bjh guideline

Guidelines for the use of hydroxycarbamide in children and adults with sickle cell disease

A British Society for Haematology Guideline

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Methodology

This guideline was compiled according to the British Society of Haematology (BSH) process at b-s-h.org.uk. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org

Literature review details (Appendix 1)

A literature search was conducted on 15 June 2016. Databases searched include MEDLINE (OVID) and Embase (OVID) from 1995 to July, week 1, 2016. Key words were: Hydroxycarbamide; Hydroxyurea, Sickle cell disease; Sickle cell anaemia; Mode of Action: HbF; Pain; Chest crisis; stroke; silent infarct; cerebral flow velocities; primary prevention of stroke; secondary prevention of stroke; end organ damage; renal function; nephropathy; avascular necrosis; pulmonary hypertension; reduced morbidity; reduced mortality; toxicity; side effects; bone marrow suppression; infertility; spermatogenesis; teratogenicity; cancer; leukaemia, death, dosing, monitoring, long term follow-up; paediatrics; infants; children; adults. Exclusions included non-human and single case reports, no abstracts or irrelevant to guideline.

Review of manuscript

Review of the manuscript was performed by the BSH Guidelines Committee General Haematology Task Force, the BSH Guidelines Committee and the General Haematology sounding board of BSH. It was also placed on the members section of the BSH website for comment. The manuscript was also reviewed by the Sickle Cell Society; this organisation does not necessarily approve or endorse the contents.

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Introduction

Sickle cell disease (SCD) is a generic term for an inherited group of disorders that includes homozygous sickle cell anaemia (SS), sickle cell/haemoglobin C (SC) sickle cell/βthalassemia (S/β thal) and other compound heterozygous conditions. SCD is characterised by the presence of the mutated β-globin gene, *HBB*^{s} (also termed β^{s}-globin). On de-oxygenation, this forms a polymeric structure resulting in deformed, rigid red blood cells, and is associated with a chronic haemolytic anaemia due to shortened red cell life span and vaso-occlusion causing frequent episodes of severe bony pain (vaso-occlusive crises) and other acute and chronic complications. These include an increased risk of stroke, pulmonary hypertension, acute and chronic lung damage, chronic renal failure and leg ulcers. Fetal haemoglobin (haemoglobin F, HbF, $\alpha_2\Upsilon_2$) is protective against these complications and infants are relatively protected in the first few months of life before HbF in infancy is replaced by HbS ($\alpha_2\beta^S{}_2$) rather than adult haemoglobin (HbA, $\alpha_2\beta_2$). Co-inheritance of raised HbF levels is also associated with a milder phenotype (Perrine *et al*, 1978; Platt *et al*, 1994).

Hydroxycarbamide (also known as hydroxyurea) is currently the only medication licensed in the UK for the prevention of recurrent painful crisis in patients with SCD. The randomized controlled Multicenter Study of Hydroxyurea (MSH) study showed definitively that treatment with hydroxycarbamide could decrease episodes of pain and acute

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chest syndrome (ACS) and reduce the need for transfusion (Charache *et al*, 1995). Since then, multiple trials have confirmed its efficacy in disease modification in children and in the prevention of additional disease complications, and have shown an improved survival in patients taking hydroxycarbamide (Steinberg *et al*, 2010; Voskaridou *et al*, 2010; Lobo *et al*, 2013). Despite the clear benefits of hydroxycarbamide, it remains under-utilized due to reluctance in both clinicians and patients to use it and there is marked variability in its use across the UK (http://www.wmqrs.nhs.uk/review-programmes/view/haemoglobin-disorders-2014-16-reviews-adults-and-children). This is partly due to concerns about its side effects, which include myelosuppression, with a need for regular blood monitoring, and uncertainties about its effect on spermatogenesis and misconceptions about possible teratogenicity.

This guideline aims to outline the current evidence for specific indications and to provide clinician aids for consultation and monitoring of hydroxycarbamide. This will enable joint decision-making between clinicians and patients and will improve equity of access to hydroxycarbamide. As with any medical intervention, specific recommendations are to be utilised within the context of informed consent, verbal or written, and shared decision-making process and on-going discussion between the provider and patient.

The majority of available evidence has been obtained only for patients with genotypes SS and Sβ^0thalassaemia (S β^0) and its role in other sickle genotypes (e.g. SC, Sβ^+thalassaemia) is discussed separately.

Mode of action

Hydroxycarbamide is an inhibitor of ribonucleotide reductase and has been used as an oral anti-proliferative drug for several decades. Its mode of action in SCD is based on both its ability to increase HbF levels, which was first shown in the 1980s (Platt *et al*, 1984; Veith *et al*, 1985), and its ability to reduce intercellular adhesion and hence improve blood flow. The effect on HbF levels is thought to be partly due to the induction of mild intermittent bone marrow suppression, which results in a state of stressed erythropoiesis, where production of HbF is increased relative to steady state. This is not an immediate effect and it may take several months of dose escalation to achieve an optimal rise in HbF levels. The effect of hydroxycarbamide on HbF levels is variable and this is partly due to genetic variants which cause variation in baseline HbF levels, including polymorphisms in the *XmnI* site, *BCL11A* and *SALL2* (Green & Barral, 2014; Sheehan *et al*, 2014) and further studies to understand HbF-inducing genes are ongoing.

Hydroxycarbamide has also been shown to have beneficial effects in SCD outside its modification of HbF and acts via multiple mechanisms to improve blood flow and reduce vaso-occlusion (Green & Barral, 2014). In part, this is due to decreased expression of integrins and other adhesion molecules on red cells, white blood cells (WBCs) and vascular endothelium. The interactions between these cells are involved in neutrophil migration and red blood cell flow and reduction of adhesion leads to decreased vaso-occlusion. Nitric oxide (NO) levels are decreased in patients with SCD and stimulation of NO production by hydroxycarbamide may result in local vasodilation, which will improve blood flow and reduce vaso-occlusion.

Laboratory effects of hydroxycarbamide

In addition to the increase in HbF%, the laboratory effects of hydroxycarbamide also include raised haemoglobin concentration (Hb) levels and mean cell volume (MCV) and a reduction in absolute reticulocyte count (ARC) and WBC count; these effects have been shown to be consistent and sustained across all ages (Charache *et al*, 1992; Ferster *et al*, 1996; Kinney *et al*, 1999; Zimmerman *et al*, 2004; Voskaridou *et al*, 2010).

The clinical benefits of hydroxycarbamide have been correlated with a rise in Hb, HbF and MCV (Ferster *et al*, 1996; Italia *et al*, 2009; Singh *et al*, 2010; Mellouli *et al*, 2013; Quarmyne *et al*, 2015).

Rationale for hydroxycarbamide

Reduction in mortality

The reduction in mortality in both adults and children on hydroxycarbamide treatment is a compelling reason for using hydroxycarbamide (Wang, 2016). Observational data has suggested that increased survival is associated with hydroxycarbamide use. This may be related to the reduction in acute pain episodes, chest crises and hospital admissions in patients on hydroxycarbamide or may be due to effects of hydroxycarbamide in reducing or preventing end organ damage.

