Annals of Case Reports
Yahouédéhou SCMA, et al. Ann Case Rep: 7: 920.
www.doi.org/10.29011/2574-7754.100920
www.gavinpublishers.com

OPEN ACCESS

GAVIN PUBLISHERS

Research article

CAT -21A>T Variant Alters Hydroxyurea Pharmacokinetic Parameters in Brazilian Children with Sickle Cell Anemia

Sètondji Cocou Modeste Alexandre Yahouédéhou[1,2], Joelma Santana dos Santos Neres[1], Natalia Valadares de Moraes[3], Francine Johansson Azeredo[3], Luciana Magalhães Fiuza[1], Caroline Conceição da Guarda[1], Suéllen Pinheiro Carvalho Valverde[1,2], Rayra Pereira Santiago[1], Isa Menezes Lyra[4-6], Elisângela Vitória Adorno[2], Ananda Freitas Fonseca[7], Ana Leonor Godoy[7], Marilda Souza Goncalves[1,2*]

[1]Laboratório de Investigação em Genética e Hematologia Translacional, Instituto Gonçalo Moniz / Fiocruz-BA, Brazil

[2]Laboratório de Pesquisas em Anemia, Faculdade de Farmácia, Universidade Federal da Bahia, Brazil

[3]Center for Pharmacometrics and Systems Pharmacology, Department of Pharmaceutics, College of Pharmacy, University of Florida, Florida, USA

[4]Complexo Hospitalar Universitário Professor Edgard Santos, Universidade Federal da Bahia, Brazil

[5]Ambulatório, Fundação de Hematologia e Hemoterapia da Bahia, Brazil

[6]Curso de Medicina, Escola de Ciências da Saúde e Bem-Estar, Universidade Salvador, Brazil

[7]Laboratório de Toxicologia, Faculdade de Farmácia, Universidade Federal da Bahia, Brazil

***Corresponding author**: Marilda Souza Goncalves, Laboratório de Investigação em Genética e Hematologia Translacional, Instituto Gonçalo Moniz / Fiocruz-BA, Brazil

Citation: Yahouédéhou SCMA, Neres JSS, Moraes NV, Azeredo FJ, Fiuza LM, et al (2022) *CAT* -21A>T Variant Alters Hydroxyurea Pharmacokinetic Parameters in Brazilian Children with Sickle Cell Anemia. Ann Case Report 7: 920. DOI: 10.29011/2574-7754.100920

Received: 16 August 2022, **Accepted:** 20 August 2022, **Published:** 23 August 2022

Abstract

This study investigated the effects of the *CAT* -21A>T (rs7943316) variant on pharmacokinetic (PK) parameters in sickle cell anemia (SCA) children undergoing HU therapy. Plasma HU concentration of 12 SCA children was quantified using an HPLC/MS. Hematological and biochemical parameters were assessed by electronic methods, and polymorphisms were investigated by PCR-RFLP. The mean HU oral clearance was 40 ± 16 L/h, while HU Cmax and AUC0-inf were 9998.25 ± 4023.02 ng/mL and 22605.46 ± 10041.57 ng*h/mL, respectively. The heterozygote (*CAT* -21AT) genotype was found in 07 (58.33%) children, while the variant (*CAT* -21TT) genotype was found in 03 (25%) of them. Association analyses showed that children with the variant genotype had increased HU clearance and decreased HU Cmax, using codominant and recessive genetic models. Moreover, the multivariate linear regression analysis confirmed the associations between the variant *CAT* -21T allele in homozygous and HU clearance increase and Cmax decrease. In summary, data showed a lower HU plasma exposure in Brazilian SCA children. Interestingly, we observed the association of *CAT* -21A>T variant with alterations in crucial HU PK parameters, suggesting that it may be a potential genetic marker related to HU PK.

Keywords: Sickle cell anemia; Hydroxyurea; *CAT*; Variant; Pharmacokinetic parameters

