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Cutaneous Side Effect of Hydroxurea in a Sickle Cell Anaemia Child-A Case Report

A. O. Salako[1], S. O. Ogunmefun[1] and O. W. Aworanti[2*]

[1]Abbys Paediatric Care, Omole Phase II, Ikeja, Lagos, Nigeria.
[2]Department of Haematology, National Reference Laboratory, Synlab Nigeria, Lagos, Nigeria.

Authors' contributions

This work was carried out in collaboration among the authors. Authors AOS and OWA made the draft. Authors AOS, SOO and OWA managed the literature searches. Authors AOS and OWA corrected the draft. All the authors read and approved the final manuscript.

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Case Study

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ABSTRACT

Background: Hydroxyurea (HU) has redefined the quality of life of children with sickle cell anaemia and their care givers. Despite the acclaimed benefits of HU, the drug could be associated with variable side effects affecting different systems in the human body, including the skin and integuments. The aim of this report is to raise the awareness about the less common side effects of HU.

Case Report: A 5-year 8 months old homozygous sickle cell anaemia child presented with pruritic hyperpigmented lesions on the trunk, arms and the legs, four weeks after commencement of HU. HU was initially discontinued for two weeks and thereafter recommenced with a different brand but there was worsening skin lesions despite at a daily low dose of 10 mg/kg. The rashes eventually resolved with low dose once in 3 days HU therapy. She had recurrent episodes of acute painful crisis; average of three [3] episodes per year warranted hospital admission prior to commencement, but with HU therapy, there has been significant improvement in the crisis.

Discussion: Cutaneous lesions are uncommon side effect of hydroxyurea. This side effect is dependent on genetic predisposition and photosensitivity. However, with the established benefit of

**Corresponding author: E-mail: aworantioladapo@yahoo.com;*

HU in the management sickle cell anaemia, it is important for the sickle cell experts to continue to monitor closely the children for both the common and rare side effects and to individualize therapy to ensure maximal benefit with minimal or no side effects.

Keywords: Hydroxyurea; sickle cell anaemia; side effects; hyperpigmented; rashes.

1. INTRODUCTION

In the 19th century, the benefits of Hydroxyurea in the management of sickle cell disorder came to limelight with continuous improvement on its use in individuals living with the sickle cell disease. The mechanism of action of Hydroxyurea in sickle cell disease is still under evaluation. The proposed mechanisms by which the drug increases Hb F include specific destruction of sickled precursor red cells in the bone marrow, increase in the red cell precursors, which includes fetal erythroblasts that lead to production of Hb F reticulocytes and reduction in the cellular inflammatory mediators (monocytes and neutrophils) [1-3].

In homozygous sickle cell anaemia (HbSS), the pharmacologic effects of Hydroxyurea (HU) revolved around the production of Hb F and the corresponding effect of the Hb F to arrest polymerization; thus, there is increased red cells water content, enhancing deformability of sickled cells, and altering inflammatory cellular mediators and red blood cells(RBC) adhesions to the vascular endothelium [1,4-6].

The effects of HU described above results in overall improved quality of life vis-a-vis reduced frequency of pain (vaso-occlusive) crises, decrease morbidity and mortality in individual living with sickle cell anaemia (Hb SS) [7-9,10].

Despite the acclaimed benefits of Hydroxyurea in sickle cell anaemia management, it is associated with some side effects. These side effects are grouped into common side effects (anaemia, leucopenia/neutropenia, macrocytosis and thrombocytopaenia), less common (alopecia, hyperpigmented skin lesion, ichythyosis, nail discolouration and poor appetite) and rare (skin cancer, leukaemia, azoospermia and dysuria). These could be dependent on dose, duration or individual idiosyncratic reaction/response. These effects could be predictable and reversible after discontinuation of the drugs. However, most people do not experience all of the side effects listed. There is no relationship between the presence or severity of side effects and the effectiveness of the medication [11-13].

Adverse skin reactions from HU are less common and the mechanism of such reactions are not fully understood with several ongoing research to enhance the understanding. This paper reports this uncommon cutaneous reaction due to the use of HU.

2. CASE REPORT

About one year ago, a five year eight-month old female child with Homozygous Sickle Cell Disorder presented for evaluation prior to commencement of Hydroxyurea on account of recurrent vaso-occlusive crisis of more than six episodes in the previous one year. Past medical history of this young girl revealed recurrent episodes of painful crisis, approximately, three out of these crises warranted hospitalization. Last episodes of admission on account of vaso-occlusive crisis was 2 months prior to her presentation during which the parents were counselled on possible commencement of HU.

