Hydroxyurea in Sickle Cell Disease: A Treatment Guide

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Before starting Hydroxyurea

Indications

All patients with diagnosed sickle cell disease **'SS' or 'Sickle-β Thalassemia'** after the age of 6 month.

Contraindication

1. Pregnancy

Precaution

2. Breastfeeding – breastmilk should be discarded for first 3 hours of taking hydroxyurea.
3. Stop at least 3 months before conception (stop in both male and female)

Baseline Investigation before starting Hydroxyurea.

- Complete blood count – Hb, MCV, WBC, Absolute neutrophil count
- SGPT, Sr. Creatinine
- UPT (must in every woman of reproductive age group with doubtful LMP, or in every visit)
- Reticulocyte count (if available)

How to start hydroxyurea?

- Start Hydroxyurea 20 mg/kg/day in children and 15 mg/kg/day in adults.
- It can be taken once or twice daily, should be taken at the same time every day.
- It can be taken with or without food.
- **For children** – 1 capsule of 500 mg Hydroxyurea is dissolved in 10 ml of drinking water and give according to the dosing chart.
- **In chronic kidney disease** – if creatinine clearance is **< 60 ml/minute** or in end stage renal disease start Hydroxyurea with 5 - 10 mg/kg/day with smaller increment.

Preparing hydroxyurea solution for children

- Hydroxyurea is currently available as 500mg capsules. No liquid preparation is available. Parents need to be counselled that one capsule of hydroxyurea need to be dissolved in water as described above and give to the child. This solution can be safely stored in room temperature for use without losing its potency.

Hydroxyurea dose chart in SCD

*Hydroxyurea should never be used in sickle cell carrier (AS)

Pediatric dose (age<12 years)- start with 20 mg/kg/day, titrate to maximum tolerated dose or up to 35 mg/kg/day which ever is less.

***Dissolve one capsule in 10 mL drinking water**

Weight Bands	Mon	Tue	Wed	Thurs	Fri	Sat	Sun	No of 500mg capsules/month
05-08 kg	2mL	2mL	2mL	2mL	2mL	2mL	2mL	10*
08-12 kg	5mL	5mL	5mL	5mL	5mL	5mL	-	16*
12-16 kg	1	-	1	-	1	-	1	20
16-20 kg	1	1	1	1	1	-	-	24
20-25 kg	1	1	1	1	1	1	1	30
25-30 kg	1	1	1	1	1	1	2	36
30-35 kg	1	1	1	1	1	2	2	40
35-40 kg	1	2	1	2	1	2	1	46
40-45 kg	2	2	2	2	2	2	2	60

Adult dose (age>12 years)- start with 15 mg/kg/day, titrate to maximum tolerated dose or maximum daily dose is 2000 mg/day whichever is less.

Weight Bands	Mon	Tue	Wed	Thurs	Fri	Sat	Sun	No of 500mg capsules/month
25-30 kg	1	1	1	1	1	1	-	28
30-35 kg	1	1	1	1	1	1	1	30
35-40 kg	1	1	1	1	1	1	2	36
40 kg and above	1	2	1	2	1	2	1	46

HYDROXYUREA TREATMENT FLOW CHART

Contraindication

1. Pregnancy

Precaution

2. Breastfeeding – breastmilk should be discarded for first 3 hours of taking hydroxyurea.
3. Stop at least 3 months before conception (stop in both male and female)

Start Hydroxyurea – See dosing chart
< 12 years – 20 mg/kg/day
> 12 years - 15 mg/kg/day
(In CKD – 5 – 10 mg/kg/day)

Monitor CBC every month for first 3 months. Then once in 2 – 3 months

Absolute Neutrophil counts	> 1500	< 1500
Hemoglobin	> 4.5 gm%	< 4.5 gm%
Platelets	> 80,000	< 80,000

Continue Hydroxyurea as per the dose chart.

Increasing dose
- After 8 – 12 weeks of starting Hydroxyurea, if clinical response is **sub-optimal***, dose is increased by 5 mg/kg/day.
- Dose can be increased after every 8 – 12 weeks until there is evidence of clinical benefit.
- Dose can be raised maximum up to 35 mg/kg/day

If any one of three values is reduced **Stop Hydroxyurea for 2 - 3 weeks** and do repeat CBC after 1 week. Check this weekly. Once improved

Monitor SGPT, Sr. Creatinine (every 6 - 12 months)

SGPT	> 2 times normal value
Sr Creatinine	> 1.5 times previous values

Repeat SGPT and Sr Creatinine after 2 - 3 weeks***. If it's normal***

Restart at lower dose:
reduce by either.
- 2.5-5mg/kg/day in children
- 1500 mg/week in adults (3 cap of 500 mg)

* **Sub-optimal response**
Persistent

1. Pain episodes
2. Need of blood transfusion
3. Other crises or hospitalisation

How do we know that the patient is responding to hydroxyurea?

