Published in final edited form as:

Pediatr Blood Cancer. 2014 September ; 61(9): 1536–1539. doi:10.1002/pbc.25073.

Do Difficulties in Swallowing Medication Impede the Use of Hydroxyurea in Children?

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Abstract

Background—Use of hydroxyurea (HU) in children with sickle cell disease (SCD) may be hampered by its formulation as a capsule and the limited availability of liquid HU.

Procedure—At four Pediatric SCD clinics, parents of children with SCD ages 5–17 years were surveyed about their children's medication use and ability to swallow medication. Data were stratified by HU therapy and analyzed using descriptive statistics, Chi square tests, Fisher exact tests and univariate analysis.

Results—Of the 116 parents surveyed, 97% were the primary caregiver. One fourth (26%) of parents reported that their child's difficulty swallowing medication interfered with daily medication use. Age-related differences were found in ability to swallow medication, but not by HU use. Children taking HU were more likely to take multiple daily medications, with more frequent dosing schedules. Among 65 HU users, children using the liquid formulation (28%, n = 18) were younger than capsule users ($P < 0.0001$). Nonetheless, half of liquid HU users were aged 8–13. Children using liquid HU were more likely to have difficulties swallowing medication than those who use HU capsules (OR 4.29, 95% CI 1.14–16.18, $P = 0.032$). Few had received training for swallowing medication.

Conclusions—One fourth of surveyed parents viewed swallowing as challenging to daily medication use. These findings suggest that difficulty swallowing capsules is a fairly frequent barrier to for children prescribed HU, especially for younger children. HU use appears more likely

in families with daily and more complex medication schedules. Coaching for swallowing capsules may improve HU utilization and adherence.

Keywords

adherence; capsules; hydroxyurea; medication; swallowing

INTRODUCTION

Hydroxyurea (HU) is a major pharmacologic intervention for children with sickle cell disease (SCD). Reduced disease complications by HU in children are reported for children as young as 1 year of age [1,2]. Despite its effectiveness, HU is widely underutilized in the United States [3–5], with barriers at provider, family and systems levels [4,6–9]. Even if prescribed, challenges to a daily medication regimen for children may result in suboptimal adherence [6,10,11]. Current approval by the Food and Drug Administration (FDA) for HU use for SCD is limited to adults (http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/016295s041s042lbl.pdf, accessed 1.7.2014). Off-label use in children can be a barrier to its uptake [7].

FDA-approved formulations are limited to capsule form. Young children commonly have difficulty swallowing medications, especially capsules [12,13]. A liquid form of HU is distributed through compounding pharmacies, rendering it less widely available, not standardized, and with potentially incomplete coverage by Medicaid [13]. Anecdotally, some parents of children prescribed HU report that their children struggle to swallow the capsules, potentially impeding pediatric uptake and adherence. In a multi-site survey of parents, we compared children based on HU use regarding their medication regimen, their ability, strategies or difficulties in swallowing forms of medication, and if swallowing posed logistic barriers to pediatric HU use. Our hypothesis was that HU use in children is hampered by its formulation as a capsule and its limited availability of liquid HU.

METHODS

Following approval by the Institutional Review Board at each site, a self-administered anonymous survey of parents of children with SCD ages 5–17 years was offered to parents of children attending the pediatric SCD clinic at four institutions (see author affiliations). Parents could select the English or Spanish survey versions. The survey had 46 multiple-choice and two open-ended questions, and took 10–12 minutes to complete. In families with more than one child with SCD, a survey was completed for each eligible child. In addition to child and parent demographics, parental views were assessed on their child's medication regimen, including HU; ability to swallow medication and what strategies were employed; whether difficulties swallowing pills or capsules interfered with the child taking daily medication; and if children had received training for medication swallowing. Data were stratified by HU therapy and analyzed using descriptive statistics, Chi square tests, Fisher exact tests and logistic regression, with a *P*-value of <0.05 considered as statistically significant, using SAS software version 9.3 (SAS Institute, Inc., Cary, NC).

