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The efficacy of hydroxyurea in decreasing transfusion requirements and hospital admission in children with sickle cell disease

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THE EFFICACY OF HYDROXYUREA IN DECREASING TRANSFUSION REQUIREMENTS AND HOSPITAL ADMISSIONS IN CHILDREN WITH SICKLE CELL DISEASE

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfilment of the requirement for the degree of Master of Medicine in the branch of Paediatrics

Johannesburg 2000

DECLARATION

I, Diane Mackinnon, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the branch of Paediatrics in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

.....

.....10th..... day of .....March..... 2000

ABSTRACT

The burden of sickle cell disease lies in Africa where resources are limited. Hydroxyurea may be an affordable treatment option for these patients.

Purpose

To assess whether hydroxyurea has any effect in reducing vaso-occlusive crises, hospitalization and transfusion requirements in children with homozygous sickle cell anaemia. To evaluate the toxicity of hydroxyurea.

Methods

This is a retrospective, descriptive study of clinical and haematological outcomes in children with sickle cell anaemia treated with hydroxyurea.

Results

Ten patients were evaluated. Hydroxyurea decreased the rate of vaso-occlusion and decreased the transfusion requirements. The clinical and haematological benefits were greatest when foetal haemoblobin was maximal. There was no short-term toxicity.

Conclusion

Hydroxyurea ameliorates symptoms in sickle cell disease. Ongoing studies are needed to assess long-term effects.

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1.0 INTRODUCTION

The haemoglobinopathies are some of the most common inherited diseases of mankind, probably because of the survival advantage conferred by the carrier state against falciparum malaria (1). The most common haemoglobinopathy is sickle cell anaemia which has autosomal co-dominant inheritance. In Africa the incidence of sickle cell trait is highest in West Africa (30-40%) and lowest in South Africa (about 1%) (2). Sickle cell anaemia constitutes a huge public health problem in some developing countries. The enormous burden is due to the fact that the disease is common and chronic. As primary health care improves the number of surviving homozygotes will increase, and with an expected average of one to two admissions per year the burden on the family as well as society will increase. About 120 000 babies with sickle cell anaemia are born yearly, but less than two percent survive to the age of five years. High technology treatment will benefit the fortunate few, but to have an important effect any treatment must be translated into a form that can be applied to the less developed and poorer countries.

Normal haemoglobin consists of a heme ring and four globin chains. During embryonic and foetal life the globin genes are sequentially activated and inactivated. The control mechanism of globin chain switching remains incompletely understood. During the third trimester of gestation, gamma chain production gradually diminishes and foetal haemoglobin (HbF $2\alpha 2\gamma$) is replaced by adult haemoglobin (HbA $2\alpha 2\beta$).

A single base substitution in the gene encoding the human β-globin unit, with the resulting replacement of $\beta 6$-glutamic acid by valine, leads to sickle cell anaemia in homozygous individuals. Sickle cell trait (heterozygous individual) is a benign carrier state, important for its genetic counselling implications.

Under normal circumstances haemoglobin is a highly soluble protein. The cause of sickle cell disease is the substitution of valine for glutamic acid at the sixth position of the β-globin chain. This results in a hydrophobic interaction between haemoglobin molecules when deoxygenated, resulting in an aggregation of sickle haemoglobin into large polymers. Polymerization of deoxygenated sickle haemoglobin results in a distortion of the shape of the red blood cell and a decrease in its deformability, resulting in vaso-occlusion and vascular injury. Sickle haemoglobin also has adverse effects on the red blood cell membrne that cause

oxidative damage, cellular dehydration, abnormal phospholipid asymmetry and increased adherence to endothelial cells (3). The nett result of these cellular abnormalities is a shortened red cell lifespan (i.e. haemolysis) and intermittent episodes of vascular occlusion that cause tissue ischaemia and acute and chronic organ dysfunction.

Haemolysis causes variable degrees of chronic anaemia and jaundice. Sickle cell anaemia places patients at risk for aplastic crises, caused by infection with human parvovirus and for the formation of gallstones (3). Delays in physical growth and in the onset of puberty are also common and correlate with the severity of the haemolysis.

Vaso-occlusion is initiated and sustained by interactions among sickle cells, endothelial cells and constituents of plasma. Repeated sickling and unsickling causes membrane damage and consequent potassium efflux followed by loss of water which increases cell density and the tendency of sickle haemoglobin (HbSS)to polymerize. Adhesive interactions between sickle cells and endothelial cells occur as a result of injury to cell membranes. As sickle cells perturb the endothelium, the balance between vasodilators and vasoconstrictors may be changed to favour vasoconstriction. Activated platelets release thrombospondin, which promotes the adherence of sickle cells to endothelial cells. Reticulocytes that are prematurely released from the bone marrow display additional adhesive ligands that facilitate interaction between sickle cells and endothelial cells.

