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Impact of Pharmacogenetic Variability on Praziquantel Pharmacokinetics and Treatment Efficacy in Tanzanian School-Aged Children with Schistosomiasis

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ABSTRACT

Despite the widespread use of praziquantel (PZQ) for schistosomiasis, little is known about how genetic differences influence its plasma levels and treatment outcomes. This study examined the relationship between pharmacogenetic variations and both drug exposure and therapeutic response in Tanzanian school-aged children infected with Schistosoma mansoni. A total of 340 participants received a single PZQ dose. Stool samples were analyzed using the Kato-Katz technique, and treatment success was evaluated three weeks later. Adverse events were monitored within four hours of drug administration. Plasma concentrations of PZQ and its metabolite trans-4-OH-PZQ were measured four hours post-dose using UPLC-MS/MS, and genotyping for CYP3A4*1B, CYP3A5 (*3, *6, *7), CYP2C19 (*2, *3, *17), and CYP2C9 (*2, *3) was performed by real-time PCR. Participants had a median age of 12 years (range 7–17). Variations in CYP2C19 were significantly linked to PZQ plasma levels and the metabolic ratio (trans-4-OH-PZQ/PZQ). Specifically, carriers of CYP2C19 (*2, *3) exhibited higher PZQ concentrations than those with CYP2C19 *1/*1 or 17 (ultra-rapid metabolizers) ($p = 0.04$), while the metabolic ratio was elevated in CYP2C1917 carriers compared to CYP2C19 (*2, *3) ($p = 0.01$). No genotype significantly influenced treatment efficacy or overall adverse events, although baseline infection intensity and CYP3A5 genotype predicted drug-related side effects. These findings demonstrate that CYP2C19 polymorphisms meaningfully affect PZQ pharmacokinetics and metabolism, underscoring for the first time the clinical relevance of pharmacogenetic variability in schistosomiasis management.

Keywords: CYP2C19, Schistosomiasis, Praziquantel, Pharmacogenetics, Treatment outcomes, CYP3A5

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Introduction

Praziquantel (PZQ) has been the cornerstone of schistosomiasis control since its introduction in 1984, forming the basis of global mass drug administration (MDA) initiatives [1]. Currently, it remains the only WHO-endorsed medication for schistosomiasis, demonstrating efficacy against all major Schistosoma species, including S. haematobium and S. mansoni. Despite extensive use, schistosomiasis continues to affect hundreds of millions globally, with over 800 million people at risk and roughly 250 million requiring treatment [2, 3]. In Tanzania, the disease was first documented in 1895 and remains endemic nationwide despite decades of interventions [4-6]. In 2017 alone, more than 99 million individuals received treatment worldwide, including over 80 million school-aged children [7]. The WHO aims to achieve control of heavy infections (<5%) and elimination as a public health concern (<1%) by 2025 [8].

Preventive chemotherapy, particularly targeting school-aged children through PZQ MDA, constitutes the mainstay of schistosomiasis control in endemic regions [1]. This approach has successfully reduced morbidity and mortality linked to severe infections [9]. However, the standard 40 mg/kg dose has produced variable outcomes across populations, with both cure rates and adverse event profiles showing considerable heterogeneity, particularly in S. mansoni infections [10-12]. Such variability arises from multiple factors, including genetic

differences, environmental influences, and the severity of infection, all of which may alter drug metabolism and distribution [13]. Studies in other infectious diseases—such as malaria, tuberculosis, and HIV—have demonstrated that genetic polymorphisms can significantly impact both therapeutic efficacy and the risk of adverse events [14-16].

Despite these insights, the role of genetic variation in shaping PZQ pharmacokinetics and treatment outcomes remains poorly understood [17]. Although individualized dosing is challenging within MDA programs, understanding the influence of genetic polymorphisms on plasma drug levels and treatment response is critical for optimizing therapy [18, 19]. Recent research in Africa highlights the potential of pharmacogenetic data to improve treatment outcomes [20], and genetic variation may partially explain observed differences in PZQ exposure, cure rates, and adverse event profiles [21].

