Long-term hydroxyurea treatment in children with sickle cell disease: tolerance and clinical outcomes

Mariane de Montalembert
Valentine Brousse
Caroline Elie
Françoise Bernaudin
Junxin Shi
Paul Landais
for the French Study Group on Sickle Cell Disease

Two hundred twenty-five SCD children have been enrolled in a study assessing the tolerability of hydroxyurea treatment. Mean age at inclusion was 9.2 ± 4.4 years, median duration of treatment was 3.8 years. Ten and 75 patients have been treated respectively for more than 10 and 5 years. No severe side effect was related to hydroxyurea treatment, which was discontinued in 81 children mainly for treatment failure (30 cases) or non-compliance (17 cases). Treatment was also withdrawn in 5 of 6 children who had developed hypersplenism, in 3 because of a pathological transcranial Doppler, and in 2 after a stroke.

Key words: sickle cell disease, hydroxyurea, tolerance of hydroxyurea.

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Service de Pédiatrie Générale, Hôpital Necker (MdM, VB), Service de Biostatistiques et Informatique Médicale, Hôpital Necker, Paris (CE, JS, PL); Service de Pédiatrie, Centre Hospitalier Intercommunal de Créteil, France (FB).

Correspondence:
Mariane de Montalembert,
Service de Pédiatrie Générale,
Hôpital Necker-Enfants Malades,
149, rue de Sèvres, 75015 Paris,
France.
E-mail: mariane.demontal@nck.ap-hop-paris.fr

Hydroxyurea is a cytostatic myelosuppressive drug that reactivates fetal hemoglobin synthesis. Via this mechanism, and also most probably via pleiotropic effects on red cell deformability, red cell endothelial interactions, leukocyte reduction and nitric oxide (NO) release, it alleviates the burden of sickle cell disease (SCD) in most patients affected by severe forms of this illness. In SCD children, hydroxyurea has been shown to decrease the rate and the intensity of painful events and the number of days of hospitalization.[1-3] Its clinical and biological effects have been sustained in children for up to 9 years of therapy.[4-6] Given the benefits well established in several controlled studies, hydroxyurea is currently prescribed for SCD children affected by severe, recurrent pain crises or repeated acute chest syndrome.[7] Extension of treatment to other indications, mostly for the prevention of organ dysfunction in very young children[8] and primary or secondary prevention of strokes,[9] is under debate. So far, reports concerning short and medium-term tolerability are reassuring, in particular with regard to growth and pubertal development.[4-6,10-12] However, considering that hydroxyurea is an antineoplastic drug, theoretically capable of increasing the risk of developing of leukemia or cancer, long-term studies are needed. We, therefore, studied a a large number of children who received hydroxyurea treatment for a median of 3.8 years.

Design and Methods

Patients

The study population consisted of 225 patients (88 females, 137 males) who were treated in 50 French centers. Five centers treated more than 10 patients each, and 7 centers 5 to 10 patients each. The mean age at inclusion was 9.2 ± 4.4 years (range, 17 months to 19 years). Five children were younger than 2 years at the initiation of hydroxyurea treatment. Two hundred and twelve patients were homozygous for HbS, three had sickle hemoglobin C, eight had sickle β-thalassemia, and two had Hb SD-Punjab.

Reasons for initiating hydroxyurea therapy

This study was primarily supported by the Institut National de la Recherche Medicale and subsequently by the Delegation à la Recherche Clinique. After approval from the Necker Hospital Ethics Committee, in the first period of the study (from 1992 to 1996) children who had suffered at least three painful crises necessitating hospital admissions during the previous year were enrolled.[3] Subsequently (1997-2003), patients were no longer treated according to a centralized protocol. New indications for treatment were considered: recurrent episodes of acute chest syndrome,[7] severe chronic anemia (defined, depending on the centers, as a baseline hemoglobin level lower than 6 or 7 g/dL), stroke in children with severe red cell allo-immunization or reluctance to be regularly transfused,[6,9] abnormally high transcranial Doppler (TCD) velocity,[13] and cardiac ischemia.[14] A letter informing parents that the potential long-term toxic effects of hydroxyurea are unknown, especially regarding subsequent fertility and occurrence of secondary leukemia or cancer, was provided by the collaborating centers. Females of childbearing age were strongly encouraged to use contraception. The storage of frozen sperm was offered to mature boys.