Vaso-occlusion and tissue ischaemia can result in acute and chronic injury to virtually every organ in the body. Twenty-five to forty-five percent of infants and young children with sickle cell anaemia (SCA) experience at least one episode of dactylitis and many older patients experience repeated episodes of musculo-skeletal or abdominal pain (3). Acute and chronic injury to three major organs - the spleen, the lungs and the brain - are responsible for much of the morbidity and most of the mortality seen in childhood (3). In a given year, about sixty percent of patients with SCA will have an episode of severe pain (4). Vaso-occlusion is the most common reason for hospitalization in patients with SCA and the frequency of crises has prognostic significance for life expectancy. Only forty percent of young adults with more than three crises per year survive beyond forty years of age. Decreasing the frequency of crises may not necessarily increase the lifespan of patients with SCA (5) but recurrences of painful episodes or organ dysfunction are clearly associated with a poorer prognosis and early

mortality in adulthood. The acute chest syndrome, a frequent and often fatal complication, affects about forty percent of all people with SCA. It is most common, but least severe, in children, and when recurrent can lead to chronic respiratory insufficiency.

1.1 BLOOD TRANSFUSION IN SCA

Until recently, supportive therapy has been the mainstay of treatment for SCA. Indications for blood transfusion include

- symptomatic episodes of acute anaemia
- severe symptomatic chronic anaemia
- prevention of recurrent strokes
  (50% of children with SCA and stroke who do not receive frequent transfusions will have another stroke within three years compared with 10% who receive transfusions)
- acute chest syndrome with hypoxia
- surgery under general anaesthesia. (4)

There are many complications associated with blood transfusion.

1.1.1 Effects of transfusion on viscosity

The viscosity of blood is determined by the total haematocrit and the deformability of the red blood cells. As erythrocytes are transfused the haematocrit rises, resulting in a significant increase in viscosity. In normal patients oxygen transport increases as blood is transfused until the haematocrit reaches 40%. Once the haematocrit is above forty-five percent the viscosity increases dramatically and oxygen transport starts to fall. In patients with SCA the viscosity of a red blood cell suspension at full oxygenation is already higher than normal and the viscosity rises progressively with deoxygenation. When a patient with SCA receives a simple blood transfusion the increase in haematocrit with a constant sickle crit leads to an increase in viscosity thus limiting the improvement in oxygen delivery, despite the improved oxygen-carrying capacity. It is probably the combination of increased blood viscosity with decreased efficiency of oxygen delivery that causes the

sickle complications that have been reported to occur during or even soon after transfusion as well as after the cessation of hyper-transfusion. The complications are generally either painful vaso-occlusive crises, or neurological events (1).

1.1.2 Allo-immunization

Allo-immunization to red blood cell antigens in SCA has been reported to occur in eight to fifty percent of UK and North American SCA patients (1). The development of antibodies appears directly related to the number of transfusions and the frequency continues to rise as the number of transfusions increases. This is partly because, in these areas, the SCA patients are of different racial origins from the donor population. Up to one-third of antibodies to red blood cell antigens in SCA are transitory and therefore may not be detected on pre-transfusion testing, so that there is a risk of developing delayed haemolytic transfusion reactions, which can mimic the complications of SCA, including painful crises and hepatic sequestration. Matching donors for racial origin will decrease the risk, but is not recommended for cost reasons.

1.1.3 Transfusion transmitted infection

Pre-donation questioning and exclusion of high risk donors combined with new technologies have dramatically decreased the risk of transfusion transmission of HIV-I and II, as well as the hepatitides including hepatitis B and C. This remains a major concern for patients with SCA receiving transfusions in some developing countries. Unfortunately there is a high prevalence of these viral infections in the parts of the world where SCA is common. Leucocyte depletion, using filters that achieve three to four log reductions in white cells, is also effective at preventing transmission of a number of other infections including cytomegalovirus, Chagas disease and HTLVI.

1.1.4 Iron overload

Frequent blood transfusions result in iron overload and haemosiderosis. Iron deposition in the organs interferes with normal function and is fatal without chelation therapy. Iron overload is monitored most simply by serum ferritin, but optimally by biochemical assay of hepatic iron stores.

Plasma ferritin is an acute phase reactant, which rises as part of a non-specific response to inflammation including vaso- occlusion as well as infection. Hence repeated estimations of serum ferritin are required to indicate iron overload. Presently the only proven way to avoid an adverse outcome is by the regular use of infusions, generally subcutaneously of desferrioxamine. This is given by a syringe-driver pump over eight to twelve hours at least five to six nights each week. Unfortunately, the experience worldwide is of very poor compliance related to the inconvenience, social unaccept- ability as well as the local side-effects which include swelling, itching and irritation. Chelation therapy is understandably very costly.