Introduction

Sickle cell anemia (SCA) is a severe hematological disease caused by the recessive autosomal inheritance of the beta (β) S globin gene that affects approximately 300,000 to 400,000 newborns worldwide each year [1-3]. SCA individuals present clinical heterogeneity, and those with a severe clinical profile, i.e, recurrent vaso-occlusion crises and acute chest syndrome, the occurrence of osteonecrosis and retinopathy, as well as stroke risk, are commonly indicated to use hydroxyurea (HU). HU (CAS Registry Number, 127-07-1) is an antineoplastic drug approved by the U.S. Food and Drug Administration to treat SCA due to its anti-sickling potential [4,5]. However, inter-individual variations in the therapeutic response to HU are frequently observed, and this may be attributed to several factors, including variations in the metabolic profile of the individuals [6]. Despite its broad indication and usage, the HU metabolism has yet to be completely elucidated. Evidence has shown that the first step of the HU conversion into nitric oxide (NO) is mediated by catalase [7]. Moreover, Juul et al. [8] demonstrated that HU effects depend on its direct target for catalase and suggested that it could act as a catalase-activated pro-drug. Catalase (CAT; EC 1.11.1.6) is an endogenous antioxidant enzyme crucial in neutralizing reactive oxygen species. This enzyme, encoded by the *CAT* gene, located on chromosome 11 (11p13.31), is most expressed in the liver, kidney, and erythrocytes [9,10]. Although controversial, the polymorphism -21A>T (rs7943316) in the promoter region of the *CAT* gene has been linked to changes in *CAT* transcription and enzymatic activity [10-13]. The present study investigated the effects of the *CAT* -21A>T variant on pharmacokinetic (PK) parameters in SCA children undergoing HU therapy.

Material and Methods

Subjects and ethical aspects

We included 12 SCA children (HbSS) undergoing HU therapy, all seen at the University Hospital Professor Edgard Santos (HUPES) outpatient clinic in Salvador, Brazil. All children reported regular use of folic acid and were in disease steady-state, defined as the absence of acute crisis and no blood transfusion in the three months before blood collection. The exclusion criteria were chronic transfusion therapy, active infection, or inflammatory diseases. This research protocol received approval from the Institutional Review Board of HUPES (protocol number: 2.823.416), and individuals or their legal guardians provided a signed term of informed consent before enrollment in the study. The study protocol was performed in accordance with the Helsinki Declaration of 1975 and its later amendments.

Pharmacokinetic and laboratory parameters

Blood samples were collected by venipuncture in the morning, after 12h of fasting, under standardized conditions, before HU administration (T0), and 45, 90, 120, 150, 180, 240, 360, and 480 minutes later, in tubes containing heparin for PK assay. The quantitative measurement of the plasma HU concentration was performed by high-performance liquid chromatography with a mass spectrometry detector (HPLC/MS). The PK profile of each patient was obtained from non-compartmental analysis using PKanalix® 2021R1 software (Lixoft, France). PK parameters such as the area under the concentration-time curve from time zero to last time or infinity (AUC0–t or AUC0-inf), apparent elimination rate constant (Lambda), mean residence time (MRT), apparent total clearance (CL/F), and apparent volume of distribution (V/F), were determined. At T0, blood samples were collected in tubes without anticoagulant or with anticoagulant EDTA for laboratory parameters analysis. Hematological, biochemical, and

inflammatory parameters were assessed using a Beckman Coulter LH 780 Hematology Analyzer (Beckman Coulter, Brea, California, USA), an A25 spectrophotometer autoanalyzer (Biosystems SA, Barcelona, Spain), and an Access 2 Immunoassay System (Beckman Coulter, Fullerton, CA, USA), respectively.

Molecular analysis

CAT -21A>T variant was investigated from genomic DNA using the polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique [10]. Moreover, the genetic modifier, β^S haplotypes, was also investigated by PCR-RFLP [14].

Statistical analysis

Statistical analyses were performed using GraphPad Prism 8.0 and SPSS 17.0, with $p<0.05$ considered statistically significant. The frequencies of the categorical variables were calculated, and to test whether *CAT* -21A>T variant was in Hardy-Weinberg equilibrium, a goodness-of-fit χ^2 was used. Association analyses between PK parameters and *CAT* -21A>T variant were performed using codominant and recessive genetic models. In the codominant genetic model, ANOVA or Kruskal Wallis was used to compare mean values between 03 genotype groups (wild type *vs*. heterozygote *vs*. variant). Regarding the recessive genetic model, we performed an unpaired t-test or Mann-Whitney U test to compare mean values between 02 groups (wild type and heterozygote *vs*. variant). Moreover, multivariate linear regression analyses were performed to confirm the influence of the variant on PK parameters in the presence of confounding variables. Data were expressed as mean ± standard deviation, median (minimum-maximum), or number or frequency where appropriate.

Results

Socio-demographic, laboratory, and pharmacokinetic data

The median age of the children was 13 years (range: 8-17 years), and four (33.33%) of them were female. The HU dosage ranged between 15.94 and 24.90 mg/kg/day (median: 20.26), and the average duration of HU treatment was 52 months. Table 1 presents laboratory parameters. Data shows increases in fetal hemoglobin (HbF), reticulocytes, MCV, MCH, RDW, iron serum, LDH, AST, and total and indirect bilirubin, as well as reductions in red blood cell count, hemoglobin, and hematocrit when compared to reference values. Table 2 presents estimated HU PK parameters, and Figure 1 shows HU plasma concentration *vs*. time data after administering oral doses of HU in SCA children. The mean HU oral clearance was 40 ± 16 L/h, while HU Cmax and AUC0-inf were 9998.25 ± 4023.02 ng/mL and 22605.46 ± 10041.57 ng*h/mL, respectively.

