Case study

CUTANEOUS SIDE EFFECT OF HYDROXUREA IN A SICKLE CELL ANAEMIA CHILD-A CASE REPORT

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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 system 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 8months 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 10mg/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 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.

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 mechanism by which the drug increases Hb F includes specifically destruction of sickle 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.

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 I, II and III

She was commenced on Oral Hydroxyurea at 370mg [15mg/kg] [HYDRINE Caps [R] 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 I

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 Figures 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 4years.

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 10mg/kg (250mg) per day [Hydroxyurea capsules, USP- Par Pharmaceutical] as against the initial 375mg 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 10months now without any episode of painful crisis since commencement of HU.

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, it was discontinued with resolution of rashes 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 [<10-15mg/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.

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.

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Consent: After adequate counselling and consent given by the caregivers/parent.

Ethical approval: It is not applicable

REFERENCES

1. Steinberg MH (1999) Management of sickle cell disease. N Engl J Med 1999;340: 1021-1030. 2.
2. Hankins JS, Ware RE, Rogers ZR, Wynn LW, Lane PA, et al. Long-term hydroxyurea therapy for infants with sickle cell anemia: the HUSOFT extension study. Blood 2005;106: 2269-2275.
3. Steinberg MH, Nagel RL, Brugnara C. Cellular effects of hydroxyurea in Hb SC disease. Br J Haematol,1997; 98: 838-844.]
4. Ballas SK, Marcolina MJ, Dover GJ, Barton FB. Erythropoietic activity in patients with sickle cell anaemia before and after treatment with hydroxyurea. Br J Haematol,1999; 105: 491-496. 7
5. Ballas SK, Dover GJ, Charache S. Effect of hydroxyurea on the rheological properties of sickle erythrocytes in vivo. Am J Hematol 1989; 32: 104-111.

6. Scott JP, Hillery CA, Brown ER, Misiewicz V, Labotka RJ. Hydroxyurea therapy in children severely affected with sickle cell disease. J Pediatr. 1996, 128(6):820-8
7. Steinberg MH, McCarthy WF, Castro O, Ballas SK, Armstrong FD, et al. The risks and benefits of long-term use of hydroxyurea in sickle cell anemia: A 17.5-year follow-up. Am J Hematol 2010; 85: 403-408. 6. 8.
8. [Charache S, Terrin ML, Moore RD, Dover GJ, Barton FB, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the Multicenter Study of Hydroxyurea in Sickle Cell Anemia. N Engl J Med 1995; 332: 1317-1322.]
9. Odenheimer DJ, Sarnaik SA, Whitten CF, et al. The relationship between fetal hemoglobin and disease severity in children with sickle cell anemia. Am JMed Genet. 1987;27(3):525–535.
10. Steinberg MH, Barton F, Castro O, Pegelow CH, Ballas SK, et al. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia: risks and benefits up to 9 years of treatment. JAMA 2003; 289: 1645-1651.
11. Hydroxyurea. Hydrea®, Draxia™, Mylocel™. 2002-2019 by Chemocare.com®. carewww.chemocare.com.
12. Package insert Hydroxyurea, Par Pharmaceutical, Chestnut NY 10977.2016
13. Package insert Oxyurea Capsules, Bond Chemical Industries LTD, Plot 20-26 Adesakin Layout Oyo State Nigeria.
14. Package insert (2011) Hydroxyurea, Bristol Myers Squibb Company: Princeton NJ.
15. Ballas SK, Singh P, Adams-Graves P, Wordell CJ. Idiosyncratic Side Effects of Hydroxyurea in Patients with Sickle Cell Anemia. J Blood Disorders Transf 2013; 4: 162. doi: 10.4172/2155-9864.1000162.
16. De Montalembert M, Bégué P, Bernaudin F, Thuret I, Bachir D, et al. Preliminary report of a toxicity study of hydroxyurea in sickle cell disease. French Study Group on Sickle Cell Disease. Arch Dis Child 1999; 81: 437-439. 11.