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 ($P = 0{\cdot}04$) (Steinberg *et al*, 2003). After a 17·7-year follow-up period the analysis of mortality in 3-month intervals according to hydroxycarbamide usage in the interval, showed that death rates were reduced by 40% during 3-month intervals when patients were taking hydroxycarbamide (Steinberg *et al*, 2010). Twenty-four percent of deaths were due to pulmonary complications and 87·1% of these occurred in patients who never took hydroxycarbamide or took it for <5 years. In an observational Belgian study of 469 adults and children (Lê *et al*, 2015), the 185 patients treated with hydroxycarbamide had a higher 15-year survival than those not treated with the drug (99·4% compared with 95·4% $P = 0{\cdot}04$). In a prospective, non-randomised study from Greece, outcomes in 131 adults with SCD (SS, S β^0thal and

S β $^{+}$thal) treated with hydroxycarbamide were compared with outcomes in 199 untreated patients. The probability of 10-year survival was 86% for those on hydroxycarbamide, compared with 65% for those not on hydroxycarbamide ($P = 0{\cdot}001$), even though the treated group had more severe disease. HbF levels were a significant independent predictor of survival (Voskaridou *et al*, 2010).

The Brazilian paediatric hydroxycarbamide programme retrospectively analysed data from the first 9 years of the programme, reviewing the data of 1760 children aged 3–18 years, of whom 267 were selectively on hydroxycarbamide treatment (Lobo *et al*, 2013). Survival was significantly greater in the group treated with hydroxycarbamide compared with those who were untreated (99·5% vs. 94·5% $P = 0{\cdot}01$) due primarily to fewer deaths from ACS and infection. In a retrospective analysis of an East Mediterranean cohort including 735 patients (102 children, 633 adults) over a median follow-up of 66 months, hydroxycarbamide use was significantly associated with reduced mortality ($P = 0{\cdot}009$) (Karacaoglu *et al*, 2016).

Reduction in acute pain complications and ACS

Hydroxycarbamide has proven efficacy in the reduction of painful episodes and chest crises. This was first shown in the double blind randomised Multicenter Study of Hydroxyurea (MSH) (Charache *et al*, 1995). In this trial, 152 adults with SS who received hydroxycarbamide were compared with 147 who received placebo. In the group receiving hydroxycarbamide the median number of painful crises over the 2-year follow-up period was significantly reduced, from 4·5 to 2·5 (44% reduction $P = 0{\cdot}001$), median time to crisis was increased from 1·5 to 3 months ($P = 0{\cdot}01$), and time to second crisis was increased from 4·6 to 8 months ($P = 0{\cdot}0001$). In addition the incidence of ACS was reduced over a 2-year follow-up (25 vs. 51, $P = 0{\cdot}001$) and transfusion need was reduced (48 patients vs. 73 patients, $P = 0{\cdot}001$) in patients on hydroxycarbamide. A randomised cross-over trial of children and young adults with SS (Ferster *et al*, 1996) who were administered hydroxycarbamide or placebo in randomised order, with a washout period between, showed an absence of pain events requiring hospitalisation in 16/22 patients (73%) during the hydroxycarbamide treatment period compared with only 3/22 (14%) during the placebo treatment ($P = 0{\cdot}0016$). It also showed a reduction in mean hospital stay in the treated group. Participants were treated with 20 mg/kg of hydroxycarbamide, increased to 25 mg/kg unless cytopenia developed.

A further double-blind randomised study in India looked at 60 children with SS aged 5–18 years, with half receiving 10 mg/kg/day hydroxycarbamide and half receiving placebo (Jain *et al*, 2012) and showed a significant decrease in pain crises, blood transfusions and hospitalisations in the treated group.

The clinical benefits of hydroxycarbamide have also been shown in very young children. Demonstration of clinical benefits was a secondary objective in the BABY HUG study (Wang *et al*, 2011) a randomised double-blinded trial of children aged 9–18 months with SS and Sβ^0thalassaemia. Participants were unselected for severity and treated with a standard dose of 20 mg/kg. Ninety-six children in the hydroxycarbamide group were compared with 97 children in the placebo group and showed reduction in pain (177 events in 62 patients vs. 375 events in 75 patients; 2·2-fold lower rate of pain, $P = 0{\cdot}002$), dactylitis (24 events in 14 patients vs. 123 events in 42 patients; 5·2-fold lower rate, $P = 0{\cdot}0001$), and a reduction in ACS $P = 0{\cdot}02$ (3·5-fold lower rate). Hydroxycarbamide use was associated with reduced transfusion requirements ($P = 0{\cdot}03$) and hospital admission rates ($P = 0{\cdot}05$), higher Hb, HbF and MCV ($P = 0{\cdot}001$), reduced WBC count ($P = 0{\cdot}005$) and it was well tolerated, with only transient reduction in absolute neutrophil count (ANC). Of this cohort ($n = 176$), 163 (93%) consented to further follow-up over 36 months (Rogers *et al*, 2011) and all clinical and laboratory benefits were sustained compared with the placebo group. Despite mild myelosuppression, there was no increase in bacteraemia or serious infection. These data provided important safety and efficacy information for hydroxycarbamide in very young children with SS and Sβ^0thalassaemia. In addition, in sub-analysis of an asymptomatic cohort (52 hydroxycarbamide, 49 placebo) there were fewer episodes of dactylitis and hospitalisation ($P = 0{\cdot}006$), higher HbF%, and lower WBC count and ARC compared with placebo and in those with higher baseline Hb, hydroxycarbamide significantly reduced pain episodes (relative risk 3·05 $P < 0{\cdot}001$) (Wang *et al*, 2012). This confirmed that hydroxycarbamide has clinical value even in asymptomatic young children and American guidelines (NHLBI, 2014) have changed their approach from targeted (offering hydroxycarbamide to those with severe symptoms) to non-selective where hydroxycarbamide is offered to all children, even those with asymptomatic disease.

At the time of writing this guideline, initial follow-up data (i.e., 3 years), has shown no adverse events in very young children due to hydroxycarbamide exposure. However the on-going follow-up of the Baby HUG study will be important in describing the long-term effects of hydroxycarbamide in a larger cohort of children treated since infancy.

Reduction in hospitalisation and pain in the community

Observational studies have shown a significant reduction in hospitalisation for pain crises (de Montalembert *et al*, 1997; Deshpande *et al*, 2016) and reduced hospitalisation for pain and chest crises (Koren *et al*, 1999). Further studies have shown patients on hydroxycarbamide have both a significant reduction in visits to the emergency department ($P = 0{\cdot}011$) (Raj *et al*, 2015) and a significant reduction in hospital admission rates $P = 0{\cdot}001$ (Nottage *et al*, 2013). This reduction in

hospitalisation rate has been translated into public health cost benefits of taking hydroxycarbamide (Wang *et al*, 2013).