Considering the cost and complications associated with blood transfusion, alternative safe and effective forms of treatment for SCA are required.

1.2 FOETAL HAEMOGLOBIN AND ITS INDUCTION

Polymerization is dependant on the cellular concentrations of sickle haemoglobin (HbS), implying that small reductions in the concentration of HbS may have important clinical benefits (6). High foetal haemoglobin (HBF) concentrations decrease the severity of SCA by preventing the formation of HbS polymers. HbF inhibits polymerization by reducing the intracellular HbS concentration. Also a glutamic residue at position gamma-87 prevents a critical lateral contact in the double strand of the sickle fibre (7). The solubility of equal amounts of HbS and HbF is about twice that of HbS alone.

Individuals with SCA have variable levels of HbF. HbF levels of more than ten percent in patients with SCA are associated with a milder clinical course, including a decreased risk of stroke and acute chest syndrome. HbF levels of more than twenty percent seem to protect against most vaso-occlusive events (8). In support of this clinical observation, in vitro solutions containing more than thirty percent HbF inhibit polymerization of deoxy HbS (8).

Hydroxyurea (HU) is an orally administered antitumour agent. The precise mechanism by which it produces its antineoplastic effect is unknown. Various studies support the hypothesis that HU causes an immediate inhibition of DNA synthesis by acting as a ribonucleotide reductase inhibitor. HU has been shown to increase the production of HbF in patients with SCA and ameliorate symptoms (9,10,11). The

exact mechanism by which hydroxyurea stimulates HbF production is unknown, but is most likely due to the recruitment of early red blood cell precursors with a higher inherent capacity for generating erythroblasts containing HbF (12). This appears to be accompanied by an improvement in rheologic properties of the red blood cell, including red blood cell survival, red blood cell density distribution and cell deformability. Hydroxyurea may also alter the adhesive receptors expressed on red blood cells and the vascular endothelium, increasing the possibility that vascular complications can be prevented (13). The benefit of hydroxyurea treatment may also be due in part to a decrease in the number of reticulocytes and young low-density red blood cells, since these cells are particularly likely to adhere to the vascular endothelium. Early interruption of the vaso-occlusive process may also prevent damage to vital organs. Hydroxyurea is relatively non-toxic, its myelosuppressive effects are readily reversible and it is not known to induce tumours.

Other agents have been used experimentally to induce HbF e.g. short-chain fatty acids (butyrate). Membrane-active drugs like clotrimazole and magnesium have also been used. However, results of these studies have been disappointing and currently hydroxyurea is the only drug in widespread use for the palliation of SCA.

1.3 LITERATURE REVIEW

After a double blind placebo controlled trial of HU in 299 adults it appeared that HU significantly decreased the frequency of painful crises, acute chest syndrome and blood transfusion requirements (11). These promising results in adult patients together with the absence of toxic effects or malignancy observed during long-term HU administration in a series of young patients with cyanotic congenital heart disease have encouraged investigation of this treatment in young SCD patients. Studies of HU in young children and adolescents are just beginning, and to date there are few studies available with small sample sizes. Short-term toxicity appears to be mild and infrequent and includes nausea, alopecia and cytopaenias (5). The frequency of these side-effects may increase as new studies are reported. Questions remain concerning long-term risks, e.g. carcinogenesis, gametogenesis, marrow toxicity, growth failure and chromosonal damage. Long-term studies are needed to answer these questions.

de Montalembert et al (14) gave HU in an uncontrolled study to thirty-five children with sickle cell disease. They showed that HbF was increased in all the children except one. The increase in HbF was related to the HU dose and inversely to the patient's age. They also noted an apparent reduction in crises which did not seem strictly correlated with the rise in HbF. They had two patient failures which they could not explain. They did not experience any serious haematological complications.

Similarly, Scott et al (8) found that HU induced statistically significant increases in haemoglobin and HbF in thirteen patients. Their toxic effects included three episodes of reversible myelotoxicity. They did not show a statistically significant decrease in hospitalization. They performed the pre-therapy analysis for the twelve to twenty-four month period prior to starting HU to control for the seasonal variation and episodic nature of vaso-occlusive crises.

Jayabose et al (5) also showed a significant increase in haemoglobin and HbF in fourteen patients treated with HU. They showed a significant decrease in vaso-occlusive crises and hospital admissions, although the duration of crises during HU treatment was not significantly reduced. There were two patient failures. For this study they took into account the whole duration of follow-up prior to starting HU as they thought this was more likely to give them a true pre-treatment rate.

In the only randomized trial, Ferster et al (15) studied the biologic and clinical benefit of HU by randomizing twenty-five patients to receive either HU or a placebo for six months. The patients were switched to the other arm for the next six months. Among twenty-two evaluable patients, six experienced no change in the number of crises requiring hospitalization. In these patients there was only a very slight increase in HbF. The remainder of the patients showed significant benefits.