17. Chaine B, Neonato MG, Girot R, Aractingi S. Cutaneous adverse reactions to hydroxyurea in patients with sickle cell disease. Arch Dermatol 2001;137: 467-470. 12.
18. Salmon-Ehr V, Leborgne G, Vilque JP, Potron G, Bernard P. Secondary cutaneous effects of hydroxyurea: prospective study of 26 patients from a dermatologic consultation. Rev Med Interne 2000; 21: 30-34. 13.
19. Vassallo C, Passamonti F, Merante S, Ardigò M, Nolli G, et al. Mucocutaneous changes during long-term therapy with hydroxyurea in chronic myeloid leukaemia. Clin Exp Dermatol 2001; 26: 141-148.
20. UtaÅŸ S, Kulluk P. A case of hydroxyurea-induced longitudinal melanonychia. Int J Dermatol 2010; 49: 469-470.
21. 15. Aste N, Fumo G, Contu F, Aste N, Biggio P. Nail pigmentation caused by hydroxyurea: report of 9 cases. J Am Acad Dermatol 2002; 47: 146-147.
22. Tshilolo L, Tomlinson G, Williams TN, Santos B, et al. Hydroxyurea for Children with Sickle Cell Anemia in Sub-Saharan Africa. N Engl J Med 2019; 380:121-131
23. Harminder Singh, Nana Dalhani, Bithika Nelkumar, Prabhalla Singh, Pawan Tiwari. Effective Control of Sickle Cell Disease with Hydroxyurea therapy. Indian J Pharmacol 2010;42(1):32-35.
24. Butungeshwar Pradhan, Bipin K. Kulla, Sagnika Tripatha, Nayan K. Patel. Low Dose Oral Hydroxyurea Prophylaxis Improves All Clinico-haematological Parameters Amongst Sickle Cell Disease Patients. Int J Res Med Sci 2018; 6(6):1950-1955.
25. Titilola S .Akingbola, Santosh L. Saraf, Binal N. Shah, Chinedu Anthony Ezekekwu, Omowunmi Sonubi, Lewis L. Hsu et. al. Hydroxyurea for Treatment of Sickle Cell Disease in Adults in Africa.Blood 2016; 128: 1305

Table I: Haematological Parameters

HAEMOTOLOGICAL PARAMETERS	AT PRESENTATION	2WEEKS AFTER COMMENCEMENT	AFTER TEMPORARY DISCONTINUATION	8 WEEKS AFTER RE-COMMENCEMENT
PCV (%)	22	24	24	21.1
WBC [$\times 10^3$/ul]	9.2	12.3	13.6	14.4
GRANULOCYTES	5.2	10.6	10.0	8.2

[×10^3/ul]				
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

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PARAMETERS	**VALUES**
Sodium [Na]	135mmol/L
Potassium [K]	4.3mmol/L
Bicarbonate	22mmol/L
Chloride	99mmol/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 III: 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	

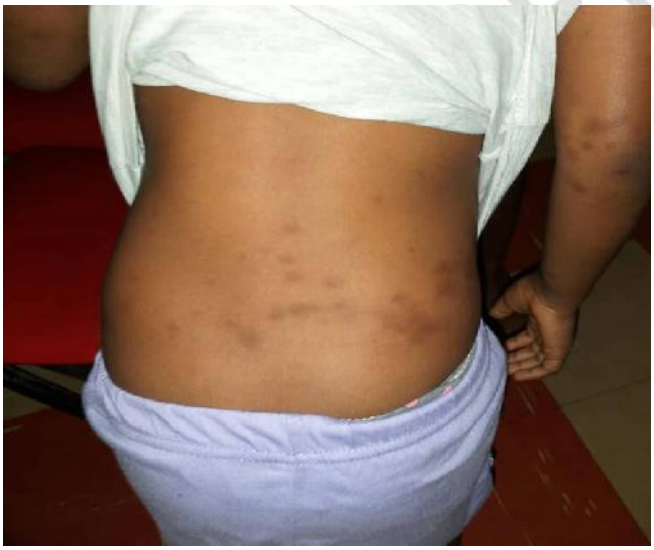

Figure 1: Hyperpigmented rashes on the posterior trunk

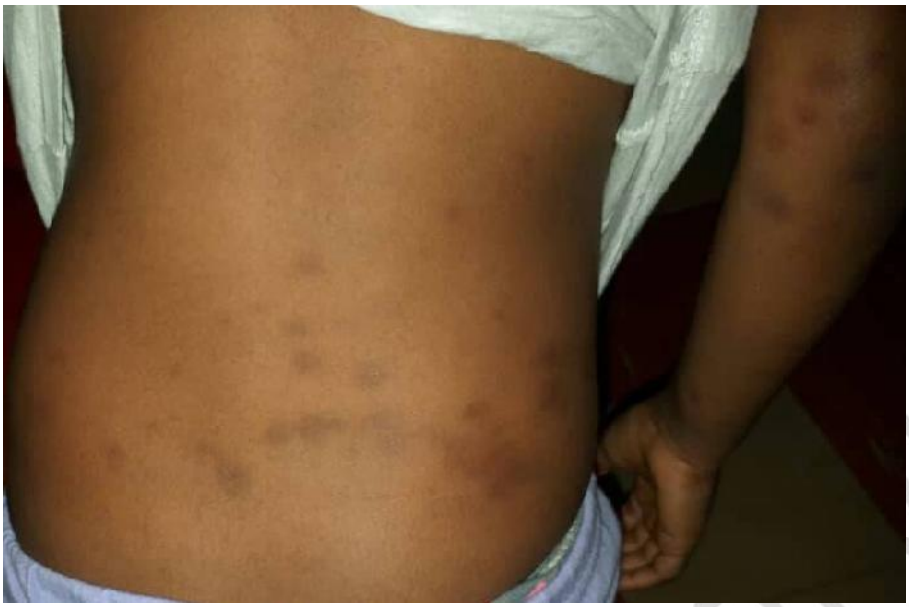

Figure 2: Hyperpigmented rashes on the trunk and the right upper limb