Pain in the community, when patients do not present to hospital, can seriously affect a patient's daily quality of life and is much more difficult to measure. Diaries/hospital visits were analysed on the 299 patients from the MSH study (Ballas *et al*, 2010) and it was found that hydroxycarbamide not only significantly shortened duration of admission and cumulative days of admission ($P = 0{\cdot}022$) but also decreased the amount of opioid used at home ($P = 0{\cdot}015$). Smith *et al* (2011) compared daily pain, and home analgesic use among ambulatory adults in the MSH study. Patients rated their sickle cell pain intensity, which was lower on hydroxycarbamide ($P = 0{\cdot}0007$), as was use of analgesics ($P < 0{\cdot}0001$). The reduction in pain was related to HbF treatment response.

Recommendations

- **The benefits of hydroxycarbamide should be discussed with all parents of children, adolescents and adults with SS/Sβ^0 to enable informed joint decision-making. There should be on-going discussion between provider and patient (1B)**
- **In infants with SS/Sβ^0 aged 9–42 months, offer hydroxycarbamide regardless of clinical severity to reduce sickle cell complications (pain, dactylitis, acute chest syndrome (ACS), anaemia (1A)**
- **In children aged >42 months, adolescents and adults with SS/Sβ^0, offer treatment with hydroxycarbamide in view of the impact on reduction of mortality (1B)**
- **In adults and children with SS/Sβ^0 who have 3 or more sickle cell-associated moderate to severe pain crisis in a 12-month period, treat with hydroxycarbamide (1A)**
- **In adults and children with SS/Sβ^0 who have sickle cell pain that interferes with daily activities and quality of life, treat with hydroxycarbamide (1C)**
- **In adults and children with SS/Sβ^0 and a history of severe and/or recurrent ACS treat with hydroxycarbamide (1A)**
- **Ongoing informed consent should be confirmed for all patients on hydroxycarbamide, at least at each Annual Review (1D)**

Stroke prevention

Risk factors for acute ischaemic stroke in childhood include abnormal Transcranial Doppler (TCD) 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. In adults, the risk factors are potentially different and the role of hydroxycarbamide in primary and secondary stroke prevention has not been fully investigated.

Primary stroke prevention. Abnormal TCD velocities in the middle cerebral and anterior cerebral arteries confer a significant risk of childhood acute ischaemic stroke. A number of studies have demonstrated a reduction in TCD velocities with use of hydroxycarbamide (Gulbis *et al*, 2005; Kratovil *et al*, 2006; Lagunju *et al*, 2015).

In the BABY HUG trial, one stroke occurred in 98 subjects randomised to the placebo arm and 4 children (1 on the hydroxycarbamide arm) had abnormal TCD velocities by the end of the study. This was not statistically significant. Some of these children were asymptomatic at trial entry and adverse events in these children were separately analysed, but this did not include neurological events or TCD change. The average increase in the TCD velocity during the study was however significantly lower in the hydroxycarbamide group (Wang & Dwan, 2013). Overall reduction in TCD velocity in the hydroxycarbamide group was seen, suggesting hydroxycarbamide could be considered for primary stroke prevention.

Sparing Conversion to Abnormal TCD Elevation (SCATE) (Hankins *et al*, 2015) was a phase 3 randomised clinical trial designed to study the efficacy of hydroxycarbamide in preventing conversion from conditional to abnormal TCD. Although this trial was terminated early due to slow recruitment and only recruited 38 patients, in *post hoc* analysis in the group treated with hydroxycarbamide, fewer children converted to abnormal TCD and a reduction was seen in mean TCD velocity after a mean of 10 months of treatment in children on hydroxycarbamide. This difference did not reach statistical significance in the intention-to-treat analysis.

Hydroxycarbamide therapy has not been formally tested as first line therapy for children with high risk TCDs but feasibility data suggest reductions in TCD velocity can occur as early as 3 months after starting treatment (Galadanci *et al*, 2015). Transfusions have an established role in the primary prevention of paediatric acute ischaemic stroke (Adams *et al*, 1998).

The role of hydroxycarbamide as an alternative to transfusions was investigated in the TWiTCH (TCD With Transfusions Changing to Hydroxyurea) trial (Ware *et al*, 2016). This was a phase 3 non-inferiority trial, in which 121 children who had received at least 1 year of regular transfusions for primary stroke prevention were randomised to continuing regular transfusions with iron chelation therapy or hydroxycarbamide and venesections. Children with magnetic resonance angiography (MRA)-defined severe vasculopathy were excluded and the mean age at enrolment was similar [9·5 years SD 2·6 (standard arm) and 9·7 years SD 3·2 (alternative)]. Children were eligible from the age of 4 years and the mean age at enrolment was 6·5 years. At the first scheduled interim analysis, non-inferiority was demonstrated with no new infarctions identified in either arm, therefore the trial was terminated early. It was concluded that hydroxycarbamide is an effective alternative to transfusion in primary stroke prevention. Some children reverted to high cerebral flow velocities whilst escalating to maximum tolerated dose

of hydroxycarbamide (Bernaudin *et al*, 2016) and in the TWiTCH trial transfusions were not stopped until hydroxycarbamide therapy was established. For silent cerebral infarcts, hydroxycarbamide may confer some protection against progression, defined as new silent ischaemia or vascular stenosis (Nottage *et al*, 2016). For children aged 5–15 years, regular transfusions have been shown to have a significant impact in reducing recurrence of overt stroke, but not silent cerebral ischaemia (DeBaun *et al*, 2014).

Vasculopathy and MR changes—Hydroxycarbamide therapy may also protect against progression of magnetic resonance imaging abnormalities, including leucoencephalopathy and cerebral vasculopathy, by altering risk factors when started in early childhood (Sommet *et al*, 2016). Further studies are required to establish the impact of hydroxycarbamide on preventing cerebral vasculopathy but the benefits may be less overt in older children and earlier initiation may be more favourable.

Secondary stroke prevention. For secondary stroke prevention, transfusion therapy remains the standard of care. Data from the only randomised controlled trial (Stroke with Transfusions changing to Hydroxyurea – SWiTCH) exploring use of hydroxycarbamide in secondary stroke prevention demonstrate a higher likelihood of stroke recurrence when paediatric patients were switched to hydroxycarbamide therapy and venesections compared to continued transfusions and chelation therapy (Ware & Helms, 2012). This trial was not designed to compare transfusion with hydroxycarbamide directly but rather as a non-inferiority trial. Allowance was made for an increased number of recurrent stroke events but the combined benefit of hydroxycarbamide with venesections in reducing iron overload was hypothesised. In this study, 7 strokes occurred in 67 subjects randomised to hydroxycarbamide/venesection compared with 0 strokes in 66 subjects on transfusion/chelation. The rate difference (0·10) remained within the non-inferiority margin. All patients had severe vasculopathy and 6 of the strokes occurred during the venesection phase. Hydroxycarbamide therapy has, however, been shown to reduce stroke recurrence rates and should be considered where transfusions are contraindicated or unavailable (Sumoza *et al*, 2002; Ali *et al*, 2011; Greenway *et al*, 2011; Lagunju *et al*, 2013).

