Hydroxyurea in Sickle Cell Disease: Drug Review

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Abstract Hydroxyurea, a myelosuppressive agent, is the only effective drug proven to reduce the frequency of painful episodes. It raises the level of HbF and the haemoglobin level. It usually decreases the rate of painful episodes by 50 %. It was first tested in sickle cell disease in 1984. It also decreases the rate of ACS episodes and blood transfusions by ~50 % in adults. It was developed as an anticancer drug and has been used to treat myeloproliferative syndromes-leukemia, melanoma, and ovarian cancer. It was approved for use by FDA in adults. Side effects includes neutropenia, bone marrow suppression, elevation of hepatic enzymes, anorexia, nausea, vomiting and infertility.

Keywords Hydroxyurea · HbF level · Neutropenia

Introduction

Hydroxyurea has many characteristics of an ideal drug for sickle cell anemia (SCA) and provides therapeutic benefit through multiple mechanisms of action. Over the past 25 years, substantial experience has accumulated regarding its safety and efficacy for patients with SCA. Early proof of principle studies were followed by prospective phase 1/2 trials demonstrating efficacy in affected adults, then adolescents and children, and more recently infants and toddlers. The phase 3 National Heart, Lung and Blood Institute—sponsored multicenter study of hydroxyurea trial

proved clinical efficacy for preventing acute vaso-occlusive events in severely affected adults. Based on this cumulative experience, hydroxyurea has emerged as an important therapeutic option for children and adolescents with recurrent vaso occlusive events; recent evidence documents sustained long-term benefits with prevention or reversal of chronic organ damage. Despite abundant evidence for its efficacy, however, hydroxyurea has not yet translated into effective therapy for SCA. Because many healthcare providers have inadequate knowledge about hydroxyurea, patients and families are not offered treatment or decline because of unrealistic fears. Limited support for hydroxyurea by lay organizations and inconsistent medical delivery systems also contribute to underuse. Although questions remain regarding its long-term risks and benefits, current evidence suggests that many young patients with SCA should receive hydroxyurea treatment. In the discussion of harms of hydroxyurea treatment, the panel of National Institutes of Health Consensus Conference wrote, “The risks of hydroxyurea are acceptable compared with the risks of untreated sickle cell disease” [1].

Mechanism of Action

Given the abundant evidence for laboratory and clinical efficacy of hydroxyurea therapy in children and adults with SCA, it is perhaps surprising that its mechanisms of action for HbF induction remain incompletely understood. Current evidence suggests that several potential mechanisms of action by hydroxyurea may be relevant for patients with SCA, which together lead not only to HbF induction but also to additional benefits. Perhaps the most important mechanism of action is inhibition of ribonucleotide reductase (RR), the enzyme involved in transforming

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ribonucleosides into deoxyribonucleosides that serve as building blocks for DNA synthesis. Hydroxyurea is a potent RR inhibitor that reduces intracellular deoxynucleotide triphosphate pools and acts as an S-phase-specific agent with inhibition of DNA synthesis and eventual cellular cytotoxicity. Hydroxyurea directly inhibits the RR M2 subunit, but spontaneous regeneration of the active enzyme occurs when hydroxyurea is removed. For this reason, the *in vivo* effects of hydroxyurea on RR are predictably transient, resulting from the rapid absorption, metabolism, and excretion of hydroxyurea in mammalian systems. Presumably with once-daily dosing in SCA, hydroxyurea causes intermittent cytotoxic suppression of erythroid progenitors and cell stress signaling, which then affects erythropoiesis kinetics and physiology and leads to recruitment of erythroid progenitors with increased HbF levels.

