Review Article

Hydroxyurea: Modifier of Pathophysiology in Sickle Cell Anemia

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Abstract

Sickle cell anemia (SCA) patients have a point mutation in the 6th codon of the hemoglobin gene in which adenine is replaced by thymine resulting in replacement of glutamic acid with valine on the 6th amino acid in the β globin chain of the hemoglobin. Despite identical basic genetic mutation in all SCA patients, significant variation in clinical severity occurs. Clinical severity of SCA varies from mild to very severe types requiring more intensive medical interventions such as use of hydroxyurea (HU) and stem cell transplantation. Use of HU has improved clinical outcome in SCA and is recommended for moderate-to-severe varieties of SCA. This review brings to the fore mode of action, indications, commencement of therapy, monitoring, toxicity, and discontinuation of HU in selected SCA patients.

Keywords: Hydroxyurea, pathogenesis, sickle cell anemia

Introduction

Sickle cell anemia (SCA) was first described in 1910 by Dr. James Herrick in a Dental student in Chicago, USA.[1] A point mutation in the 6th codon of the hemoglobin gene in which adenine is replaced by thymine (GAG → GTG) is responsible for the sickle cell gene. The consequence of the mutation is the replacement of glutamic acid with valine on the 6th amino acid in the β globin chain of the hemoglobin molecule. Despite the presence of basic identical genetic mutation (GAG → GTG) in all SCA patients, significant variation in clinical severity occurs.[2] Well established causes of the variations of clinical severity in SCA have been reported, these include hemoglobin haplotypes and fetal hemoglobin (HbF) concentrations,[3] socioeconomic status,[4] coinheritance of α-thalassemia,[5] expression of adhesion molecules on white blood cells (WBCs),[6] steady-state neutrophil counts and function,[7] plasma level of IgG and in particular IgG3,[8] levels of circulating immune complexes,[9] and levels of transferrin and C-reactive protein.[10] Clinical severity varies from mild to very severe requiring more intensive medical interventions such as use of hydroxyurea (HU) and stem cell transplantation.[11]

Pathogenesis of Vaso-occlusion in Sickle Cell Anemia and the Role of Hydroxyurea

Chronic hemolysis in SCA is associated with hemoglobinemia. Hemoglobin is an avid scavenger of nitric oxide (NO), resulting in the reduction of intracellular NO which is associated with numerous complications of SCA such as, priapism and acute chest syndrome (ACS) among others. Metabolism of HU generates NO, which compensates for the loss of endogenous NO from chronic hemolysis and hemoglobinemia, thus ameliorating the effects of NO deficiency. Furthermore, the NO available from HU metabolism stimulates soluble guanyl cyclase which in turn increases HbF concentration.[12] Similarly, HU inhibits two iron molecules of the cellular's ribonucleotide reductases enzymes, which favors the production of HbF because the latter red-cell progenitors divide less rapidly unlike hemoglobin S (HbS) whose production is severely depressed because of its rapidly dividing precursors.[13]

The accentuated chronic intravascular and extravascular hemolysis resulting from membrane damage causes a reduction in intravascular NO secondary to hemoglobinemia which results in increased vascular tone and pulmonary artery hypertension.[14,15] Apart from NO depletion secondary to chronic hemolysis and hemoglobinemia, the pathogenesis of painful crises, ACS, functional asplenia and acute stroke in

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SCA are majorly due to high levels (concentrations) of HbS in red cells of SCA patients. HbSS red cells lose deformability when deoxygenated, the consequences of this are vascular obstruction and ischemia.

High steady-state leukocytes count has been reported to directly impact on clinical severity.[7] HU induces cytoreduction and decreases inflammatory reactions, thus decreasing vascular injury, hemolysis and vaso-occlusion.

Finally, the abnormal surfaces of the damaged red cells predispose to increased adherence to and impair the vascular endothelium, thus provoking vascular proliferative lesions through the activation of WBC and platelets with production of cytokines, growth factors, and coagulation proteins leading to acute vaso-occlusion.

