

Role of hydroxycarbamide in prevention of complications in patients with sickle cell disease

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Abstract: Sickle cell disease (SCD) is a genetically inherited condition caused by a point mutation in the beta globin gene. This results in the production of the abnormal hemoglobin, sickle hemoglobin (HbS). Hydroxycarbamide, is an antimetabolite/cytotoxic which works by inhibiting ribonucleotide reductase, blocking the synthesis of DNA and arresting cells in the S phase. In sickle cell anemia, it promotes fetal hemoglobin (HbF) synthesis, improves red cell hydration, decreases neutrophil and platelet count, modifies red cell endothelial cell interactions and acts as a nitric oxide donor. Trials have shown the clinical benefit of hydroxycarbamide in a subpopulation of adult patients with SCD, with a 44% reduction in the median annual rate of painful crises, a decrease in the incidence of acute chest syndrome and an estimated 40% reduction in overall mortality over a 9-year observational period. Its use in pediatrics has also been well established; trials have shown it is well tolerated and does not impair growth or development. In addition it decreases the number and duration of hospital attendances. A number of emerging uses of hydroxycarbamide currently are being investigated, such as stroke prevention.

Keywords: sickle cell anemia, hydroxycarbamide, hydroxyurea, maximum tolerated dose, vaso-occlusive crisis

Introduction

Sickle cell disease (SCD) is a genetically inherited condition caused by a point mutation causing the substitution of valine for glutamic acid at position 6 in the beta globin gene. This results in the production of the abnormal hemoglobin, sickle hemoglobin (HbS). The clinical phenotype can be seen in patients with homozygous sickle cell disease (HbSS), but also in patients who are compound heterozygotes of HbS and another abnormal hemoglobin such as hemoglobin C, D, E or O-Arab or beta thalassemia. Sickle cell disease is now the most common genetic disorder in the UK, affecting over 1 in 2000 live births and up to 1 in 300 births in some urban areas, and there is a worldwide annual birthrate of over 200,000 of which more than 90% are in Africa.¹ HbS polymerizes at low oxygen levels, making the red cell initially more rigid, and eventually irreversibly sickled. These red cells are less deformable and this results in vaso-occlusion within the end organ capillaries, leading to pain and organ dysfunction. In addition, ongoing hemolysis has an important role in disease pathophysiology by causing nitric oxide (NO) deficiency and vascular instability.² Red blood cell dehydration and red cell adhesion to the endothelium, with subsequent endothelium activation also contribute to the pathophysiology of this condition.³ Despite being a single gene disorder there is considerable heterogeneity in the clinical severity seen, and this is thought to be in part due to the role of other genetic factors, such as the co-inheritance

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of alpha thalassemia, and the presence of several single nucleotide polymorphisms (SNPs).⁴

Despite being one of the first inherited diseases characterized, treatment for SCD in the UK has lagged behind that in many other conditions. Hydroxycarbamide (also known as hydroxyurea), has a FDA license for the prevention of the complications of SCD in adults and is associated with improvements in morbidity in the adult and pediatric sickle populations.

Hydroxycarbamide – mechanism of action

Hydroxycarbamide has been used for decades in many hematological disorders, in particular the myeloproliferative disorders as a myelosuppressive agent. The first investigations into hydroxycarbamide as an agent that could potentially alter the production of fetal hemoglobin (HbF) was in anemic baboons,^{5,6} and it was first shown to raise levels of HbF in patients with SCD in 1985.⁷

Hydroxycarbamide belongs to a class of compounds called hydroxamic acids, which can bind metals. It inhibits ribonucleotide reductase by binding to two iron molecules on the reductase and inactivating a critical tyrosyl radical.⁸ This accounts for its cytotoxic effect which is beneficial in many ways; it targets rapidly dividing cells, which in red cells tend to be those with a high level of HbS, and favors the production of red cells with a high HbF, as these tend to arise from red cells that divide less rapidly.

Another potential mechanism of action is the production of NO caused by the metabolism of hydroxycarbamide. Hydroxycarbamide activates guanylate cyclase, an enzyme containing heme, via a NO-dependent mechanism, which results in the production of HbF, as shown in vitro. The mechanism by which hydroxycarbamide generates NO is thought to be related to the NO/guanosine 3,5-cyclic monophosphate (cGMP) pathway in erythroid progenitor cells.⁹ The production of NO may also compensate for the loss of endogenous NO due to intravascular hemolysis.