Interventions to prevent stroke in adults has been less well studied. One observational study suggested a limited benefit from hydroxycarbamide in SS/S$\beta^{0/+}$ (Rigano *et al*, 2013). Other studies suggest hydroxycarbamide may have a role in preventing progression of neuro-vascular abnormalities but this has not been formally tested in a randomised controlled trial.

Recommendations

- **Children who have started regular blood transfusions for abnormal Transcranial Doppler (TCD) can be switched to hydroxycarbamide therapy (with or without venesection) if they have received at least 1 year of regular transfusions and have no magnetic resonance angiography-defined severe vasculopathy (1A)**
- **In children who are treated for primary stroke prevention who are changing from regular blood transfusions to hydroxycarbamide therapy, transfusion should be continued until they have reached maximum tolerated dose of hydroxycarbamide (1C)**
- **Children with TCD velocities in the range 170–200 cm/s (conditional risk category) should be treated with hydroxycarbamide therapy to help prevent progression from conditional to abnormal TCD velocity (1B)**
- **When treating children with conditional TCD velocities with hydroxycarbamide, the dose should be escalated to maximum tolerated dose (1C)**
- **In children and adults with a previous history of acute ischaemic stroke or infarcts, hydroxycarbamide should be recommended as second line therapy for secondary stroke prevention when transfusions are contraindicated or unavailable (1B)**
- **There is insufficient data to advise commencing hydroxycarbamide therapy for primary stroke prevention in adults (1D)**

End organ damage

There is accumulating evidence that hydroxycarbamide may prevent chronic organ damage in children with SS and may preserve organ function in adults. This benefit may be optimal when hydroxycarbamide is given in doses that achieve higher levels of HbF. Hydroxycarbamide use has not been associated with improvement of organ function over time (Fitzhugh *et al*, 2015) and therefore hydroxycarbamide should ideally be administered before organ damage occurs. The evidence for efficacy on separate organ systems is outlined below.

Splenic function. Loss of splenic function in SS has been identified as early as 4–6 months of age, and by 5 years of age most of children with SS are functionally asplenic. Small observational studies show that hydroxycarbamide therapy may preserve splenic function in children (Hankins *et al*, 2008; Nottage *et al*, 2014). Thirty-six children (median age 8·8 years) enrolled in the Hydroxycarbamide Study of Long-Term Effects (HUSTLE) had baseline ^{Tc}99 scans of liver and spleen and 36% showed preserved or improved splenic infiltrative function after 3 years of treatment (Nottage *et al*, 2014); younger age, higher baseline HbF and time to drug response were significantly associated with preserved splenic function. This is further supported in a study by Santos *et al* (2002) where 21 patients, aged 3–22 years, had liver/spleen scintigraphy before and after 6 and 12 months of hydroxycarbamide therapy; spleen function improved in 10 patients

(50%). Improvement in splenic function was also seen in the extension of the Hydroxycarbamide Safety and Organ toxicity trial (HUSOFT extension study) (Hankins *et al*, 2005). Twenty-one infants (mean age 3·4 years) were enrolled on treatment at 20 mg/kg/day for 2 years with escalation to 30 mg/kg/day in the extension study. Fourteen had splenic function assessed at baseline, year 2 and year 4. Only 6 (43%) were functionally asplenic upon study completion in contrast to the expected 94% incidence of asplenia among untreated age-matched children with SS based on red-cell counts ($P < 0{\cdot}001$).

The randomised clinical trial, BABY HUG, which treated infants with SS/Sβ^0 thalassaemia with 20 mg/kg/day of hydroxycarbamide or placebo for 2 years, did not show a difference in splenic function (qualitative uptake on ^{99}Tc spleen scan) between the two groups (Wang *et al*, 2011). Further data are awaited to determine the effect of hydroxycarbamide on splenic function.

Renal function. Renal changes in SCD are common and are associated with significant morbidity and mortality.

In the randomised controlled BABY HUG study of infants with SS/Sβ^0 thalassaemia, those treated with hydroxycarbamide showed better urine concentrating ability ($P = 0{\cdot}007$) and less renal enlargement than those on placebo ($P = 0{\cdot}007$) but there was no change in estimated glomerular filtration rate (eGFR) (Alvarez *et al*, 2012).

The observational HUSTLE study showed a reduction in estimated glomerular hyperfiltration in 23 children who had been treated with hydroxycarbamide for 3 years ($P = 0{\cdot}016$) (Aygun *et al*, 2013). Observational studies in children have also reported a reduction in microalbuminuria with hydroxycarbamide treatment. Tehseen *et al* (2017) analysed 288 children aged >8 years with SS/Sβ^0 thalassaemia and showed that new and persistent albuminuria was less frequent in those treated with hydroxycarbamide (21% vs. 24%), as was intermittent albuminuria (12·5% vs. 25·3%; $P = 0{\cdot}045$).

Observational data on adults suggest that treatment with hydroxycarbamide may improve renal dysfunction. Observational data of 149 adults on hydroxycarbamide over 11 years has shown a lower prevalence of albuminuria (34·7% vs. 55·4% $P = 0{\cdot}01$) than in a comparator group (Laurin *et al*, 2014).

The mode of action for this renal benefit may be via suppression of damaging proteins; lower levels of monocyte chemoattractant protein 1 are expressed in children on hydroxycarbamide (dos Santos *et al*, 2015).

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/S$\beta^{0/+}$ 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 ($P = 0{\cdot}005$), suggesting induction of HbF levels with hydroxycarbamide may have a protective effect on the development retinopathy in children (Estepp *et al*, 2013).

Pulmonary hypertension. Pulmonary hypertension occurs in around 10% of adult patients with SS/Sβ^0 and is associated with an increase in all-cause mortality (Gordeuk *et al*, 2016).

There is no direct evidence to support the use of hydroxycarbamide in pulmonary hypertension in children or adults.

Pulmonary artery pressures can increase acutely during episodes of vaso-occlusive and chest crises, triggering right heart failure (Machado *et al*, 2007). The latter group of patients are at an increased risk of death both during and after hospital admission. The benefits of hydroxycarbamide therapy may therefore be to decrease the rate of vaso-occlusive crisis and hence avoid precipitation of heart failure and death.

Cardio-pulmonary benefits. In children, hydroxycarbamide has been associated with statistically significant improvement in pulmonary function tests, increase in daytime ($P = 0{\cdot}001$) and average overnight oxygen saturation ($P = 0{\cdot}01$) (Narang *et al*, 2015), significant improved aerobic exercise tolerance and physical fitness (Wali & Moheeb, 2011). These cardiovascular benefits may be due to the associated increase in haemoglobin.