The main indication for inclusion was severe pain crises (n=181) (sole symptom in

155 patients). The second indication episodes of acute chest syndrome (n=41) (sole symptom was in 14 patients). Twenty patients were included because of severe anemia (sole symptom in 12 patients) and six because of stroke (sole symptom in two patients). Five patients were included because they had previously had a pathological TCD result (time-averaged mean of the maximum velocity above 200 cm/sec), which had normalized after 0.5 to 1.1 years of transfusion. Hydroxyurea was prescribed together with regular transfusions for 3 months and thereafter alone. TCD assessments were repeated quarterly in these five children after transfusions had been stopped.[15] Three children had been treated for cardiac ischemia (sole symptom in two patients).

Hydroxyurea treatment regimen

In the first period (1992-1996), based on published data,[16] hydroxyurea was prescribed at the dose of 20 mg/kg of body weight over 4 consecutive days each week. In the absence of toxicity, this dose was increased to a maximum of 40 mg/kg/day. Median daily doses (total weekly doses divided by seven) were 27.3±5.8 mg/kg at 3 months and 32.5±7.4 mg/kg at 3 years of treatment. In the second period (1997-2003), the dosing regimen was progressively switched to daily administration. However, the availability of only one dosage form (500 mg tablets) impaired dosage adaptation and meant that administration protocols varied (four, five, or six days a week, or every day). No attempt was made to reach the maximal tolerated dose. In the absence of clinical benefit after 6 months of hydroxyurea at 20 mg/kg/day, or if severe anemia persisted, doses could be increased up to 40 mg/kg/day. If Doppler velocities exceeded 200 cm/sec, hydroxyurea was withdrawn and regular transfusions or bone marrow transplantation considered. For the 139 children persistently under hydroxyurea treatment in November 2003, the mean daily dose was 21.2±6.1 mg/kg and the median daily dose was 20 mg/kg (range, 6.25-42). Two-thirds of the patients received a daily dosage of hydroxyurea in the range of 15-25 mg/kg/day. The drug was taken daily by 138 patients and 4 days/week by 45 patients.

All patients were regular by followed-up every 2 to 3 months, and treatment compliance was checked by questioning. Non-compliance signified that families or children admitted that the treatment was not administered. The median duration of treatment was 3.8 years (range, 1 day-12.7 years) (Figure 1). Ten patients have been treated for more than 10 years and 75 for more than 5 years.

Efficacy and safety variables

Case report forms were designed to collect data on adverse events, if any, with their description, an assessment of their severity, their relationship with hydroxyurea, the action taken, and the outcome of the adverse event. In parallel, the characteristics of the hydroxyurea treatment were collected, taking into account the date of starting treatment, current dose, dosing scheme, date of withdrawal if appropriate, and reason for withdrawal.

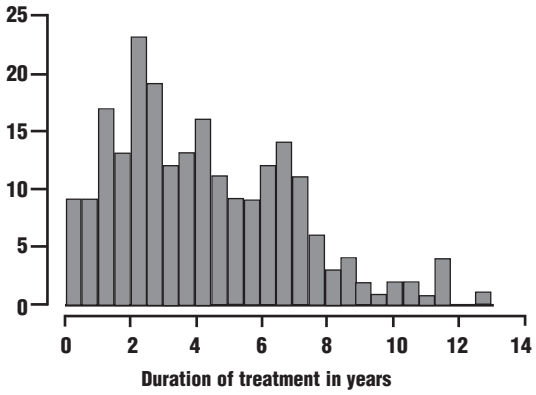

Figure 1. Median duration of hydroxyurea treatment (years).

