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Evaluation of pediatric hydroxyurea prescriptions for patients with sickle cell disease

Fernanda Alice Tanimoto Duque[1] Elaine Ferreira Dias[2] Jéssica Soares Malta[2]
Priscila Cezarino Rodrigues[1] Lucas de Faria Martins Braga[3] Josiane Moreira da Costa[2]

[1] Fundação Hemominas. Belo Horizonte/MG, Brasil.
[2] Universidade Federal de Minas Gerais – UFMG. Belo Horizonte/MG, Brasil
[3] Rede Mater Dei de Saúde. Belo Horizonte/MG, Brasil.
E-mail: fernandatanimoto@gmail.com

Abstract

Hydroxyurea (HU) was one of the main advances in the treatment of sickle cell disease. The use of the drug in children in Brazil is still off-label and is only available in solid pharmaceutical form. The objective of the present study is to evaluate the strategies for adapting the solid dosage form for use in children with sickle cell disease. This is a descriptive study, with the analysis of pediatric HU prescriptions and the application of questionnaires to those responsible in the period from January to March 2018. 43 prescriptions were analyzed, and two forms of adaptation were identified, 1) conventional dilution: dilution of the drug in a pre-prescribed quantity - determined amount of water, followed by administration of part of the solution obtained (22) (51%), and 2) use of the holiday or intermittent dose recommendation (21) (49%). All patients using the conventional dilution strategy discarded the remainder of the drug from the domestic sewage system. In addition, incorrect administration of the drug was identified in one patient. The lack of an appropriate pharmaceutical form for the pediatric population can lead to risks of incorrect administration and unnecessary expenses with drug disposal, in addition to improper disposal that compromises environmental factors. This study reinforces the need to develop pharmaceutical forms that are more suitable for children.

Keywords: Sickle cell disease. Sickle Cell Anemia. Hydroxyurea. Pediatrics. Dose.

INTRODUCTION

Sickle cell disease (SCD) is considered one of the most common genetic diseases in the world, affecting mainly people of African descent[1,2,3]. In Brazil, due to genetic diversity, SCD is not restricted to a group of individuals, it is estimated that the number of live births with the disease each year is around 3,000 to 3,500[2,3]. Clinical manifestations are basically due to vaso-occlusion and hemolysis phenomena, caused by the polymerization of Hemoglobin S (HbS) inside the blood vessels[3,4].

The use of hydroxyurea (HU) was one of the main advances in the treatment of patients with SCD[1]. The drug is classified as an antimetabolite and antineoplastic drug, and is primarily indicated for the treatment of specific types of cancer[5,6]. The mechanism of action is not fully elucidated, but it is known that the drug acts by increasing fetal hemoglobin synthesis, decreasing the number of neutrophils and

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erythrocyte adhesion molecules, and patients with SCD can have a significant improvement in quality of life with the use of HU[1,3,5]. The literature demonstrates a reduction in the number of vaso-occlusive crises, a reduction in hospitalizations and the need for transfusions, as well as a lower occurrence of acute chest syndrome[1,2,4,5,7].

The use of HU in children in Brazil remains off-label, which reinforces the identification of the need to carry out more robust pharmacokinetic studies[5,6]. In Brazil, this drug is only available in solid dosage forms, in 500 mg capsules[8,9].

The dose of HU used for the treatment of SCD is based on the patient's weight and can vary from 15 to 35 mg/kg/day[1,10]. It is possible to start treatment in children from 9 months of age, and it is necessary to adapt the solid presentation for use in pediatric patients with a dose lower than 500 mg per day[10,12].

It is known that the adaptation of the fixed-dose dosage form of HU for use in pediatrics is complex, as there is a risk of incorrect dilution and administration and the use of higher daily doses than recommended, among others, which may compromise the safe use of the drug[5,12,13,14].

The National Commission for the Incorporation of Technologies in the Unified Health System (Sistema Unica de Saude - SUS) (CONITEC) released a report in 2013, where the annual impact of the acquisition of HU, 500 mg capsule, was estimated at R$ 1,530,000.00[14]. At that time, the drug was authorized for children over 2 years of age, currently with the increase in the age range of use to 9 months and older, associated with the increase in patient survival, it is understood that the cost of acquiring the drug is even greater[14]. In the same document, in 2013, CONITEC gave a favorable opinion for the acquisition of 100 mg capsules more appropriate for the recommended dosage for children; however, to date, this form is not available in the Brazilian market[14].

When considering the high governmental investment associated with the purchase, distribution, and dispensing of HU, the frequent need to indicate the manipulation of this drug in the home environment for administration to children, the risks and losses inherent in this process, the present study aims to evaluate the strategies of prescribed solid drug preparation for use in pediatric patients with SCD.

