Hydroxycarbamide (Hydroxyurea) Use in Paediatric Sickle Cell Disease

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Written by: Dr Emma Astwood
Peer reviewer: Dr Jeanette Payne
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Intended Audience

This document contains information and clinical guidelines for management of children attending the Sheffield Children’s Hospital Haematology department. This guideline is for staff at SC(NHS)FT involved in the care of children with sickle cell disease who are taking Hydroxyurea.

Purpose

This document is to be referred to for children receiving/starting Hydroxyurea for the management of their sickle cell disease who attend Sheffield Children’s Hospital Haematology department. It will give instructions on how to start, monitor and dose changes. It is for guidance only as all decisions should be made by a consultant haematologist.

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The decision to treat with Hydroxycarbamide (also called Hydroxyurea) should be made by a consultant haematologist after discussion with the child and their parents, outlining the possible benefits and side effects.
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1. Indications for Treatment

The benefits of hydroxycarbamide should be discussed with all children and adolescents with Sickle cell disease (HbSS) and Sickle Cell/Beta 0 Thalassaemia (HbSβ°) to enable informed joint decision-making. Hydroxycarbamide should be offered to all infants and children >9 months to reduce sickle cell complications (pain, dactylitis, acute chest syndrome, anaemia) and to impact on reduction in mortality.

Specific indications to commence Hydroxycarbamide include:

- 3 or more sickle cell associated moderate/severe painful crises in a 12 month period
- Children who suffer from sickle cell pain that interferes with daily activities and affects quality of life
- In children with HbSS/HbSβ° and a history of severe and/or recurrent acute chest syndrome

Consider hydroxycarbamide in the following situations:

- Children receiving regular transfusions for abnormal transcranial Doppler (TCD) – these children can switch if they have received at least 1 year of regular transfusions and have no magnetic resonance angiography-defined severe vasculopathy.
- Children with TCD velocities in the 'conditional range' should be treated with hydroxycarbamide to help prevent progression from conditional to abnormal TCD velocity.
- In children with a previous history of acute ischaemic stroke or infarct consider as second line therapy to prevent stroke when transfusions are contraindicated.
- In children with sickle nephropathy with persisting proteinuria despite angiotensin-converting-enzyme inhibitors consider the addition of hydroxycarbamide.
- In children with chronic hypoxia
- In children who suffer from symptomatic chronic anaemia
- In children with sickle cell disease with genotypes other than SS and Sβ° Thalassaemia who have recurrent pain, acute chest syndrome or episodes of hospitalisation.

A very few patients with thalassaemia intermedia benefit from low dose Hydroxycarbamide and need monitoring, but do not need aggressive dose escalation.
2. Treatment

Patients and parents must be willing to comply with the treatment regimen and the increased monitoring required. Patients should be encouraged to maintain a high daily oral fluid input.

Baseline investigations must be completed before commencing therapy: see below in monitoring.

There is an information sheet available which should be given to parents after discussion with the consultant haematologist and before starting treatment ‘Starting Hydroxyurea (Hydroxycarbamide) for sickle cell disease: Information for families’ PIS 1422 available via Dr Emma Astwood (Red Cell Lead Consultant) or Louise George/Shaun Emmitt (Benign Haematology Nurse Specialists)

| Hydroxycarbamide (Hydroxyurea) oral | Capsules 500mg, tablets 100mg (the tablets are not soluble but can be dispersed in water) | Liquid (must be ordered in advance, short expiry 30 days from opening) | 20mg/kg each evening. Increase every 8-12 weeks by 5mg/kg according to response and toxicity to maximum 35mg/kg/day. |

All hydroxycarbamide is prescribed on Chemocare and a record of the blood test results can be viewed on that system. When authorising Hydroxycarbamide please contact Pharmacy by phone to let them know a prescription has been authorised, or if also prescribing other drugs for that patient, write on the HOP (Hospital Out Patient) prescription that Hydroxycarbamide has been authorised.
Response

Response is defined as:

- fewer painful crises,
- HbF increase to 15-20%, or more
- increased Hb if severely anaemic,
- improved well-being,
- acceptable myelotoxicity.

