

British Society for Haematology guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease, May 2018

The new British Society for Haematology guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease were published in May 2018. This has resulted in a change in practice across the UK, and you are likely to be offered hydroxycarbamide if you are not already on treatment.

I have summarised the guidelines below in what I hope is patient-friendly language. Please read and ask your medical team about starting hydroxycarbamide treatment at your next clinic appointment.

Hydroxycarbamide (also known as hydroxyurea) is the only medication licensed in the UK for the prevention of recurrent painful crisis in patients with sickle cell disease. In 1995 the randomized controlled Multicenter Study of Hydroxyurea (MSH) showed that treatment with hydroxycarbamide could decrease episodes of pain and acute chest syndrome and reduce the need for transfusion. Other trials confirmed its effectiveness in sickle cell disease, including in preventing disease complications and improving survival.

Despite the clear benefits of hydroxycarbamide, it remains under-used because of reluctance in both clinicians and patients to use it, and there is marked variability in its use across the UK. This is partly due to concerns about side effects, which include bone marrow suppression with a need for regular blood monitoring, and uncertainties about effects on sperm production and misconceptions about possible teratogenicity (damage to the developing baby if the medicine is taken by a pregnant woman).

Hydroxycarbamide's mode of action in sickle cell disease is based on its ability to increase HbF levels, first shown in the 1980s, as well as its ability to improve blood flow by reducing adhesion between cells. The effect on HbF levels is not immediate and may take several months of dosing to achieve optimal levels. The effect on HbF levels is variable, partly due to genetic variants which cause variation in pre-treatment HbF levels.

Hydroxycarbamide has other beneficial effects by causing improved blood flow due to decreased expression of integrins and other adhesion molecules on red blood cells, white blood cells and the lining of blood vessels (vascular endothelium). Nitric oxide levels are reduced in patients with sickle cell disease. Stimulation of nitric oxide production by hydroxycarbamide may result in widening of blood vessels (vasodilation) which improves blood flow.

Measurable laboratory effects of hydroxycarbamide treatment include increased haemoglobin F%, haemoglobin and mean cell volume and a reduction in the reticulocyte count and white blood cell count. These effects are consistent and sustained in all age groups. Clinical benefits of hydroxycarbamide occur with a rise in haemoglobin, haemoglobin F% and MCV.

The rationale for hydroxycarbamide:

The **reduction in mortality** in both adults and children on hydroxycarbamide is a compelling reason for treatment. Data shows increased survival associated with hydroxycarbamide use. Adults entered into the randomised controlled MSH study were subsequently entered into a nonrandomised observational study. At 9 years of follow-up, use of hydroxycarbamide was associated with a 40% reduction in mortality.

Hydroxycarbamide leads to a **reduction of painful episodes and chest crises**. This was first shown in the double blind randomised Multicenter Study of Hydroxyurea (MSH) in which 152 adults with HbSS who received hydroxycarbamide were compared with 147 who received placebo.

The clinical benefits of hydroxycarbamide have also been shown in very young children in the BABY HUG study - a randomised double-blinded trial of children aged 9–18 months with HbSS and HbS β^0 thalassaemia. Participants were unselected for severity and treated with a standard dose. 96 children in the hydroxycarbamide group were compared with 97 children in the placebo group and showed reduction in pain, dactylitis (swollen painful fingers and toes) and a reduction in acute chest syndrome (3-5-fold lower). In the BABY HUG study, Hydroxycarbamide use was associated with a statistically significant reduction in transfusion requirement and hospital admission rates, higher haemoglobin, HbF, MCV, and a reduced WBC count. The American guidelines (NHLBI, 2014) and UK

guidelines (2018) have changed their approach from offering hydroxycarbamide to those with severe symptoms, to a non-selective approach where hydroxycarbamide is offered to all children, even those with no current symptoms from their disease.