A remarkable attribute of hydroxyurea is the observation that treatment has multiple potential benefits for patients with SCA. Beyond HbF induction, the cytotoxic effects of hydroxyurea also reduce marrow production of neutrophils, reticulocytes and also reduce no of platelets which is an important mediator of inflammation. Because an elevated WBC has been associated with both morbidity and mortality of SCA [2, 3], lowering the WBC count in SCA is itself potentially therapeutic. Both neutrophils and reticulocytes promote vaso-occlusion through vascular adhesion; hydroxyurea lowers their absolute numbers and reduces surface expression of adhesion receptors [4]. Additional benefits of hydroxyurea treatment include salutary effects on the circulating erythrocytes. A frequently observed effect of hydroxyurea treatment is an elevated mean corpuscular volume, despite reduced reticulocytosis. Peripheral erythrocytes undergo numerous morphologic and physiologic changes during hydroxyurea dose escalation to maximum tolerated dose (MTD), including macrocytosis, increased mean corpuscular hemoglobin, better hydration, more targeting, less hemolysis, and fewer sickled forms. Overall blood flow is improved, with a higher haemoglobin concentration and lower LDH and bilirubin levels. Concerns about deleterious effects related to a higher hemoglobin concentration causing higher blood viscosity do not appear clinically relevant, presumably because of counteracting benefits from increased cellular hydration and deformability, decreased adhesiveness, and overall improved rheology. Finally, the hydroxyurea molecule contains an NO moiety that can be released directly through unknown metabolic processes [5]. NO has beneficial effects on vascular endothelium, including local vasodilatation, and could help offset proposed hemolysis-related NO consumption. This effect may help explain the clinical improvement some patients feel soon after initiating hydroxyurea treatment, before reaching MTD with maximal HbF induction.

Pharmacodynamics and Pharmacokinetics

Hydroxyurea is readily absorbed after oral administration. Peak plasma levels are reached in 1–4 h after an oral dose. With increasing doses, disproportionately greater mean peak plasma concentrations and AUCs are observed. There are no data on the effect of food on the absorption of hydroxyurea. It distributes rapidly and widely in the body with an estimated volume of distribution approximating total body water. Hydroxyurea concentrates in leukocytes and erythrocytes. Up to 50 % of an oral dose undergoes conversion through metabolic pathways that are not fully characterized. In one minor pathway, hydroxyurea may be degraded by urease found in intestinal bacteria. Excretion of hydroxyurea in humans is a nonlinear process occurring through two pathways. One is saturable, probably hepatic metabolism; the other is first-order renal excretion.

Clinical Efficacy

Hydroxyurea has become an accepted therapeutic option for many patients with SCA. For SCA, an ideal therapeutic intervention would require the following characteristics:

- (1) General features: single-agent, inexpensive, orally administered, once-daily dosing
- (2) Laboratory efficacy: increases HbF and total Hb, reduces WBC and reticulocytes, and lowers LDH
- (3) Clinical efficacy: ameliorates anemia, leads to fewer vaso occlusive events and hospitalizations, decreases hemolysis
- (4) Treatment goals: works in all age groups, prevents acute events and chronic organ dysfunction
- (5) Sustainability: benefits continue over time without medication resistance or tolerance
- (6) Side effects: few short-term toxicities that might limit adherence, wide therapeutic index
- (7) Safety: no major short-term toxicities, plus no known long-term sequelae or complications of therapy.

Based on currently available data, hydroxyurea treatment fulfills these criteria for SCA and should be offered much more frequently, especially to young patients before the development of chronic complications and end-organ damage.

Among published predictors of clinical severity, the amount of fetal haemoglobin (percentage HbF) is the most critical laboratory parameter. HbF is protective against clinical severity; low-percentage HbF is associated with a higher risk of developing vaso-occlusive complications, organ damage, and early death [2, 3]. Accordingly, pharmacologic induction of HbF is a logical treatment goal in SCA, and recent reviews have focused on this topic [6, 7].

An increased WBC count has also been associated with poor clinical outcomes, and more recently, elevated serum lactate dehydrogenase (LDH, reflecting intravascular hemolysis) has been associated with morbidity and mortality in SCA [8]. Hydroxyurea has emerged as an exciting therapeutic agent because of its ease of oral administration, modest toxicity profile, predictable laboratory efficacy for increasing percentage HbF and reducing hemolysis, and proven clinical efficacy for preventing acute vaso-occlusive events.

Clinical experience has been accumulating for more than 25 years regarding the safety and efficacy of hydroxyurea therapy for patients with SCA. In the early 1990s, an important prospective phase 1/2 study in adults [9] using hydroxyurea at MTD was followed by the pivotal NHLBI-sponsored double-blinded, placebo-controlled phase 3 MSH trial, which was halted early because of clinical efficacy for preventing vaso-occlusive events. Subsequently, reports described the short-term safety and efficacy for pediatric patients receiving open-label hydroxyurea treatment [10, 11]. The prospective NHLBI sponsored phase 1/2 pediatric trial (HUG-KIDS) [12] demonstrated that laboratory efficacy and toxicities of hydroxyurea were mild, and similar for children and adolescents as observed for adults with SCA.