Hydroxycarbamide has additional effects including a reduction in the numbers of white cells and platelets, potentially reducing their roles in vascular injury¹⁰ and also improves red cell hydration and decreases red cell adhesiveness to the endothelium.^{11,12}

Role of hydroxycarbamide in prevention of acute painful crises and acute chest crises

Systematic reviews have looked at all randomized or quasi-randomized controlled trials comparing the use of

oral hydroxycarbamide with placebo, standard therapy or other interventions for the treatment of patients with SCD.^{13,14} Only 2 out of 7 studies^{15,16} were suitable for inclusion in these reviews and they are described in detail below. One further study is ongoing.¹⁷ These reviews concluded that hydroxycarbamide appeared effective in severely affected adults with HbSS over a 2-year period; however, further studies are required to elucidate its role in other patient groups. In addition all individuals should be counseled prior to commencing therapy relating to the known and potential risks.

Adult trials

Multicenter Study of Hydroxyurea (MSH)¹⁵

This was the first phase III double-blind, randomized controlled trial to look at the efficacy of hydroxycarbamide in reducing the frequency of painful sickle crises. Two hundred and ninety-nine adults with HbSS and a history of 3 or more crises a year were included and were randomly assigned to receive hydroxycarbamide (n = 152) or placebo (n = 147). Hydroxycarbamide was initiated at 15 mg/kg/day and increased every 12 weeks by 5 mg/kg/day until the maximum tolerated dose (MTD) was reached. If marrow depression occurred, it was stopped until blood counts recovered and restarted at a dose 2.5 mg/kg lower than the previous dose, starting a new 12-week cycle. The patients were seen every 2 weeks and blood samples taken. A painful crisis was defined as a visit to a medical facility lasting more than 4 hours and requiring parenteral or oral narcotics. In addition patients filled out daily pain diaries, reviewed at each clinic visit.

There was a median rate of 2.5 crises per year in the hydroxycarbamide group, compared to 4.5 in the placebo group, which represented a 44% difference ($P < 0.001$). When crises severe enough to warrant hospitalization were compared, the median annual rates were 1.0 in the hydroxycarbamide group and 2.4 in the placebo group ($P < 0.001$). The incidence of chest syndrome also differed significantly with 25 patients developing acute chest syndrome (ACS) in the hydroxycarbamide group vs 51 in the placebo group ($P < 0.001$). Both the frequency of blood transfusions (48 vs 73, $P = 0.001$) and number of red cell units transfused (336 vs 586, $P = 0.004$) were decreased in the group receiving hydroxycarbamide. There was no significant difference in the incidence of death, stroke and hepatic sequestration between the two groups.

The trial was stopped early, after 21 months of follow-up because of the beneficial results observed. Hb, mean cell volume (MCV), HbF and proportion of HbF cells were higher in the hydroxycarbamide group than the placebo

group at the time of study closure, and white blood cell count (WBC), platelets and reticulocyte counts were lower. They found the beneficial effects of hydroxycarbamide do not become manifest for several months, differences between the two groups in terms of MCV and HbF percent becoming apparent from 8 weeks. No deaths owing to treatment were described in the trial and no patients developed neoplastic disorders. Treatment was permanently stopped in 14 patients in the hydroxycarbamide group for medical reasons and 6 in the placebo group. Treatment ceased temporarily in almost all of the patients treated with hydroxycarbamide because of marrow depression; blood counts recovered within approximately 2 weeks. Hydroxycarbamide was associated with a raised hemoglobin in 11 patients, and despite it exceeding 12 g/dL, there were no adverse events.

This was an important study which demonstrated the clinical benefit of hydroxycarbamide in patients with severe homozygous SCD, which significantly reduced the median annual rate of painful crises and the incidence of ACS. It left further questions to be answered about optimal dose, further application, any benefit to prevent long-term organ damage, and long-term safety and tolerability data.

The MSH subsequently published 9-year follow-up observational data¹⁸ which estimated that there was a 40% reduction in overall mortality in the patients who had taken hydroxycarbamide. Complete data for 233 out of the original 299 patients were obtained for the full 9 years, and during the follow-up study they were able to continue, stop or start hydroxycarbamide and were seen yearly from 1996 to 2001. Data were included from the beginning of the original MSH trial, which showed that 96 patients (31%) never received hydroxycarbamide, 48 (16%) received hydroxycarbamide for less than 1 year and 156 (52%) received hydroxycarbamide for 1 or more years. From the initial patient cohort, 25% (75) died during the trial or follow-up, 28 of the deaths being due to pulmonary complications. When the deaths were analyzed in terms of original randomized patient subgroups, there were no differences between the hydroxycarbamide and placebo arms, but this did not take into account the patients' treatment after the original randomized phase was completed. There was a difference in cumulative mortality between the 2 subgroups, although this was not statistically significant ($P = 0.35$). Patients with reticulocyte counts less than 250,000/mm³ and hemoglobin levels <9 g/dL had increased mortality ($P = 0.002$). Cumulative mortality at 9 years was 28% when HbF levels were 0.5 g/dL or higher ($P = 0.03$). Individuals who had ACS during the trial had 32% mortality compared with 18% of individuals without ACS ($P = 0.02$).