RESULTS

Demographics

A convenience sample of 116 adults completed the survey, with 27–32 surveys obtained from each site. Fewer than 10 people refused to participate, many of whom stated that they were not the parent. Of survey respondents, 97% self-identified as parents and as the child's primary caregiver (Table I). Half of all children were ages 8–13 years, and 22% were 7 or younger (Table I). Groups were designated by HU use (56%, $n=65$) or no use (44%, $n=51$). Groups did not differ by parent or child age or use of the Spanish survey version. Parents of children taking HU had a higher level of education ($P=0.015$). While 96% of all the children were prescribed medication, children taking HU were more likely to be taking medication on a daily basis (98% vs. 55%, $P<0.001$), taking multiple medications ($P<0.001$), including a medication regimen requiring more than once daily dosing ($P=0.001$; Table I).

Medication Swallowing

Parental determination *post hoc* was used to assess the swallowing patterns of the children. No statistically significant differences by HU use were found in overall ability to swallow medication in any form. Of children whose parents were surveyed, nearly all (98%) could swallow liquid medication, with the majority (65.5%) able to do so by 1 year of age, and an additional 25.7% by age 6 (Fig. 1). In contrast, a total of 75.5% of the children could swallow pills, with 32.1% able to do so by age 4, an additional 36.6% by age 10 and 4.5% by age 17. A similar total proportion was able to swallow capsules, with 20.2% by age 4, another 36.8% by age 10 and 5.5% by age 17. In all, only 72.5% of the children could swallow capsules. Among the children who could not swallow either pills or capsules, 75% of this sub-group was unable to swallow either form of medication.

In a separate question, parents were asked: "Is swallowing pills or capsules so hard that your child sometimes misses a day?" One quarter (26%, $n=28$) of parents reported that their child's difficulty swallowing medication interfered with the medication regimen, with no difference by HU use, study site or even age. Among these 28 children, 25% ($n=7$) were 7 years, 50% ($n=14$) were 8–13 and 25% ($n=7$) were 14–17 (Fig. 2). In total, 11% ($n=13$) of children had received training for medication swallowing. Most of the parents of these children perceived the training as helpful to their child, including for the children on HU.

Among HU users ($n=65$), HU use did not vary significantly by clinic site ($P=0.11$). HU users comprised 60–65% of children of participating parents at three sites, and 36% at the fourth site. HU users reported to have difficulty swallowing medication did not differ by clinical site ($P=0.179$).

Among HU users, 28% ($n=18$) reported taking the liquid form. As a group, those children taking liquid HU were younger than those taking HU capsules ($P<0.001$). Only 6.5% ($n=3$) of capsule users were 7 years and 54% ($n=18$) were 8–13, while 50% ($n=9$) of the liquid takers were 8–13 (Fig. 3). Use of the liquid formulation varied by site ($P<0.001$), with 72% ($n=13$) at Duke, 11% and 17% ($n=2$ and 3) at Columbia and Milwaukee, respectively, and none at Kansas City.

Among the 51 HU capsule users, 17% (n=9) reported needing to open the capsule and mix contents with a liquid or soft food to aid swallowing. That practice also varied by site ($P < 0.001$), with highest number (6) at Columbia. By univariate logistic regression of children taking HU, those using the liquid form of HU were more likely to have difficulty swallowing medication than those who use HU capsules (OR 4.29, 95% CI 1.14–16.18, $P = 0.032$).

DISCUSSION

Children with SCD commonly require daily medications for treatment of their disease, as well as for other concurrent medical conditions [11]. Clinical trials for children with SCD have demonstrated substantial benefit from HU use for broadening indications (recently reviewed in Refs. [14,15]) and for very young children [1,2]. Addressing barriers to its use in the expanding pediatric demographics of clinical indication and age is critical for improving disease outcomes. To our knowledge, this multi-site study is the first published report of parental perspectives on challenges to medication swallowing for children with SCD.

The majority of parents surveyed did not view medication swallowing as an impediment to daily use of medications, including HU, by their children with SCD ages 5–17. As expected, children learn to swallow pills and capsules, but that skill acquisition appears to level off by age 10 years. These data suggest that difficulty swallowing medication is not a universal barrier to pediatric HU use. However, one fourth of surveyed parents viewed swallowing as an impediment to daily medication use, and this same proportion of children could not readily swallow pills or capsules. Children under five were especially challenged, but problems extended through all age ranges. Even among HU users ages 8–13, many reported use of the liquid form. Children who take HU and have trouble swallowing medication were more likely to avoid that problem by using the liquid form.

