Cutaneous Adverse Reactions to Hydroxyurea in Patients With Sickle Cell Disease

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Background: Treatment with hydroxyurea may alleviate the symptoms of sickle cell disease (SCD). Because treatment with hydroxyurea may be responsible for several cutaneous side effects and is often lifelong in patients with SCD, we conducted this study to evaluate the risk of cutaneous adverse reactions in SCD patients treated with hydroxyurea.

Observations: Seventeen adult patients with SCD treated with hydroxyurea at one institution were examined by a dermatologist. Hydroxyurea was given for a mean of 3.04 years (range, 0.42-6.5 years). None of the patients had skin cancer, but 5 (29%) had disabling hydroxyurea-induced leg ulcers. Four of these 5 patients had a previous history of SCD ulcer, compared with none of the 12 patients without hydroxyurea-induced leg ulcers (P<.05). The mean age of patients with induced ulcers was 35.8 years and for those without ulcers was 23.5 years (P<.01).

Conclusions: Our rate of hydroxyurea-induced leg ulcers (29%) is higher than that reported for patients with myeloproliferative syndromes (9%). In addition, use of hydroxyurea has induced ulcers mainly in patients with previous SCD ulcers, suggesting that hydroxyurea could act in conjunction with other vascular abnormalities. Careful attention should be required when giving hydroxyurea to patients with SCD with previous ulcers as well as in older patients with SCD.

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Sickle cell disease (SCD) is a chronic disabling disease for which only symptomatic treatments were available until hydroxyurea’s efficiency was demonstrated in the early 1990s.1 Hydroxyurea stimulates the production of fetal hemoglobin in red cells,2-4 which level is correlated to a lower rate of sickle polymer formation, and, consequently, to a significant improvement of the disease. The administration of hydroxyurea leads to a decrease in the number of vaso-occlusive crises and acute chest syndrome in severely ill patients,3,7 resulting in shorter hospital stays and a decrease in the need for blood transfusions. However, it is not yet known if hydroxyurea prevents chronic organ damage.6 Several cutaneous adverse events may develop in patients treated with hydroxyurea.8-10 Although most of the reported cutaneous reactions were benign, some were severe or life-threatening, leading to the withdrawal of hydroxyurea. These severe events included the development of painful leg ulcers or cutaneous squamous cell carcinomas in 9% and 3% of cases, respectively.11,12 In contrast with myeloproliferative disorders (MPD), in which hydroxyurea is given for a few years to primarily middle-aged white patients, in SCD, hydroxyurea is given lifelong to young black patients. Because hydroxyurea represents a new opportunity for the management of SCD and because the occurrence and the natural course of severe cutaneous adverse events is unknown in such a population, we conducted a study of all patients treated with this drug in our institution.

RESULTS

Seventeen patients were included in the study. There were 9 women and 8 men, with a mean age of 27.1 years (range, 19-51 years). Hydroxyurea was given for a mean of 3.04 years (range, 0.42-6.5 years), and the mean daily dose was 20.23 mg/kg (range, 14-28 mg/kg). The effectiveness of hydroxyurea in all patients was evident: the number of pain events and/or acute chest syndrome was significantly reduced and fetal hemoglobin level increased. Of note, 2 patients had small leg ulcers at the time hydroxyurea treatment was initiated.

Results of cutaneous evaluation are presented in the Table. Briefly, 5 (29%) of...
PATIENTS AND METHODS

Among all adult patients with SCD observed in our institution, all those receiving treatment with hydroxyurea were selected. Diagnosis of SCD was done by standard laboratory procedures and family history. Sixteen patients were homozygous for SCD; one was compound heterozygous for sickle cell–β-thalassemia. Hydroxyurea had been given to all for pain and/or acute chest syndrome. A letter was mailed to all these patients explaining the aim of the study and proposing a clinical evaluation by the same dermatologist (B.C.). When examined, the dose and the duration of hydroxyurea as well as careful analysis of previous complications of SCD were recorded. All the skin symptoms that have been reported as possible adverse events to hydroxyurea in previous series were systematically checked (Table). Ulcers were attributed to hydroxyurea treatment if (1) they appeared or worsened while hydroxyurea was given and SCD was not active, (2) there was neither arterial nor venous underlying cause, (3) repeated blood transfusions were unsuccessful, and (4) the ulcers disappeared or greatly improved after withdrawal or reduction of hydroxyurea. To evaluate risk factors for hydroxyurea-induced leg ulcers, comparison of groups with or without this complication was done by the Fisher exact test.

