SPAH
SCOTTISH PAEDIATRIC AND ADULT HAEMOGLOBINOPATHIES NETWORK

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Use of Hydroxycarbamide in adults with Sickle Cell Disease

NOTE

This guideline is not intended to be construed or to serve as a standard of care. Standards of care are determined on the basis of all clinical data available for an individual case and are subject to change as scientific knowledge and technology advance and patterns of care evolve. Adherence to guideline recommendations will not ensure a successful outcome in every case, nor should they be construed as including all proper methods of care or excluding other acceptable methods of care aimed at the same results. The ultimate judgement must be made by the appropriate healthcare professional(s) responsible for clinical decisions regarding a particular clinical procedure or treatment plan. This judgement should only be arrived at following discussion of the options with the patient, covering the diagnostic and treatment choices available. It is advised, however, that significant departures from the national guideline or any local guidelines derived from it should be fully documented in the patient's case notes at the time the relevant decision is taken.

Hydroxycarbamide is currently the only medication licensed in the UK for the prevention of painful crises in sickle cell disease. It has been shown in a large randomised-controlled study to decrease the frequency of painful vaso-occulusive crises and of chest crises in adults with homozygous sickle cell disease. It has more recently been shown to lessen the risk of other sickle-related complications and there is evidence to indicate a survival benefit.

Side effects include bone marrow suppression with the need for regular blood monitoring, gastro-intestinal disturbances, and increased skin and nail pigmentation. It is potentially teratogenic so contraception should be used whilst on the drug. It may affect male fertility and sperm storage should be discussed for males before commencement. There is no evidence of leukaemogenesis with long term follow-up of patients on the drug.

The main aim of therapy is to optimise HbF% without causing excess bone marrow suppression – achievement of maximum tolerated dose.

Indications for use in adults

It is good practice to discuss the benefits and risks of hydroxycarbamide with all patients with sickle cell disease (HbSS/Sβ^0) regardless of the severity of their condition.

Moderate or severe sickle cell disease (HbSS/Sβ^0) – patients should be offered hydroxycarbamide therapy.

- 3 or more episodes of moderate or severe painful crises in a 12 month period
- sickle cell pain that interferes with daily activities and quality of life
- 1 or more life threatening complications of the disease, such as acute chest syndrome
- hydroxycarbamide should be recommended as second line therapy for secondary stroke prevention when transfusions are contraindicated or unavailable
- sickle nephropathy with persisting proteinuria despite angiotensin-converting-enzyme inhibitor/angiotensin receptor blocker therapy, consider the addition of hydroxycarbamide therapy
- recurrent priapism
- chronic hypoxia
- other indications (such as pulmonary hypertension, AVN) and the use of hydroxycarbamide in other genotypes eg.HbSC should be discussed with consultant colleagues within the network

Exclusions:

- Pregnancy or not practicing active contraception (if sexually active)
- Active hepatitis
- Hb<6g/dl, WCC<1x10^9/l, Plts<100x10^9/l Prior to commencing drug
- eGFR < 30 ml/min/1·73 m^2.

Requirements prior to starting therapy:

- The benefits and hazards of using hydroxycarbamide should be considered for each patient individually, and discussed
- Ensure that the patient is willing to attend regularly to monitor blood counts
- Discuss the unknown effects on fertility with male patients. Offer sperm banking.
- It is important to discuss the possible teratogenic effects of hydroxycarbamide and recommend contraceptive use whilst on the drug.

Baseline investigations

- FBC and reticulocytes
- HbF%
- U+Es, LFTs, Urate, LDH

Regimen details:

- Commence at 15mg/kg/day orally rounded to nearest 500mg
- 5–10 mg/kg/day starting dose if the patient has chronic kidney disease (eGFR < 60 ml/min/1·73 $m^{2)}$.
- The dose can be escalated by 5 mg/kg/day every 8–12 weeks, aiming for a neutrophil count of 2–3 × 10^9/l and stopping if neutrophils fall below 1 × 10^9/l or if there is other haematological toxicity or until maximum dose of 35mg/kg/day. This is the maximum tolerated dose.
- An optimal clinical and laboratory response to treatment with hydroxycarbamide may take 12 months

Monitoring:

- Weekly FBC for first 4 weeks
- Fortnightly FBC for next 8 weeks
- FBC 2-3 monthly thereafter if counts stable
- 2-3 monthly U+Es, LFTs, Urate, LDH and HBF%