METHODS

This is a descriptive study, in which, from January to March 2018, the HU prescriptions of pediatric patients, aged 0 to 5 years, with SCD under follow-up at the Blood Center of Belo Horizonte were analyzed. The project was approved by the Ethics and Research Committee of Fundação Hemominas, under CAAE 79284017.0.0000.5118, and the study was carried out in accordance with the Declaration of Helsinki.

Study location

The outpatient clinic of the Blood Center in Belo Horizonte is a reference center in the diagnosis and treatment of coagulopathies and hemoglobinopathies, including SCD. In this institution, patients have access to follow-up with a multidisciplinary team.

Patients are received in the outpatient's waiting room, undergo a medical consultation, and then proceed to the pharmacy. Medical

prescriptions are issued by a computerized system integrated with the electronic medical record, and have a header with the patient's name, mother's name, medical record number, date of prescription and patient's age.

Inclusion criteria

Children with SCD, followed up at the Blood Center of Belo Horizonte, aged between 0 and 5 years, using HU, and with prescriptions that recommended adaptation of the solid dosage form of this drug were included in the study.

In order to choose the age group from 0 to 5 years old, the minimum age for starting the use of HU (9 months of age) and the maximum age that would possibly need to use the fractionated dose were considered[10]. This calculation was performed considering the estimated weight of children according to age, from the World Health Organization (WHO)[15], associated with the recommended dose in milligrams of the drug per weight per day[10]. Thus, it was identified that in the age range between 0 and 5 years old would be the population in which the largest number of children with a dose lower than 500 mg/day would be identified.

Exclusion criteria

Patients who did not attend scheduled medical appointments were excluded from the study.

Data collection and analysis

Those responsible for the patients were approached on the day of the medical consultation, when visiting the pharmacy or the waiting room of the blood center. Here the invitation to participate in the research was carried out, with a presentation of the purpose of the study and the Informed Consent Form (ICF). If they agreed, in order to better understand the guidelines recorded in the prescriptions, the person responsible for the child was interviewed, through a questionnaire tested in a pilot phase, addressing questions about previous use of the drug, as well as evaluation of the disposal of the drug.

After the application of the questionnaire, access to the medical prescription of HU occurred. In the prescriptions, the variables age of the patient, drug dosage, and strategy for adapting the solid drug's preparation were collected.

Data collection was performed by the researcher in charge, who works at the institution as a pharmacist, and by an undergraduate intern of the pharmacy course, previously trained by the researcher. The times and days of data collection were based on the medical agenda and the presence of the researcher and/or the intern at the outpatient clinic during patient care hours.

The collected data were recorded in a Microsoft Excel® 2010 spreadsheet (Microsoft®, NY, USA), followed by descriptive analysis in Minitab® (Minitab Inc. Pennsylvania, USA). Absolute and relative frequency distribution was performed for categorical variables and measures of central tendency (mean) for quantitative variables.

RESULTS

Data collection

In the period from January to March 2018, there were 56 patients who were candidates to participate in the study, of which 9 were not approached by the researchers because they missed the medical appointment or

because of difficulties in data collection, such as the availability of a professional to collect data full-time.

Sample characteristics

Prescriptions of 47 patients were analyzed, and 4 patients were excluded because they had a dosage greater than 500 mg per day, without the need to adapt the solid preparation. No responsible person approached refused to participate in the research.

Among the 43 patients, 25 were male, the median age of the participants was 3 years old. No patient in the study was less than one year old.

Analysis of prescriptions

In the analysis of the prescriptions, two main strategies for adapting the solid preparation of the drug for use in children were identified: i) conventional dilution: dilution of the drug in a predetermined amount of water, followed by administration of part of the solution obtained, and ii) use of the holiday or intermittent dose recommendation. Holiday or intermittent dosing consists of distributing the daily dose over a week of treatment, that is, in children who would need 350 mg/day, they would use 2,450 mg per week, with a 500 mg capsule being prescribed five days a week.

The prescriptions corresponded to six prescribers from the Blood Center of Belo Horizonte, with the frequency of dosage recommendation, according to the doctor, specified in table 1.

Different recommendations for preparation, dilution and administration techniques were also identified in the medical prescriptions, as shown in table 2.

The specifications of the two groups of patients, regarding sex, age, daily dose, disposal, and need for dilution, can be seen in table 3.

Table 1 – Specification of the number of prescriptions with holiday dosage recommendation, and conventional fractionation, according to the prescriber. Belo Horizonte, MG, 2018.

