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Preventing Inappropriate Hydroxyurea Dosing in Children by Introducing a Child-Appropriate Preparation

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ABSTRACT

Hydroxyurea (HU) is the only FDA- approved disease- modifying drug for sickle cell disease, by inducing the production of fetal hemoglobin and thus decreasing the sickling of red blood cells. Till recently HU was available only in adult doses of 1000 mg. This meant that to aim at the standard dose of 20 mg/kg/d, most young children had to be overdosed, or the doses had to be fluctuated daily to achieve the aimed mean dose. Because adherence improves with unchanged daily dose, and due to the more than 10 fold variability in HU pharmacokinetics in children, there was an urgent need for a pediatric formulation of HU.

This issue has been solved with FDA approval of the French-originated orphan HU, Siklos, a preparation of 50 and 100 mg, which prevents the risk of inappropriate dosing in children.

Keywords: Hydroxyurea, Sickle cell disease, Sickle cell crisis, Children, Siklos, Fetal hemoglobin, Pharmacokinetics.

INTRODUTION

Sickle cell disease (SCD) is a genetic disorder of the red blood cell affecting up to 100,000 Americans, and millions of people worldwide [1]. When children inherit the sickle hemoglobin gene (Hb SS) from both parents, or the Hb SS gene from one parent and another abnormal Hb gene from the other parent, their erythrocytes tend to be deoxygenated, dehydrated, and reshaped as crescents ("sickled") (Figure 1).

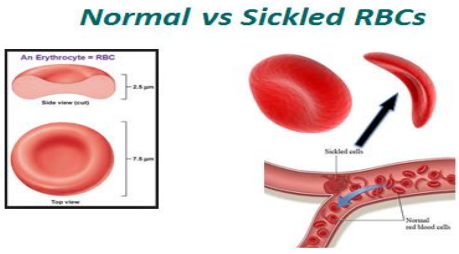

Figure 1: Normal *vs.* sickled RBCs.

Sickling can also be caused by additional, less common sickle syndromes from other genotypes, such as SCD-S beta, SCD-SC among other [2]. This results in red blood cell aggregation, sticking to blood vessels, blocking blood flow to different organs, leading to attacks of acute pain ("sickle cell crisis"). SCD causes permanent damage to a variety of organs, including the heart, brain, lungs, kidneys, liver, and bone, among other (Figure 2).

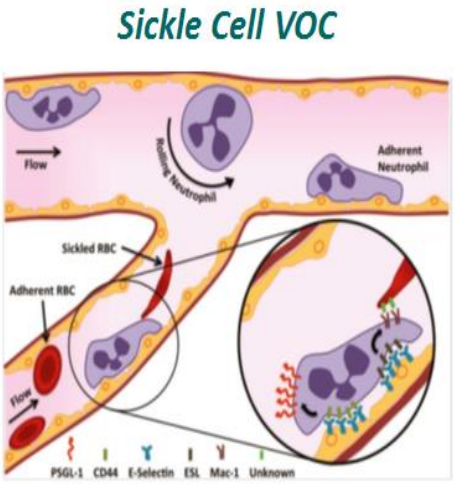

Figure 2: Schematic presentation of veno occlusive events in sickle cell disease.

These crises typically lead to hospitalization for pain control, rehydration and oxygen administration [2]. The most serious adverse event in SCD is the chest crisis, typified by hypoxia which may be life threatening [3]. This serious chronic disease results in shortened life span and seriously impaired quality of life.

A breakthrough in the management of SCD came about in 1984, when HU, originally developed as an antimetabolite drug for leukemia, melanoma and ovarian cancer, was shown to induce the production of fetal hemoglobin, thus diluting the proportion of Hb SS [4]. This was based on earlier observations showing that levels of fetal hemoglobin are inversely related to the numbers of sickle cells [5]. A threshold of 20% of fetal Hb has been generally accepted as the level needed to decrease the severity of SCD symptoms. Randomized, placebo control studies in both adults and children have shown consistently that HU induces the production of fetal hemoglobin and decreases the frequency of acute painful episodes by 66-80%, the need for transfusion by 40-90%, the incidence of acute chest syndrome by 25-59%, decrease the numbers and duration of hospitalization by 73% and decrease mortality at 8 year follow up by 40% [2]. Originally, HU was approved for adults in 1998 [1], with a standard tablet of 1000 mg. The different RCTs have shown that the maximal tolerated dose is 21 mg/kg/d in adults and 26 mg/kg/d in children [2].