The case report forms were completed annually by the participating physicians, whether or not an adverse event had been observed during hydroxyurea treatment. Hydroxyurea was withdrawn temporarily if reticulocyte counts decreased $<50\times10^9$/L, polymorphonuclear counts $<1.5\times10^9$/L, or platelet counts $<100\times10^9$/L, and treatment was not resumed unless these parameters normalized. Treatment was also withdrawn if alanine transferase concentration increased 2-fold or if the serum creatinine value was more than 30% of the baseline value.

Statistical analysis

Relationships between categorical variables were tested with the χ^2 test or Fisher's exact test. Student's t-test was used to compare continuous variables between two groups.

Results and Discussion

Patients' outcomes

The majority of patients (133, 59%) have received hydroxyurea without any interruption, and six have resumed hydroyxurea after stopping treatment. Eleven (5%) were lost to follow-up after a median of 47 months (13-88). One 18-year old patient, who had received hydroxyurea for 11 months and had only a slight reduction in the frequency of painful episodes, died suddenly from asystole while he was hospitalized for a painful crisis. No autopsy was performed and death was attributed to a probable underlying SCD-related myocardiopathy. In one child, already reported,[11] a diagnosis of acute lymphoblastic leukemia with evidence of Philadelphia chromosome was made 1.5 months after starting hydroxyurea. Other reasons for discontinuation of hydroxyurea are given in Table 1. These were mainly treatment failure and poor compliance (in respectively 30 (13%) and 17 (7.5%) patients). There was no relation between the diagnosis of treatment failure and the dose. The frequency of failure was significantly different in the group of children receiving hydroxyurea 4 days/week (14 failures/45 patients: 31%) compared with the group receiving hydroxyurea 7 days/week (12 failures/138 patients: 8.7%) ($p<0.001$), but our comparison is partly historical.

Table 1. Reasons for withdrawing hydroxyurea treatment.

Reasons for withdrawal	*N*
Failure	30
Non-compliance	17
Hypersplenism	5
TCD velocities > 200 cm/s	3
Osteonecrosis of femoral head	3
Cerebrovascular event	2
Rash	2
Dizziness	2
Headache	2
Asthenia	1
Azoospermia	1
Leg ulcer	1
Planned pregnancy	1
Pregnancy	1
Middle cerebral artery stenosis	1
Leukemia	1
Systemic lupus erythematosus	1
Sarcoidosis	1
Interferon for hepatitis C	1
Not determined	5

Of the five patients switched to hydroxyurea after normalization of their TCD under transfusion, two developed velocities above 200 cm/sec and were again prescribed regular exchange blood transfusions.[15] Treatment was also stopped in another patient because of the first occurrence of pathological TCD velocities.

Hydroxyurea was initiated in six patients because of history of stroke, which was the sole indication in two of them. Hydroxyurea was prescribed without any transition period with a chronic transfusion program. There were two stroke recurrences in our cohort. One occurred after 3 months of treatment in a child in whom stroke was the only indication for hydroxyurea. The second one occurred in a child whose past history of stroke was not the reason advocated by his physician for hydroxyurea treatment, this reason being the existence of painful crises. This child had a stroke after 8 years of treatment. We did not observe any neurological event after periods of follow-up ranging from 2 to 12 years in the five other patients in whom the indication for hydroxyurea was the prevention of stroke.

Hypersplenism was observed in six Hb SS patients. Before hydroxyurea treatment, three of them had splenomegaly and two a previous history of splenic sequestration. The diagnosis was based on an increase in spleen size and concomitant thrombocytopenia; two cases, aged 6 and 7, had recurrent splenic sequestration crises. Five patients were splenectomized, three of them have restarted hydroxyurea with good tolerance. Symptoms in one patient stopped when the dose was decreased from 20 to 10 mg/kg/day.