Prescriber	Holiday Prescription N (%)	Prescriptions guiding dilution and disposal (fractional dosage) N (%)	Total prescriptions
M1	3 (75%)	1 (25%)	4 (100%)
M2	6 (50%)	6 (50%)	12 (100%)
M3	0 (0%)	10 (100%)	10 (100%)
M4	0 (0%)	3 (100%)	3 (100%)
M5	0 (0%)	1 (100%)	1 (100%)
M6	12 (92%)	1 (8%)	13 (100%)
TOTAL	21	22	47

Table 2 – Specifications of the dosage recommendations of the prescriptions by daily dose and by strategy of adaptation of the solid drug's preparation. Belo Horizonte, MG, 2018.

Daily dose (actual or calculated, in mg)	Specification of the prescribing strategy	N (%)
125	Dilute the contents of one capsule in 10 mL of filtered water. Offer 2.5 mL at night, daily and discard the rest.	1 (2.3)
150	Dilute one capsule in 10 mL of water and give 3 mL once a day. Dilute 1 capsule in 10 ml of water and mix well. Give 3 mL once a day. Discard the rest.	2 (4.7) 1 (2.3)
200	Dilute one capsule in 10 mL of filtered water and give 4 mL daily. Discard the rest.	1 (2.3)
214	Take 01 capsule on Monday, Wednesday, and Friday.	1 (2.3)
250	Dilute one tablet in 10 ml of water and give 5 ml daily. Take 1 capsule a day on alternate days. One pill on even days.	5 (11.6) 1 (2.3) 1 (2.3)
286	One tablet Monday, Wednesday, Friday, and Sunday. Take 01 capsule a day from Monday to Thursday. Take 01 capsule a day on Monday, Wednesday, Friday, and Saturday.	1 (2.3) 1 (2.3) 1 (2.3)
300	Dilute 1cp in 10 mL of water and give 6 mL once a day. Discard the rest. Dilute 1cp in 10 mL of water and give 6 mL daily. Dilute one capsule in 5 ml of water and give 3 ml daily.	1 (2.3) 2 (4.7) 1 (2.3)
350	Dilute 1cp in 10 mL of water and give 7 mL once a day.	1 (2.3)
357	Dilute one tablet in 10 ml of water and take the Monday, Tuesday, Wednesday, Thursday, and Friday. Do not take on Saturday and Sunday. Take one pill on Monday, Wednesday, Friday, Saturday and Sunday. Do not take Tuesdays and Thursdays. Dilute one capsule from Monday to Friday, do not give Saturday and Sunday. Give a pill on the Wednesday, Thursday, Friday, Saturday, and Sunday. Do not give on Monday and Tuesday. Take one capsule 5 times a week. Do not give Saturday and Sunday. Take one capsule a day from Monday to Friday.	1 (2.3) 1 (2.3) 4 (9.3) 1 (2.3) 1 (2.3) 3 (7.0)
400	Dilute 1 capsule in 10 mL of water and mix well. Give 8 mL once a day and discard the rest. Dilute 1cp in 10 mL of water and give 8 mL 1x a day.	2 (4.7) 2 (4.7)
429	Take one capsule a day from Monday to Saturday. Take 01 capsule a day from Monday to Saturday. Do not take on Sunday.	2 (4.7) 2 (4.7)
450	Dilute one capsule in 10mL of filtered water and give 9mL at night, daily. Discard the rest. Dilute the tablet in 10mL of water and give 9mL daily. Dilute 01 capsule in 5mL of water. Give 4.5 mL once a day every day.	1 (2.3) 1 (2.3) 1 (2.3)

Table 3 – Comparison between groups of patients who discard medication and those who use intermittent dosing. Belo Horizonte, MG, 2018.

Patient characteristics	Conventional dilution with drug disposal (N=22)	Intermittent Dosage (N=21)
Male	13 (59.1%)	12 (57.1%)
Female	9 (40.9%)	9 (42.9%)
Average Age (years)	2.8±1.3	3.9±1.1
Daily dose variation (actual and calculated) (mg)	125 – 450 (actual)	214 – 429 (calculated)
Average daily dose (mg)	290	344
Dilution of capsule contents in 10 mL of water	20	Not applicable
Dilution of capsule contents in 5 mL of water	2	Not applicable
Number of capsules discarded/month	238.5 caps. of 500 mg	There is no disposal
Financial loss due to disposal/year*	R$ 3,503.95	There is no disposal
Number of patients who need to dilute the drug before administering	22 (100.0%)	11(52.4%)
Number of patients who, even on holiday dosage, are not able to swallow the solid dosage form	Not applicable	13 (61.0%)
Other strategies used by caregivers to administer the drug	Not applicable	Mix capsule contents into food. Deposit the contents of the capsule on the child's tongue, without dilution.