Recently Hoppe et al reported on the use of hydroxyurea in children aged two to five years. These children responded with the same increases in haemoglobin and HbF as older children. Treatment with HU also resulted in a marked decrease in hospital admissions, total number of hospital days and transfusion needs. Short-term toxicity was virtually absent with no adverse effects on growth or development (17). As experience with the long-term administration of HU in patients with SCD increases there is appropriate

concern about the possible induction of tumours. The risk appears to be small in patients with myeloproliterative disorders who have taken the drug for up to 20 years (7).

1.4 MOTIVATION FOR THE STUDY

The burden of SCA lies in Africa, where resources are limited. Hydroxyurea, if effective, is an affordable treatment option. The cost of one unit of packed red blood cells for transfusion (R292) is equivalent to three months' treatment with HU (one hundred 500mg tablets cost R279).

Analysing the effects of HU is difficult, because of the high phenotypic diversity of the disease. We have clear indications for starting HU therapy, which selects patients who are sufficiently severe to warrant treatment. Many patients fulfilled the criteria for HU therapy long before we were using it. We have analysed the effects of HU by comparing clinical and haematological responses to HU, using the patients as their own controls from the time when HU would have been indicated.

To date, no studies have been conducted in developing countries. To have an important effect HU must be proven to be effective in these situations. The determinants of HbF response to HU have not been elucidated; postulates include biologic ability (bone marrow reserve), compliance, genetic factors and variations in drug metabolism. Nutritional factors affect bone marrow reserve and compliance is more likely to be a problem in developing countries. For these reasons we reviewed the effects of HU in our children with SCA.

2.0. MATERIALS AND METHODS

In our institution hydroxyurea has been used in the management of severely ill children with sickle cell anaemia since 1998.

The indications for hydroxyurea treatment included

- three or more vaso-occlusive events per year
- acute chest syndrome or other severe vaso-occlusive event (including cerebral vaso-occlusion)

- *splenic sequestration.*

Vaso-occlusion was defined as any painful episode involving the extremities, abdomen, back or chest, including acute chest syndrome.

Acute chest syndrome was considered to be vaso-occlusion of the lungs and was defined as an episode of respiratory distress associated with lung infiltrates on chest radiograph and which required hospital admission.

Splenic sequestration was defined as a massively enlarged spleen, associated with acute, severe anaemia.

Informed consent was obtained from parents prior to starting hydroxyurea. Parents were told that the long-term effects of hydroxyurea, including effects on the fertility of their child were unknown.

The starting dose of hydroxyurea was ten to fifteen milligrams per kilogram per day as a single daily dose. If an inadequate response was obtained, i.e.

- no clinical improvement
- persistent anaemia
- HbF<20%

then the dose was increased every eight to twelve weeks in increments of 5mg/kg/d to a maximum dose of 35mg/kg/d.

The end points for dose escalation were:

- no painful episodes
- increased HbF
- increased Hb
- myelotoxicity.

If bone marrow toxicity occurred, defined as:

- neutrophill count $<2000 \times 10^6/l$
- absolute reticulocyte count $<80000 \times 10^6/l$
- platelet count $<100000 \times 10^6/l$

then treatment was stopped. After recovery of the bone marrow, HU was re-instituted at a dose of 2-5mg/kg/d less than the toxic dose. Hydroxyurea was also temporarily stopped if there was a severe infection, vascular accident or aggravation of anaemia requiring transfusion.

2.1 STUDY DESIGN

This was a retrospective, descriptive study of clinical and haematological outcomes in children with sickle cell anaemia treated with hydroxyurea. Pre-treatment haematological parameters were compared with post-treatment values in each patient. *Clinical responses - transfusion requirements,* hospital admissions and rates of vaso-occlusive crises were also compared pre-treatment versus on treatment. These clinical responses were compared for three different time-periods

1. for the entire period of follow-up prior to starting hydroxyurea

2. for the twelve-month period prior to starting hydroxyurea

3. from the time when HU would have been indicated, based on symptomatology, had it been a treatment option.

Study population

All children with SCA, followed-up at the Chris Hani Baragwanath and Johannesburg General Hospitals, treated with hydroxyurea were included in the study. Records were analysed from the time of diagnosis of sickle cell anaemia.

Exclusion Criteria

Children receiving regular blood transfusions for the prevention of recurrent stroke were excluded from the analyses.

2.2 OBJECTIVES

Primary objective

To assess whether HU decreased transfusion requirements in children with SCA.