Age, pre-treatment infection intensity, and anemia have also been identified as determinants of treatment success in children [11, 22]. PZQ undergoes extensive metabolism primarily via CYP3A4, CYP3A5, CYP2C19, and CYP2C9, producing active metabolites such as trans-4-OH-PZQ [23-25]. Polymorphisms in these enzymes can lead to substantial inter-individual variability in plasma drug levels, potentially affecting both efficacy and safety. Pharmacokinetic-pharmacodynamic studies indicate that plasma drug concentration serves as a surrogate for tissue exposure, where suboptimal levels can compromise therapeutic efficacy and excessive exposure can increase adverse events [21, 26].

To date, no studies have systematically examined the impact of pharmacogenetic variability on PZQ plasma concentrations and schistosomiasis treatment outcomes. This study addresses this gap by evaluating the influence of CYP polymorphisms on drug exposure, cure rates, and the incidence of adverse events among Tanzanian school-aged children treated with a single PZQ dose for S. mansoni infection.

Materials and Methods

Study design and setting

This study was designed as a prospective investigation combining pharmacogenetic, pharmacokinetic, and pharmacodynamic analyses to explore how genetic variability influences praziquantel (PZQ) exposure and treatment outcomes in children infected with Schistosoma mansoni. The research was conducted from February 2017 to January 2018 in Nyamikoma, a rural village in northwestern Tanzania where intestinal schistosomiasis is endemic [6]. The community had previously received five rounds of school-based PZQ mass drug administration. A total of 340 children aged between 7 and 17 years with confirmed S. mansoni infection were enrolled.

Participant data collection

Socio-demographic data, including age and sex, were gathered through structured interviews and school records. Clinical and laboratory information—such as baseline and post-treatment infection status, adverse events, anthropometric measurements, and hemoglobin levels—was recorded in case report forms following WHO protocols.

Assessment of hemoglobin and nutritional status

Hemoglobin concentrations were measured prior to treatment using a HemoCue Hb 201+ device (HemoCue AB, Angelholm, Sweden) via finger-prick samples. Anemia was defined as hemoglobin below 11.5 g/dL [27]. Nutritional status was evaluated using height-for-age (HAZ) and body mass index-for-age (BAZ) Z-scores calculated with WHO AnthroPlus software (v1.0.4) [28]. Scores below −2 standard deviations were classified as stunting (HAZ) or wasting (BAZ).

Treatment administration and follow-up

Participants received a single 40 mg/kg dose of PZQ (Praziquantel 600 mg tablets, Batch BZ6043, S Kant Health Care Ltd., India) under direct observation following a light meal, in line with WHO recommendations for antihelminthic efficacy evaluation [29]. Children were monitored for adverse events during the first four hours post-treatment, and treatment outcomes were assessed during a follow-up visit three weeks later.

Blood sampling for genetic and pharmacokinetic analysis

Pre-treatment whole blood samples (2 mL) were collected in EDTA tubes from all participants and stored at −80°C for DNA extraction. For pharmacokinetic analysis, 2 mL of blood was drawn from 287 children four hours after PZQ administration, collected in heparinized tubes, centrifuged to separate plasma, and frozen at −80°C until shipment. Samples were transported to Karolinska Institutet, Stockholm, Sweden, for laboratory analysis.

Stool sample collection and parasitological analysis

Two stool samples were collected from each child on consecutive days at baseline and follow-up. Samples were processed using the thick smear Kato-Katz technique according to WHO guidelines [30]. Each slide was examined independently by two trained technicians, and egg counts were recorded to determine infection intensity and treatment efficacy [11].