Priapism. Case reports suggest some benefit of hydroxycarbamide to prevent recurrent ischaemic priapism (Al Jam'a & Dabbous, 2002; Saad *et al*, 2004) through its mechanism of enhancing NO bioavailability, but there is no evidence to support its role in acute episodes (Uzoma *et al*, 2015).

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 (Jena & Swain, 2006).

Recommendations

- **The potential benefits of hydroxycarbamide in preventing end organ damage (renal/splenic and retinopathy) should be discussed with all carers of children/patients with SS and Sβ^0 (1C)**
- **In patients with sickle nephropathy with persisting proteinuria despite angiotensin-converting-enzyme inhibitor/angiotensin receptor blocker therapy, consider the addition of hydroxycarbamide therapy (2C)**
- **There is insufficient evidence to treat patients with SS/Sβ^0 with pulmonary hypertension and avascular necrosis with hydroxycarbamide but it should be considered on a case-by-case basis (2C)**
- **In children and adults with chronic hypoxia, recommend treatment with hydroxycarbamide (1C)**

- **Patients should be counselled that hydroxycarbamide may prevent priapism (2D)**
- **In children and adults with SS/Sβ^0 and symptomatic chronic anaemia that interferes with daily activities or quality of life, recommend treatment with hydroxycarbamide (1C)**

Use in other genotypes

Hydroxycarbamide has been less well investigated in SCD phenotypes other than SS/Sβ^0 thalassaemia genotypes. Although there are no completed randomised clinical trials of hydroxycarbamide use in patients with sickle cell/HbC (SC) disease, cohort studies suggest a beneficial role in reducing pain events and hospitalization, particularly in older children and adults (Lebensburger *et al*, 2015; Luchtman-Jones *et al*, 2016). Haematological responses with an increase in HbF and MCV with reductions in total WBC, ANC and ARC have been noted whilst an increase in Hb was not always observed.

The efficacy of hydroxycarbamide in SCD other than SS and Sβ^0 warrants further investigation. A prospective single centre study of hydroxycarbamide in children with SC is ongoing (NCT02336373).

Recommendations

- **Hydroxycarbamide therapy should be considered in adults and children with sickle cell disease (SCD) with genotypes other than SS and Sβ^0 thalassaemia who have recurrent acute pain, acute chest syndrome or episodes of hospitalisation (2C)**
- **Hydroxycarbamide therapy should be considered in adults and children with SCD with genotypes other than SS and Sβ^0 thalassaemia for other indications on a case-by-case basis (2D)**

Concerns of hydroxycarbamide

Short-term complications. Hydroxycarbamide is well tolerated with few side effects.

Some patients may experience mild gastrointestinal symptoms (Kinney *et al*, 1999), or hyperpigmentation of the skin and darkening of nails, which is not dose-dependant (O'Branki *et al*, 2001). 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 (Charache *et al*, 1995). Marrow suppression, which is transient and reversible, is the most expected short-term effect. This side effect also contributes to the clinical benefits (see section on *Dosing and monitoring*).

Medium and long term concerns

No risk of leukaemogenesis. There is now compelling evidence that hydroxycarbamide, when used in the treatment of patients with haemoglobinopathies, carries no increased risk of leukaemogenesis (Algiraigri & Radwi, 2014; Castro *et al*, 2014). In a 17-year follow-up of patients in the LaSHS (Voskaridou *et al*, 2010) and MSH (Steinberg *et al*, 2010) studies there were no cases of myelodysplastic syndrome or leukaemia. In extended follow-up from a small teenage cohort from HUSOFT (with 15 years of treatment from infancy) there was no evidence of myelodysplastic syndrome (Hankins *et al*, 2015).

There is medium-term data (up to 8 years) in 107 children (median age 11 years) treated with hydroxycarbamide showing no increased number of genetic mutations (Zimmerman *et al*, 2004).

Data from the HUSTLE study, a prospective study in children evaluating long-term cellular and molecular effects of hydroxycarbamide with up to 12 years exposure, mean age (13·2 ± 4·1 years), has shown no difference in chromosome stability compared with rates in untreated patients (Flanagan *et al*, 2010). There does not seem to be increased chromosome damage in cells from children on hydroxycarbamide and there was no evidence of increased genotoxicity in data from the BABY HUG study (McGann & Ware, 2011; McGann *et al*, 2012). These observations provide important safety data regarding long-term risks of hydroxycarbamide exposure for children with SS/Sβ^0 and suggest no *in vivo* mutagenicity or carcinogenicity.

Normal growth and development. The data on 8 adolescents enrolled as infants (aged 6 months to 2 years) with 15 years exposure to hydroxycarbamide (median age 17·6 years) shows growth rates that continued on the 50th centile for both height and weight, and puberty occurred without delay. Cognitive development was also normal (Hankins *et al*, 2014). The results of the long-term follow-up cohort of the BABY HUG study will be important in describing the long-term efficacy and toxicity of hydroxycarbamide in a larger cohort of children treated in infancy.

Fertility. There is no available evidence in females or males that hydroxycarbamide affects fertility.

In a study by Ballas *et al* (2009) that followed up MSH patients 17 years post-randomisation, 28 female participants had 51 pregnancies (18·3% of female participants had at least 1 pregnancy).

In males, the effect of hydroxycarbamide on spermatogenesis remains unclear. Most studies are case reports with few prospective studies, making evidence-based counselling of risk of developing sperm abnormalities or infertility challenging. Baseline sperm abnormalities exist in men with sickle cell disease. Berthaut *et al* (2008) carried out a retrospective multicentre study and 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. This abnormality is seen whether or not clinical priapism or testicular infarction has been documented.

Hydroxycarbamide is an antimetabolite and slows DNA synthesis. Animal studies have shown that doses equivalent to 25 mg/kg of hydroxycarbamide in mice increases testicular germ cell apoptosis and reduces spermatogenesis (Shin *et al*, 1999; Jones *et al*, 2009). In the study reported by Berthaut *et al* (2008), all sperm parameters seemed to be adversely affected less than 6 months into treatment with hydroxycarbamide, later reaching a plateau. Whilst there was no statistical significance in sperm parameters in 30 patients before hydroxycarbamide treatment and in 4 patients after cessation of treatment, 3 out of those 4 patients had severe reduction in sperm count. Length of hydroxycarbamide exposure may be related to sperm abnormalities. A 12-year follow-up of 2 children revealed azoospermia (Lukusa & Vermylen, 2008). Two recent studies have attempted to show the effect of hydroxycarbamide on spermatogenesis. Sahoo *et al* (2017) included 100 males aged 15–45 years and performed seminal fluid analysis before starting hydroxycarbamide and every 3 months after its initiation. Among 50 SCD patients without hydroxycarbamide therapy 18% were oligospermic and 4% were azoospermic. Among 50 patients treated with hydroxycarbamide, 20% developed oligospermia and 10% developed azoospermia. There was a significant reduction in sperm concentration, motility and normal morphology ($P = 0{\cdot}0001$) during therapy. Seminal fluid parameters reverted to normal after stoppage of hydroxycarbamide for 3 months in 11 (73%) of 15 oligospermic and azoospermic patients. One criticism of this study was that sperm samples of patients not treated with hydroxycarbamide were not compared over time so there was no control group. A prospective multicentre study from France (Berthaut *et al*, 2017) assessed the effect of 6 months of hydroxycarbamide treatment on total sperm count (TSC). Thirty-five men with SS (age range 20–51 years) were evaluated. Before hydroxycarbamide treatment 40% of patients had abnormal TSC, one had cryptozoospermia and none had azoospermia. After 6 months of treatment with hydroxycarbamide there was a significant decrease in TSC and twice as many patients had an abnormal TSC. Five patients had cryptozoospermia and six had azoospermia. This study did not examine if these changes are reversible and did not address the impact on fertility. These studies are small, and it is not possible to confirm the degree to which hydroxycarbamide impairs spermatogenesis and the reversibility of its effects, however 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 (Milardi *et al*, 2012) and the effect of hydroxycarbamide on male fertility have not been evaluated.