Secondary objectives

a) To assess whether hydroxyurea decreased hospitalization in children with SCA

b) To document any toxicity associated with hydroxyurea

- nausea, vomiting, gastro-intestinal tract disturbance
- alopecia
- bone marrow toxicity

c) To compare the rates of vaso-occlusive events in the two groups

d) To compare the HbF levels in the two groups

2.3 MEASUREMENTS

Data was obtained from patient records

Records were analysed from the time of diagnosis of SCA

Baseline investigations included

- FBC with differential and reticulocyte count
- HbF
- serum chemical values (urea and electrolytes)
- liver function tests.

FBCs were performed monthly and HbF levels three-monthly.

Data extracted from patient records included:

- age, sex
- anthropometric measurements (height, weight)
- transfusion requirements and indications for transfusion
  - symptomatic episodes of acute anaemia (cardiac failure, Hb <7g/dl)
  - severe symptomatic chronic anaemia
  - acute chest syndrome or other severe vaso-occlusive episode
  - bone marrow toxicity
- number of hospitalizations, duration of hospitalization and indications for hospitalization
- rate of vaso-occlusive events and their severity

- symptoms of toxicity recorded on questioning

- Laboratory Data

  ~ FBCs which had been done monthly

    Haemoglobin, mean cell volume, platelet count and white cell count were recorded

    (FBCs were analysed via the Technikon H*3RTX which uses light scatter and hydrodynamic focussing techniques)

  ~ Differential counts and reticulocyte counts (which were assessed manually)

  ~ HbF (which was determined by the alkaline denaturation test)

  ~ The maximal HbF achieved by each patient, as well as when it occurred

- The dose of HU, expressed in milligrams per kilogram.

2.4 DATA ANALYSIS

Data was analysed using a statistical software package (Statistix), with the aid of a statistician. For the comparison of means the Wilcoxan matched pairs signed ranks test was used because of the small sample size. To assess the correlation between significant results a non-parametric test, the Spierman rank correlation test, was used. A 'p' value of less than 0.05 was used to indicate statistical significance.

2.5 ETHICAL CLEARANCE

Ethical clearance was obtained from the Committee for Research on Human Subjects (Protocol number M00/2/21). This certificate has been included.

UNIVERSITY OF THE WITWATERSRAND, JOHANNESBURG

Division of the Deputy Registrar (Research)

COMMITTEE FOR RESEARCH ON HUMAN SUBJECTS (MEDICAL)
Ref: R14/49 Mackinnon

CLEARANCE CERTIFICATE PROTOCOL NUMBER M00/2/21

PROJECT	To Assess The Effficacy Of Hydroxyurea In Decreasing Transfusion requirements And Hospital Admissions In Children With Sicklelell Disease
INVESTIGATORS	Dr DJ Mackinnon
DEPARTMENT	Paediatrics Department, Baragwanath Hospital
DATE CONSIDERED	00/02/25

DECISION OF THE COMMITTEE *

Approved unconditionally

DATE 00/02/28 CHAIRMAN.....(Professor P E Cleaton-Jones)

* Guidelines for written "informed consent" attached where applicable.

c c Supervisor: Dr L Wainright
Dept of Paediatrics Department, Baragwanath Hospital

Works2\lain0015\HumEth97.wab\M 00/2/21

DECLARATION OF INVESTIGATOR(S)

To be completed in duplicate and ONE COPY returned to the Secretary at Room 10001, 10th Floor, Senate House, University.

I/we fully understand the conditions under which I am/we are authorized to carry out the abovementioned research and I/we guarantee to ensure compliance with these conditions. Should any departure to be contemplated from the research procedure as approved I/we undertake to resubmit the protocol to the Committee.

DATE 10/3/2000 SIGNATURE .....

PROTOCOL NO.: M 00/2/21

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

3. RESULTS

There were ten patients who had been treated with hydroxyurea available for evaluation.

Age
The median age was 9 years with a range from 2 to 14 years.

Sex
There were four males and six females.

Duration of Follow-Up
The median duration of follow-up was 13 months with a range from 3 to 20 months.

Toxicity or Cessation of Treatment
There was no documented toxicity either symptomatically or in terms of bone marrow suppression.

Dose at Twelve Months
The mean dose of hydroxyurea was 22,2 mg/kg/day
The median dose 23,75 mg/kg/day
The maximum dose 30 mg/kg/day

3.1 CLINICAL OUTCOMES

The rate of vaso-occlusive crises (episodes per year), the frequency and duration of hospitalisation (days per year) and transfusion requirements were compared before and during hydroxyurea treatment. For vaso-occlusive crises and hospitalisation three different time periods were compared. Firstly the whole period of follow-up prior to starting HU; secondly, the twelve month period preceding HU treatment; and thirdly from the time when HU would have been indicated on the basis of disease severity.

Patient number one presented with a splenic crisis, had a history of recurrent crises, and was started on hydroxyurea. There was therefore no pre-treatment data available for this patient.