- **Clinical and haematological benefit of hydroxyurea takes up to 8 – 12 weeks to appear**. Thus, it is used as the preventive therapy in sickle cell disease and not in acute crisis conditions.
- There is no specific feature that can be used to determine whether an individual treated with Hydroxyurea will obtain a clinical benefit or the magnitude of the benefit. Some features can guide if the hydroxyurea is working or not *(could not find clear criteria*).
- Reduction in pain episodes.
- Increase in baseline haemoglobin.
- Increase in MCV value.
- Reduction in WBC.
- Overall feeling of wellbeing – better school attendance, playing, less frequent falling ill.
- If improvement is sub-optimal, dose of the hydroxyurea needs to be increased as described below.

How to increase dose of Hydroxyurea to get desired benefit?

- The therapeutic dose range of Hydroxyurea is 15 – 35 mg/kg/day. Hydroxyurea
    - is initiated at a low dose and gradually increased to a dose that does not cause severe hematologic toxicity.
- After 8 – 12 weeks of starting Hydroxyurea, if clinical response is sub-optimal, dose is increased by 5 mg/kg/day. Dose can be increased after every 8 – 12 weeks until there is evidence of clinical benefit.

When to stop increasing dose of Hydroxyurea?

Till patient is reached at Maximum Tolerated Dose (MTD). MTD can be reached with following criteria.

- Clinical benefit is attained **OR**
- Maximum dose of 35 mg/kg/day or 2000 mg/day is achieved **OR** one of the following criteria is attained.
    1. Absolute neutrophil count (ANC) - 1500 – 3000/microL
    2. Platelet count - 80,000 – 150,000/microL
    3. Absolute reticulocyte count (if available) – 80,000 – 100,000/microL

When to stop hydroxyurea?

Hydroxyurea should be continued life-long. It needs to be ***halted*** for 2 – 4 weeks in following situations.

- When ***any one*** of these is observed
    - Absolute Neutrophil count is < 1500.
    - Platelet count is < 80,000.
    - Hemoglobin is < 4.5 gm%
    - Serum creatinine increased by > 1.5 times of baseline value or value in previous visit.
    - SGPT/ALT increased by > 2 times of the normal range.
    - Reticulocyte count is < 80,000.

Stop Hydroxyurea for 1 – 2 weeks and check CBC every 1-2 weeks.

- Both women and men attempting conception, and during pregnancy and breastfeeding.

How to re-start hydroxyurea?

Restart Hydroxyurea when,

- Absolute Neutrophil count is > 1500.
- Platelet count is > 80,000.
- Hemoglobin is > 4.5 gm%

Restart with reduced dose than previous, reduce by either.

- 2.5 – 5 mg/kg/day or
- 1500 mg/week or 3 capsules/week of 500 mg

Hydroxyurea in pregnancy and breastfeeding

- Hydroxyurea needs to be stopped 3 months before planning conception among women.
- Among men – It is advisable to stop Hydroxyurea 3 – 6 months before planning conception.
- During pregnancy – It should be stopped. If there is risk of complications such as vaso-occlusive crisis during pregnancy starting hydroxyurea should be discussed with obstetrician followed by patient's counselling.
- During breastfeeding – *(There are no clear guidelines*) Breastmilk for first three hours after taking Hydroxyurea should be discarded.

Adverse effect of hydroxyurea and its management

Evidence from over 30 years of use in individuals with SCD has demonstrated that long-term use of hydroxyurea is not associated with clinically significant adverse effects on growth or development.

S. N.	Side effects	Monitor	Treat
1	Headache, nausea/vomiting, abdominal pain	History taking	Start night-time dose. Symptoms subsides with time
2	Myelosuppression (decreased TLC, Neutrophil count, platelet count)	Monitor TLC, DLC, Platelet count	Withhold Hydroxyurea for 1-2 week and restart as described above.
3	Hepatic & Renal dysfunction	Monitor Serum creatinine and SGPT	Withhold Hydroxyurea for 1-2 week and restart as described above.
4	Skin ulcers, erythematous skin changes	History and examination	Stop Hydroxyurea. Start supportive treatment. Restart Hydroxyurea once symptoms are relieved with low dose.
5	Teratogenicity	History and UPT (in childbearing women)	Stop hydroxyurea
6	Pulmonary-interstitial pneumonitis	Monitor for respiratory symptoms and where needed chest X-ray and CT scan	Stop hydroxyurea
7	Neurological-rarely dizziness, disorientation, seizures	History	Stop hydroxyurea

How to assess non-response to hydroxyurea?

- Hydroxyurea should be continued for at least 6 months on the maximum tolerated dose (explained above) in order to assess a response.
- Non-response to hydroxyurea is rare.
- Patients with SCD on Hydroxyurea who fail to show an adequate increase in HbF (foetal haemoglobin) are more likely to be non-compliant with medication than non-responders.
- It needs to be ensured that the patient is taking regular treatment by checking with parents and family members, and if needed through home visits.
- If the patient is taking the drug as directed and not experiencing any clinical benefit and is not having the expected hematologic changes, we may discontinue the medication, as the risks of continuing therapy, albeit small, may no longer be justified.

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