Patients with 3 or more painful episodes per year during the trial had 27% mortality compared with 17% of patients with less frequent episodes ($P = 0.04$). There were 3 cases of cancer, 1 case of in situ cervical cancer who had received 63 months of hydroxycarbamide, 1 of breast carcinoma after 47 months of hydroxycarbamide and 1 patient died of endometrial carcinoma after 9 years of hydroxycarbamide.

Analyzing mortality in 3-month intervals according to hydroxycarbamide usage in the interval, death rates were reduced 40% during the 3-month intervals when patients were taking hydroxycarbamide ($P = 0.04$). Overall, the follow-up trial showed that adult patients taking hydroxycarbamide for frequent painful sickle episodes appear to have reduced mortality after 9 years of follow-up, and estimated this to be in the order of 40% overall reduction. Survival was related to HbF levels and frequency of vaso-occlusive events. These results must be interpreted with care as this is an observational study in which patients could choose whether or not they took the hydroxycarbamide.

Pediatric trials

Belgian study¹⁶

This randomized single blind placebo crossover trial of hydroxycarbamide, looked at 25 children and young adults with a median age of 9 years (range 2 to 22 years). They were randomized between placebo and hydroxycarbamide at a dose of 20 mg/kg/day for 2 weeks and the dose was increased to 25 mg/kg/day if there was no increase in HbF. After 6 months they were switched to the other treatment. Three patients on the placebo and 16 on the hydroxycarbamide had no hospitalizations during the 6 months of treatment, and there were no clinically relevant toxicities, implying that hydroxycarbamide decreased the incidence of painful crises in children as well as in adults.

Belgian Registry data^{19,20}

Data from the Belgian Registry were initially published in 2001²⁰ and updated in 2004.¹⁹ One hundred and twenty-seven patients with SCD were enrolled into the registry between 1993 and 2002 and started on hydroxycarbamide; 99 for 2 or more vaso-occlusive crisis (VOC), 21 for an ACS, 7 for stroke, 1 for transient ischemic attack (TIA), and 18 for abnormal trans-cranial dopplers (TCDs) only. One hundred and nineteen patients had HbSS, 4 HbSβ⁰ thalassemia, 3 HbSC and 1 HbSD. The median age at entry was 6 years (8 months to 19 years) and mean follow up was 47 months (1 to 8 years).

Hydroxycarbamide dosing was started at 20 mg/kg/day and escalated in increments of 5 mg/kg if felt appropriate by

the treating physician. The mean number of hospitalizations and duration of hospital admissions dropped significantly during the 8 years of hydroxycarbamide treatment ($P < 0.05$). Ninety-two out of 109 (85%) patients treated with hydroxycarbamide for conventional clinical criteria were free of major events requiring hospitalization at 1 year. At 7 and 8 years after initiation of treatment 6/24 (25%) and 5/14 (36%) patients respectively, remained so.

Thirty-two patients with HbSS were monitored for 6 years to assess the long term effects of hydroxycarbamide therapy. The median age at entry was 6 years (range 8 months to 19 years). Hospitalizations, acute painful crisis and ACS were more frequently observed during the fourth to sixth year of treatment than during the first 3 years. During the 6 years of hydroxycarbamide treatment 8/32 (25%) patients remained free from any SCD-related event requiring hospitalization. No strokes or TIA occurred in the 31 patients without a previous history of neurological events. There was 1 recurrent stroke in an 8-year-old girl, 6 years after the initial event. The hydroxycarbamide dose was reduced over time with no effect on the hematological indices.

In the registry, 14 patients were less than 2 years old at the time of enrolment and of these 10 had a minimum follow-up of 2 years hydroxycarbamide therapy. Their clinical events and hospitalizations were similar to those in older age groups over the same time period, the hospitalization durations being longer in the younger group.

HUG-KIDS study²¹

This was a phase I–II pediatric hydroxycarbamide trial used to determine if hydroxycarbamide would have a detrimental effect on the growth of school-aged children with HbSS.¹⁹ This prospective observational trial enrolled 68 children and adolescents who had an age range of 5 to 16 years and included 28 female and 40 male patients. Patients were eligible if they had severe SCD with 3 or more painful events in 1 year or 3 or more episodes of ACS in the 2 years before trial entry and hydroxycarbamide was escalated to MTD. In addition they needed a minimum of 6 documented height and weight measurements recorded for at least 2 years preceding entry. They had serial height, weight and Tanner stage measurements during the study. Comparison data were obtained from the data from the Co-operative Study of Sickle Cell Disease (CSSCD), and 3 groups were compared: pretreatment HUG-KIDS, on-treatment HUG-KIDS and the CSSCD group. In girls, there were no significant differences in height or weight among the pre-treatment, on-treatment and CSSCD groups. Compared with the CSSCD groups,

HUG-KIDS boys were heavier from 9 years of age (although not statistically significant) and pre-treatment HUG-KIDS boys were taller from 7 years of age ($P > 0.05$). The Tanner stage transitions took place at appropriate ages. This study showed that treatment with hydroxycarbamide had no adverse effect on height or weight gain or pubertal development in school-aged children with SCD.