3.1.1 VASO-OCCLUSIVE CRISES

a. The frequency of vaso-occlusive crises (VOCs) before treatment and during treatment are presented in the following table (3.1).

Patient	Age, Sex	Before treatment			During treatment		
		Total Number	Duration of follow up (months)	VOCs per year	Total Number	Duration of Follow up (months)	VOCs per year
1	3 yrs, male				1	14	0,85
2	5 yrs, male	3	38	0,95	0	7	0
3	10 yrs, female	1	49	0,25	0	4	0
4	10 yrs, male	1	18	0,66	1	14	0,85
5	7 yrs, female	1	48	0,25	0	12	0
6	12 yrs, female	1	48	0,25	0	13	0
7	14 yrs, female	5	139	0,43	1	13	0,92
8	2 yrs, male	4	14	3,4	0	3	0
9	8 yrs, female	7	54	1,5	2	11	2,18
10	14 yrs, female	8	18	5,3	3	20	1,8
	Total	31	426	0,87	8	111	0,86

	Before treatment		During treatment	
Mean number VOCs/yr	1,44	vs	0,62	
Minimum number VOCs/yr	0,25	vs	0	p = 0,24
Median number VOCs/yr	0,66	vs	0,43	
Maximum number VOCs/yr	5,3	vs	1,8	

b. Similarly, VOCs were compared for the year prior to starting hydroxyurea with those on treatment.

Before treatment			During treatment	
13 VOCs in 108 months giving 1,44 VOCs/yr		vs	8 VOCs in 111 months giving 0,86 VOCs/yr	
Mean number VOCs/yr	1,44	vs	0,62	
Minimum number VOCs/yr	0	vs	0	
Median number VOCs/yr	1	vs	0,43	p = 0,05
Maximum number VOCs/yr	7	vs	1,8	

c. VOCs were also compared from the time when hydroxyurea would have been indicated on the basis of crises to those occurring on treatment.

Before treatment			During treatment	
28 VOCs in 278 months giving 1,2 VOCs/yr		vs	8 VOCs in 111 months giving 0,86 VOCs/yr	
Mean number VOCs/yr	3,09	vs	0,62	
Minimum number VOCs/yr	0,25	vs	0	
Median number VOCs/yr	1	vs	0,43	p = 0,05
Maximum VOCs/year	16,8	vs	1,8	

3.1.2 HOSPITALIZATION

a. Table 3.2 Number of days per year spent in hospital before treatment compared to on treatment.

Patient	Before treatment			During treatment		
	Total Number Days	Duration of follow up (months)	Days per year	Total Number Days	Duration of Follow up (months)	Days per year
1				7	14	6
2	13	38	4	0	7	0
3	6	49	1,5	0	4	0
4	5	18	3,3	9	14	7,7
5	9	48	2,25	0	12	0
6	5	48	1,25	0	13	0
7	15	139	1,31	5	13	0
8	15	14	12,8	0	3	0
9	58	54	12,8	8	11	8,8
10	85	18	56,6	27	20	16,2
Total	211	426	5,9	56	111	6

Before treatment			During treatment	
Mean number of days/yr	10,64	vs	4,26	
Minimum number of days/yr	1,25	vs	0	p = 0,12
Median number of days/yr	3,3	vs	2,3	
Maximum number of days/yr	56,6	vs	16,2	

b. Hospitalization was also compared for the year prior to treatment versus during treatment.

Before treatment			During treatment	
There were 105 days spent in hospital in 108 months, giving a weighted average of 11,6 days/year			There were 56 days of hospitalization in 111 months, giving an average of 6 days/year	
Mean number of hospitalized days/year were:	11,67	vs	4,26	
Minimum number	0	vs	0	p = 0,28
Median number	5	vs	2,3	
Maximum number	79	vs	16,2	

c. When comparing hospitalization from the time when hydroxyurea would have been indicated on the basis of crises, there was a significant difference before treatment compared to during treatment.

Before treatment			During treatment	
198 days were spent in hospital in 278 months, giving a weighted average of 8,55 days/year			56 days were spent in hospital in 111 months, giving a weighted average of 6 days/year	
Mean number of days spent in hospital per year:	28,55	vs	4,26	
Minimum number	1,47	vs	0	
Median number	3,55	vs	2,3	p = 0,04
Maximum number	189,9	vs	16,2	

3.1.3 TRANSFUSION REQUIREMENTS

Table 3.3
Transfusion requirements before treatment compared to on treatment

Patient	Before treatment			During treatment		
	Total Transfusions	Duration of follow up (months)	Transfusions per year	Total Transfusions	Duration of Follow up (months)	Transfusions per year
1				1	14	0,85
2	1	38	0,3	0	7	0
3	2	49	0,49	0	4	0
4	2	18	1,3	1	14	0,85
5	24	48	6	0	12	0
6	28	48	7	0	13	0
7	18	139	1,6	1	13	0,92
8	1	14	0,85	0	3	0
9	16	54	3,5	4	11	4,3
10	13	18	8,6	0	20	0
Total	105	426	3	7	111	0,75