CAT -21A>T and β^S haplotypes frequencies

CAT -21A>T variant was found to be in Hardy-Weinberg Equilibrium ($\chi^2 = 0.34$, df = 1, $p = 0.545$). Two (16.67%) children had the wild type (*CAT* -21AA) genotype, while 07 (58.33%) and 03 (25.00%) had heterozygote (*CAT* -21AT) and variant (*CAT* -21TT) genotypes, respectively (Figures 2A and 2E). β^S haplotypes allelic distribution is presented in Figure 3.

Association between *CAT* -21A>T variant and PK parameters and multivariate linear regression analyses

Association analyses were performed to investigate the influence of the *CAT* -21A>T variant on PK parameters. Using a codominant genetic model, we observed a significant association between variant *CAT* -21TT genotype and an increase in HU clearance, while in the recessive genetic model this genotype was significantly associated with an increase in HU clearance and a reduction in HU Cmax (Figure 2). Table 3 presents data of the multivariate linear regression. The proposed model significantly predicted Cmax, F (2, 9) = 4.542, $p = 0.043$. The adjusted $R^2 = 0.392$ depicts that this model explains 39.2% of the variance in Cmax, where the variant *CAT* -21TT genotype was significantly associated with a reduction in Cmax ($\beta = -0.635$, $p = 0.025$). HU clearance was also significantly predicted by the proposed model, F (2, 9) = 7.337, $p = 0.013$. Moreover, the adjusted $R^2 = 0.535$ shows that the model explains 53.5% of the variance in clearance, where the variant *CAT* -21TT genotype presented a significant association with an increase in clearance ($\beta = 0.768$, $p = 0.005$).

	SCA children (M±SD)	**Reference**
Hemoglobin		
HbF, %	10.51±6.72	<2.0
HbS, %	80.50±9.22	---
Erythrogram		
RBC, $x10^9$/mL	2.40±0.29	4.1 – 5.1
Hemoglobin, g/dL	8.36±0.89	12.0 – 16.0
Hematocrit, %	25.55±2.38	36.0 – 46.0
MCV, fL	107.00±7.95	80.0 – 99.0
MCH, pg	35.01±2.83	27.0 – 32.0
MCHC, %	32.68±0.80	31.5 – 35.5
RDW, %	17.95±2.20	11.0 – 15.0
Leukogram		
WBC, /mL	10058.33±3560.25	3700 – 10000
Neutrophil, /mL	4714.25±1556.44	1800 – 10000
Eosinophil, /mL	331.17±218.87	1 – 600
Lymphocyte, /mL	4271.58±1999.37	1000 – 5000
Monocyte, /mL	728.42±401.87	80 – 1200
Basophil, /mL	12.92±44.74	0 – 200
Platelets		
Platelet, $x10^3$/mL	358.08±201.42	150 – 450
Plateletcrit, %	0.25±0.14	
MPV, fL	8.23±0.99	6.5 – 12.0
PDW, %	14.40±5.85	
Hemolysis		
Total bilirubin, mg/dL	2.68±1.26	<1.2
Direct bilirubin, mg/dL	0.33±0.18	<0.4
Indirect bilirubin, mg/dL	5.06±9.81	0.9
Lactate dehydrogenase, U/L	1169.92±678.06	<480
Reticulocyte, %	4.33±1.59	0.5 – 1.5
Iron serum, mcg/dL	109.83±45.54	<50
Lipids and glucose		
Total cholesterol, mg/dL	114.33±18.66	<170
HDL-C, mg/dL	33.75±4.86	>40 or >35
LDL-C, mg/dL	64.93±17.92	<110.0
VLDL, mg/dL	15.65±9.89	<40

Triglycerides, mg/dL	78.25±49.46	<100
Glucose, mg/dL	85.00±5.89	65 – 99
Renal panel		
Urea, mg/dL	17.00±3.69	15 – 45
Creatinine, mg/dL	0.41±0.11	0.40 – 1.30
Hepatic panel		
Aspartate aminotransferase, U/L	52.08±20.82	<42
Alanine aminotransferase, U/L	25.17±12.45	<45 or <37
γ-glutamyl aminotransferase, U/L	23.50±14.16	<58 or <39
Total protein, g/dL	7.65±0.45	6.0 – 8.0
Albumin, g/dL	4.37±0.25	3.5 – 5.5
Globulin, g/dL	3.28±0.45	2.3 – 3.5
RELAG	1.34±0.25	1.0 – 2.5
Alkaline phosphatase, U/L	470.00±176.66	<645
Inflammatory markers		
Uric acid, mg/dL	4.29±0.79	1.9 – 6.0 or 0.9 – 5.0

RBC: red blood cell, HbS: variant S hemoglobin, HbF: Fetal hemoglobin, MCH: mean corpuscular hemoglobin, MCV: mean corpuscular volume, MCHC: mean corpuscular hemoglobin concentration, RDW: Red Cell Distribution Width, WBC: white blood cell, MPV: mean platelet volume, PDW: Platelet Distribution Width, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein cholesterol, VLDL-C: very low-density lipoprotein cholesterol, M ± SD: mean ± standard deviation

Table 1: Laboratory parameters of SCA children undergoing HU therapy.