After adequate counselling and consent given by the caregivers/parent. The baseline complete blood count, liver function test and Haemoglobin profile were done, they are presented in Tables 1, 2 and 3 respectively.

She was commenced on Oral Hydroxyurea at 370 mg [15 mg/kg] [HYDRINE Caps ®] Korea United Pharm Inc.] daily for 2 weeks, after which she presented in the hospital for observation.

Repeat Complete blood count was done, as shown in Table 1 after four weeks of HU use, she was noticed to have developed numerous hyper pigmented, diffuse, macular and patch-like rashes which was initially on the posterior trunk and gradually involved the lower and upper extremities. This is presented in Figs. 1 & 2.

The rashes were characteristically pruritic, affected her sleep most of the nights. At this time, she was not on any other drugs except routine folic acid, vitamin B complex and Proguanil tablet which she has been on in the last 4 years.

Table 1. Haematological parameters

Haemotological parameters	At presentation	2 weeks after commencement	After temporary discontinuation	8 weeks after re-commencement
PCV (%)	22	24	24	21.1
WBC [×10^3/ul]	9.2	12.3	13.6	14.4
Granulocytes [×10^3/ul]	5.2	10.6	10.0	8.2
Lymphocytes [×10^3/ul]	3.1	1.3	2.7	4.9
Monocytes [×10^3/ul]	0.9	0.4	0.9	1.3
Platelet [×10^3/ul]	476	352	439	429

Table 2. Liver function test profile

Parameters	Values
Sodium [Na]	135 mmol/L
Potassium [K]	4.3 mmol/L
Bicarbonate	22 mmol/L
Chloride	99 mmol/L
Urea	3 mg/dl
Creatinine	0.2 mg/dl
Serum Bilirubin	2.5 mmol/L
Total Protein	7.3 mg/dl
Albumin	4.2 mg/dl
Alanine Transaminase [ALT]	36 mg/dl
Aspartate Transaminase [AST]	64 mg/dl
Alkaline Phosphatase [ALP]	191 mg/dl

Table 3. Haemoglobin quantitation

	Before commencement	8 weeks after commencement
Haemoglobin A2	3.3%	2.8%
Haemoglobin F [HbF]	14.3%	18.4%
Haemoglobin S	82.4%	78.8%
Haemoglobin Phenotype	Homozygous Sickle cell	