Mean number of transfusions/year	3,29	vs	0,71	
Minimum number per year	0,3	vs	0	
Median number per year	1,6	vs	0	p = 0,00001
Maximum number per year	8,6	vs	4,3	

3.2 HAEMATOLOGICAL RESPONSES

Table 3.4
Laboratory Values Before and During Treatment with Hydroxyurea

	Before Treatment	At HbF max*	3 mo	6 mo	9 mo	12 mo
1. Hb g/dl						
Mean	7,16	8,09	7,7	8,03	8,4	8,0
Minimum	5,5	6,2	5,5	6,2	7,2	7,2
Median	7,3	8,2	8,1	7,8	8,2	8,0
Maximum	8,1	9,9	9,2	9,9	10,7	9,2
p value		0,0092	0,02	0,01	0,08	0,04
2. HbF %						
Mean	4,55	18,22	14,97	17,4	12,3	10,14
Minimum	2,7	2,5	1,9	2,5	2,6	5,7
Median	3,95	7,9	6,8	5,2	4,2	7,5
Maximum	10,3	54,7	39,2	54,7	41,3	23,7
p value		0,01	0,15	0,24	0,32	0,11
3. MCV (fl)						
Mean	91,7	99,8	100,7	98,9	98,1	105
Minimum	78	92	83	84	84	92
Median	92	95	97,5	99,5	101	102
Maximum	104	117	125	117	110	129
p value		0,08	0,04	0,13	0,13	0,11
4. Reticulocytes %						
Mean	27,7	13,7	19,0	13	7,0	10
Minimum	12,4	4,1	8,4	0,6	0,3	4,1
Median	25,2	12,7	19,3	14,5	3,7	7,9
Maximum	54	29,0	31,0	20,3	17	20
p value		0,02	0,14	0,005	0,05	0,15

* HbF max refers to the point in time when a maximal HbF level was obtained.

At no time during treatment was there any significant difference in the absolute neutrophil count ($p = 0,5$) or the platelet count ($p = 0,1$).

4.0 DISCUSSION

In terms of clinical response to HU, there was no difference in the number of vaso-occlusive crises for the entire period prior to treatment compared with the number on treatment ($p=0.24$). Jayabose et al (5) showed a significant difference when comparing these two groups and felt that comparing the number of crises for the entire period gave a better indication of the true pre-treatment rate. However, many of the children had been followed-up from a young age, when they were relatively asymptomatic in terms of vaso-occlusion possibly because of the physiologically higher HbF in young children. Also, because of the small sample size, the results may be skewed by a non-responder. There was no pre-treatment data available for patient 1, and the follow-up for patients 3 and 8 was short, which may have influenced the results. To control for season variation and the known episodic nature of VOCs we also performed the pre-therapy analysis for the twelve-month period prior to starting hydroxyurea. Here there was a significant difference in the frequency of crises ($p=0.05$). Because this was an uncontrolled study we compared the rates of VOCs from the time when HU would have been indicated on the basis of crises. All the patients except one (patient 3) fulfilled the criteria for HU therapy long before we started using it. Once again there was a statistically significant decrease in crisis rate ($p=0.05$). The difference in VOCs (i.e. VOC rate before treatment minus the VOC rate on treatment) correlated significantly with the maximal HbF ($p<0.05$) i.e. a large reduction in vaso-occlusion was associated with a high HbF.

In terms of hospitalization there was again no significant difference in the number of days per year prior to treatment compared with on treatment ($p=0.12$). There was also no difference in hospitalization in the year prior to treatment versus on treatment ($p=0.28$). There was, however, a significant decrease in hospitalization when compared from the time when HU would have been indicated ($p=0.04$). This reduction in hospitalization correlated with the reduction in vaso-occlusion ($p<0.05$).

There was a significant decrease in transfusion requirements on HU treatment ($p=0.00001$) even when compared with the entire pre-treatment period. Although there was also a significant increase in haemoglobin, the decrease in transfusion requirements is slightly biased. Prior to HU treatment patients were often transfused if their haemoglobin was less than 7g/dl, even though no patients were on strict transfusion programmes. Once on HU, transfusion was

avoided and patients were more likely to be allowed to continue with haemoglobins of less than 7g/dl if they were asymptomatic. The difference in transfusion requirement was not significantly related to the maximal HbF and was not related to any difference in vaso-occlusion or hospitalization.

There was a significant increase in haemoglobin on HU treatment. The increase was maximal when HbF was maximal, irrespective of when HbFmax occurred. The increase in haemoglobin was sustained and was significantly related to the decrease in vaso-occlusion, but not significantly related to hospitalization or transfusion.