ID	AUC0-t (ng*h/mL)	AUC0-inf (ng*h/mL)	AUC % ext.	CL/F (L/h)	V/F (L)	Lambda_z (h-1)	MRT (h)	Cmax (ng/mL)
1	6681.94	7078	5.6	71	220	0.32	2.09	4979.83
2	21120.5	21296.8	0.83	47	66	0.71	2.05	10060.24
3	7024.98	7206.4	2.52	69	100	0.69	2.17	3523.32
4	24057.5	24223.2	0.68	41	55	0.75	2.5	11262.12
5	41088.1	41230.3	0.34	24	28	0.88	2.21	17647.9
6	29399.3	30320	3.04	33	100	0.32	2.14	15461.9
7	22895	23311.3	1.79	21	30	0.72	2	10861.6
8	20059.4	20273.9	1.06	25	42	0.58	2.21	8942.48
9	27425.4	30833.7	11.05	32	93	0.35	3.24	8460.48
10	11984.7	12177.4	1.58	41	63	0.65	1.87	6723.65
11	27134	28236.1	3.9	35	87	0.41	2.45	12421.5
12	24533.6	25078.4	2.17	40	76	0.52	2.49	9634

Median	23476.25	23767.25	1.98	38	71	0.62	2.21	9847.12
Q1	16022.05	16225.6	0.94	29	49	0.38	2.06	8026.27
Q3	29267.75	41230.3	3.47	44	97	0.71	2.32	11552
Mean	21950.37	22605.46	2.88	40	81	0.57	2.26	9998.25
SD	9770.37	10041.57	2.98	16	52	0.19	0.34	4023.02

ID: Identification, AUC: area under the concentration-time curve, CL/F: clearance, V/F: volume of distribution, Lambda_z: apparent elimination rate constant, MRT: mean residence time, Q1: 25th percentile, Q3: 75th percentile, SD: standard deviation

Table 2: Estimated HU pharmacokinetic parameters in SCA children.

Dependent variable	Independent variable	Adjusted R^2	β	t-value	F-test	*p*1	*p*2
Cmax	*CAT**	0.392	-0.635	-2.684	4.542	0.043	0.025
	Body weight		0,391	1.654			0.132
CL/F	*CAT**	0.535	0.768	3.73	7.337	0.013	0.005
	Age		0.225	1.092			0.303

Cmax: maximum plasma concentration; CL/F: apparent total clearance; *CAT**: *CAT* was defined using recessive genetic model, where 0 represent wild type or heterozygote genotype and 1 the variant genotype, R^2: coefficient of determination, β: coefficient of regression; *p*1, p value of the model, *p*2: p value of the independent variable. The final predictive equations of the dependent variables were Cmax = 5243.899 - 0.635(*CAT*) + 0.391(body weight) and CL/F = 15.864 + 0.768(*CAT*) + 0.225(age).

Table 3: Multivariate linear regression models of *CAT* -21A>T variant in SCA children undergoing HU therapy.