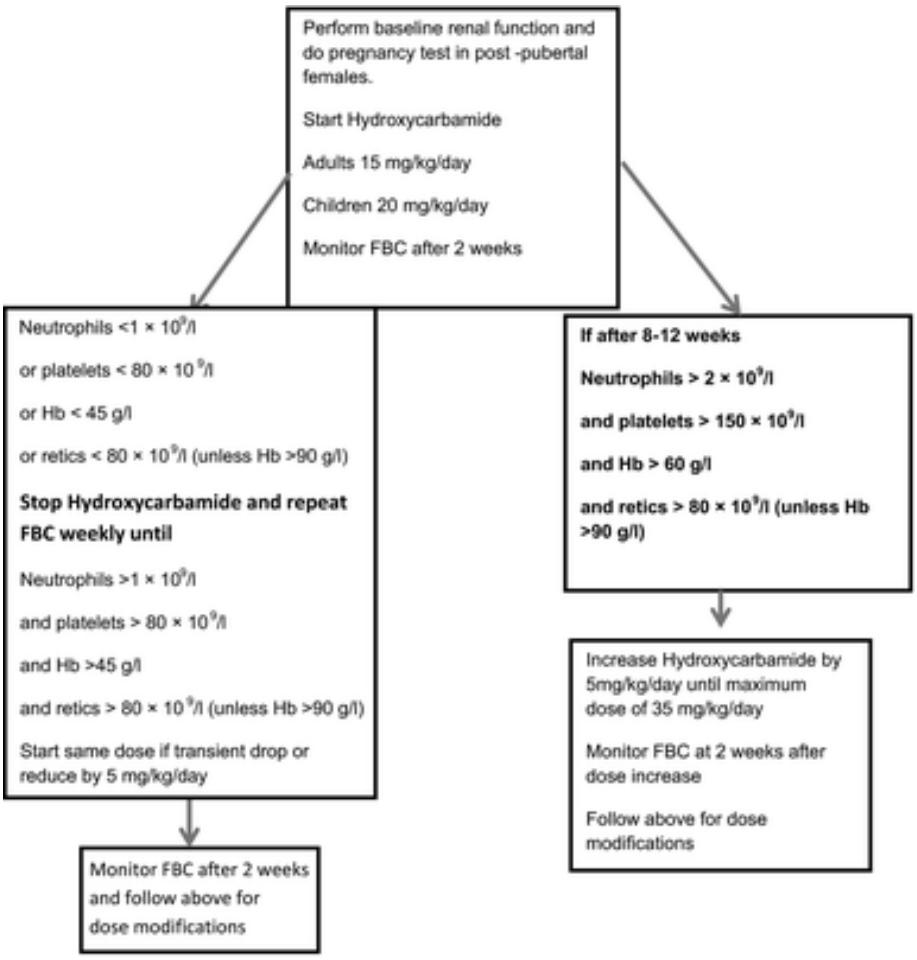
Toxicity:

- Neutrophils < 1.0 x 10^9/l
- Platelets < 80 x 10^9/l
- Reticulocytes < 80 x 10^9/l (unless Hb >90g/l)
- Haemoglobin <45 g/l or 30g/l from baseline
- If any of the above problems with FBC encountered, stop hydroxycarbamide, until full blood count has recovered

- Restart at 5mg/kg/day (or 1 capsule – 500mg) lower. This is the maximum tolerated dose (MTD)

Figure 1

Algorithm for hydroxycarbamide dosing and monitoring (From BCSH guideline)



Caution

- If there is a significant rise in Hb (>110g/l in HbSS) stop the hydroxycarbamide and consider venesection
- If there is a downwards trend in FBC parameters, increase frequency of monitoring
- Use with caution in renal impairment: start at a lower dose and increment more cautiously
- Hydroxycarbamide therapy should be continued during hospitalizations or illness unless due to febrile neutropenia or bleeding with thrombocytopenia

Preconception and Pregnancy

- Consider stopping hydroxycarbamide pre-conception in male and female patients and in pregnant women if the patient is not at high risk of serious complications relating to sickle cell disease
- Prenatally and during pregnancy, consider a transfusion programme if there is a severe clinical phenotype as an alternative to hydroxycarbamide treatment

Toxicities

Common: Bone marrow suppression and cytopenias.
Nausea and vomiting
Diarrhoea
Skin rash
Mouth ulcers

Uncommon: Alopecia
Leg ulcers
Hyperpigmentation of nails and skin

Unknown: Decreased sperm count and function
Low risk of malignancy in sickle cell

British Society for Haematology: Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease
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