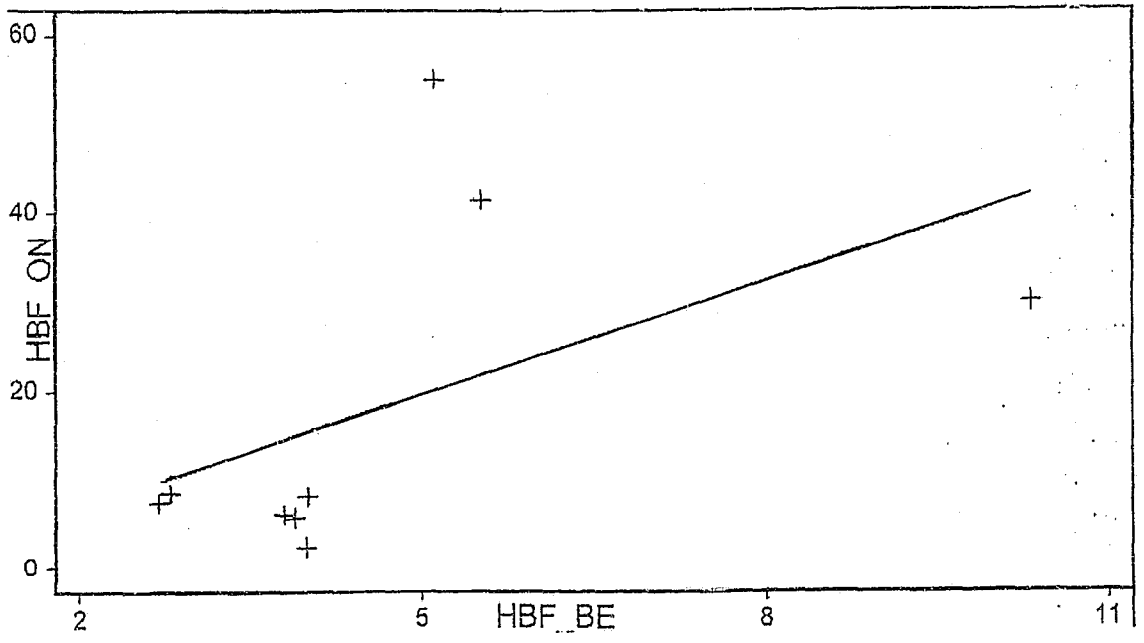
There was marked variation in the HbF response. HbF was only significantly increased when recorded at its maximum. HbFmax occurred at varying points in time, but both the mean and median time to reach HbFmax was nine months. The difference in HbF was significantly related to the difference in vaso-occlusion and haemoglobin, but not to hospitalization. It is uncertain what determines a patient's HbF response. In this study the dose of HU was not related to HbFmax or any difference in vaso-occlusion. The dose was also not related to any difference in haemoglobin. Compliance is undoubtedly a problem in all patients, but probably more so in those of lower socio-economic class. In 10 to 25 percent of adult patients hydroxyurea does not cause an increase in HbF, possibly due to variations in drug metabolism, genetic factors or bone marrow reserve (4). However, Maier-Redelsperger et al (16) found no correlation between myelotoxic events and HbF increase, suggesting that marrow reserve does not influence HbF response in children. Although there was a trend towards greater HbFmax's in patients with higher baseline HbFs, this was not statistically significant, possibly because of the small sample size (Fig 4.1).

There was no significant increase in mean cell volume ($p=0.07$). Mean cell volume was not significantly related to HbFmax. Other studies have shown a relationship between HbF and mean cell volume and have suggested that the increase in mean cell volume be used to monitor HbF response.

There was a significant decrease in reticulocyte percentage which was related to HbFmax. There was no significant difference in absolute neutrophil count or platelet count. The decrease in reticulocytes was therefore likely to be secondary to a decrease in haemolysis rather than a bone marrow suppressive effect, especially as it was associated with an increase in haemoglobin.

Fig 4.1 Scatter plot of HbF ON vs HbF BE

HbF ON is the maximal HbF attained
HbF BE is the baseline HbF



5.0 CONCLUSION

Hydroxyurea decreases the rate of vaso-occlusion in severely affected children with sickle cell anaemia and decreases the transfusion requirements. These clinical benefits are secondary to increased haemoglobin levels and HbF percentages. The clinical and haematological responses are greatest when HbF is maximal. HbFmax is not dose-related. The determinants of HbF response have still to be evaluated. There was no short-term toxicity associated with hydroxyurea. Because long-term effects are still unknown, hydroxyurea should be reserved for patients who have complications that are sufficient to justify treatment. Ongoing studies are needed to assess long-term effects.

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