Our findings also suggest that HU use is more likely in families committed to daily medication use and more complex medication schedules, or for children with medical needs requiring additional medication beyond once daily HU. Three of the centers typically offer HU for use in children at ages 1–3 years, depending on clinical complications and parental preference. One center (Kansas City) initiates HU at age 5, which may have contributed to the absence of liquid users among their patients surveyed despite their in-house compounding pharmacy. Few children received training for swallowing medication, an intervention that nearly all their parents found to have been helpful.

Limitations of this study include the reliance on anonymous parental report of their child's pattern of medication swallowing rather than direct observation by study staff. Probable over-representation of children taking HU likely reflects the increased frequency of clinic attendance by those taking HU [7,16]. The heterogeneity of clinical sites, parental demographics and children's ages reflect that a cross section of children and their medication swallowing practices were obtained. Use of an anonymous survey did not enable us to discern what impact, if any, higher parental education had on HU swallowing or surmounting other barriers to HU use. Variability in the number of users of liquid HU by

site may reflect local factors such as accessibility of compounding pharmacies, provider preference and/ or insurance coverage. The survey did not address whether HU was ever specifically discontinued due to swallowing difficulties, or if the liquid preparation was continued into older years because of swallowing difficulties rather than simply as the preparation in use.

Our results suggest that challenges to swallowing HU capsules are fairly frequent among children and is not limited to the youngest patients. Furthermore, opening HU capsules to aid in swallowing the contents may be a hazardous exposure to skin or other site from this chemotherapeutic agent. Ideally, medications formulated for pediatric use are palatable [17], stable, widely available in standardized liquid and other easily ingested forms [13,18] and pharmacologically comparable to other oral forms [17] outside of a study setting [19]. Expanding pediatric use of HU for SCD may be facilitated by FDA approval of a liquid form for individuals who cannot swallow capsules, especially younger children. Clinicians should address potential impediments to HU such as swallowing capsules and complex medication regimens. Swallowing training programs, as well as instructing parents about correct techniques for opening capsules onto soft foods, should be targeted to the subset of children with difficulty swallowing medications.

Acknowledgments

Grant sponsor: NIH; Grant number: 1R21NR013745

This study received support from NIH 1R21NR013745 (Green and Smaldone, PIs).

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Fig. 1.
Age when children with SCD learned to swallow medication (N =116).

Fig. 2.
Proportion of children with SCD and difficulty swallowing medication, by age (N =116).

Fig. 3.
Formulation of HU taken, by age (N =65).

TABLE I

Demographics and Medication Regimen, by HU Use

Takes HU (N =65)						No HU (N =51)		P-Value
Demographics		%	N	%	N			
Parent or guardian of child								
Yes	96.9	63	98.0	50	1.0			
No	3.1	2	2.0	1				
Most responsible for the child's medical care								
Yes	96.9	63	96.1	49	1.0			
No	3.1	2	3.9	2				
Age of parent (years)								
18–25	1.6	1	5.9	3	0.588			
26–35	37.5	24	39.2	20				
36–45	43.8	28	35.3	18				
45	17.2	11	19.6	10				
Main language in the home								
English	83.1	54	88.2	45	0.404			
Spanish	15.4	10	7.8	4				
Other	1.5	1	3.9	2				
Parent education								
Grade school	1.6	1	7.8	4	0.015			
High school	26.6	17	15.7	8				
Some college	39.1	25	60.8	31				
College grad	32.8	21	15.7	8				
Age of child (years)								
7	18.8	12	27.5	14	0.331			
8–13	53.1	34	39.2	20				
14–17	28.1	18	33.3	17				
Medication used daily ^a								
Yes	100	64	54.9	28	<0.0001			
# different medications ^a								

Demographics	Takes HU (N =65)		No HU (N =51)		P-Value
	%	N	%	N	
0	0	0	29.2	15	<0.0001
1-2	42.9	27	58.4	30	
3	57.1	36	12.5	6	
Medication times daily ^a					
0	0	0	30.6	14	0.001
1	35.5	22	16.3	8	
2	59.7	37	51	25	
3	4.8	3	2	1	

^aHU users N =62-64, depending on numbers of responses omitted for responder inconsistencies.