Toxicity

Toxicity is defined as:

- Myelotoxicity: Neutrophils <1.0 x 10^9/L
  Or platelets <80 x 10^9/L
  Or Hb <45g/L
Or Retics <80 x 10^9/L (unless Hb >90g/L)

- Increase in ALT to >2 x normal
- Increase in creatinine to >2 x baseline

If toxicity occurs stop hydroxy carbamide and monitor FBC weekly until:

- Neutrophils >1 x 10^9/L
- and platelets >80 x 10^9/L
- and Hb >45g/L
- and retics >80 x 10^9/L –

Restart at the same dose if transient drop in counts or reduce by 5mg/kg/day.

This defines the maximum tolerated dose (MTD) - do not increase further. (but remember a dose increase may be needed due to weight gain to maintain the MTD
Monitor FBC after 2 weeks after any modifications.

Dose Escalations:

If after 8-12 weeks the FBC shows:

- Neutrophils >2 x 10^9/L
- and platelets > 150 x 10^9/L
- and Hb >60g/L
- and retics >80 x 10^9/L (unless Hb >90g/L)
Increase hydroxycarbamide by 5mg/kg/day every 8-12 weeks until maximum dose of 35mg/kg/day is reached. Monitor FBC 2 weeks after any dose increase.

Document in the notes any good or adverse effects and document dose (including mg/kg), and when the patient is to return for blood tests and when for clinical review. Remind the parents of what side effects to look out for (see below) and keep the GP informed with letters from clinic. HbF and MCV can be used to monitor effect and compliance.

Failure to respond i.e. failure of Hb F (or MCV) to increase, may be due to biological inability to respond to treatment or poor compliance with treatment.

In the absence of transfusion support or illness suppressing erythropoiesis, a trial period of 12 months is probably adequate and hydroxyurea can be stopped if no benefit is experienced, despite increasing dosage as described above. Some patients claim subjective benefit even without increase in HbF.
3. Monitoring

Tests:

<table>
<thead>
<tr>
<th>Pre-treatment</th>
<th>After dose increase/decrease</th>
<th>On maintenance dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight</td>
<td></td>
<td>Every 6 months</td>
</tr>
<tr>
<td>FBC with MCV</td>
<td>2 weeks after increase or decrease. Monitor weekly whilst off treatment due to toxicity.</td>
<td>every 8 – 12 weeks</td>
</tr>
<tr>
<td>Reticulocytes</td>
<td>2 weeks after commencing treatment or dose change</td>
<td>every 8 – 12 weeks</td>
</tr>
<tr>
<td>HbF%, (high HbF &gt;10% does not preclude a favourable response to therapy.)</td>
<td>Every 8 – 12 weeks</td>
<td>6 monthly</td>
</tr>
<tr>
<td>U+Es and LFTs</td>
<td>2 weeks after increase, or 1 week after recommencing after renal/hepatic toxicity</td>
<td>every 8 – 12 weeks</td>
</tr>
</tbody>
</table>

Ask about side effects:

- rash/hyperpigmentation of skin
- nails – flaky/brittle
- GI symptoms
- hair loss
- bleeding/bruising tendency
- leg ulcers
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4. Cautions

- Special caution should be taken in patients with abnormal renal or hepatic function.
- Advise about teratogenicity and the need for contraception in teenage patients.
- Parents should be advised that capsules should not be opened.
- Parents should be advised to report symptoms suggestive of infection or bleeding promptly.
- Some patients have had a marked response to Hydroxyurea – consider dose reduction/venesection if Hb >100g/L because of effect on blood viscosity.
- Concomitant use of hydroxycarbamide with a live virus vaccine may result in severe infection. Current advice is to avoid yellow fever vaccine. Other live vaccines are deemed safe to give.

References:

Sheffield Teaching Hospitals Sickle cell disease guidelines.

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