In the recently completed decade, the time line is shortened with important studies published almost every year. The phase 1/2 HUSOFT trial reported that infants tolerate hydroxyurea (liquid formulation) without short-term adverse events and have substantial laboratory and clinical efficacy [13]. Predictors of response to hydroxyurea in HUG-KIDS were published [14], along with evidence for normal growth and development [15]. Sustained laboratory benefits were reported for school-age children [16] and infants. Long-term clinical efficacy with reduced mortality has been reported with long-term hydroxyurea usage [17]. More recently, salutary effects of hydroxyurea on prevention and treatment of organ dysfunction are being reported.

Benefits

- (1) Reduces number of painful events along with hospitalisations in adults and children [10].
- (2) Preserve splenic function in infants receiving hydroxyurea [13].
- (3) Hydroxyurea has clinical efficacy for children with variable sickle-related organ damage, including proteinuria, spleen dysfunction, hypoxemia, pulmonary hypertension, glomerular hyperfiltration [18], neurocognitive delay, silent brain infarcts, elevated transcranial Doppler (TCD) velocities [18, 19], primary

stroke prevention [19], and secondary stroke prevention [20].

- (4) In both school-age and very young patients with SCA, open label hydroxyurea has been associated with excellent growth and development [15, 17].
- (5) Sexual maturation, including menarche, has occurred without apparent delay [12, 15].
- (6) For toddlers on open-label hydroxyurea, impact-on-family scores improved after 2 years of treatment [18].
- (7) Useful to treat acute vaso-occlusive events in adults as well as children.

Indications in SCA [21]

A. *Standard indications* (any of the following)

- Frequent pain crises.
- Acute chest syndrome.
- Severe or symptomatic anemia (Hb < 7 g/dL).
- Hemolytic alloantibodies/autoantibodies.
- Severe complications without benefit from standard therapy (priapism, leg ulceration).

B. *Scenarios to be considered* (not proven efficacious)

- Chronic transfusion therapy precluded by presence of multiple allo-antibodies.
- Abnormal TCD refusing transfusion therapy.
- History of stroke refusing/non-compliant with transfusion/chelation therapy.

Contraindications [21]

- Pregnancy or sexually active and unwillingness to use contraception.
- Active liver disease (HBV or HCV infection).
- History of severe HU toxicity or hypersensitivity.
- History of significant non-compliance with recommended medical care.

Drug of Administration

A. *Documentation*

- Document informed consent with patient and/or parent/guardian of minor patients. Should include discussion of required monitoring, potential toxicity, potential teratogenicity/carcinogenicity, and need for contraception/abstinence.
- Signed written consent not required as hydroxyurea is FDA approved in adults with SCA and Phase II safety studies have been performed on children >age 5 years.

- Additional information to be given to parents of younger children re: availability of data on their age group and potential concerns.

B. Baseline investigation

- Documented complete physical exam (all vital signs including weight, height, and pulse oximetry).
- Hb electrophoresis with quantitative HbF %.
- CBC with differential and reticulocyte count.
- Chemistry profile (electrolytes, LDH, Total protein, Albumin, Total bilirubin).
- Liver function tests (AST, ALT).
- Renal function (BUN, Cr).
- Serum B-12 and folate (to ensure HU-related macrocytosis does not mask deficiency).
- Serum iron, TIBC, ferritin (to ensure HU related-macrocytosis does not mask Fe-deficiency).
- Hepatitis B, Hepatitis C, Parvovirus B19 and HIV serology.
- Pregnancy test for post-menarchal females.

C. Dosing

- Initial dose 10–15 mg/kg/day given as a single daily dose [17, 22]. Divided dosing unnecessary and may decrease compliance.
- Dose escalation by 5 mg/kg every 4–6 weeks.
- Increase dose until one of the following:
 - Evidence of hematological toxicity (see below) and thus “maximal tolerated dose” (MTD)
 - Goal ANC 2000–3000 achieved
 - 35 mg/kg/day dose achieved.
- If clear positive clinical and/or hematological effect is observed before MTD can consider stopping escalation, although there is some evidence of dose response that would suggest continuing to MTD may enhance clinical effect further.
- Re-evaluation of dosage (mg/kg) will occur with each monitoring visit.
- How supplied: 500 mg capsules.
- Liquid formulation can be prepared by compounding pharmacy using published guideline [22]. Alternatively, capsules may be opened and dissolved into a glass of water with vigorous stirring.