Observational studies show a **reduction in hospitalisation for pain crises** and **reduced hospitalisation for pain and chest crises in those on hydroxycarbamide**. Studies also showed significant reductions in visits to the emergency department and hospital admission rates.

Pain in the community, when patients do not present to hospital, can seriously affect a patient's daily quality of life and is more difficult to measure. Diaries/hospital visits were analysed on the 299 patients from the MSH study and it was found that hydroxycarbamide significantly shortened duration of admission and cumulative days of admission and also decreased the amount of opioid used at home. The reduction in pain was related to HbF treatment response.

Stroke prevention - Risk factors for acute ischaemic stroke in childhood include abnormal transcranial Doppler velocities, cerebral vasculopathy, silent cerebral infarction, low Hb and low HbF%. By modifying these risk factors, hydroxycarbamide may have a role to play in limiting the risk of childhood stroke.

Organ damage - There is accumulating evidence that hydroxycarbamide may prevent chronic organ damage in children and may preserve organ function in adults. Hydroxycarbamide use has not been associated with improvement of organ function over time and therefore hydroxycarbamide should ideally be started before organ damage occurs.

Spleen function - Loss of spleen function has been identified as early as 4–6 months of age, and by 5 years of age most children with HbSS/Sβ⁰ are functionally asplenic (lack a functioning spleen). Thirty-six children enrolled in the Hydroxycarbamide Study of Long-Term Effects (HUSTLE) had baseline Tc⁹⁹ scans of liver and spleen and 36% showed preserved or improved splenic infiltrative function after 3 years of treatment.

Kidney function - kidney changes in sickle cell disease are common and are associated with significant morbidity and mortality. In the randomised controlled BABY HUG study of infants with SS/Sβ⁰ thalassaemia, those treated with hydroxycarbamide showed better urine concentrating ability and less renal enlargement than those on placebo. Observational data on adults suggest that treatment with hydroxycarbamide may improve renal dysfunction.

Damage to the retina of the eye (retinopathy) - A low level of HbF seems to be a risk factor for the development of retinopathy; an observational study of 123 children with SS/Sβ^{0/+} showed that children with HbF < 15% have a significantly higher odds of developing retinopathy whether or not hydroxycarbamide was being taken. In children treated with hydroxycarbamide, those who developed retinopathy had lower HbF levels compared with those who did not have retinopathy, suggesting that induction of HbF levels with hydroxycarbamide may have a protective effect on the development of retinopathy.

Cardio-pulmonary benefits - In children, hydroxycarbamide has been associated with statistically significant improvement in lung function tests, increase in daytime and average overnight oxygen saturation, and significant improved aerobic exercise tolerance and physical fitness.

Priapism - Case reports suggest some benefit of hydroxycarbamide to prevent recurrent ischaemic priapism (painful sustained erection of the penis) through its mechanism of enhancing nitric oxide bioavailability.

Bone damage (Avascular necrosis, AVN) - A prospective non-randomised study compared outcomes in adults with early AVN, with 46 receiving hydroxycarbamide and 18 not receiving treatment. Pain and radiological findings were improved in the patients on hydroxycarbamide, with a significant HbF rise in the treated group.

Hydroxycarbamide has been less well investigated in sickle cell disease types other than HbSS/Sβ⁰thalassaemia. Cohort studies in patients with sickle cell/HbC (HbSC) disease suggest a beneficial role in reducing pain events and hospitalization.

Hydroxycarbamide is well tolerated with few side effects. Some patients experience mild gastrointestinal symptoms or hyperpigmentation of the skin and darkening of nails. Some patients note hair thinning. Skin ulcers have been reported but do not seem to be any more frequent than in those not on hydroxycarbamide. Marrow suppression, which is transient and reversible, is the most expected short-term effect. This side effect also contributes to the clinical benefits.

There is compelling evidence that hydroxycarbamide, when used in the treatment of patients with haemoglobinopathies, carries no increased risk of leukaemia or myelodysplastic syndrome.