Hydroxyurea Safety and Organ Toxicity trial (HUSOFT)

The original HUSOFT trial²² investigated the short term feasibility of hydroxyurea administration, toxicities, hematologic effects and effect on spleen function in infants with SCD. This was a prospective, multicenter, open-label, single arm, pilot study. In the 2-year initial study, 28 infants with HbSS or HbS β^0 thalassemia, all unselected for disease severity between 6 and 28 months (median 15 months), were prospectively treated with hydroxycarbamide. This was given orally once a day at the fixed dose of 20 mg/kg as a liquid formulation.

Twenty-one infants completed 2 years of hydroxycarbamide treatment. Hydroxycarbamide was well tolerated, produced mild toxicities, predominantly transient neutropenia, which was associated with a presumed viral infection in 70%. None had an associated invasive viral infection. Persistent or recurrent neutropenia required a decrease in dose in 3 patients. Anemia and thrombocytopenia were rare and no significant hepatic or renal toxicity was observed. Two patients had accidental overdoses of hydroxycarbamide, which resulted in a mild transient neutropenia in both. No adverse effects on growth were observed compared with untreated controls. There was maintenance of relatively stable elevated hemoglobin and HbF levels, showing a clear response to hydroxycarbamide therapy. The study also suggested a possible beneficial effect on preservation of splenic function, but the numbers were too low for statistical significance.

The HUSOFT extension study followed on from this pilot study.²³ This reported on the long-term efficacy and toxicity of hydroxycarbamide in infants. All 21 infants completing the original 2-year pilot study were offered continued liquid hydroxycarbamide therapy, and their dose was escalated by 5 mg/kg every 6 months to a maximum dose of 30 mg/kg/day. Of the 21 patients enrolled, 1 was removed because of non-compliance and 1 patient did not tolerate the dose increase, because of neutropenia. This patient required a permanent dose reduction to 27.5 mg/kg/day. Seventeen completed an additional 4 years, and 11 were treated for a total of 6 years. Removal from the study before 6 years was

due to non-compliance (in 4), parents' request (4) recurrent ACS (1) and death from pneumococcal sepsis (1).

Increased and sustained values of Hb, MCV, HbF and F cells were observed during the extension trial. All patients who tolerated the dose escalation responded to hydroxycarbamide by raising the percentage of HbF. Levels of WBC, platelet count and reticulocyte levels were lower than those expected in untreated children and were lower at year 6 than year 3, possibly because of dose escalation. The treated patients had significantly fewer ACS events than untreated SCD patients; however there was no difference in the incidence of pain. This was attributed to the method of data collection as in this trial pain was recorded monthly whereas in some other trials, eg, the CSSCD study, pain frequency was recorded annually retrospectively.

Hydroxycarbamide was generally well tolerated, with 8% cases of neutropenia compared to 10% in the pilot study above. Growth was not impaired among these children treated with hydroxycarbamide compared to standard growth curves. There was improved growth in some children, especially boys, a finding which has previously been demonstrated in boys²¹ and school-age children.²⁴ A trend towards a delay in functional asplenia was observed and recovery of splenic function in was seen in 2 cases. There was no decrease in the rate of silent infarcts after 4 years of hydroxycarbamide therapy (21%), compared to the prevalence reported in untreated SCD children.

In conclusion, the extension study supported the findings of the initial pilot study described above that hydroxycarbamide is effective in young children, with little acute toxicity. In addition it showed the use of oral liquid formulation of hydroxycarbamide at a dose of 30 mg/kg/day is feasible, results in sustained hematological efficacy with relatively limited adverse events, decreases the ACS rate, and may improve growth.