In the subgroup of 20 patients treated for severe anemia, the mean hemoglobin level was 6.6±0.5 g/dL prior to hydroxyurea and increased to 8.2±1.5 g/dL after 1 year of therapy. Treatment was considered a success in 12 patients, whereas one was lost to follow-up. Hydroxyurea was stopped in seven of these patients (one because of headache, one because of hypersplenism, one because TCD velocity became abnormal, and four because of treatment failure). Overall, among the children who stopped treatment, 29 (13% of the whole cohort) are now on regular transfusions, 35 (16%) are not taking any alternative treatment, and 10 (4.4%) underwent bone marrow transplantation (1 died, 9 were cured). As expected, the most frequent minor adverse events which did not lead to cessation of treatment were mild hematologic toxicities (thrombocytopenia, neutropenia/leukopenia, reticulocytopenia and pancytopenia in respectively 8, 8, 5, and 1 patients) that returned to baseline values after decreasing the dose.

Hydroxyurea has led to a major improvement in the management of SCD children affected by frequent, painful vaso-occlusive crises. Combining our data with those of Zimmerman[5] and Gulbis[6] shows that hydroxyurea has already been administered to more than 470 SCD children and young adults, with good short- and middle-term hematologic and clinical tolerability. No serious toxicity was found to be related to the use of hydroxyurea over periods of more than five years by either Zimmerman, Gulbis, or our group in, respectively, 36, 32, and 75 patients. The predominance of males in the cohort can be explained by greater severity of SCD in males, or by the fact that parents were more reluctant to allow daughters to enter the study because of the consequences on fertility. Though freezing of sperm was systematically offered to mature boys before starting hydroxyurea, no patient accepted. The mean age at initiation of treatment, 9.2±4.4 years, is comparable to that of other series. We recommend that hydroxyurea is prescribed after the age of 2 years, given the uncertainties on potential growth impairment in infants.[17]

When our study started in 1992, stroke was not considered as an indication for hydroxyurea treatment, and our case report form did not collect data on past histories of patients, but on indication(s) for hydroxyurea therapy. Consequently, our study may underestimate the efficacy of hydroxyurea on preventing the recurrence of stroke since we do not know the exact prevalence of patients with a past history of stroke who have been treated with hydroxyurea. Hypersplenism, which was diagnosed in six patients, is a classical complication of SCD, but recurrent splenic sequestration episodes are unusual in children aged 6 and 7 years, Hb SC children excepted, and suggest hydroxyurea-induced hypersplenism. This agrees with previous reports on delaying functional asplenia in very young children,[8] and on splenic regeneration in older patients.[18,19] Studies on splenic uptake of Tc99m sulphur colloid in SCD infants treated with hydroxyurea showed a lower proportion of asplenic children in the treated group (43%) than the expected proportion in an untreated age-matched population (94%).[20] All these observations converge to suggest that hydroxyurea can prevent or delay functional asplenia, increasing the risk and lengthening the at-risk period for acute splenic sequestration episodes. We, therefore, recommend careful evaluation of spleen size and blood tests at each evaluation in children with previous splenomegaly or a past history of splenic sequestration before starting hydrox-

yurea. Among the six children in our cohort who developed hypersplenism, hydroxyurea could be safely administered to five after splenectomy and to one after a dose decrease (from 20 to 10 mg/kg/day). One malignancy occurred in our cohort, but analysis of this case led us to conclude that, most probably, the leukemia pre-existed the hydroxyurea administration, since the leukemia was diagnosed 1.5 months after starting hydroxyurea therapy. This short interval strongly suggested that the bone pains which had prompted hydroxyurea treatment were in fact the first manifestation of the leukemia. However, assessment of the carcinogenic and leukemogenic risks of hydroxyurea will require continuous long-term follow-up of large cohorts of patients.[21]

