

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

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 on alternate day 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, 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.

25 **Introduction**

26 In the 19th century, the benefits of Hydroxyurea in the management of sickle cell disorder came to
27 limelight with continuous improvement on its use in individuals living with the sickle cell disease. The
28 mechanism of action of Hydroxyurea in sickle cell disease is still under evaluation. The proposed
29 mechanism by which the drug increases Hb F includes specifically destruction of sickle red cells in the
30 bone marrow, increase in the red cell precursors, which includes fetal erythroblasts that lead to production
31 of Hb F reticulocytes and reduction in the cellular inflammatory mediators (monocytes and neutrophils).<sup>(1-
32 3)</sup>.

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

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

40 Despite the acclaimed benefits of Hydroxyurea in sickle cell anaemia management, it is associated with
41 some side effects. These side effects are grouped into common side effects (anaemia,
42 leucopenia/neutropenia, macrocytosis and thrombocytopenia), less common (alopecia, hyperpigmented
43 skin lesion, ichthyosis, nail discolouration and poor appetite) and rare (skin cancer, leukaemia,
44 azoospermia and dysuria). These could be dependent on dose, duration or individual idiosyncratic
45 reaction/response. These effects could be predictable and reversible after discontinuation of the drugs.

46 However, most people do not experience all of the side effects listed. There is no relationship between the
47 presence or severity of side effects and the effectiveness of the medication. ⁽¹¹⁻¹³⁾

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

51 **Case Report**

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

58 After adequate counselling and consent given by the caregivers/parent. The baseline complete blood
59 count, liver function test and Haemoglobin profile were done, they are presented in Tables I, II and III

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

62 Repeat Complete blood count was done, as shown in Table I

63 After four weeks of HU use, she was noticed to have developed numerous hyper pigmented, diffuse,
64 macular and patch like rashes which was initially on the posterior trunk and gradually involved the lower
65 and upper extremities. This is presented in Figures 1&2

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

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

70 After the two weeks off HU use, she was recommenced on another brand of Hydroxyurea at a lower dose
71 of 10mg/kg (250mg) per day [Hydroxyurea capsules, USP- Par Pharmaceutical] as against the initial
72 375mg per day

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

78 **DISCUSSION**

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

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

86 This index patient was noticed to have developed skin rashes after commencement of HU, it was
87 discontinued with resolution of rashes but on recommencement of HU, the rashes reoccurred even with a
88 different brand. The rashes however disappeared completely with low dose with less frequency of three
89 times weekly. This is contrary to earlier report that showed that the skin reaction disappears once the drug
90 is discontinued and does not reoccur after recommencement.⁽¹⁵⁾ Furthermore, acute cutaneous
91 manifestation which includes hyperpigmentation of the skin and nails, scaling of the hand and foot, oral
92 sores, stomatitis, hair loss has been associated with overdose of HU and in adults with myeloproliferative
93 disease on HU.^(12,14,16-19), our patient was however on therapeutic dose of the drugs when the rashes were

94 noticed. Even at low dose [$<10-15\text{mg/dl}$] recommended for children with sickle cell anaemia, the rashes
95 were spreading

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

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

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

108 CONCLUSION

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

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UNDER PEER REVIEW

HAEMOTOLOGICAL PARAMETERS	AT PRESENTATIO N	2WEEKS AFTER COMMENCEMEN T	AFTER TEMPORARY DISCONTINUATIO N	8 WEEKS AFTER RE- COMMENCEMEN T
PCV (%)	22	24	24	21.1
WBC [$\times 10^3$ /ul]	9.2	12.3	13.6	14.4
GRANULOCYTES [$\times 10^3$ /ul]	5.2	10.6	10.0	8.2
LYMPHOCYTES[$\times 10^3$ /ul]	3.1	1.3	2.7	4.9
MONOCYTES[$\times 10^3$ /ul]	0.9	0.4	0.9	1.3
PLATELET[$\times 10^3$ /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

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208 ***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	

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UNDER PEER REVIEW



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224 Figure 1: Hyperpigmented rashes on the posterior trunk

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

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