Subsequently, HU was approved as Siklos by the FDA as an orphan drug for children older than 2 years of age in December 2017 [6]. However, because the dose units available on the market were aimed at adults, this meant the individualized dose per kg for children has been in most cases different from the intended dose.

In this review, we elaborate on the need for accurate dosing of HU in children, and introduce the breakthrough achieved by the recent introduction of child-appropriate dose units.

Toxicology of HU

HU is an anticancer drug, and as such, has predictable dose dependent adverse effects on the bone marrow. Dosing guidelines for HU acknowledge this toxicological profile and have set clear guidelines for dose decreases when [2]:

1. Neutrophil count is below 1000 per micro L
2. Hemoglobin is below 7.0 g/ dL with low reticulocyte count (below 100 K per mcL), or a 20% decrease from the previous count.
3. Platelets count is below 80 K per micro L.

Studies have shown that in some cases bone marrow suppression continues long after discontinuation of HU [7]. Putting these facts into the reality of pediatric prescribing of the drug. Please consider an infant of 7 kg who would need 22 mg/kg/d to a total of 154 mg. With the available adult dose of adult preparation of Droxia of 200 mg, s/he would receive with one tablet 30% more drug than they need. An overdose of 30% is more likely to increase the risk for bone marrow suppression and attendant infections. If one considers a 12 kg infant, the dose needed would be 264 mg a day. This means that a 200 mg Droxia would result in an under dosing of 32%. As therapeutic drug monitoring of HU serum concentrations is not practiced to date in most academic centers the dose schedule is monitored by follow up of leucocyte counts as outlined above.

One approach that has been practiced among children who need to use adult forms of HU was to alternate the daily dose over 2 or more days, to arrive at the aimed cumulative dose. However, there is evidence that this results in decreased adherence to the drug, as consistent unchanged daily dose leads to favorable adherence [2].

Moreover, it is now more and more evident that there is very wide pharmacokinetic variability HU. Wiczling et al. have recently documented a 15 fold variations in HU concentrations 15-20 minutes after a dose, 10 fold differences at one hour and 20 fold by 180 minutes. Systemic exposure measured by the area under concentration-time curve (AUC) varied two fold [8]. The recommended starting dose, based on therapeutic drug monitoring ranged between 16.7 and 33.3 mg/kg/d. This large pharmacokinetic variability appears to be quite similar to the results in adult studies [9]. The future of personalized prescription of HU is driven by pharmacogenetic variability in transporters such as the organic anion transporter 1B which drives the secretion of the drug in the kidney [10]. Such degree of variability in dosing will certainly demand the ability to tailor dose schedules which cannot be achieved with the available adult's forms?

The first pediatric- designed HU

In December 2017 the FDA approved Siklos for the reduction of the frequency of painful crises and to reduce the need for blood transfusions in children 2 years of age and older with SCD and recurrent moderate to severe painful crises [6]. The drug is produced by Addmedica Inc. in France. The FDA based the approval on the open label single arm ESCORT study, which included 405 children 2-18 years of age. In that study there was a sub cohort of 141 children with SCD who had not received the drug prior to joining the study. After one year of treatment, there was a significant decrease in fraction of patients with vaso -occlusive episodes, transfusions and SCD repeated hospitalizations. The more common adverse events of Siklos were neutropenia and infections [6].

In another study, the Hydroxyurea Study of long-Term Effects, the team examined the effects of initiating HU and escalating it to its maximal tolerated dose in children younger than 5 years of age, before experiencing the physiologic decline in fetal hemoglobin. The maximal tolerated dose was defined by achieving a neutrophil count of 2-4 x 10/L or other hematologic toxicity. Adherence was measured by records of purchase of the drug. Children who started HU before 5yr of age (n=49) had a safe and effective course, not different from the children who started later (n=102) [11].

