Hydroxyurea (Hydroxycarbamide) -
Guidelines for treating children with Sickle Cell Disease

Patient selection

The benefits of hydroxycarbamide should be discussed with all parents/carers of children with Sickle Cell Anaemia (HbSS and Hb/Sβ^0) to enable informed joint decision-making. It may also be useful in selected patients with other types of sickle cell disease such as HbSC disease.

Indications:

As a standard of care, Hydroxyurea should be discussed with parents/carers of all children with HbSS/Sβ^0 thalassemia in the first year, and then the information revisited at a later date as appropriate. In the USA some centres offer it as early as 9 months of age, irrespective of clinical severity (Wang et al, 2011).

It should also be offered to patients with severe complications:

- 3 or more episodes of acute vaso-occlusive painful episodes each year, which are causing significant disruption to education or family life;
- Recurrent or severe Acute Chest Syndrome

Other indications include:

- conditional velocities on Transcranial Doppler scans (TCD)
- significant cerebral vasculopathy when blood transfusions are unacceptable
- progressive cerebral vasculopathy despite adequate blood transfusions
- persistent low haemoglobin (<60g/l)
- hypoxaemia
- significant proteinuria
- patients keen to avoid blood transfusions if at all possible, those with alloantibodies or a history of severe transfusion reactions
- preoperative preparation when blood transfusions are not acceptable
- patients who are changing from regular blood transfusions to maximum tolerated dose hydroxyurea for primary stroke prevention (see section below).

Use in patients with Sickle Cell Disease (HbSC, HbSE etc):

Hydroxyurea may be helpful to a minority of patients with severe complications, and therefore, can be offered to selected patients. However, the blood result ranges for monitoring and dose adjustment are different for those shown for Sickle Cell Anaemia (HbSS) and care must be taken to avoid increases in haemoglobin >100g/L, when venesection should considered.

Parent/patient information and Consent

Patient information leaflets should be given in addition to a full discussion of risks, benefits and side effects, including dose-dependent bone marrow suppression.

Hydroxyurea is a form of chemotherapy and informed consent is essential; discussions should be recorded in the notes but it is not necessary for the child or parent to sign anything.

Both males and females should be advised about the theoretical risk of teratogenicity, and the need to avoid becoming pregnant or conceiving a child whilst taking hydroxyurea; this is particularly important for the teenage patients.
The importance of adherence to the effectiveness of Hydroxyurea should be discussed. If patients miss a dose they should not take a double dose.

Fertility

There is no available evidence in females or males that hydroxycarbamide affects fertility; in males, the effect of hydroxycarbamide on spermatogenesis remains unclear. Most studies are case reports with few prospective studies, making evidence-based counselling of the risk of developing sperm abnormalities or infertility challenging. Possible irreversible subfertility should be discussed with the parents of all boys considering hydroxyurea, and sperm analysis and banking should be offered to boys who are pubertal and arranged before commencing treatment.

Many patients and carers may want to think about the issues and discuss things further, a follow-up appointment in 2-4 weeks to discuss things further should be offered.

Contacts for Sperm Analysis and Banking
Assisted Conception Unit (Guys & St Thomas'): 020 7188 2300
Assisted Conception Unit (King's) 020 3299 9000 Ext 35390 email: kch-tr.fertility@nhs.net
Andrology Dept Hammersmith Hospital (referrals from St George's): 020 3313 4680 email: lia.joannou@nhs.net

Toxicity

- Reversible increase in skin and nail pigmentation, alopecia
- Haematological – myelosuppression – see below
- Renal
- Hepatic
- Gastrointestinal – rarely - nausea and vomiting, diarrhoea – antiemetics not usually required
- Teratogenic – Hydroxyurea may, theoretically harm the unborn fetus although there is no clear human evidence of this.
- Fertility in boys – some evidence of reduced fertility in males with Sickle Cell Anaemia – exact role of Hydroxyurea unclear
- Longterm marrow effects uncertain
- No evidence of increase in malignancy in patients with SCD taking Hydroxyurea.
- Drug interactions

Baseline investigations

Prior to commencing hydroxyurea these should include:

- FBC and reticulocytes with differential count
- HbF%
- Renal function
- Hepatic function including ALT

The paediatric Clinical Nurse Specialist should be informed of all patients starting hydroxyurea to include them on the list for review in the Multidisciplinary Team Meeting.