The 17 patients had induced leg ulcers (patients 2, 6, 11, 12, and 16). Three of them had a single ulcer (patients [Figure], 12, 6, and 16), whereas multiple and bilateral ulcers were found in patient 2. In 4 of these 5 patients, clinical and ultrasound examination excluded arterial or venous disorders. The last one (patient 11) reported a previous lower leg venous thrombosis episode, but the ulcers were bilateral without venous insufficiency on the opposite leg. Three patients had long-term red cell transfusions, which did not modify the ulcers. In contrast, all ulcers were cured or at least greatly improved 4 to 6 weeks after hydroxyurea was withdrawn or the dose decreased without any other measure: in 3 of the 5 patients, dose decrease allowed the healing of the ulcers, while withdrawal was needed in 2 patients. There were no differences in sex ratio, duration of treatment, daily dose, and genotype between patients with or without hydroxyurea-induced leg ulcers. However, the age of patients with hydroxyurea-induced ulcers was 35.8 years compared with MPD (6.5 years),11 thereby strengthening the hypothesis that preexisting vascular abnormalities are implicated since these are usually worse in homozygous sickle cell anemia than in classic MPD. Although we did not find differences in sex ratio, duration of treatment, and daily doses between the hydroxyurea-treated patients with and without induced ulcers, the limited number of patients might not allow this detection.

When given to patients with MPD for years, hydroxyurea has been shown to induce many cutaneous reactions, including ulcers or cancers. As patients with SCD differ from those with MPD, particularly in respect to age and skin phototype, it seemed important to evaluate the risks of hydroxyurea given lifelong to individuals with SCD. A unique dermatologist systematically examined all patients receiving hydroxyurea for SCD disease in one center. In this study, leg ulcers attributed to hydroxyurea treatment were found in 29% of treated patients. This rate is higher than that observed among patients with MPD, which was shown to be 8.5% to 9%.11,12 This difference may be because in our study the skin was systematically examined by a dermatologist. However, it is interesting to note that hydroxyurea appears to induce leg ulcers in patients presenting with MPD or SCD, in which small vessel abnormalities may occur. However, studies of psoriasis, although older and done in patients receiving shorter courses, did not report this reaction. This may suggest that hydroxyurea induces ulcers only in conjunction with previous small vessel abnormalities. This hypothesis is strengthened by the fact that, in our series, the rate of hydroxyurea-induced leg ulcers was higher in patients who had previous SCD leg ulcers. In MPD, a previous history of leg ulcer was found in 30% of treated patients who had hydroxyurea-induced ulcers.13 In addition, the delay of leg ulcer development was shorter in patients with SCD (2.6 years in our series) compared with MPD (6.5 years),11 thereby strengthening the hypothesis that preexisting vascular abnormalities are implicated since these are usually worse in homozygous sickle cell anemia than in classic MPD. Although we did not find differences in sex ratio, duration of treatment, and daily doses between the hydroxyurea-treated patients with and without induced ulcers, the limited number of patients might not allow this detection.

The status of hydroxyurea-treated patients in relation to induced leg ulcers and past ulcers is still poorly known. Theoretically, the increase in fetal hemoglobin induced by hydroxyurea should have a beneficial effect on the ulcers of SCD since ulcers are rare among the Saudi Arabia population in which the fetal hemoglobin rate is spontaneously high.14 Indeed, a small series has shown that leg ulcers improved in one patient while being treated with hydroxyurea.15 However, this study included only 2 patients with previous leg ulcers and systematic cutaneous evaluation of all treated patients was not done, making definite conclusions about the role of hydroxyurea difficult. In another case report, multiple SCD ulcers neither improved nor worsened with hydroxyurea treatment, but healing was obtained when recombinant erythropoietin was added to the regimen.16

Only a few drugs may be responsible for ulcers at distant sites from their route of administration and therefore the pathogenesis of hydroxyurea-induced ulcers is yet unknown. Nicorandil, a drug effective in treating angina pectoris, can induce severe disabling oral ulcers.
These ulcers may be caused by the elimination in the saliva of a metabolite toxic to predisposed individuals.\textsuperscript{17} Foscarnet is another drug treatment that may be responsible for genital ulcerations secondary to the direct cytotoxic effect of the molecule excreted in urine on genital skin occluded under the foreskin.\textsuperscript{18} Pathogenesis of hydroxyurea-induced ulcers remains unknown. Nevertheless, whatever the mechanism, initiation and choice of the dose of hydroxyurea in patients with a previous history of ulcers as well as in older patients should be carefully considered. In these cases, to lower the risk of induced ulcers, it may be useful to give no more than 20 mg/kg per day or use alternate administration.