Finally, the most frequent problem of hydroxyurea treatment currently encountered is the secondary lack of efficacy observed in a few patients, whether this is attributed to treatment failure or to poor compliance (observed in 30 (13%) and 17 (7.5%) patients, respectively of our series). Using analyses of laboratory parameters, review of peripheral blood smears and pill counts when possible, Zimmerman estimated that non-compliance led to hydroxyurea withdrawal in 12% of her patients. The way information was collected in our study, in an open, uncontrolled manner, did not allow any reliable distinction to be made between treatment failure and non-compliance. The prescription of different schedules of hydroxyurea during the two periods of the study (1992-1996 and 1996-2003) makes the interpretation of results more difficult. The rate of side effects in the first period was significantly higher than that observed in the second period (p=0.007), but this retrospective analysis cannot reliably attribute this finding either to a longer follow-up in the first period-patients or to the different schedules of administration. A better knowledge of the metabolism and phamacodynamics of the drug in children with SCD would definitely contribute to a better understanding of both efficacy and safety data. Clarification of the optimal dose is also needed. American studies have increased hydroxyurea doses up to the maximal tolerated dose (17% of Zimmerman's patients received more than 30 mg/kg/day), whereas European studies have not attempted to reach this maximal tolerated dose and mean daily doses (around 20-25 mg/kg/day) are usually slightly lower in European studies than in American ones. A 12-year follow-up of hydroxyurea use in SCD children allows us to consider that this drug is a very potent therapeutic option for the management of severe forms of the disease. However, a special warning must be made concerning the potential occurrence of splenic adverse effects such as hypersplenism. These data contribute to the debate on the therapeutic options for children with severe forms of SCD, and underline the need for pharmacokinetic studies of hydroxyurea in SCD children.

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Physicians collaborating in the study: C. Allisy (Argenteuil), R. Amira (St Denis), D. Asensi (Pontoise), D. Bachir (Créteil), B. Bader-Meunier (Bicêtre), P. Bégué (Paris), E. Bellaton (Bicêtre), M. Belloy (Gonesse), P. Benhaim (Bondy), C. Berger (St-Etienne), F. Bernard (Montpellier), F. Bernaudin (Créteil), A. Broyart (Aulnay sous Bois), M. Chalumeau (Paris), A. Champolion (Angicourt), O. Charara (Versailles), S. Claeyssens (Toulouse), A. Devidas (Corbeil), C. Dollfus (Paris), J.P. Dommergues (Bicêtre), C. Dumontet (Lyon), G. Elana (Le Lamentin), C. Galambrun (Lyon), D. Gendrel (Paris), R. Girot (Paris), B. Gombert (La Rochelle), F. Gouraud (Meaux), M.D. Guilloy (St Germain en Laye-Poissy), D. Kauffmann (Caen), E. Lachassine (Bondy), A. Lambilliotte (Lille), J. Landman-Parker (Paris), A. Leblanc (Evry), A. Lehnert (Montargis), F. Lionnet (Argenteuil), L. Lutz (Strasbourg), C. Martel (Morlaix), A. May (Evry), A. Meyer (Dourdan), M.Micheau (Bordeaux), B. Monier (Montmorency), M. Monlouis-Eugénie (Le Lamentin), J. Nicolas (Montpellier), M.H. Odièvre (Colombes), C. Olivier-Weil (Colombes), C. Orzechowski (Bry sur Marne), C. Pajot (Toulouse), B. Pautard (Amiens), M.O. Peter (Mulhouse), N. Philippe (Lyon), D. Plantaz (Grenoble), C. Pondaré (Lyon), B. Quinet (Paris), O. Reman (Caen), B. Rétali (Pontoise), M. Russo (Fontainebleau), J.L. Salomon (Mantes), P. Schneider (Rouen), G. Sibille (Basse Terre), C. Soler (Nice), J.L. Stéphan (St Etienne), P. Talon (Montfermeil), G. Tchernia (Bicêtre), I. Thuret (Marseille), J. Vedrenne (Fontainebleau), F. Vitrey (Vesoul).

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