D. Monitoring visits

(1) Dose escalation

- Laboratory evaluation every 2–4 weeks:
 - CBC, differential, reticulocyte count.
 - Bilirubin, ALT, BUN, Cr every dose escalation.
 - Inquiry regarding side-effects, sexual activity and birth control.

- Clinical examination visits every 4 weeks (more frequently if education or compliance needs reinforcement).

- Weight, BP, vital signs and pulse SaO₂.
- Hematological system and toxicity focused physical exam each visit.
- Quantitative HbF Q 3–6 months.

- Record all lab values and evidence of toxicity and side effects on flow sheet. A brief clinical note to be completed for each visit.
- Continue until patient has been at stable or maximal tolerated dose for 8 weeks without toxicity.

(2) Stable/maximal tolerated dose

- Clinical and laboratory examination visits every 4–8 weeks.
 - CBC with differential and reticulocyte count every 4–8 weeks.
 - Quantitative HbF every 6–12 months.
 - ALT, AST, BUN, Cr every 6 months.
- Weight, BP, vital signs and pulse SaO₂.
- Hematological system and toxicity focused physical exam each visit.
- Inquiry regarding side-effects, sexual activity and birth control.

Adverse Effects

Side effects of hydroxyurea therapy in young patients with SCA are usually mild, and most children tolerate hydroxyurea without difficulty. Occasionally, patients will describe headache or mild gastrointestinal symptoms, including abdominal discomfort or nausea [12]. Some children develop dermatologic changes, including skin hyperpigmentation or darkening of the nails (melanonychia), which are sporadic and not dose-dependent. Hepatic and renal dysfunction from hydroxyurea treatment has not been reported. Clinical experience confirms that the most common short-term hydroxyurea toxicity in patients with SCA is transient and reversible myelosuppression, primarily neutropenia, although in some young patients reticulocytopenia can be dose-limiting [12]. Marrow suppression and mild peripheral blood cytopenias represent predictable toxicities of daily hydroxyurea therapy and are actually desired effects during escalation to MTD [12, 23]. Neutropenia is the most common laboratory toxicity, but its incidence depends on the absolute neutrophil count (ANC) threshold used for toxicity and dose adjustments (usually 1.0–2.0₁₀ [9]/L); severe cytopenia is rare. Even with the

conservative ANC toxicity threshold used (2.0_10 [9]/L), little toxicity was observed. The phase 1/2 HUSOFT pilot study documented feasibility of hydroxyurea for very young children with SCA between the ages of 6 and 24 months and evaluated its safety and toxicity profile. Twenty-eight infants with HbSS at 4 centers were enrolled in an open-label study; the fixed hydroxyurea dose of 20 mg/kg/day was well tolerated with few hematologic toxicities [13]. An extension study on these patients with hydroxyurea dose escalation to MTD did not reveal additional toxicities [17].

Based on tens of thousands of exposure years now accumulated, hydroxyurea used at therapeutic doses in young patients with SCA does not appear to confer an increased risk of malignancy. There are no any teratogenic effects of hydroxyurea. In 2009, Ballas et al. [24] reported on pregnancy outcomes in patients with sickle-cell disease receiving hydroxyurea during a controlled trial, which failed to show evidence of increased teratogenic risk. Concurrent use of folic acid decreases the risk of neural tube defects. Counsel the parents that SCD does not impair fertility.

Conclusions

We do not treat diabetes simply to avoid ketoacidosis, or asthma just to avert intubation; similarly, we should not treat SCA with the goal of simply reducing acute complications requiring hospitalization. We owe our patients with SCA the opportunity to enjoy healthy and productive lives with good quality. We should make every effort to treat children and adolescents with SCA before they develop chronic, inexorable, and ultimately fatal organ damage. The recent observation that mortality rates for older children with SCA have not changed in 20 years indicates the need for new approaches to disease management, especially regarding therapeutic intervention. At the current time, curative therapy with stem cell transplantation remains an unavailable option to most patients with SCA, although newer successful approaches may increase interest in this modality. Until something better becomes available that has a similar wide spectrum of efficacy and safety, hydroxyurea appears to be the best available treatment option for children and adolescents with SCA.

Conflict of Interest None.

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