The effect of hydroxycarbamide on male spermatogenesis and fertility when the drug is started in pre-pubertal children are unknown.

Ballas *et al* (2009) reported that the female partners of 27 male MSH participants had 40 pregnancies (18·5% of the MSH male participants had a female partner with at least 1 pregnancy). These 40 pregnancies resulted in 42 pregnancy outcomes. This data indicates that men who have taken hydroxycarbamide have fathered children.

In view of these uncertainties it has been suggested that it is reasonable to offer post –pubertal male patients sperm analysis and cryopreservation prior to starting treatment with hydroxycarbamide (Berthaut *et al*, 2008; NTP-CERHR, 2008).

There are cost implications of sperm cryopreservation and this needs to be highlighted to NHS England and included within tariffs for specialised commissioning. It is not clear if hydroxycarbamide therapy should be interrupted to allow sperm cryopreservation in male patients who were not previously offered this or who were pre-pubertal at commencement. A research study to evaluate the effect of hydroxycarbamide on spermatogenesis is a priority. Data are needed on sperm function in males with SCD, whether on hydroxycarbamide or not, the effects of hydroxycarbamide on spermatogenesis and also if sperm function is affected, whether this is reversible and how long hydroxycarbamide would have to be discontinued to reverse any effect. It is also important to know how reduction in sperm function correlates with fertility.

Teratogenicity

Hydroxycarbamide at high (superpharmacological) 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, including early fetal loss or anomalies. An expert panel report from the NTP in the USA expressed concern about potential teratogenicity with hydroxycarbamide and possible harmful effects to the baby when breastfeeding (NTP-CERHR, 2008).

At present, until further data are available, the use of contraception is recommended for both male and female patients whilst taking hydroxycarbamide. Despite this precautionary measure, some women have become pregnant while they or their male partners were on hydroxycarbamide.

Specifically, in the study reported by Ballas *et al* (2009), there were 28 female MSH participants who had 51 pregnancies. Only six had definite exposure to hydroxycarbamide and there were two live births, one spontaneous abortion and three elective abortions. For male MSH study participants who had known hydroxycarbamide usage at conception, the 10 pregnancy outcomes of the female partners resulted in five live births (full term), one live birth (premature), two elective abortions (gestational age <24 weeks) and two spontaneous abortions; no teratogenic changes were found.

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.

However 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 of teratogenicity. These risks should be carefully discussed with the patients to enable them to make an informed choice.

Recommendations

- **Post-pubertal male patients should be considered for sperm analysis and cryopreservation prior to starting treatment with hydroxycarbamide (1C)**
- **Consider stopping hydroxycarbamide pre-conception in male and female patients and in pregnant women (1C) 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. (1C)**
- **Contraception is advised for patients on hydroxycarbamide (1C)**

Dosing and monitoring

HbF and maximum tolerated dose

The main aim of therapy is to optimise HbF% without causing excess bone marrow suppression.

In a retrospective cohort study of 383 patients, those with highest HbF% were more likely to be alive ($P = 0{\cdot}04$) and high HbF% was correlated with highest hydroxycarbamide dose (Fitzhugh *et al*, 2015). This benefit was not observed in those patients with lower HbF levels. Different doses of hydroxycarbamide have been used in studies and trials, from 10 mg/kg (Jain *et al*, 2012, 2013; Sharef *et al*, 2013; Keikhaei *et al*, 2015) up to >25 mg/kg, all showing clinical benefit (Ware, 2010; Phillips *et al*, 2018). A higher dose, of 26 mg/kg hydroxycarbamide, was shown by Phillips *et al* (2018) to give a significantly higher HbF (29·2% vs. 20·4%, $P = 0{\cdot}015$).

Dosing should start at 15 mg/kg/day for adults (rounded up to the nearest 500 mg) (Charache *et al*, 1995) and 20 mg/kg/day for children (Wang *et al*, 2012). Use 5–10 mg/kg/day as the starting dose if the patient has chronic kidney disease (estimated glomerular filtration rate [eGFR] < 60 ml/min/1·73 m^2) and hydroxycarbamide should be avoided if eGFR < 30 ml/min/1·73 m^2. The dose can be escalated by 5 mg/kg every 8–12 weeks, aiming for a neutrophil count of 2–3 $\times$ 10^9/l and stopping if neutrophils fall below 1 $\times$ 10^9/l or if there is other haematological toxicity. This is the maximum tolerated dose.

Most patients will sustain HbF induction with hydroxycarbamide although there is considerable inter-individual variability of the amount of HbF produced. Although poor response may be due to poor compliance, possible genetic modifiers of HbF induction have been identified and adults often display more myelosuppression than children and cannot tolerate the doses needed to induce a high HbF response. Baseline elevation of HbF should not affect the decision to initiate hydroxycarbamide therapy (NHLBI, 2014).

Neutrophil, platelet and Hb threshold for stopping hydroxycarbamide

There is significant variation in the neutrophil count, platelet count and Hb used to indicate the need for dose modification in patients treated with hydroxycarbamide. Neutrophils and platelets are an important part of the pathogenic process of organ damage in sickle cell disease. Mild to moderate neutropenia and thrombocytopenia should not be considered an adverse event but rather a therapeutic effect. We know from clinical practice in haemato-oncology in children and young adults with acute lymphoblastic leukaemia that chemotherapy treatment is not stopped or modified unless the neutrophil count is <0·75 $\times$ 10^9/l as an infection risk at this level is small. Also bleeding is not generally experienced with a platelet count greater than 50 $\times$ 10^9/l.

Most of the data for neutrophil thresholds used to recommend treatment interruption are from trials in children, which are much older studies and cumulative experience is high. The NHLBI guidelines suggest a lower limit of 1·25 $\times$ 10^9/l in children and 2 $\times$ 10^9/l in adults (NHLBI, 2014). The SWiTCH study recommended a lower neutrophil count limit of 1·5 $\times$ 10^9/l before stopping hydroxycarbamide (Ware & Helms, 2012) and/or adjusting dosage. We suggest that clinicians should stop treatment if the neutrophil count is ≤1 $\times$ 10^9/l.