History of Hydroxyurea

In 1970s, patients with SCA who had increased red blood cell HbF were observed to have less severe presentations.[16,17] Following a decade of relative inactivity, Platt *et al*. in 1984 reported HU induced an increase in HbF in red blood cell of SCA.[18]

HU was approved in February 1988 after four years of clinical trials for adult sickle cell disease patients by the United States Food and Drug Authority. The National Heart Lung and Blood Institute also recommended its daily use on some selected SCD patients in 2002.[19-21]

In 2007, the use of HU in SCD was approved by the European Medicines Agency for recurrent vaso-occlusive crises (VOC) and ACS in pediatric and adult patients.[22]

By 2008, the National Institutes of Health Consensus Development held a Conference on the use of HU in the treatment of SCD[23] following a published comprehensive systematic review by Agency for Healthcare Research and Quality.[24] The use of HU secondary to its approval and recommendation in adult SCA by various agencies and organizations, resulted in observed clinical improvements which have been incontrovertibly reported to significantly reduce the frequencies of VOC and ACS and the rate of blood transfusions in SCA by several studies[25-30] Several studies have also demonstrated the decreased rate of hospitalization in patients on HU compared to pre-HU era.[29,31,32]

Pharmacology of Hydroxyurea

HU belongs to the group of drugs described as anti-metabolites. First synthesized in 1869 in Germany by Dressler and Stein,[33] it has a molecular weight of 76.05 with a structural formula of $CH_4N_2O_2$. HU is converted to NO *in vivo.* The NO diffuses into cells inhibiting ribonucleotide reductase's two iron molecules, thus inactivating its tyrosyl free radical. This selectively inhibits DNA synthesis causing cell death in S phase.[13]

HU exists in 100, 200, 300, 400, and 500 mg formulations. Individual reactions to use of HU in SCD are variable for unknown reasons, thus limiting its usefulness in some individuals.[34,35] It modifies SCD pathogenesis[36] decreasing the incidence of VOC,[37] priapism,[38] and overall mortality in adults.[39]

The effects of HU's clinical improvement in SCD are mediated majorly through increased HbF concentrations. It is also known to increase erythrocyte volume and hydration, decrease steady-state neutrophils count and activation, decrease adhesion of red cells and granulocytes to vascular endothelium as well as increased NO production with resultant improved cellular oxygen perfusion. Apart from its usefulness in HbSS, it is use in the management of HbSC was recommended by some authors[40] but neither recommended nor discouraged in another study.[41]

Metabolism of Hydroxyurea

HU belongs to the class of hydroxamic acids. It has ability to bind metals and also inhibits ribonucleotide reductase. This inhibition reduces the production of HbS and increases production of HbF. It also reduces WBCS and platelet counts, thus reducing their roles in vascular injury and occlusion. When metabolized, it generates NO. NO stimulates soluble guanylate cyclase resulting in the production of HbF. NO generated also compensates for NO loss in intravascular hemolysis. The half-life of HU is 3–4 h; it is well absorbed orally and excreted through the kidneys.

Indications for Hydroxyurea

HU indications recommended by National Heart Lung, and Blood Institute is presented in Table 1. Summary of indications for use of HU recommended by Wong *et al.*,[42] include

1. Adults with SCA who have ≥3 moderate-to-severe VOC in 1 year (Grade 1A)
2. Adults and children with SCA who have history of ACS or symptomatic anemia (Grade 1B)
3. In children with SCA who have ≥3 moderate-to-severe VOC in 1 year (Grade 1 B)
4. In patients with SCA with a history of stroke and contraindications to chronic transfusion (Grade 2 B)
5. In adults with HbS β^+ thalassemia with ≥3 moderate to severe VOC in a one year period or a history of ACS (Grade 2C)
6. In patients with HbSC and children with HbS β^+ thalassemia, there is insufficient evidence to provide recommendations for HU therapy.

Footnotes of the grading as follows:

- Grade 1A – Very strongly recommended, Grade 1B – Strongly recommended
- Grade 2B – Recommended, Grade 2C – Weakly recommended.

Starting Hydroxyurea

Mandatory baseline investigations are weight, height, oxygen saturation, full blood count (FBC), and HbF quantification, liver function test, urea, and creatinine. Viral screen includes HbsAg, HCV, HIV, and Parvo virus B19 serology. Lactate

dehydrogenase levels and pregnancy tests for women in reproductive age group are important. Starting dose is 15 mg/kg/day. However, if creatinine clearance is <60 ml/min, starting dose is reduced to 7.5 mg/kg/day.[43]

Monitoring Hydroxyurea Use

Table 2 gives an overview of monitoring hydroxyurea use.

