note that these effects are reversible upon discontinuation of the drug, often necessitating lifelong therapy in most cases (6-8). Beyond the increase in Hb F levels and the subsequent reduction in sickling, Hydroxyurea may offer additional benefits in SCD through other mechanisms (1, 4, 6):

Nitric Oxide (NO): Hydroxyurea can increase NO levels, both by reducing hemolysis and by promoting intracellular NO production. NO is a potent vasodilator, and increased levels may improve blood flow in specific vascular beds, such as the pulmonary vasculature (1, 4, 6).

Red Blood Cell (RBC) Rheology: Hydroxyurea may improve RBC volume, density, adhesivity, and passage through the microcirculation independently of its effects on Hb F levels. This improvement may be due to a reduction in the proportion of reticulocytes and young, low-density RBCs prone to adhere to vascular endothelium (1, 4, 6).

White Blood Cells (WBC): Reduced white blood cell (WBC) counts and decreased neutrophil adhesion to vascular endothelium may contribute to reduced vaso-occlusion. In vitro studies have shown that individuals with SCD have enhanced WBC binding to fibronectin and increased activation. Clinical trials have suggested lower neutrophil counts are associated with fewer pain episodes in individuals receiving Hydroxyurea treatment (1, 4, 6).

INDICATIONS AND EVIDENCE FOR EFFICACY:

Hydroxyurea (also known as hydroxycarbamide, Droxia, Hydrea, Siklos) has proven to be effective in reducing complications and potentially increasing the life expectancy of individuals with sickle cell disease (SCD), especially those with the most severe genotypes (such as Hb SS and sickle beta0 thalassemia). It is important to note that Hydroxyurea is not a treatment for acute complications but rather a preventive measure (1, 4, 6).

Infants aged 6 to 9 months with symptomatic disease (e.g., severe anemia, dactylitis, acute pain episodes) may be considered for Hydroxyurea therapy. This recommendation is based on indirect evidence from older children and the potential benefits of maintaining high fetal hemoglobin levels. Limited evidence in this age group suggests that early initiation of Hydroxyurea results in higher total hemoglobin levels and lower neutrophil counts at 24 months (1, 4, 6). For infants aged nine months and older, as well as children and adolescents, Hydroxyurea is recommended regardless of disease severity. This recommendation aligns with the 2014 guidelines for SCD management from the National Heart, Lung, and Blood Institute (NHLBI) in the United States (1, 4, 6). The use of Hydroxyurea in individuals with other SCD genotypes, such as Hb SC disease or sickle beta+ thalassemia, is determined on a case-by-case basis depending on disease severity, which varies more in these genotypes. Hydroxyurea may be considered for those with clinical manifestations similar to Hb SS or sickle beta0 thalassemia, but it is not typically recommended for individuals with milder disease. Various guidelines, consensus statements, and the practices of SCD experts support this approach (1, 9). Hydroxyurea was initially approved for use in adults with SCD by the US Food and Drug Administration (FDA) in 1998 and by the European Medicines Agency in 2007. In 2017, the FDA extended its approval to include children with SCD (1, 9).

Hydroxyurea can be administered with other medications, such as L-glutamine, voxelotor, or crizanlizumab, and these combinations have demonstrated more significant benefits than using any single agent alone (1, 9).

EVIDENCE FOR EFFICACY:

The initial evidence supporting the efficacy of Hydroxyurea in SCD primarily came from studies conducted in adults, with subsequent studies involving children and infants. Over the years,

prospective observational studies have consistently shown a reduction in mortality associated with long-term Hydroxyurea use (1, 10). Additionally, Hydroxyurea may offer other advantages, including improved quality of life and daily functioning. This improvement may lead to better school attendance and fewer missed workdays. Studies have shown that children with SCD treated with Hydroxyurea reported better overall health-related quality of life and better physical compared to those who did not receive the medication. Cost savings may also result from fewer clinical encounters and hospitalizations for individuals on Hydroxyurea therapy. Furthermore, Hydroxyurea may have a positive impact on neurocognitive function. Studies have shown that earlier initiation of Hydroxyurea was associated with higher neurocognitive test scores in patients with Hb SS or Hb S beta0 thalassemia. This benefit remained significant even after adjusting for various factors, including social vulnerability, sex, and duration of treatment. Across different genotypes, Hydroxyurea-treated patients exhibited a six-point increase in intelligence quotient (IQ) compared to untreated patients (1, 10).

ADMINISTRATION AND DOSING:

Hydroxyurea is initiated at a low dose and gradually increased to a level that does not cause severe hematologic toxicity. The medication is typically administered once daily, although divided doses can be considered for patient preference and adherence. For infants under one year of age with good kidney function (creatinine clearance >60 mL/minute), the initial dose is usually 20 mg/kg per day. It is worth noting that Hydroxyurea is not available commercially as a liquid, and compounding pharmacy support is required to prepare an oral solution from capsules. The oral solution is chemically stable at room temperature for up to six months (1, 10).

In older children, adolescents, and adults who can take Hydroxyurea in pill form, the initial dose is determined based on the patient's weight and creatinine clearance. Capsules are available in various sizes, typically 200 mg to 500 mg. The recommended initial oral dose for children with creatinine clearance >60 mL/min is 20 mg/kg per day, rounded to the nearest 2.5 mg/kg per day. The dosing for adults may vary, with lower doses recommended for older adults and those with normal to mildly reduced glomerular filtration rates (1, 10).

ADVERSE EFFECTS

Common side effects, experienced by more than 10% of patients, include neutropenia, anemia, oral ulcers, mild gastrointestinal discomfort, hyperpigmentation, rash, and changes in nail appearance. Less frequent side effects, observed in 10% or fewer of patients, encompass ankle ulcers, mouth, and skin lesions resembling lichen planus, nausea, and diarrhea. Rare adverse effects encompass fever and abnormalities in liver function tests. (1, 10).

CONTRAINDICATIONS

Hydroxyurea should not be used in cases of severe bone marrow suppression, such as significant neutropenia or thrombocytopenia (1, 10).

In conclusion, Hydroxyurea decreases vaso-occlusive events, including pain and acute chest syndrome, in individuals afflicted with sickle cell disease. The primary mechanism responsible for this effect is the elevation of fetal hemoglobin levels, which in turn diminishes the polymerization of sickle hemoglobin (Hb S), mitigating sickling and the occurrence of vaso-occlusive events..

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