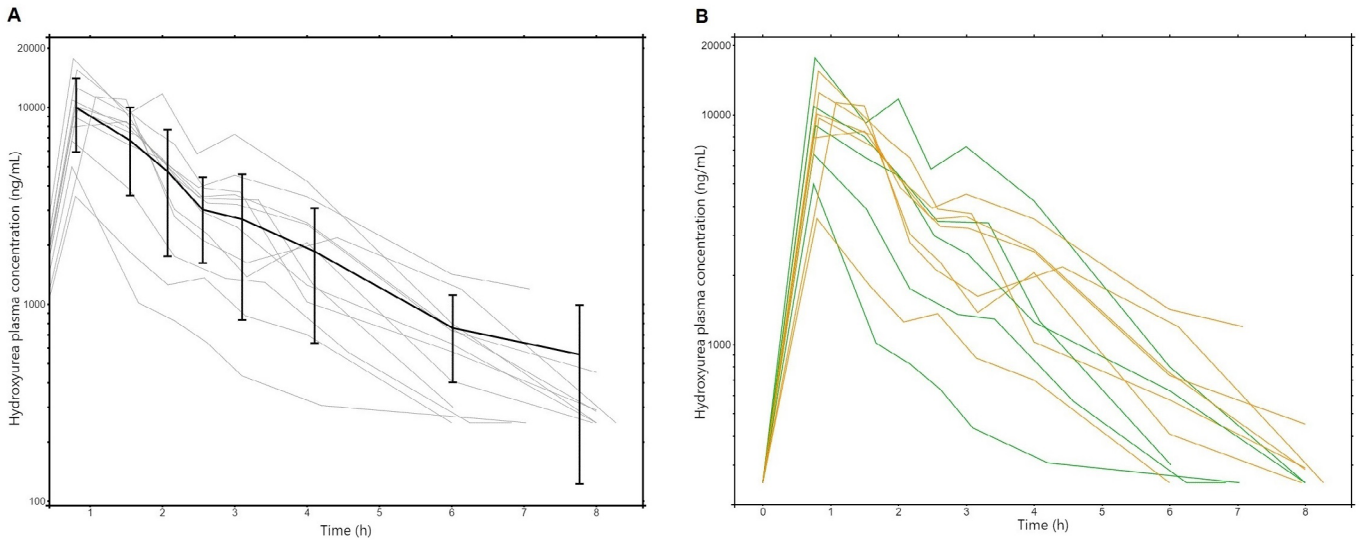

Figure 1: Spaghetti plots of the HU plasma concentration vs. time. (A) Individual profiles (gray lines) and mean plasma concentration profile (black line). (B) Individual profiles according to patient age (green lines: 8-13 years; orange lines: 14-17 years).

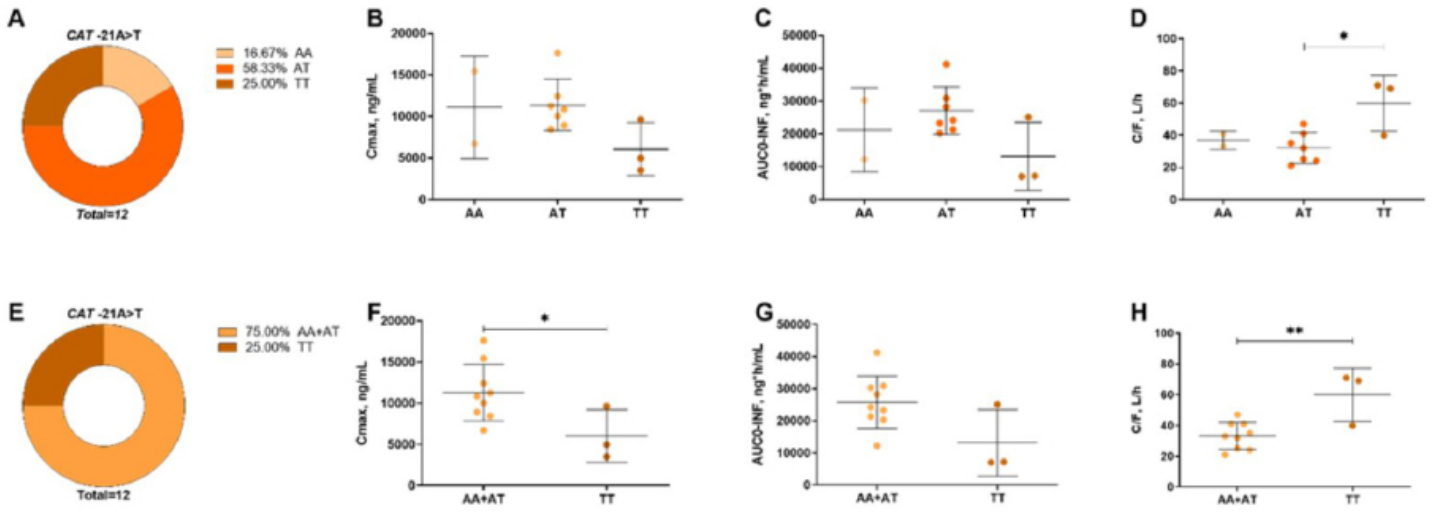

Figure 2: Frequency of *CAT* -21A>T in SCA children undergoing HU therapy (A and E) and its association with PK parameters using the codominant (B-D) and recessive genetic model (F-H). The codominant genetic model compared three genotype groups (wild type *vs*. heterozygote *vs*. variant), while the recessive genetic model compared two genotype groups (wild type/heterozygote *vs*. variant). AUC: area under the curve, C/F: clearance, Cmax: maximum concentration, *p<0.05 and **p<0.01.