Finally, cutaneous carcinoma and actinic keratosis were not found in our patients, in contrast to patients with sickle cell disease who have an increased risk of these neoplasms.\textsuperscript{19} Patients with homozygous sickle cell disease also have an increased risk of developing myelodysplasia.\textsuperscript{20,21}

\begin{table}
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
Patient No./
Sex/Age, y & Geographic Origin & Treatment Duration, y & Daily Dosage, mg/kg & Cutaneous Manifestations & Phenotype; Genotype† \\
\hline
1/M/28 & Congo & 1.5 & 20 & Cutaneous xerosis, longitudinal ungual pigmentation (feet), palatine pigmentation & SS; 4 \textsuperscript{a}BaBa \\
\hline
2/M/30 & French West Indies & 3.5 & 20 & Internal bilateral malleolar ulcers, moderate palmar-plantar keratoderma & SS; 4 \textsuperscript{a}BeBe \\
\hline
3/M/27 & French West Indies & 1.5 & 16 & Ichthyosis, longitudinal ungual pigmentation (hands) & SS; 4 \textsuperscript{a}BeBe \\
\hline
4/F/19 & Congo & 0.83 & 16 & Longitudinal ungual pigmentation (hands and feet), diffuse cutaneous pigmentation & SS; 3 \textsuperscript{a}BaBa \\
\hline
5/M/23 & Algeria & 6 & 21 & Cutaneous xerosis, diffuse cutaneous pigmentation & S\textsuperscript{thal}Ba; 4 \textsuperscript{a}Be\textsuperscript{thal} \\
\hline
6/F/51 & Cameroon & 6 & 18 & Longitudinal ungual pigmentation (hands and feet) and total (feet), cutaneous pigmentation (forehead, palms, soles), lingual pigmentation, cutaneous xerosis, internal malleolar ulcer, mouth ulcers & SS; 3 \textsuperscript{a}BaBe \\
\hline
7/F/27 & Cameroon & 0.42 & 14 & Cutaneous xerosis & SS; 4 \textsuperscript{a}BeBe \\
\hline
8/F/24 & Haiti & 3 & 22 & Nail pigmentation, cutaneous pigmentation (knees) & SS; 4 \textsuperscript{a}BeBe \\
\hline
9/F/25 & Togo & 4 & 17 & Longitudinal ungual pigmentation (hands) & SS; 3 \textsuperscript{a}BeBe \\
\hline
10 (sister of 9)/F/20 & Togo & 0.5 & 17 & Longitudinal ungual pigmentation, lower lip depigmentation & SS; 3 \textsuperscript{a}BeBe \\
\hline
11/F/39 & French West Indies & 6 & 25 & Internal and external bilateral malleolar ulcers & SS; 5 \textsuperscript{a}BeBe \\
\hline
12/F/38 & Cameroon & 2.5 & 17 & Diffuse cutaneous pigmentation, total ungual pigmentation (hands), left malleolar internal ulcer & SS; 3 \textsuperscript{a}BeBe \\
\hline
13/M/22 & Cameroon & 1.5 & 25 & None & SS; 3 \textsuperscript{a}BeBe \\
\hline
14/M/21 & Congo & 2 & 25 & None & SS; 4 \textsuperscript{a}BaBa \\
\hline
15/F/22 & Togo/Benin & 6 & 26 & None & SS; 4 \textsuperscript{a}BeBe \\
\hline
16/M/21 & Mali & 6.5 & 28 & Longitudinal ungual pigmentation (hands, feet) and transversal (feet), palatine pigmentation, left malleolar external ulcer & SS; 4 \textsuperscript{a}SeSe \\
\hline
17/M/24 & Benin & 6 & 17 & Plantar keratoderma, cutaneous xerosis & SS; 3 \textsuperscript{a}BeBe \\
\hline
\end{tabular}
\caption{Characteristics of 17 Patients Treated With Hydroxyurea\textsuperscript{*}}
\end{table}

\textsuperscript{*}SS indicates homozygous sickle cell; \textsuperscript{a}\textsuperscript{}\textsuperscript{-}\textsuperscript{}\textsuperscript{a}-globin (gene number); Be, Benin; Ba, Bantou, Se, Senegal; and S\textsuperscript{thal}, sickle cell–\textsuperscript{thal}asemia.

\textsuperscript{†}By \textsuperscript{b}-globin gene cluster haplotype analysis.
with MPD.\textsuperscript{19} This difference is probably the consequence of the phototype of patients with SCD who were all black or had tanned skin,\textsuperscript{20} as well as from the short duration of the hydroxyurea treatment (3 years) and the young age of the patients (27 years). Finally, various benign cutaneous lesions were disclosed among 82\% of all treated patients. Most of these consisted of pigmentary disorders. This rate is higher than the one observed among patients with MPD, which was 35\%.\textsuperscript{9} But here too, our study was a systematic analysis made by one dermatologist. Decrease in dose or withdrawal of hydroxyurea was never requested in view of these symptoms.

This study points out an unexpectedly high risk of leg ulcers when hydroxyurea is given for treatment of SCD. Although the cause is unknown, the risk appears to be higher in older patients, particularly if they had previous SCD ulcers, suggesting that hydroxyurea may act in conjunction with small vessel abnormalities. Interestingly, not only withdrawal but also dose decrease of hydroxyurea may be sufficient to cure the ulcers. Careful attention should be given to skin changes during hydroxyurea treatment in patients with SCD.

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