Monitoring and dosing of hydroxycarbamide

Hydroxycarbamide has only recently been licensed for use in SCD in the UK, and the majority of UK patients are currently being prescribed the unlicensed formulation. In view of this, and the lack of long-term follow up data for hydroxycarbamide, it is vital that full informed consent is taken from patients who are commenced on hydroxycarbamide therapy and the use of a patient information sheet is advised. Hydroxycarbamide therapy is usually commenced at a starting dose of 15 mg/kg (rounded to the nearest 500 mg), as in the MSH study¹⁵ and the full blood count should be checked 2 weeks after initiation and after

each dose increase. Once stable the full blood count should be checked every 6 to 8 weeks. If the patient is still symptomatic, then dose escalation should take place every 4 weeks until the blood count falls. At this point the hydroxycarbamide should be stopped until the full blood count has recovered and restarted at 2.5 mg/kg or 500 mg lower. This is the MTD. Liver function tests and urea and electrolytes should be checked every 8 weeks. HbF levels should also be checked regularly as this gives a good indication of response as does an increase in MCV. There are no studies looking at optimal timing of dose escalation and blood monitoring but UK expert opinion would support the above strategy.²⁵

Hydroxycarbamide is renally excreted so dosage should be adjusted in patients with evidence of renal impairment, and a starting dose of 7.5 mg/kg should be given in patients with a glomerular filtration rate of less than 60 mL/minute.²⁶

Maximum tolerated dose or minimum effective dose?

The majority of trials using hydroxycarbamide, including MSH, have commenced treatment at 15 mg/kg or 20 mg/kg and escalated treatment to the MTD or a maximum dose of 30 mg/kg. It is not clear on current evidence whether it is necessary to dose escalate in this way, or whether patients should be treated with the minimum effective dose. Although the patients enrolled in the MSH study were intended to dose escalate to the MTD, many did not, only 33% of patients receiving the MTD by 6 months, and 53% at the time of study closure, suggesting that hydroxycarbamide is effective at doses lower than the MTD. Hydroxycarbamide therapy at the MTD has been shown to be well tolerated and has sustained hematologic efficacy over several years of therapy.²⁷ In this trial hydroxycarbamide was initiated in 122 patients with severe SCD (106 HbSS, 7 HbSC, and HbS/ β thalassaemia and 2 HbS/O_{Arab}) at a median age of 11.1 years (range 0.5 to 19.7 years). Hydroxycarbamide was escalated to the MTD, with an average dose of 25.4 ± 5.4 mg/kg/day. The average duration of treatment was 45 ± 24 months. Of the 122 patients, 21 received doses higher than 30 mg/kg/day (median 31.1 mg, range 30.1 to 36.1 mg/kg/day). It was discontinued in 15 children with poor compliance.

There were significant increases for all of the 122 patients in hemoglobin level, MCV, and HbF level. When analyzed according to genotype, the increase in hemoglobin concentration was significant in all but the 8 patients with HbSC or HS/ β^+ . Hydroxycarbamide led to a decrease in the rate of hemolysis, as shown by significant decreases in reticulocyte count and bilirubin levels. In addition, there were significant

decreases in WBC and platelet counts. Mild transient neutropenia occurred in 5% of patients, but there was no hepatic or renal toxicity. There were no adverse effects on growth while on therapy, and many children had improved growth.

HbF induction was sustained for up to 8 years reaching levels of up to 20% which is the level suggested to provide clinical benefit.²⁸ This was achieved without adverse effects on growth or increased numbers of DNA mutations as measured by the quantitative VDJ assay to look for acquired somatic mutations. No child on hydroxycarbamide in this study acquired myelodysplasia, leukemia or any other malignancy. These data showed that escalating the dose of hydroxycarbamide to the MTD in children could achieve the maximum and sustained beneficial hematologic effects on percentage HbF and WBC count but they did not show that a decrease in clinical severity paralleled the dose increases.

In adults, it has been shown that it is not always necessary to reach the MTD to produce good clinical effects.²⁹ There is no current evidence to suggest that either MTD or minimum effective dosing regimes are safer or more efficacious and there are no long-term safety data beyond 8 years in children and 9 years in adults.

Adverse effects of hydroxycarbamide

The most common short-term side effect of hydroxycarbamide is myelosuppression, which requires careful monitoring with regular blood tests.

There is no established evidence of malignancy caused by the use of hydroxycarbamide in SCD, but there have been a small number of cases of leukemia and lymphoma reported.^{15,30} This needs to be discussed with the patient and balanced against the improvement in symptoms and mortality.

Animal studies have shown hydroxycarbamide to be embryotoxic/teratogenic,³¹ causing a number of birth defects. There have been 58 pregnancies reported in 57 women exposed to hydroxycarbamide during pregnancy which include one case of a fetal death and reduced growth and several minor malformations.³² The advice given currently to both male and female patients is not to conceive while on hydroxycarbamide and for 3 months after cessation. Clinicians should ensure that their patients are aware of the recommendation to use contraception whilst on hydroxycarbamide. If a woman becomes pregnant while on hydroxycarbamide she should stop it immediately and should not recommence until breast feeding has stopped.