*Calculation based on the maximum government sale price, CMED Medicines Price List, version of 02/25/2018, available at http://portal.anvisa.gov.br/listas-de-precos[16].
By questioning those responsible for the patients, it was observed that 100.0% of those responsible discarded the medication in the domestic sewage network (sink or toilet). In addition, one (2.3% of the total) patient was identified who used the medication in a greater amount than prescribed. According to the reports, most patients (34; 79.1%) had started using the drug a month or more before, as seen in table 4.

Table 4 – Report of the guardians about the beginning of medication use. Belo Horizonte, MG, 2018.

	Reports of those responsible				
Report of initiation of drug use	Would still start	Started less than a month ago	Started more than a month ago (less than a year)	Started over a year ago	Does not remember or was unable to inform
Total N 43 (100.0%)	3 (6.9%)	4 (9.3%)	16 (37.2%)	18 (41.9%)	02 (4.7%)

DISCUSSION

Although the Ministry of Health Protocol allows the use of the drug from 9 months of age, the non-identification, in the present study, of patients younger than 1 year may be due to the greater rigidity of the protocol in the inclusion criteria for initiation of the HU for children under 2 years of age[10].

No studies were found that compared safety or effectiveness between the two forms of prescription: conventional dilution (with fixed doses lower than 500mg/day) and intermittent dosing.

A similar study, published in 2018, evaluated the effectiveness of intermittent

dosing of HU in children with SCD in Angola, and concluded that both intermittent dosing and fixed (undiluted) doses of 500 mg of HU are effective in the treatment[17]. Thus, it is understood that criteria such as offering risks to patients, environmental risks and/or losses should be considered when choosing the prescribed dosage.

Table 1 shows the prevalence of the type of strategy prescribed according to the medical doctor (M3: 100% of prescriptions as conventional dilution, M6: 92% of prescriptions based on holiday dosage). The only prescriptions from physicians M1 and M6 that indicated conventional dilution were from patients originally not followed up by these physicians. The low number of prescriptions by certain physicians (M4 and M5) may be due to the characteristics of the patients seen by these physicians, such as age group above 5 years old and a greater prevalence of coagulopathies.

Table 2 also shows a lack of standardization among the analyzed prescriptions. For the same daily dose of HU (357 mg), up to six ways of prescribing the intermittent dosing strategy were observed. Furthermore, for the same daily dose of HU (250 mg), both adaptation strategies were observed (conventional dilution and intermittent dosing). The choice between one of the prescribing strategies seems to be individual and based on the judgment of the prescribing physician. The Ministry of Health, in a document published in 2014, advises that the dilution of the capsule content be administered to children. No official documents or studies were found that suggest the use of intermittent dosing for prescribing HU in SCD.

The lack of appropriate dosage forms for use in children is a problem that affects several classes of drugs, with solid oral dosage forms representing the majority of drugs with inadequate dosage for the pediatric population[18]. Clinical studies in the field of pediatrics come up against ethical and legal issues, which contributes to the fact that the prescriptions of some drugs for children are based on extrapolations of the results of studies carried out in adults[19].

HU is on the Food and Drug Administration (FDA) and European Medicines Agency (EMA) list of non-marketable drugs or "orphan drugs". This definition of the Orphan Drug Act created in the USA, made these regulatory agencies encourage research leading to the registration of drugs with no commercial interest. As a result, unlike in Brazil, HU is already registered in 100 mg, 200 mg, 300 mg, and 400 mg formulations on the international market[20,21], and in 2017, HU was approved for use in children by the FDA[21,22]. The FDA-approved drug is available in 100 mg and 1 g tablet forms, with 1 g tablets having grooves that allow for divisions into 4 parts of 250 mg. In addition, the tablet allows for dispersion in water immediately before administration[22]. These forms would facilitate the composition of daily doses of HU for children and adults according to the weight of each patient.

In Brazil, despite a favorable opinion from CONITEC in 2013, for the incorporation of the 100 mg form of HU in SUS[15], until the present day, the Brazilian market has only 500 mg capsules of this drug, and its use in children remains off-label.

As an alternative to the lack of an appropriate pharmaceutical form, the Ministry of Health recommends that, for administration to children, the content of the HU capsule be diluted in 10 mL of water, which would facilitate the calculation of the dose and administration[10]. There is no definite consensus on the stability of the suspension obtained after dilution of the

drug in water, especially when handling it in a domestic environment[5,8,10]. This fact influences pediatricians, when they choose the conventional dilution, to recommend the daily disposal of the rest of the prepared suspension.