There is no available evidence in females or males that hydroxycarbamide affects fertility. In a study that followed up MSH patients 17 years post-randomisation, 28 female participants had 51 pregnancies. In males, the effect of hydroxycarbamide on spermatogenesis remains unclear. Baseline sperm abnormalities exist in men with sickle cell disease. A retrospective multicentre study evaluated the sperm parameters and fertility of 44 patients and the potential impact of hydroxycarbamide. At least 1 sperm parameter was found to be abnormal in 91% of patients pre-treatment.

The abnormalities seen in sperm parameters in men with sickle cell disease do seem to be increased by hydroxycarbamide. The association of abnormal sperm parameters and fertility is not clear as men with low sperm number and abnormal morphology can still be fertile. The female partners of 27 male MSH participants had 40 pregnancies. These 40 pregnancies resulted in 42 pregnancy outcomes. This data indicates that men who have taken hydroxycarbamide have fathered children. It is reasonable to offer post-pubertal male patients sperm analysis and cryopreservation prior to starting treatment with hydroxycarbamide.

Hydroxycarbamide at high (superpharmacological – higher than usual treatment levels) doses is teratogenic in animals leading to abnormalities in the central nervous system, vertebral bodies, craniofacial tissue, skull and limbs in mammals. There is limited data on adverse outcomes in pregnant women. At present, until further data are available, the use of contraception is recommended for both male and female patients while taking hydroxycarbamide. Despite this precautionary measure, some women have become pregnant while they or their male partners were on hydroxycarbamide, resulting in normal infants. Both women and men should have a discussion with their physician about the risks and benefits of stopping hydroxycarbamide prior to planned conception, or in pregnancy and whether alternative therapies, such as transfusion, are indicated to prevent sickle cell complications. If women do conceive whilst taking hydroxycarbamide, stopping the drug should be considered in the first trimester and a detailed anomaly scan should be performed at 20 weeks gestation.

In men and women who have a severe disease phenotype and/or are difficult to transfuse, the risks of stopping hydroxycarbamide prenatally and for women during pregnancy may outweigh any possible risks.

The effectiveness of hydroxycarbamide depends on adherence to daily dosing. Hydroxycarbamide therapy should be continued during hospitalization or illness unless due to a high fever associated with a low neutrophil count or bleeding with a low platelet count. Patients should present to hospital if unwell with high fever and infection and hospital staff should perform a full blood count to check for a low neutrophil count.

The British Society for Haematology recommendations that:

- **The benefits of hydroxycarbamide be discussed with all parents of children and adolescents and all adults with SS/Sβ⁰ to enable informed joint decision-making.**
- **In infants with SS/Sβ⁰ aged 9–42 months, offer hydroxycarbamide regardless of clinical severity to reduce sickle cell complications**
- **In children aged >42 months, adolescents and adults with SS/Sβ⁰, offer treatment with hydroxycarbamide in view of the impact on reduction of mortality**

Conclusion

Hydroxycarbamide has been shown to increase survival in sickle cell disease patients. There is high quality evidence that it is effective in reducing episodes of pain and chest crisis and reducing conditional cerebral blood flow velocities in children. It also prevents events in asymptomatic children.

It is well tolerated and has no long-term mutagenic effect. It is the only disease-modifying therapy available to patients with sickle cell disease. Its significant benefits should be discussed with all patients and parents of children with sickle cell disease.

Failure to take a correct daily dose is the main reason that some patients do not obtain the full benefit of treatment. When taken regularly and at the correct dose, clear changes in the full blood count, including a higher haemoglobin, higher haemoglobin F levels, higher mean cell volume and lower white cell count and reticulocyte counts, will be seen.

Below is an example of the microscopic blood film appearances of a typical sickle cell disease patient before treatment (A), during early treatment (B), and after full treatment (C) with hydroxycarbamide.