There are limited data on male fertility after ceasing hydroxycarbamide, and there is some evidence that fertility does not return to normal in all patients, even several months after cessation. Males' sperm counts have been well described to be

affected during therapy with hydroxycarbamide, predominantly in animal studies but also in a number of case studies,³² one study showing up to 40% of men had decreased sperm counts while on hydroxycarbamide.³³ There are several case reports showing a long-term effect of hydroxycarbamide on sperm counts, including a case of a sickle patient who became azoospermic after 7 months' treatment with hydroxycarbamide who still had significantly reduced sperm count and sperm motility at 1 year after cessation of treatment.³⁴ A retrospective review of 4 patients on hydroxycarbamide, 3 with sickle cell and 1 with myeloproliferative disease (MPD), showed variable effects on spermatogenesis. Unfortunately no pre-hydroxycarbamide data were available. The MPD patient was azoospermic while on hydroxycarbamide, and regained a normal sperm count, but with many abnormal forms and motility 3 months after cessation. Once hydroxycarbamide was restarted he again became azoospermic. A second patient had a normal count throughout treatment but reduced motility, although sperm count fell once treatment was ceased. The 3rd and 4th patients did not have data both on and off hydroxycarbamide.³⁵

A further study has looked at the effects of hydroxycarbamide on sperm parameters, in 4 patients with sequential data, on and off hydroxycarbamide therapy.³³ Of these, one became azoospermic, which persisted 4 years after cessation. Two others developed reduced sperm counts on hydroxycarbamide, which did not recover 3 to 5 years after stopping treatment. One patient's sperm count was not affected during treatment, but there were concerns about the patient's compliance.

The data from the above observational studies, although in small numbers, raise the question for the need to provide analysis and possible sperm banking for males starting hydroxycarbamide. The authors would recommend that sperm analyses and banking are offered to all men about to commence hydroxycarbamide therapy, and that semen analysis is performed annually during therapy and when therapy is stopped. Ideally this should be done as part of a clinical trial.

Other side effects include hyperpigmentation of nails, nausea and vomiting, skin rash, alopecia and diarrhea. There was no evidence of an increased incidence of leg ulcers in the MSH study, despite the association of hydroxycarbamide therapy and leg ulcers in myeloproliferative disease.³⁶

UK guidelines – current indications for hydroxycarbamide

In the UK, there are recently published standards for the clinical care of adults and children with SCD which outline the indications for the use of hydroxycarbamide.^{37,38}

These are peer-reviewed documents based on literature review and expert opinion. In adults³⁷ hydroxycarbamide therapy is recommended for patients with moderate to severe SCD who have had 3 painful crises per year over the past 2 years requiring hospital admission, or have recurrent crises in the community which are severe enough to interfere with their activities of daily living, or who have had 2 or more acute chest syndromes, or 1 severe acute chest syndrome requiring ventilation.

Further possible indications, based on observational studies or anecdotal reports, include the following: Patients who have had a previous stroke, but are no longer willing or able to continue a transfusion program; patients with excessive hemolysis causing anemia; patients with repeated gallstone formation; or patients with anemia owing to renal disease, especially if they are not willing or able to have blood transfusion, pulmonary hypertension and priapism.

The pediatric guidelines³⁸ recommend that hydroxycarbamide should be considered in patients who have recurrent episodes of acute pain (more than 3 admissions in the previous 12 months, or are very symptomatic in the community) or who have had 2 or more episodes of acute sickle chest syndrome, or 1 acute chest syndrome requiring ventilation. They also state that the decision to start hydroxycarbamide should be made by the specialist center, although the local hospital will have a role in monitoring blood counts and side effects. The specialist center should have a written protocol which is shared with the local hospital. This should include information about dose regimen, frequency of blood test monitoring, management of myelosuppression and contraindications for use of hydroxycarbamide. In addition the patient and/or their parents should be given a patient information sheet and the use of hydroxycarbamide should be discussed with them on at least 2 separate occasions. Current knowledge about side effects, including cytopenias and the possible risk of leukemia or other malignancies, should be discussed. This discussion should be documented in the patient's notes.

The guidelines also state that there are still some areas which need clarification. These are the optimal dose; impact on long-term organ function; and risk of malignancy. For these reasons, they recommend that its use should be monitored with collection of data about long-term outcomes.

Emerging indications for hydroxycarbamide

Use of hydroxycarbamide to prevent stroke
Transcranial doppler (TCD) ultrasound is now recommended as a routine screening test for children with SCD from

2 to 16 years of age, to identify patients at highest risk for primary stroke.^{39,40} There are emerging data that hydroxycarbamide may have a beneficial effect in primary or secondary prevention of stroke in children but its role relative to that of blood transfusion has not been defined by prospective trials. Until more data are available, blood transfusion is the modality of choice in treatment and prevention of stroke in SCD.