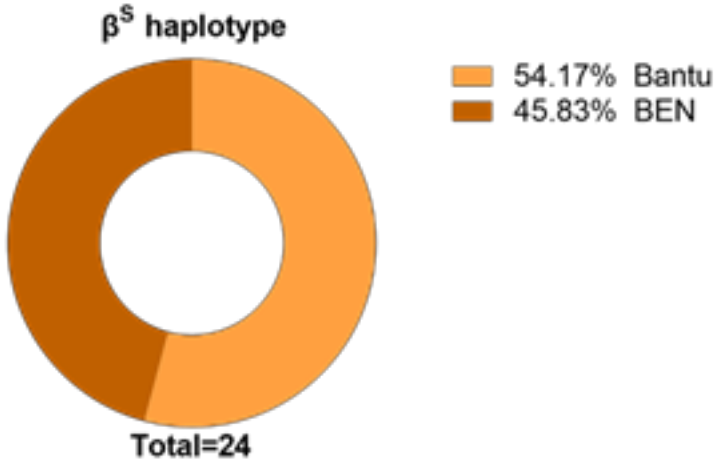

Figure 3: Allelic frequency of β^S haplotypes in SCA children undergoing HU therapy. BEN: Benin haplotype, β: beta

Discussion

To elucidate variability in HU response, we performed the present study, which investigated the effects of the *CAT* -21A>T variant on PK parameters in SCA children undergoing HU therapy. Commonly, SCA children have lower HbF levels, with some exceptions depending on their genetic background. As expected, HU use was associated with higher HbF levels. Moreover, analyses showed that higher number of children had the Bantu haplotype (54.17%), which is generally associated with HbF<5%. Therefore, these data corroborate previous studies, which demonstrated the potential of HU to increase HbF and reduce variant S hemoglobin (HbS) polymerization, hemolysis, and vaso-occlusion processes [3,15]. The reduced red blood cell count, hemoglobin, and hematocrit, as well as increased reticulocytes, compared to reference values, suggest hemolysis occurrence, despite HU therapy. This hypothesis is

reinforced by the elevated concentrations of hemolytic biomarkers (iron serum, LDH, AST, and total and indirect bilirubin) and corroborates the findings of previous studies [16,17]. Moreover, children had MCV, MCH, and RDW higher than reference values, which probably resulted from HU use, as shown in other studies [18,19]. PK parameters are critical for understanding drugs' efficacy and safety. In the present study, we observed in the SCA children a mean HU oral clearance (40 L/h) higher than in some reports, ranging from 4.5 to 27.1 L/h [20-25]. In contrast to data from previous studies [25,26], we also observed a lower HU plasma exposure, characterized by lower AUC and Cmax, in the investigated children. These discrepancies between Brazilian children and other study populations may be due to various factors, including sociodemographic and genetic characteristics, and deserve to be better elucidated. Reports demonstrated the crucial role of polymorphisms in genes encoding drug-metabolizing enzymes and drug transporters in therapeutic response [27,28]. In the present study, we focus on catalase, an endogenous antioxidant enzyme associated with HU conversion. The genotypic and allelic frequencies of the *CAT* -21A>T variant observed in the present study are consistent with our previous findings [28]. This data also corroborates frequencies previously published [10]. Analyses showed that the *CAT* -21A>T variant is associated with HU PK parameters. Despite the limited sample size, the *CAT* variant (*CAT* -21TT) genotype was significantly associated with increased HU clearance and decreased Cmax, using a codominant and recessive genetic model. Furthermore, multivariate linear regression analysis confirmed associations between the variant genotype and the observed alterations in PK HU, considering patient age or body weight as confounding variables. Indeed, previous studies used these variables to test population PK models of HU [22,29]. Dong et al. demonstrated that body weight might be a significant predictor for both maximum elimination rate and apparent volume of distribution [22]. These results suggest that the variant *CAT* -21T allele in homozygous trends to increase HU clearance decreasing Cmax. Reports regarding the effect of variant -21A>T in *CAT* expression are controversial [10-13]. Of these studies, only Saify et al. [13] investigated the association between this variant and *CAT* expression. Taking into account its association with an increase in *CAT* mRNA and the fact that HU can act as a catalase-activated pro-drug [8], our findings suggest that carriers of the variant -21TT genotype produce higher pro-drug levels. This hypothesis correlates with lower HU Cmax and higher clearance observed in individuals with the variant genotype when compared to those with the *CAT* -21AA or AT genotype. Moreover, the reduced levels of the pro-inflammatory biomarker alpha-1 antitrypsin previously reported in *CAT* -21 TT carriers [28] suggest that higher exposure to the active metabolite may influence HU response. The main limitation of the present study is the low number of individuals included. However, this does not detract from the results since the *CAT* -21A>T variant was in Hardy-Weinberg Equilibrium. Contrarily, the findings arouse interest in continuing the investigations in this line.