The recommended dose schedule is 20-35 mg/kg/d, starting with 20 mg/kg/d and titrate it by 5 mg/kg/d q8 week. Because HU is eliminated mostly by the kidney, the dose should be reduced by 50% at CrCl below 60 [12].

The ability to give young children tablets of the 50 (i.e. the scored 100 mg tablet) instead of the 200, 300, 400, 500 or 1000 mg adult preparations, increases substantially the ability to titrate dose schedules according to the child's body weight and maximal tolerated dose, as shown in Table 1.

Table 1: Siklos *vs.* adult HU preparations in achieving appropriate pediatric dosing.

Pediatric Patient-based Model

HAVING A 100 MG TAB

	AGE	NB PATIENTS	AVERAGE DAILY DOSE (MG)	DOSAGE BASED TREATMENT: SIKLOS 100 MG TAB	SIKLOS SCORED TAB*	SIKLOS 1000 MG TABLETS Triple-scored 250	500	750	1000	DROXIA Capsules 200	300	400	HYDREA Caps 500	Diagnosed & Treated Patients %	Nb.
				100	50/50										
15 mg/kg	[0-1]	2,578	62	1	1									25%	645
	[1-2]	2,560	171	2	2									25%	640
	[2-3]	2,541	212	2	2					1				25%	635
	[3-4]	2,523	248		2.5	1				1				25%	631
	[4-5]	2,504	280		2.5	1					1			25%	626
	[5-6]	2,485	309	3	3						1			25%	621
	[6-7]	2,467	344	1	3.5	1						1		25%	617
	[7-8]	2,448	374	1	3.5	1						1		25%	612
	[8-9]	2,430	409	1	4	1						1		25%	608
	[9-10]	2,411	450	2	4.5	1						1		25%	603
	[10-11]	2,393	489				1						1	25%	598
	[11-12]	2,374	531				1						1	25%	594
	[12-13]	2,355	582	1			1				2			25%	589
	[13-14]	2,337	649	2			1				1	1		25%	584
	[14-15]	2,318	732					1				2		25%	580
	[15-16]	2,300	820	1				1				2		25%	575

* Where available

This allows for much more accurate achievement of the maximal tolerated dose based on white blood cell counts of 2-4 x 10/L. With the advance of personalized dosing, the child's specific pharmacokinetic and pharmacodynamics characteristics will be very important for chronic, lifelong conditions [13]. Avoiding the need to change the daily dose every day or couple of days, as happens with the adult preparation is important for maintaining good adherence of HU.

Medication non-adherence

Medication non-adherence is a major issue in SCD with any type of medication needed, including HU. While in short randomized control studies adherence was as high as 90% [14], in clinical practice less than half of patients achieve high adherence rates of HU [15,16]. Studies show that children with poor adherence to HU exhibit worse health outcomes and higher health care cost than those who adhere well [2,16]. There are several reasons for the low adherence rates for HU in the USA. Most of these children are African American, more likely to be poor and face medication adherence barriers such as medication accessibility and cost [17]. SCD is a chronic illness necessitating lifelong daily medication even when there are no apparent symptoms. These conditions have been shown to adversely affect adherence. Adherence has been shown to be low if a key family member or the child is not supportive of the treatment with HU [2]. Presently, in certain clinics pediatric dosing of HG consists of 500 mg capsules as follows: one capsule per day, one capsule alternating with two capsules per day (i.e. 750 mg/d), two capsules per day etc [2]. However, adherence is improved when the same dose is administered daily [2]. This however, cannot be achieved with the adult dose units, and is an important advantage of Siklos. In summary, FDA approval of the French-originated orphan HU, Siklos in preparations of 50 (as scored 100 mg), prevents the risk of inappropriate dosing of the drug in children. This should encourage all involved in pediatric medicine, from health care physicians, to the pharmaceutical industry and regulators to act similarly in other therapeutic areas where inappropriate pediatric dose schedules are endangering the health and wellbeing of children.

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