Primary prevention

The Belgian Registry data included a subgroup of 18 patients who were treated with hydroxycarbamide because they were at risk of stroke on the basis of an abnormal TCD. They did not meet the conventional criteria for commencing hydroxycarbamide. Eleven of these 18 patients were prospectively followed by TCD, and 2 had velocities that returned to normal/conditional on hydroxycarbamide. In addition 8 patients at risk of secondary stroke were treated with hydroxycarbamide and followed for a median of 6 years. At trial entry only 5 of the 8 were still receiving chronic transfusion. Recurrent stroke occurred in 1 patient during the 6 years of follow-up. Thirty-four patients from the entire Belgian Registry (of 127 patients) were considered to be at risk of primary stroke on the basis of abnormal TCD, and only 1/34 presented with a cerebrovascular accident during an evaluation of 96 patient years. Evidence of silent infarction or neuropsychological change was not examined in this population.¹⁹

A prospective phase II trial has also looked at the efficacy of hydroxycarbamide in primary prevention.⁴¹ TCD velocities were examined in 59 children who were initiating hydroxycarbamide therapy because of clinical severity. Thirty-seven out of the 59 had increased flow velocities (>140 cm/second) at enrolment. The TCD velocities were then measured at MTD and at 1 year later. At the MTD, significant decreases were observed in the right and left middle cerebral artery velocities ($P < 0.001$). The magnitude of TCD velocity decline was significantly correlated with the maximal baseline TCD value. At hydroxycarbamide MTD, 14/15 children with conditional baseline TCD values improved, while the TCD reduction of 5/6 patients with abnormal TCD velocities whose families refused transfusions decreased to <200 cm/second. These TCD changes were sustained at follow-up. A further prospective single-center trial has been reported which followed up 14 infants for 80 weeks or more. This group had a median age of 35 months (range 21 to 53 months) and was treated with the MTD of hydroxycarbamide. Three patients had a conditional TCD at trial entry and these all reverted to the normal range by the end of the trial. No new MRI or MRA lesions were seen during the trial.⁴²

Secondary prevention

In 16 patients with SCD and previous stroke, transfusion therapy was prospectively discontinued and hydroxycarbamide was initiated. At the time of reporting the patients had been off transfusion for a median of 22 months (3 to 52 range). Their average hemoglobin was 9.4 ± 1.3 d/dL and 14 patients underwent phlebotomy. Three patients (19%) had neurological events considered recurrent stroke, each 3 to 4 months after discontinuing transfusions, but before maximal hydroxycarbamide effects. These data suggested that some patients may be able to discontinue chronic transfusions and use hydroxycarbamide therapy to prevent stroke recurrence.⁴³

A further study⁴⁴ looked at hydroxycarbamide as an alternative to transfusion in 5 children with SCD who had had a stroke, 3 after the first episode and 2 after the second CVA. Four had had an infarctive stroke, and 1 a TIA. None of the 5 patients had recurrence during 2 to 112 months of observation.

Phase III Stroke With Transfusions Changing to Hydroxyurea (SWiTCH) trial

A phase III trial⁴⁶ is currently underway including approximately 130 children (5.0 to 18.9 years of age with 65 subjects per treatment arm) with SCD who have had symptomatic cerebral infarctions and have been treated with red cell transfusions for at least 18 months. After completing baseline screening studies, half the participants will be switched to a therapeutic program of hydroxyurea and phlebotomy. Half of the participants will remain on transfusion and chelation. The composite primary endpoint

is to compare two modalities of treatment for the prevention of secondary stroke and management of iron overload. Hopefully this will provide some clear guidance as to the definitive role of hydroxycarbamide in the prevention of secondary stroke.

Conclusions from current evidence are that blood transfusion should be the treatment of choice for primary or secondary stroke prevention, but that hydroxycarbamide should be considered in patients who refuse or are unable to receive blood transfusion therapy. Further information will be obtained from the SWiTCH trial.

Effects on splenic function

There is emerging evidence, although not at all conclusive, that hydroxycarbamide may positively affect splenic function in children. The HUSOFT study suggested a possible delay in the progression toward functional asplenia corroborated in the HUSOFT extension study.²³ After 4 years of treatment with hydroxycarbamide there was a lower proportion of asplenic patients on hydroxycarbamide treatment (43% vs the expected 94%), suggesting that hydroxycarbamide may be able to prevent the loss of splenic function. It does however raise the possibility of a prolonged risk of acute splenic sequestration in these patients which will need further investigation.