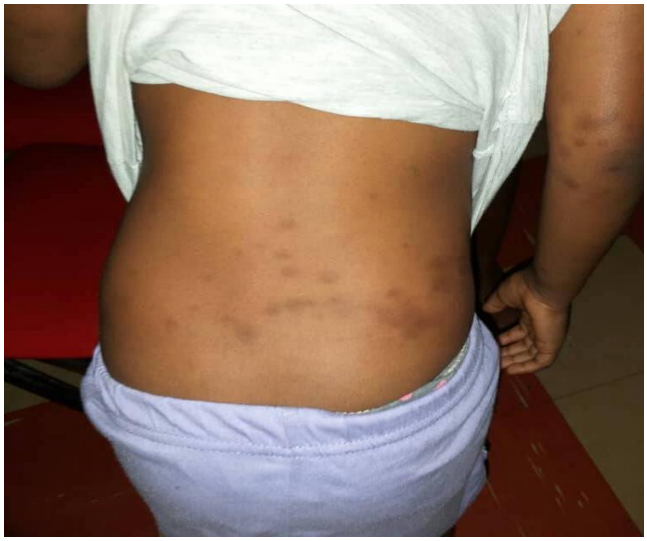

Fig. 1. Hyperpigmented rashes on the posterior trunk

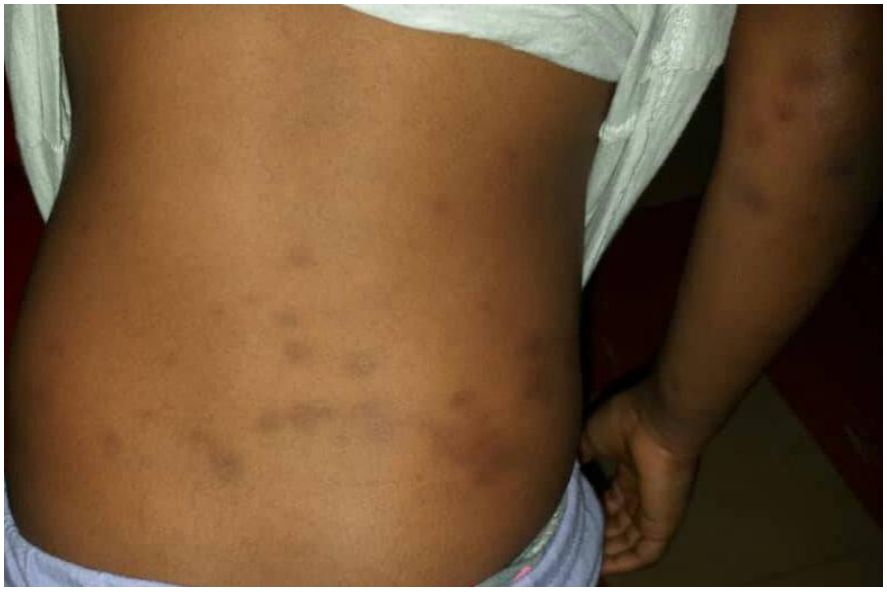

Fig. 2. Hyperpigmented rashes on the trunk and the right upper limb

The oral Hydroxyurea (HU) was then discontinued for two weeks in view of sudden development of rash.

After the two weeks off HU use, she was recommenced on another brand of Hydroxyurea at a lower dose of 10 mg/kg (250 mg) per day [Hydroxyurea capsules, USP- Par Pharmaceutical] as against the initial 375 mg per day.

However, child was noticed to have worsening hyper pigmented skin lesion with the daily dose of 250mg; thus drug was administered once in 3 days and the rash was noticed to recede in character and itchy, with subsequent disappearance of rash and resolution of body itch afterwards. She has been on the hydroxyurea continuously for about 10 months now without any episode of painful crisis since commencement of HU.

3. DISCUSSION

The use of HU in the management of sickle cell anaemia patient has become more acceptable, considering the benefits of reduced morbidity and mortality from sickle cell related manifestations and complications. Though despite this positive trend, there is need to be aware and watchful of the possible side effects of the drug.

From this presentation, the belief that the adverse dermatologic effects of Hydroxyurea (HU) is as a result of the excipient and not the HU itself remain uncertain, because this could depend on variable factors, which could be as a result of the individual or the drug itself [14,15].

This index patient was noticed to have developed skin rashes after commencement of HU, this was discontinued and the rashes resolved but on recommencement of HU, the rashes reoccurred even with a different brand. The rashes however disappeared completely with low dose with less frequency of twice weekly. This is contrary to earlier report that showed that the skin reaction disappears once the drug is discontinued and does not reoccur after recommencement [15]. Furthermore, acute cutaneous manifestation which includes hyperpigmentation of the skin and nails, scaling of the hand and foot, oral sores, stomatitis, hair loss has been associated with overdose of HU and in adults with myeloproliferative disease on HU. [12,14,16-19], our patient was however on therapeutic dose of the drugs when the rashes were noticed. Even at low dose [<10-15 mg/dl] recommended for children with sickle cell anaemia, the rashes were spreading.

The mechanism of HU resulting in the skin changes is not absolutely elucidated. The pathophysiologic mechanism of hyperpigmentation of the skin and nails is reported to be as a result of genetic predisposition, photosensitivity and increased production of melanin by the HU [20,21].

The frequency of vaso-occlusive crisis has also reduced significantly in the index child and the hospital visit now, is essentially for routine follow-up visit rather than for care in crisis. This is in consonance with previous report across variable age group on the benefit of hydroxyurea [2,6,22].

Also, there is significant improvement in fetal haemoglobin level after commencement of HU and reduction in Haemoglobin S, this is consistent with previous reports [23,24,25]. There is no significant change in the haematocrit and white blood cell count, this is in keeping with previous work done by Harminder Singh et al. (2010) but contrary to other reports where there was increase in haematocrit and reduction in white cell count [24,25]. Lack of significant change in the haematocrit and white blood cell count may be as a result of low dose of HU and frequency it is been administered.

4. CONCLUSION

As the use of HU in the management of sickle cell anaemia increases and aimed towards routine use, we implore the sickle cell experts of the need to pay special attention to the possible alterations from the use of HU and the need to continue to individualize therapy to ensure individual benefit maximally for care with minimal or no side effects.

CONSENT

After adequate counselling and written consent has been given by the caregivers/parent.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist

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