The majority of trials have used a lower platelet threshold consensus of 80 $\times$ 10^9/l. However in experienced hands and with close monitoring this threshold could be lower.

There is also variation regarding the advice for Hb threshold for stopping hydroxycarbamide.

The HUG-KIDS trial (Kinney *et al*, 1999) used an Hb of less than 45 g/l with low reticulocytes <80 $\times$ 10^9/l or 50% from baseline or a 20% decrease in baseline Hb lasting for more than 1 week.

In view of the risk of marrow suppression, a full blood count and reticulocyte count should be checked 2 weeks after commencement and after every dose increment and then at least every 8–12 weeks for the entirety of treatment. Figure 1

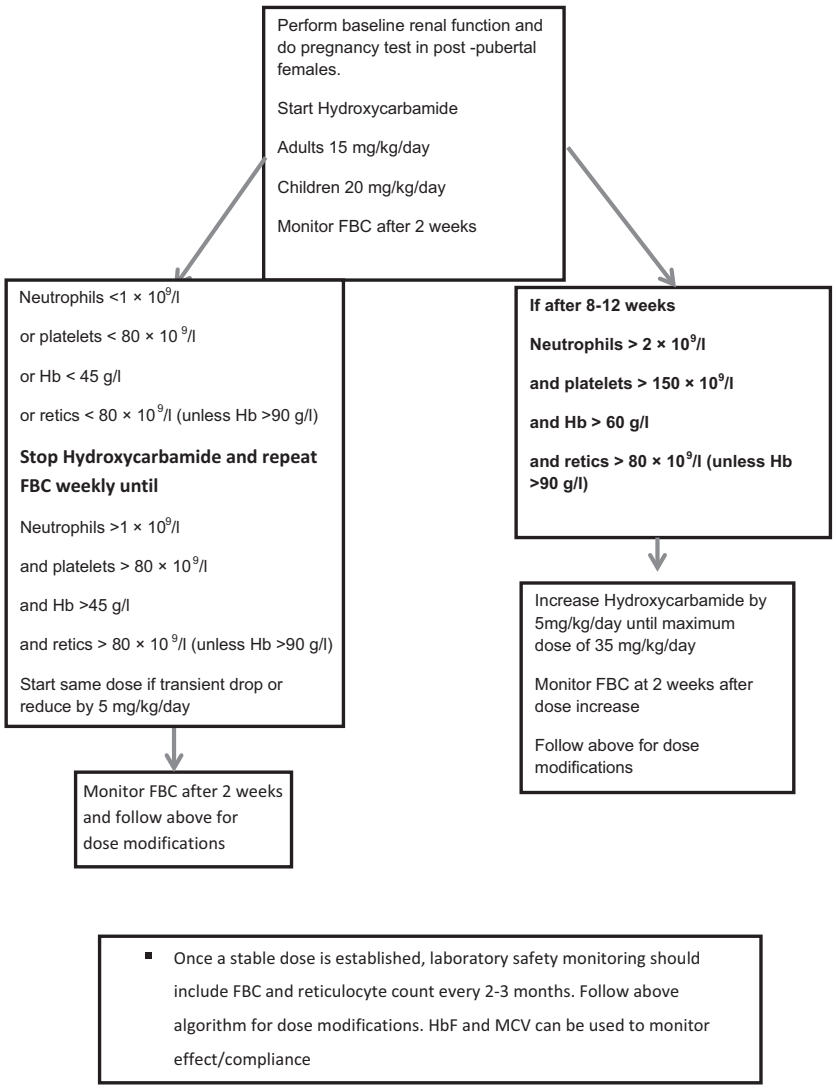

Fig 1. Algorithm for hydroxycarbamide dosing and monitoring. FBC, full blood count; Hb, haemoglobin; HbF, fetal haemoglobin; MCV, mean cell volume.

shows an algorithm for hydroycarbamide dosing and monitoring.

Definition of failure to respond to hydroxycarbamide

Hb, MCV and HbF levels should be monitored for evidence of consistent laboratory response. An optimal clinical and laboratory response to treatment with hydroxycarbamide may take 12 months. Therefore, a 6-month trial on the maximum tolerated dose is required prior to considering discontinuation due to treatment failure, whether due to lack of adherence or failure to respond to therapy. Patients and families should have the length of therapy before clinical effect explained so as not to give up too early.

For the patient who has a clinical response, long-term hydroxycarbamide therapy is indicated.

A failure to respond to hydroxycarbamide can be classified as failure to improve frequency and severity of painful episodes or ACS. Failure of response should be based on clinical criteria rather than laboratory data, as benefit can be seen even at a low HbF% (NHLBI, 2014).

A significant proportion of failure to respond to hydroxycarbamide is due to non-adherence/compliance or failure to escalate to the maximum tolerated dose.

Every effort should be made to re-counsel patients and families as to the benefits of hydroxycarbamide, to assess and address reasons for non-compliance. Support, including nurse specialist and psychologists, may be helpful to improve adherence.

Further advice for hydroxycarbamide use

Patients should be reminded that the effectiveness of hydroxycarbamide depends on their adherence to daily dosing. They should be counselled not to double up doses if a dose is missed.

Hydroxycarbamide therapy should be continued during hospitalizations or illness unless due to febrile neutropenia or bleeding with thrombocytopenia.

Other cautions include avoiding use with didanosine, stavudine and clozapine and caution with yellow fever vaccine (although risks and benefits should be considered).

Review treatment if cutaneous vasculitic ulcerations develop.

Patients should be informed to present to hospital if unwell with high fevers and infection and inform hospital staff to perform a FBC in case of neutropenia.

See in Patient Information sheet Appendix 2.

Consultation guidance can be found in Appendix 3.

Recommendations

- **Guidelines for the indications, initiation and monitoring of hydroxycarbamide therapy should be available at all sites caring for patients with sickle cell disease (Grade 1D)**

Conclusion

Hydroxycarbamide has been shown to increase survival in SCD patients. There is high quality evidence that it is effective in reducing incidence of pain and chest crisis and reducing conditional cerebral flow velocities in children, which has also been substantiated in the recent Cochrane review (Nevitt *et al*, 2017). It also prevents events in asymptomatic children. It is well tolerated and has no long-term mutagenic effects. The long-term follow-up of the BABY HUG study and further follow-up data in young children will provide important safety data on the long-term use of hydroxycarbamide in very young children. This long-term data and further trials are also required to show if early use of hydroxycarbamide can reduce long-term organ damage, including the risk of pulmonary hypertension and chronic renal disease. Further studies are also warranted to analyse quality of life of patients on hydroxycarbamide. One remaining important research question is the effect of hydroxycarbamide on spermatogenesis. The question of whether sperm function is adversely affected, the impact of abnormal sperm function on fertility and if any effect is reversible, needs to be answered. Sperm banking should be considered for all post-pubertal male patients. The effect on pre pubertal spermatogonial stem cells is also unknown. The potential importance of testicular preservation in younger children needs to be raised, although the ability to transplant this tissue successfully in the future remains to be proven. The cost of cryopreservation should be incorporated into specialised commissioning, as it has been in patients undergoing chemotherapy. At present, hydroxycarbamide is the only disease-modifying therapy available to patients with SCD. Its benefits, which are significant, and side effects should be discussed with all patients and parents of children with SCD. The data of patients on hydroxycarbamide in each centre should be included in clinical dashboards as it improves both the quantity and quality of life of a patient with SCD. Further support for patients is required to encourage adherence, which is the main reason why its benefits are not experienced.