Additionally, a more recent retrospective review looked at splenic function at baseline and on treatment with hydroxycarbamide in 43 children.⁴⁶ After a median of 2.6 years (range 0.2 to 8.6 years) of hydroxycarbamide at the MTD, 6 patients (14%) completely recovered splenic function and 2 (5%) had preserved splenic function. These 8 children had a greater hemoglobin concentration on hydroxycarbamide therapy than

Table I Current UK indications for use of hydroxycarbamide in adult and pediatric sickle cell disease

Indications in adults ³³		Indications in children ³⁴
Absolute indications (grade A evidence)	Possible indications (based on observational studies or anecdotal reports)	Absolute indications (grade A evidence)
3 painful crises per year over the past 2 years requiring hospital admission	Previous stroke, but are no longer willing or able to continue a transfusion program	Recurrent episodes of acute pain (>3 admissions in the previous 12 months, or are very symptomatic in the community)
Recurrent crises in the community which are severe enough to interfere with their activities of daily living	Excessive hemolysis causing anemia or repeated gallstone formation	2 acute chest syndromes
	Anemia due to renal disease	
	Pulmonary hypertension	
	Priapism	
	Leg ulcers	

those without splenic function (9.1 vs 8.6 g/dL, $P = 0.01$). Although retrospective, the data suggest that hydroxycarbamide at MTD possibly preserves spleen and can even result in recovery of splenic function. In addition they suggest higher final hemoglobin concentration during therapy is a significant laboratory predictor of improved splenic function.

Use in renal impairment

A prospective single center trial has been reported which followed up 14 infants for 80 weeks or more. This group had a median age of 35 months (range 21 to 53 months) and was treated with the MTD of hydroxycarbamide. DTPA glomerular filtration rate (GFR) was measured at trial entry and exit. Five children had a raised GFR of over 150 mL/minute at trial entry, implying hyperfiltration and early renal damage. At trial entry the GFR had not risen as expected in the group of patients with a normal GFR at trial entry and the GFR in two patients with a raised GFR at trial entry had returned to normal.⁴² A retrospective analysis of hydroxyurea in combination with enalapril in children with SCD and sickle nephropathy⁴⁷ has looked at the laboratory effects of the two drugs. Enalapril reduced the urinary protein excretion and normalized serum albumin. There was a suggestion that the addition of hydroxycarbamide further normalized the urine/protein creatinine ratio. This would merit further investigation.

Future areas for research

Role of hydroxycarbamide in different genotypes

The majority of trials listed above have been limited to patients with HbSS, or included small numbers of patients with other genotypes, including HbSC, HbS thalassemia, and HbSD.^{15,20,23} A decrease in frequency and severity of painful crises has been shown in studies of non-HbSS patients and this trial confirms subanalysis of other trials that patients with HbSC may tolerate lower doses of hydroxycarbamide before reaching the MTD.^{27,48} These have only involved small patient numbers and would merit further investigation.

Other indications

A single-center study has reported on an improvement in chronic hypoxia in 3 pediatric patients when treated with hydroxycarbamide. This would merit further investigation.⁴⁹

Pharmacotherapy combination

There are many other agents currently being investigated, both individually and in combination with hydroxycarbamide.

They work in a variety of ways, some inducing HbF, others by varying other mechanisms, such as inhibition of normal membrane ion exchange channels, inhibition of endothelial or cell surface adhesion molecules, and as nitric oxide modulators.⁵⁰

For example, in a recent report of the National Institutes of Health (NIH) experience,⁵¹ 13 adult patients were given a combination of hydroxycarbamide and erythropoietin. These patients were either hydroxycarbamide intolerant due to reticulocytopenia, or had renal insufficiency. Erythropoietin plays an important role in dose escalation of hydroxycarbamide, while preventing erythroid toxicity, especially in the setting of renal impairment. An ongoing NIH phase I clinical trial is investigating the combination of these agents in adult patients with SCD and renal dysfunction and/or evidence of pulmonary hypertension (<http://www.clinicaltrials.gov#NCT00270478>). This will further clarify the role of erythropoietin and hydroxycarbamide combination therapy.

Summary

The efficacy of hydroxycarbamide in defined populations with SCD, both adult and pediatric, has been established since its first use in 1985. With its use has come a decrease in morbidity supplemented by increasing standards of care.

Unfortunately it is not a drug without side effects or risk and requires detailed pre-treatment counseling and careful monitoring of blood counts, which can limit compliance to therapy. Ongoing investigation into new agents may provide some further treatments; however at present hydroxycarbamide is the only effective treatment for patients with severe to moderate SCD. Its efficacy at reducing the frequency of vaso-occlusive crisis and acute chest crisis is well established. Its precise role and effects in certain populations such as stroke prevention and organ preservation is still being established, and some questions remain.

Disclosures

The authors disclose no conflicts of interest.

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