Administration and Formulation

Hydroxyurea is given orally once a day. If a dose is missed, a double dose should not be taken.

Hydroxyurea is available as:

- Hydroxyurea capsules 500mg

Hydroxyurea capsules can be opened and the powder given to the child with a small amount of water or juice. This works well for some parents, but it should be explained that hydroxyurea is a form of chemotherapy and should not come into contact with skin or anybody other than the patient; this will mean washing the spoon very carefully and wiping up any spills immediately.
Because the capsules are only available as 500mg, giving the exact calculated daily dose can be difficult, and in general it is satisfactory to give alternating day doses such as 500mg alternating with 1g to achieve an average daily dose of 750mg, although this should be explained carefully to the carers and child.

- SIKLOS 100mg tablets

SIKLOS tablets can be mixed with a small amount of water just before being taken.

- Hydroxyurea Liquid (100mg/ml)

Liquid is often most suitable for children < 7 years old, although it has a short-shelf life, and can be difficult to obtain from local hospitals for shared-care patients. It is possible to arrange for local hospitals or pharmacies to dispense the drug, and this should be discussed with the pharmacists here.

Recommended Dose

The therapeutic dose range of hydroxyurea is 15-35 mg/kg daily and for some indications clinical response at the lower end of the range is sufficient (Lowest Effective Dose), whilst for other indications, particularly involving cerebrovascular disease, the dose is escalated to the higher end of the range, or until myelosuppression occurs (Maximum Tolerated Dose – MTD).

Most children start at a dose of 20 mg/kg daily (to the nearest 100mg), unless there is particular concern about the risk of myelosuppression, when lower doses should be used.

Dose Adjustment and Monitoring

For most patients, the dose is increased by 5mg/kg every 8-12 weeks until there is evidence of clinical benefit, which is the Lowest Effective Dose.

FBC, reticulocytes, renal and hepatic function and HbF% should be checked 2 weeks after starting, and after any dose increase, until the dose is stable and then every 8–12 weeks.

Assess clinical response and if sub-optimal, increase by 5 mg/kg every 8 weeks (maximum dose 35 mg/kg/day) until target ranges are reached or stopping if haematological toxicity occurs (see below):

Target ranges:

- Neutrophils 2.0-3.0 x 10^9/l
- Platelets ≥ 100 x 10^9/l
- Reticulocytes ≥ 80 x 10^9/l

If cytopenias occur a dose adjustment should be made - see table below for dose adjustment for haematological toxicity. This is particularly important in patients where the aim is to increase the dose to Maximum Tolerated Dose (MTD) who are more likely to experience myelosuppression.

Hydroxyurea Monitoring and Dose Adjustment when aiming for Maximal Tolerated Dose (MTD)

Neutrophils x 10^9/l	Reticulocytes x 10^9/l	Platelets x 10^9/l	Dose Adjustment
>1.0	≥ 80 or ≥ 1%	≥ 80	Continue current dose
< 1.0	< 80 or <1% Unless the Hb >90g/l	< 80	**Stop treatment** and recheck FBC weekly until • Neutrophils >1.0 x 10^9/l • Platelets >80 x 10^9/l, • Hb >45g/l and • Reticulocytes >80 x 10^9/l (unless Hb>90g/l) **Then restart at lower dose -** reduce by either • 2.5-5 mg/kg/day or • 500 mg/day (1 capsule) or • 100 mg/day (SIKLOS 1 capsule) Monitor FBC after 2 weeks and follow as above for dose modifications. **This is the Maximum Tolerated Dose (MTD**)

Other toxicities:

Renal: Increase in serum creatinine ≥ 50% baseline
Hepatic: > 100% increase in ALT

Stop Hydroxyurea, contact the family directly with instructions and arrange further tests to monitor recovery.