Disclaimer

While the advice and information in this guidance is believed to be true and accurate at the time of going to press, neither the authors, the BSH, nor the publishers accept any legal responsibility for the content of this guideline.

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Declaration of interests

The BSH paid the expenses incurred during the writing of this guidance. All authors have made a declaration of interests to the BSH and Task Force Chairs, which may be viewed on request. The following members of the writing group AQ, BK, RK, JA, SP, MA, have no conflict of interest to declare. JH is on speaker's bureau for Addmedica.

Review process

Members of the writing group will inform the writing group Chair if any new pertinent evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website (b-s-h.org.uk).

Appendix 1: Literature Search

Search overview for the use of hydroxycarbamide in sickle cell disease

Records generated

Database searched	Date searched	Results
MEDLINE (OVID) 1995 to July week 1 2016	15/7/16	1042
EMBASE (OVID) 1995 to 2016 July 14	15/7/16	2527
Total		3569
After de-duplication		2737
Further duplicates removed during review (220)		2517
Exclusions (2147)		
Non-human (78)		
Not relevant to clinical question (1649)		
Single case reports (35)		
No abstract and, from title, not likely to be useful (385)		

Breakdown of remaining results

Articles included (279)
Compliance/usage/quality of life (QOL) (37)
Dose/monitoring (22)
End-organ damage (28)
Miscellaneous (8)
Mode of action (31)
Other sickling disorders (15)
Pain/crises/hospitalisation (46)
Reviews/overall (35)
Side effects/risks (34)
Stroke/transcranial Doppler (TCD) (23)
Possible articles (91)
Possibly relevant based on title only (26)
Smaller studies (65)

Medline

1 Hydroxyurea/(7752)
2 hydroxycarbamid*.tw. (223)
3 (hydrea or hydroxyurea or oncocarbide or siklos).tw. (7747)
4 or/1-3 (10620)
5 exp Anemia, Sickle Cell/(19713)
6 (sickle adj3 (disease* or disorder*)).tw. (10758)
7 (sickle adj3 an?emia).tw. (6231)
8 (HbSS or "hbs disease*" or HbSC).tw. (1383)
9 "h?emoglobin disease*".tw. (57)
10 or/5-9 (22940)
11 4 and 10 (1191)
12 limit 11 to (english language and humans) (1107)
13 limit 12 to yr="1995-Current" (1042)

Embase

1 Hydroxyurea/(22049)
2 hydroxycarbamid*.tw. (436)
3 (hydrea or hydroxyurea or oncocarbide or siklos).tw. (10902)
4 or/1-3 (23757)
5 exp Anemia, Sickle Cell/(30248)
6 (sickle adj3 (disease* or disorder*)).tw. (16545)
7 (sickle adj3 an?emia).tw. (8293)
8 (HbSS or "hbs disease*" or HbSC).tw. (2377)
9 "h?emoglobin disease*".tw. (80)
10 or/5-9 (33852)
11 4 and 10 (2957)
12 limit 11 to (human and english language and yr="1995-Current") (2527)

Appendix 2: Patient information leaflet

Patient information leaflet on hydroxycarbamide use

Hydroxycarbamide (also known as hydroxyurea) is a drug which has been used in large numbers of patients with sickle cell disease and has been shown to reduce the incidence of daily pain experienced at home or resulting in hospital admissions and life-threatening complications (chest crisis and stroke). It can improve the quality of a patient's life by increasing exercise tolerance allowing more energy for daily activities. It may also have a role in preventing long term lung and kidney damage and increasing long-term survival.

It works by increasing fetal haemoglobin (the red cells that are seen in babies) and this protects against the damage caused by sickle cells. It also makes the blood less sticky by reducing the white cell count. It can reduce the white count to low levels and this may increase risk of infection and as a result the blood count needs to be monitored on a monthly basis until the dose is stable. This potential reduction in white count is reversible.

It may cause darkening of the skin and nails and rashes. These side effects are often mild.

It may reduce sperm production but evidence for this is unclear and no large studies have been done to prove that hydroxycarbamide affects sperm production. However we do know that sperm production can be abnormal in men with sickle cell disease, and may be more abnormal after taking hydroxycarbamide. There is no evidence that either sickle cell disease or hydroxycarbamide affect fertility. Men should consider sperm testing and storage prior to taking hydroxycarbamide.

Hydroxycarbamide may, theoretically, harm the unborn baby, although there is no clear evidence of this. Women and men should stop hydroxycarbamide when planning a pregnancy, after consultation with your doctor. The risks of

becoming unwell after stopping hydroxycarbamide need to be weighed up with theoretical risks to the baby.

If you are taking hydroxycarbamide and you are unwell with high fevers and an infection, come to the hospital and ask for an urgent full blood count in case your white cell count has dropped.

Appendix 3: Underutilisation of hydroxycarbamide and guidance for consultation and informed decision making

Despite hydroxycarbamide having clear benefits in sickle cell disease, the available literature shows that only a small fraction of eligible sickle cell patients agree to take hydroxycarbamide (Brandow & Panepinto, 2010). One reason why patients fail to take this drug is because providers do not offer or discuss it with eligible patients, sometimes because they *assume* that patients will not want to take it (Brandow & Panepinto, 2010). Doctors and patients can also have either falsely held beliefs about hydroxycarbamide or lack information. The consultation should provide corrective information, providing clear facts about hydroxycarbamide, without making false assertions. Other important psychological principles of effective consultation include the following, which can both be used to help start the patient on hydroxycarbamide but also aid compliance in subsequent consultations.

1 Expertise should not be emphasised. Instead, questions should be asked to show interest, open-mindedness, and to challenge mistaken beliefs (The change wished to be seen in others should be modelled).
2 The message should be customized according to what is important to the patient, not just what is important to the physician. This can involve both relieving any unrealistic worries and also identifying real risks they may not have considered.
3 Many people find it threatening to discover they are wrong. Good things people are doing and are right about, should be articulated as this will provide a buffer against the threat of being wrong, so they are more likely to accept the correction (Cohen *et al*, 2007).
4 The corrective message should be framed in a way that is consistent with that person's worldview, e.g., the person values their health and engages in behaviour to prevent symptoms: hydroxycarbamide also prevents symptoms. Framed in this way, taking hydroxycarbamide is consistent with the person's deeper beliefs about health.

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