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

Document Information			
Version:	2	**Date:**	July 2014
Authors (incl. job title):	Dr Moira Dick Consultant Paediatrician Sandra O'Driscoll Clinical Nurse practitioner		
Responsible committee	**Child Health Clinical Governance & Risk Committee**		
Review date:	July 2016		
Target audience:	Paediatricians, Paediatric haematologists, Haematologists , Clinical Nurse specialist		
Stakeholders/ committees involved in guideline development :	Paediatric Haematology		

For Child Health Clinical Guidelines Groups' use only	
Assessed by:	**Child Health Clinical Guidelines Group**
Assessment date:	31/07/2014
Approved by :	**Child Health Governance and Risk Committee**
Approval Date	16/09/2014
Author notified:	20/09/2014

For Trust Clinical Guidelines Groups' use only	
Ratified by:	
Date ratified:	
Reference No.:	
Date when guideline comes into effect:	

Document History

Document replaces: *please include version number .* 1 (May 2010)

Consultation distribution (before ratification)

Sent to	Version	Date	Actions taken as a result
Professor David Rees	2	May 2014	Amendment re starting dose
Dr Sue Height	2	May 2014	Amendment re taking action if febrile
Sandra O'Driscoll	2	May 2014	Amendment re change of name
Shereen Boreland	2	July 2014	Amendments accepted

Reviews and updates (including CGG comments)

Date	New version no.	Summary of Changes	Author of change/s

Dissemination schedule (after ratification)

Target audience(s)	Method	Person responsible
S Thames network	Network email	Professor David Rees

Hydroxycarbamide(hydroxyurea) in the management of children with sickle cell disease

Abstract Page

Background

This guideline covers indications for the use of hydroxycarbamide in children with sickle cell disease, frequency of blood testing for monitoring purposes and guidance for when the medication needs to be stopped . It is aimed at the paediatric, haematology and nursing members of the multi-disciplinary team and will be disseminated more widely to members of the South Thames clinical network for haemoglobinopathies.

Contents of guideline:

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

This guideline is aimed at all children in King's College Hospital with Sickle Cell Disease who are taking or might take hydroxyurea (also called hydroxycarbamide). The guideline applies to patients with sickle cell disease who are currently under the care of the Paediatric Haematology team. It is mainly aimed at being a tool for the medical team managing these patients, but any member of the multidisciplinary team may find it useful.

1. Patient selection

Each patient must be evaluated carefully before starting hydroxyurea. In general, it should be considered when patients are having significant problems related to their condition. It is mostly used in children with sickle cell anaemia (HbSS) and HbS/ thalassaemia, but may also be useful in other types of sickle cell disease such as HbSC disease. The two main indications at the moment are:

(a) More than three episodes of acute pain each year, which are causing significant disruption to education, or family life.
(b) Recurrent or severe acute chest syndrome

Other less established indications include:

(a) conditional velocities on transcranial Doppler scans
(b) significant cerebral vasculopathy when blood transfusions are unacceptable
(c) progressive cerebral vasculopathy despite adequate blood transfusions
(d) persistent low haemoglobin (<6g/dl)
(e) hypoxaemia
(f) significant proteinuria
(g) patients keen to avoid blood transfusions if at all possible
(h) preoperative preparation when blood transfusions are not acceptable

The patients with less established indications should be discussed at the multidisciplinary meeting before starting. There is a school of thought in the USA that hydroxyurea should be recommended for all children with sickle cell disease regardless of symptomatology in order to prevent organ damage.

2. Parent information and Consent

Parent information leaflets are available and should be given to parents in addition to a full discussion of risks, benefits and possible side effects, including possible bone marrow damage and subfertility. Many parents and families may want to think about the issues and discuss things further, and a follow-up appointment in 2-4 weeks should be offered. Possible irreversible subfertility should be discussed with the parents of all boys considering hydroxyurea. Hydroxyurea is a mild 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.

3. Baseline investigations

Prior to commencing hydroxyurea these should include:

FBC and reticulocytes
HbF%
Renal function
Hepatic function including ALT

4. Recommended Dose

The therapeutic dose of hydroxyurea ranges from 15-35 mg/kg daily. Most children should be started on a dose of 20mg/kg daily, unless there is particular concern about the risk of myelosuppression, when lower doses should be used. The dose is typically increased by 5mg/kg every 2-3 months until there is evidence of clinical benefit. For most patients, the lowest effective dose as assessed by clinical improvement is used. However, for some indications, such as those involving cerebrovascular disease, the dose should be increased until limited by myelosuppression.

5. Formulation

Hydroxyurea is available as 500mg capsules and as a specially manufactured liquid. Liquid is often most suitable for children under the age of seven years, 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.

It is possible to open hydroxyurea capsules and give the powder 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 only come as 500mg, it is sometimes difficult to give the exact calculated dose or increment; in general it is satisfactory to give alternating day doses such as 500mg alternating with 1g, although this should be explained carefully to the carers and child.

6. Monitoring of Patients

Order sets are on EPR under paediatrics/haematology

- The paediatric clinical nurse specialist should be informed of all patients starting hydroxyurea to allow them to be included on the list for review in the multidisciplinary meeting.
- FBC, reticulocytes, renal and hepatic function should be checked 2 weeks after starting.
- FBC, reticulocytes, HbF%, renal and hepatic function should be checked every 1-3months.
- If the dose is increased, blood tests should be performed after two weeks on the higher dose, before resuming 1-3 monthly monitoring.
- Patients on hydroxyurea should still have annual review blood tests and investigations performed, including transcranial Doppler scanning.
- Contact the family directly and inform the GP about any dose adjustments based on the blood test results.
- Stop hydroxyurea if toxicity occurs – contact the family directly with instructions and arrange further tests to monitor recovery. Markers of toxicity include:

  Haematological:
  Neutrophils $< 1.0 \times 10^9/l$
  Platelets $< 80 \times 10^9/l$
  Reticulocytes $< 80 \times 10^9/l$
  Renal:
  $\geq$ 50% or more increase in serum creatinine
  Hepatic
  > 100% increase in ALT

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

7. Admission to hospital

Hydroxyurea should be continued during an admission unless the blood results indicate bone marrow suppression or the patient is septic.

8. 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.

References

1. Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on frequency of painful crises in sickle cell anemia. *N Engl J Med* 1995; **332**: 1317-22.
2. Strouse JJ, Lanzkron S, Beach MC et al. Hydroxyurea for sickle cell disease: a systematic review for efficacy and toxicity in children. *Pediatrics* 2008; **122**: 1332-42.
3. Berthaut I, Guignedoux G, Kirsch-Noir F et al. Influence of sickle cell disease and treatment with hydroxyurea on sperm parameters and fertility of human males. *Hematologica* 2008; **93**: 988-93.
4. Zimmerman SA, Schultz WH, Burgett S, Mortier NA, Ware RE. Hydroxyurea therapy lowers transcranial Doppler flow velocities in children with sickle cell anemia. *Blood* 2007;**110**: 1043-47.
5. Singh SA, Koumbourlis AC, Aygun B. Resolution of chronic hypoxemia in pediatric sickle cell patients after treatment with hydroxyurea. *Pediatr Blood Cancer* 2008; **50**: 1258-60.
6. Fitzhugh CD, Wigfall DR, Ware RE. Enalapril and hydroxyurea therapy for children with sickle nephropathy. *Pediatr Blood Cancer* 2005; **45**: 982-85.