Conclusion

Our findings demonstrated the lower HU plasma exposure in Brazilian SCA children and the association of *CAT* -21A>T with alterations in HU PK parameters, which has never been reported. However, further studies are necessary to validate the lower HU plasma exposure from a large sample and establish a cause-effect relationship between this variant and the functional effects and metabolic profiles of SCA individuals undergoing HU therapy. Whether confirmed, variant *CAT* -21A>T might be used to propose new pharmacogenetics-guided dosing strategies for HU therapy.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Author Contributions

MSG, ALG, and SCMAY conceived and designed the research. SCMAY, JSSN, LMF, CCG, SPC, RPS, and AFF performed research. NVM, FJA, SCMAY, and JSSN analyzed data. ILM followed-up and indicated patients. MSG provided financial resource. SCMAY wrote the first draft of the manuscript. MSG, ALG, and EVA revised the draft. MSG supervised the study. All authors revised the final version of the manuscript and consented to submission.

Funding

This work was supported by grants from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) (470959/2014- 2 and 405595/2016-6; MSG) and (152408/2020-7; SCMAY); Programa Inova Fiocruz - Edital Geração de Conhecimento (VPPCB-007-FIO-18-2-66; MSG); and the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior Brasil (CAPES) (Finance Code 001; SCMAY, SPCV, RPS, and LMF). The sponsors of this study are public or nonprofit organizations that support science in general.

Acknowledgments

The authors would like to thank all of the children and their legal guardians for their kind participation in the present study. We also thank all personnel at the outpatient service of the Hospital Universitário Professor Edgard Santos (HUPES), Núcleo de Ensaios Clínicos da Bahia (NECBA); Departamento de Toxicologia e Análises Clínicas, Faculdade de Farmácia (LACTFAR-UFBA); and Serviço de Equivalência Farmacêutica

e Farmacocinética (Sefar), Fiocruz. Our special thanks to Prof. Nicolaus Albert Borges Schriefer, Maria São Pedro Bispo dos Santos Trindade, Prof. Carolina Oliveira de Souza, and Prof. Davyson de Lima Moreira.