Dose adjustment to Maximum Tolerated Dose (MTD) for patients with cerebrovascular disease

For indications such as those involving cerebrovascular disease the dose should be increased every 6 - 8 weeks by increments of 5 mg/kg/day, to a maximum of 25 - 35 mg/kg/day (maximum dose 2000 mg), or until limited by myelosuppression (Maximum Tolerated Dose – MTD):

Target blood results for MTD: Neutrophils 2.0-3.0 x 10^9/l but lower counts are tolerated (see below). The aim is for a total daily dose of Hydroxycarbamide 25 - 35 mg/kg/day.

If neutrophils < 1.0 x 10^9/l, platelets < 80 x 10^9/l or reticulocytes < 80 x 10^9/l, discontinue for 2 weeks or until recovered (see above for monitoring), and restart a lower dose (usually the dose prior to the most recent dose increase). This is the Maximum Tolerated Dose.

Parents should also be advised to bring the child to hospital for assessment and urgent blood tests if they develop symptoms suggestive of sepsis, or unusual bruising or bleeding, because of the possible risk of bone marrow suppression and neutropenia or thrombocytopenia.

Inform the GP/Shared Care Hospital team/in writing of any dose adjustments and blood test results

Admission to Hospital
Hydroxyurea should be continued during and admission unless the blood results indicate bone marrow suppression, the patient is septic or there is bleeding with thrombocytopenia.

Withdrawal of Hydroxyurea
Patients should usually be treated for at least six months before deciding to stop hydroxyurea because of lack of benefit. When hydroxyurea is associated with clinical improvement, it is typically continued for at least 2-3 years; consideration is then given to stopping it, depending on the initial indications, the views of the child and carers, and circumstances at that time. In general it is better to stop hydroxyurea during school holidays and not just before important events such as exams.

Reference:

Guidelines for the use of Hydroxycarbamide in children and adults with sickle cell disease Qureshi *et al*: British Journal of Haematology 2018 181, 460-475

For further info: The telephone numbers below are available Monday-Friday, 9am-5pm. Outside these hours, please contact your GP or go to your local Emergency Department (A&E).

Guy's and St Thomas' Hospital Consultant Haematologist: Jo Howard / Rachel Kesse-Adu Telephone: 02071882741 Out of hours – Haematology SpR or on call consultant via switchboard (02071887188)

Clinical Nurse Specialists: Neil Westerdale/Luhanga Musumadi / Tolu Adeosin Telephone – 020 7188 7188 (switchboard) then bleep 1843

Kings College Hospital Consultant Haematologist: Moji Awogbade / Sara Stuart-Smith Telephone: 02032999000 Out of hours – Haematology SpR or on call consultant via switchboard (020 32999 000)

Clinical Nurse Specialists: Giselle Padmore-Payne and Fester Ike Telephone – 020 3299 4968

St George's Hospital Consultant Haematologist: Elizabeth Rhodes and Julia Sikorska Telephone: 020 87250885 Out of hours Haematology SpR via Switchboard 0208 6721255

Clinical Nurse Specialists: Carol Rose Telephone – Switchboard 0208 6721255 or 07500 835735

Additional contacts can be found on the STSTN website

Formatted: Font: Bold
Formatted: Font: (Default) Arial, Bold, Not Highlight
Formatted: Font: (Default) Arial, 9.5 pt, Not Highlight
Formatted: Normal
Formatted: Font: (Default) Arial, 9.5 pt
Formatted: Font: (Default) Arial
Formatted: Font: Bold
Formatted: Normal, No bullets or numbering