Hydroxyurea Prescribing Guidelines

Hydroxyurea is the only oral medication available to mitigate sickle cell symptomatology. Hydroxyurea has a bone marrow modulating effect which elevates fetal hemoglobin production and has been shown to reduce the incidence of pain crises, acute chest syndrome, and unplanned blood transfusions. The increased erythrocyte life span decreases the rate of hemolysis, and by default, decreases reticulocyte counts. Hydroxyurea also reduces the level of leukocytes, which are implicated in vaso-occlusive events, and has been shown to reduce elevated transcranial velocities, which are associated with an elevated stroke risk.

Hydroxyurea is FDA approved for use in adults with sickle cell disease (SCD) and is utilized off-label in pediatrics. Over 15 years of data have supported the safety and efficacy of this medication in treating SCD in children, and randomized controlled trials in children have shown similar beneficial effects as in adults. Based on encouraging Baby-HUG results (HU and Growth in Babies), it is recommended to initiate hydroxyurea at 9 months of age in all children with HbSS or HbSβ^0thalassemia.[1] Hydroxyurea initiation should be preceded with a family discussion of risks and benefits of this therapy as well as the need for monitoring and clinic visit frequency.

Consider hydroxyurea in a child >5 years of age with HbSC or HbSβ^+thalassemia who:

- Has had > 2 hospital admissions in the past year for vaso-occlusive events
- Has had >1 SCD-related event per month in the past year
- Has missed >2 days of school per month for SCD-related complications
- Has had > 2 episodes of Acute Chest Syndrome (ACS) in their lifetime or
- Has family interest in initiating hydroxyurea

Consider hydroxyurea in adult patients with HbSS, HbSβ^0thalassemia, HbSC, and HbSβ^{0+}thalassemia who:

- Have had > 3 SCD-related moderate to severe pain crises in the past year
- Report SCD-related pain that interferes with activities of daily living
- Have a history of severe or recurrent ACS
- Have severe, symptomatic, persistent anemia that interferes with activities of daily living

Baseline Evaluation

- History and physical exam, including a review of indications for hydroxyurea therapy
- Lab evaluation: Complete Blood Count with differential and reticulocyte count, Complete Metabolic Panel (BMP + liver function tests), Fetal hemoglobin quantitation, Urine pregnancy test, if indicated
- Counsel males and females of reproductive age regarding the need for contraception while taking hydroxyurea.

Treatment Recommendations

Infants and Children >9 months

- Initiate hydroxyurea at 20 mg/kg in a single daily dose (round to the nearest 10mg). Medication should be taken at the same time every day.
- Escalate dose by 5 mg/kg/day (round to the nearest 10mg) every 8 weeks in the absence of dose-limiting cytopenias until Maximum Tolerated Dose (MTD) is achieved. MTD is defined as 35 mg/kg/day or the dose beyond which 2 episodes of drug toxicity have occurred.

- Monitor CBC with differential and reticulocyte count every 4 weeks while in dose escalation. Maintain ANC >1500/µL (goal >2000/µL). Maintain platelet count >80,000/µL.
- If neutropenia or thrombocytopenia occurs, hold hydroxyurea and repeat CBC with differential in 2 weeks. If toxicity is associated with illness and subsequently resolves, hydroxyurea should be restarted at previous dose and dose escalation may continue. If there is no associated illness, restart hydroxyurea at 5 mg/kg/day lower than dose associated with cytopenias.

Adults

- Initiate hydroxyurea at 15 mg/kg in a single daily dose (round up to the nearest 500 mg). In patients with chronic kidney disease, initial dose should be 5-10 mg/kg/day. Medication should be taken at the same time every day.
- Escalate dose by 5 mg/kg/day every 8 weeks in the absence of dose-limiting cytopenias until Maximum Tolerated Dose (MTD) is achieved. MTD is defined as 35 mg/kg/day or the dose beyond which 2 episodes of drug toxicity have occurred.
- Monitor CBC with differential and reticulocyte count every 4 weeks while in dose escalation. Maintain ANC >2000/µL. Maintain platelet count and absolute reticulocyte count >80,000/µL (absolute reticulocyte count= Total RBC count * Reticulocyte %).
- If neutropenia (ANC <1300/µL) or thrombocytopenia occurs, hold hydroxyurea and repeat CBC with differential in 2 weeks. If toxicity is associated with illness and subsequently resolves, hydroxyurea should be restarted at previous dose and dose escalation may continue. If there is no associated illness, restart hydroxyurea at 5 mg/kg/day lower than dose associated with cytopenias. If unable to escalate hydroxyurea dose beyond 20 mg/kg/day due to cytopenias, contact hematology for additional assistance.

Contraindications:

- Pregnancy, breastfeeding
- Use with caution in other hepatically metabolized medications (such as certain anti-epileptics)

Laboratory Monitoring

- Once MTD has been achieved, laboratory monitoring should include CBC with differential and reticulocyte count every 2-3 months. CMP (BMP + liver function tests) should be obtained every 6 months.
- Increases in MCV and HbF indicate an appropriate laboratory response to hydroxyurea
- Pregnancy testing should be obtained routinely in sexually active adolescents and adults as clinically indicated.

Treatment Endpoints

Patients should be counseled that hydroxyurea therapy may require up to 6 months at the maximum tolerated dose before clinical response is seen. Treatment efficacy is defined as a decreased frequency of sickle cell related-complications (e.g. VOC, ACS), increased HbF, or improved anemia with absent or acceptable treatment-related side effects.

- Effectiveness of Hydroxyurea depends on adherence to daily dosing.
- If a dose is missed, the usual dosing should be continued on the next day (do not double dose to make up for missed doses.)
- Continue Hydroxyurea therapy during hospitalizations and acute illness, unless a dose limiting toxicity is present as described above.

Hydroxyurea treatment may be discontinued for the following reasons:

- o No improvement in clinical status despite dose escalation to MTD and reassurance of adherence.
- o Documented pregnancy or refusal to use contraception in males or females of child bearing age.

References

1. National Heart, Lung, and Blood Institute. Evidence-Based Management of Sickle Cell Disease: Expert Panel Report, 2014. Bethesda, MD: National Heart, Lung, and Blood Institute, US Department of Health and Human Services; 2014.