References

1. Goncalves SM (2014) Comment on "Molecular analysis and association with clinical and laboratory manifestations in children with sickle cell anemia." Revista Brasileira de Hematologia e Hemoterapia 36: 315-318.
2. Piel FB, Steinberg MH, and Rees DC (2017) Sickle Cell Disease. N Engl J Med 376: 1561-1573.
3. Kato GJ, Piel FB, Reid CD, Gaston MH, Ohene-Frempong K, et al (2018) Sickle cell disease. Nat Rev Dis Primers 4: 18010.
4. King S. (2003). The Nitric Oxide Producing Reactions of Hydroxyurea. CMC 10: 437-452.
5. Okam MM, Shaykevich S, Ebert BL, Zaslavsky AM, and Ayanian JZ (2014) National Trends in Hospitalizations for Sickle Cell Disease in the United States Following the FDA Approval of Hydroxyurea, 1998–2008. Medical Care 52: 612-618.
6. Yahouédéhou SCMA, Adorno EV, da Guarda CC, Ndidi US, Carvalho SP, et al (2018) Hydroxyurea in the management of sickle cell disease: pharmacogenomics and enzymatic metabolism. Pharmacogenomics J 18: 730-739.
7. Huang J, Kim-Shapiro DB, and King SB (2004) Catalase-Mediated Nitric Oxide Formation from Hydroxyurea. J. Med. Chem. 47: 3495-3501.
8. Juul T, Malolepszy A, Dybkær K, Kidmose R, Rasmussen JT, et al (2010) The in Vivo Toxicity of Hydroxyurea Depends on Its Direct Target Catalase. J. Biol. Chem. 285: 21411–21415.
9. Forsberg L, Lyrenäs L, de Faire U, and Morgenstern R (2001) A common functional C-T substitution polymorphism in the promoter region of the human catalase gene influences transcription factor binding, reporter gene transcription and is correlated to blood catalase levels. Free Radic. Biol. Med. 30: 500-505.
10. Liu Y, Xie L, Zhao J, Huang X, Song L, et al (2015) Association between catalase gene polymorphisms and risk of chronic hepatitis B, hepatitis B virus-related liver cirrhosis and hepatocellular carcinoma in Guangxi population: a case-control study. Medicine (Baltimore) 94: e702.
11. Góth L, and Vitai M (1997) Polymorphism of 5′ of the catalase gene in Hungarian acatalasemia and hypocatalasemia. Electrophoresis 18: 1105-1108.
12. Saify, K, Saadat, I, and Saadat, M. (2016). Influence of A-21T and C-262T genetic polymorphisms at the promoter region of the catalase (CAT) on gene expression. Environ Health Prev Med 21: 382-386.
13. Coêlho MC, Viana Filho JMC, Souza BF de, Valença AMG, Persuhn DC, et al (2022) Genetic polymorphisms of genes involved in oxidative stress and inflammatory management in oncopediatric patients with chemo-induced oral mucositis. J. Appl. Oral Sci. 30: e20210490.
14. Sutton M, Bouhassira EE, and Nagel RL (1989) Polymerase chain reaction amplification applied to the determination of beta-like globin gene cluster haplotypes. Am. J. Hematol. 32: 66-69.
15. Steinberg MH (2008) Sickle cell anemia, the first molecular disease: overview of molecular etiology, pathophysiology, and therapeutic approaches. Scientific World Journal 8: 1295-1324.
16. Nagel RL, Fabry ME, and Steinberg, MH (2003) The paradox of hemoglobin SC disease. Blood Reviews 17: 167-178.
17. Dehury S, Purohit P, Patel S, Meher S, Kullu BK, et al (2015). Low and fixed dose of hydroxyurea is effective and safe in patients with HbSβ+ thalassemia with IVS1-5(G→C) mutation: Low Dose of Hydroxyurea on HbSβ+ Thalassemia. Pediatr Blood Cancer 62: 1017-1023.
18. Silva-Pinto AC, Angulo I L, Brunetta DM, Neves FIR, Bassi SC, et al (2013) Efeitos clínicos e hematológicos do tratamento com hidroxiureia em pacientes falciformes: Experiência de um centro no Brasil. Sao Paulo Medical Journal 131: 238-243.
19. Keikhaei B, Yousefi H, and Bahadoram M. (2015) Hydroxyurea: Clinical and Hematological Effects in Patients With Sickle Cell Anemia. GJHS 8: 252.
20. Ware RE, Despotovic JM, Mortier NA, Flanagan JM, He J, et al (2011) Pharmacokinetics, pharmacodynamics, and pharmacogenetics of hydroxyurea treatment for children with sickle cell anemia. Blood 118: 4985-4991.
21. Wiczling P, Liem RI, Panepinto JA, Garg U, Abdel-Rahman SM, et al (2014) Population pharmacokinetics of hydroxyurea for children and adolescents with sickle cell disease: The Journal of Clinical Pharmacology. The Journal of Clinical Pharmacology 54: 1016-1022.
22. Dong M, McGann PT, Mizuno T, Ware RE, and Vinks AA (2016) Development of a pharmacokinetic-guided dose individualization strategy for hydroxyurea treatment in children with sickle cell anaemia: Population PK of hydroxyurea in paediatric patients with sickle cell anaemia. Br J Clin Pharmacol 81: 742-752.
23. Estepp JH, Melloni C, Thornburg CD, Wiczling P, Rogers Z, et al. (2016). Pharmacokinetics and bioequivalence of a liquid formulation of hydroxyurea in children with sickle cell anemia. The Journal of Clinical Pharmacology 56: 298-306.
24. Boucher AA, Dong M, Marahatta A, Hausfeld A, Howard TA, et al (2019) Hydroxyurea Pharmacokinetic Profiles in Children Treated for Extreme Thrombocytosis after Total Pancreatectomy with Islet Cell Autotransplant Demonstrate Poor Absorption. Blood 134: 4893-4893.
25. McGann PT, Niss O, Dong M, Marahatta A, Howard TA, et al (2019) Robust clinical and laboratory response to hydroxyurea using pharmacokinetically guided dosing for young children with sickle cell anemia. Am J Hematol 94: 871-879.
26. Meier ER, Creary SE, Heeney MM, Dong M, Appiah-Kubi, AO, et al. (2020). Hydroxyurea Optimization through Precision Study (HOPS): study protocol for a randomized, multicenter trial in children with sickle cell anemia. Trials 21: 983.
27. Božina N, Bradamante V, and Lovrić M. (2009) Genetic Polymorphism of Metabolic Enzymes P450 (CYP) as a Susceptibility Factor for Drug Response, Toxicity, and Cancer Risk. Archives of Industrial Hygiene and Toxicology 60.
28. Yahouédéhou SCMA, Neres JSdos S, da Guarda CC, Carvalho SP, Santiago RP, et al (2020) Sickle Cell Anemia: Variants in the CYP2D6, CAT, and SLC14A1 Genes Are Associated With Improved Hydroxyurea Response. Front. Pharmacol. 11: 553064.
29. Paule I, Sassi H, Habibi A, Pham KP, Bachir D, et al (2011) Population pharmacokinetics and pharmacodynamics of hydroxyurea in sickle cell anemia patients, a basis for optimizing the dosing regimen. Orphanet J Rare Dis 6: 30.