Stopping Hydroxyurea

Stop HU temporarily if neutrophils is <2000/mm^3, platelets <80000/mm^3, hemoglobin <4.5g/dl and reticulocytes <80,000/mm^3. Recommence if blood counts recover. Hematologic recovery takes place within 2 weeks.

Increasing Dose of Hydroxyurea

Increase HU 12 weekly by 5mg if FBC is within acceptable range. The maximum tolerated dose is 35mg/kg/day.

Table 1: Hydroxyurea indications recommended by National Heart Lung, and Blood Institute

Clinical presentation	Strength of recommendation	Quality of supporting evidence
Three or more sickle cell-associated moderate-to-severe pain crisis* in a 12-month period	Strong	High
Sickle cell-associated pain that interferes with daily activities and quality of life	Strong	Moderate
History of severe and/or recurrent acute chest syndrome	Strong	Moderate
Severe symptomatic chronic anemia that interferes with daily activities or quality of life	Strong	Moderate

*A pain crisis is defined as a visit to a medical facility of >4 h requiring treatment with parenteral opiate or NSAIDs. NSAIDs: Nonsteroidal anti-inflammatory drugs

Table 2: Monitoring hydroxyurea use

Parameters	Duration
FBC	2 weekly - 1st month, then 4 weekly - every 4 month and 3 monthly every year
LFT/urea/creatinine	Weekly every 4 months, 3 monthly - every year, then 6 monthly- every year in subsequent years
HbF	Every 6 months, its level should double
Hb	Increases by 1 g/dl
Absolute reticulocyte count, bilirubin, and LDH	Reduced

FBC: Full blood count, LFT: Liver function test, HbF: Fetal Hb, Hb: Hemoglobin, LDH: Lactate dehydrogenase

Poor response to Hydroxyurea

1. Poor adherence due to fears of side effects and cost of monitoring
2. Decreased marrow reserve-precluding adequate dosing
3. Genetic factors.

Treatment endpoints

1. Increased HbF
2. Increased Hemoglobin by 15%–20%
3. Improved well being
4. Less pain/VOC.

Contraception and pregnancy

Teratogenic effects of HU have been reported from animal studies.[44] Its deleterious effects on spermatogenesis were also reported by Saalu *et al*.[45] Berthaut *et al.* reported a reduction in sperm count which failed to increase after discontinuation of HU.[46] Although the use of HU in pregnant women were described in three studies reporting pregnancy outcomes,[26,29,46] no birth defects were reported in any, however, reproductive counseling is key in adolescents and adults on HU who are of reproductive age group.

Toxicity

HU could present with the following toxicity, hematological, renal/hepatic, and gastrointestinal and dermatological [Table 3].

Risk of Malignancies

In a prospective study, assessing the risk of secondary malignancies, involving 1638 polycythemia vera patients on long-term HU,[47] no risk of leukemia attributable to HU over the use of ^{32}P, busulfan or pipobroman was reported. The study concluded that a small risk cannot be ruled out completely. On the contrary, five malignancies were reported in 951 patients on HU (0.5%) and 1 malignancy in 1736 patients not on HU (0.06%).[26,29,31] Various hematologic malignancies presenting 4-15 years after starting HU in patients with SCA were reported in three studies.[48-50]

Conclusion

The use of HU has incontrovertibly improved clinical outcome of SCA patients. However, despite its numerous advantages, its use is not risk-free. It is associated with minimal side effects if used in accordance with all recommendations.

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Conflicts of interest

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Table 3: Toxicity requiring immediate discontinuation of hydroxyurea

Parameters	Values
Hematological toxicity	
Absolute neutrophil count	<1–1.5×10^9/L
Absolute reticulocyte count	<80,000/mm^3
Hb	<4.5 g/dl
Fall in Hb concentration	≥20%
Platelet counts	<80,000/mm^3
Renal toxicity	
Serum creatinine	≥50% in, or >0.5 mg/dl
Hepatic/gastrointestinal	
Alanine transferase	≥100% increase
Dermatological	Unexplained rash or hair loss

Hb: Hemoglobin

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