Disposal of medication after dilution was reported by 22 caregivers, totaling a disposal of 238.5 capsules/month and a financial loss of R$ 3,503.95 reais per year (Table 3). In a report issued in 2013 by CONITEC, the State of Minas Gerais had an estimated 795 patients aged 2 to 5 years old with sickle cell disease and an annual impact of purchasing HU, for MG, of R$ 243,312.50[14]. This corresponds to an annual cost of approximately R$ 306.05 reais per patient. Considering the drug disposal observed with the 22 patients (R$ 3,503.95), this loss would be enough to finance the annual treatment of 11.4 patients in the State of Minas Gerais[14].

Despite the dilution guideline presented by the Ministry of Health[11], in 48.8% of the prescriptions analyzed, the holiday or intermittent dosage was chosen (Table 3). The intermittent dosing strategy has an economic and environmental advantage, since there is no drug disposal.

The use of intermittent dosing makes dose adjustment difficult, since the escalation will always depend on the fixed dose of the drug, impairing the individualization of the treatment. Another important observation is that at lower doses (125 and 150 mg) (Table 2) the physicians always opted for a dosage with conventional dilution. It is understood that in the case of very small doses, such as 125 mg, the patient on intermittent dosing would have to use less than two capsules per week, which would lead to the administration of very high doses in a single dose, and, perhaps, a greater chance of developing toxicity.

Even with intermittent dosing, 13 caregivers (61.9%) reported that the children were unable to swallow the capsule (Table 3), which makes pediatricians and caregivers who opt for this prescription strategy adopt dilution or additional strategies, such as mixing the contents of the capsule with food or dispensing the contents into the mouth of children, without prior dilution. It is noteworthy that these strategies were not recommended in the prescriptions, which suggests that those responsible use strategies unknown to the medical teams. No studies were found that addressed the consequences of using HU mixed with food or directly in the patient's mouth.

All those responsible for the patients in the study who used the conventional dilution dosage discarded the remaining unadministered solution into the domestic sewage system (sink or toilet). Mainly because it is a drug classified as cytostatic, HU would need to receive treatment that minimizes the environmental risks of this disposal[13]. In addition to the environmental risk, when diluting the drug in a domestic environment, the person responsible for handling it is also exposed to the drug with its cytotoxic potential[12].

In both prescription strategies, there are risks of incorrect administration, depending on the understanding of those responsible for administration. In the conventional dilution strategy, those responsible need to learn how to handle a syringe, to dilute the drug in a predetermined volume of water, and to measure the prescribed dose. On the other hand, the use of intermittent dosing can lead to difficulty in adherence, due to forgetting administration[5,23]. It is noteworthy that individual factors such as the level of health literacy of those responsible for administering medication can influence adherence and difficulties in conducting treatment[26], causing

a greater risk of complications[24,25,27].

Health literacy is defined as "cognitive and social skills that influence the ability of individuals to access, understand, and use health information"[28]. Considering that the success in the administration of HU depends on the interpretation of medical prescriptions, the two strategies for adapting the solid preparation can generate difficulties in understanding and problems with adherence to treatment.

The most serious cases of sickle cell disease are usually patients who have an indication for the use of HU, and they are also the patients with the greatest difficulty in accessing and with the lowest level of health literacy. 36% of the population considered black or brown were considered functionally illiterate in Brazil in 2011[29] and these are the population subgroups in which sickle cell disease is more prevalent[30].

Despite the risks of incorrect administration of HU in children, only one child was identified in the study who was using a higher dose than recommended. This can be explained by some strategies adopted by the study site, such as multidisciplinary follow-up and shorter intervals between consultations and examinations in patients using HU. In addition, the fact that most patients in the study (41.9%) had already started using the medication for more than a year may contribute to this finding.

The limitations presented by this study are: convenience sample and an unavailabile full-time researcher. However, it is believed that the data collected can contribute to demonstrate the need for the development and registration of pharmaceutical forms of HU more appropriate for the pediatric public, ensuring greater safety in the treatment of children with sickle cell disease using this drug.

CONCLUSION

The study identified a lack of standardization of HU prescribing strategies, risk of incorrect drug administration and environmental risk due to improper disposal. The choice of prescribing strategy for adapting the solid preparation of HU for use in children with sickle cell disease appears to be defined by the individual judgment of each prescriber.

The study reinforces the need to register HU capsules with lesser doses in the Brazilian market and the promotion of research that develops more appropriate drug formulations for the pediatric population.

Author statement CRediT

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All authors read and agreed with the published version of the manuscript.

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