Quantification of Praziquantel and trans-4-OH-PZQ in Plasma

Materials

All chemical standards, including racemic praziquantel (rac-PZQ) and its deuterated analog (rac-PZQ-d11) used as the internal standard, as well as trans-4-OH-PZQ and trans-4-OH-PZQ-d5, were obtained from Toronto Research Chemicals (Toronto, Canada). High-purity solvents—acetonitrile, methanol, and formic acid—were procured from Merck (Darmstadt, Germany), and ultrapure water was generated on a Milli-Q system (Merck Millipore, USA). Human plasma devoid of PZQ was supplied by the Karolinska University Hospital blood bank (Stockholm, Sweden).

Sample preparation and chromatography

Plasma concentrations of PZQ and its main metabolite were determined using a UPLC-MS/MS assay adapted from AstraZeneca's validated methods [24] with minor adjustments to accommodate high metabolite levels. Calibration and quality control samples were prepared by spiking blank plasma with known concentrations of the analytes. QC levels were categorized as low, medium, and high, covering the analytical range of 3.9–2,500 ng/mL for PZQ and 31.2–50,000 ng/mL for trans-4-OH-PZQ.

For analysis, 50 µL of plasma was mixed with 150 µL of internal standard solution containing rac-PZQ-d11 and trans-4-OH-PZQ-d5 in a 1:1 acetonitrile:methanol solution. Samples were vortexed, centrifuged, and the supernatant diluted 1:1 with ultrapure water before injecting 5 µL into the UPLC-MS/MS system. Chromatographic separation was performed on an Acquity HSS T3 column (2.1 × 50 mm, 1.8 µm) at 60°C. The gradient used water with 0.1% formic acid and 2% acetonitrile as solvent A and acetonitrile with 0.1% formic acid as solvent B. Elution progressed from 4% B to 70% B within 2.6 minutes, followed by a high organic wash to prevent carry-over, and re-equilibration before the next injection.

Mass spectrometry and quantification

Analytes were monitored using multiple reaction monitoring (MRM) transitions, with adjustments to collision energy for the high-abundance trans-4-OH-PZQ. Quantification was based on the ratio of the analyte signal to the internal standard, with calibration curves generated using a quadratic regression model weighted by 1/x. Each analytical run included a minimum of twelve calibration points and QC samples interspersed at regular intervals. Data processing was performed using TargetLynx software (Waters).

Method performance

Recovery and precision were evaluated across the three QC levels. PZQ recovery ranged from 87% to 105%, while trans-4-OH-PZQ ranged from 97% to 109%. Inter- and intra-assay variability was below 7% for both compounds at all concentrations. Calibration curves were highly linear ($r^2 > 0.98$), and no significant carry-over was observed. The method was partially validated according to EMA bioanalytical guidelines (2009).

DNA extraction and genotyping of CYP enzymes

Genomic DNA was extracted from peripheral blood leukocytes using the QIAamp DNA Midi Kit (Qiagen, Germany) following the manufacturer's guidelines. To investigate the influence of genetic variation on praziquantel (PZQ) metabolism, genotyping was performed for the relevant single nucleotide polymorphisms (SNPs) in the CYP enzymes involved in PZQ biotransformation, specifically CYP3A4 (*1B), CYP3A5 (*3, *6,

*7), CYP2C19 (*2, *3, *17), and CYP2C9 (*2, *3). The genotyping process was conducted using TaqMan® assays (Applied Biosystems, USA) for allelic discrimination, with specific assay IDs for each SNP:

- CYP3A4*1B (rs2740574),
- CYP3A5*3 (rs776746),
- CYP3A5*6 (rs10264272),
- CYP3A5*7 (rs41303343),
- CYP2C19*2 (rs4244285),
- CYP2C19*3 (rs4986893),
- CYP2C19*17 (rs12248560),
- CYP2C9*2 (rs1799853), and
- CYP2C9*3 (rs1057910).

The genotyping reactions were performed on a 7500 Fast Real-Time PCR System (Applied Biosystems, USA). For each PCR reaction, a 10 µL total volume was used, consisting of 9 µL TaqMan® Fast Advanced Master Mix and 1 µL of genomic DNA. The cycling conditions included an initial incubation at 60°C for 30 seconds, followed by a denaturation step at 95°C for 10 minutes, then 40 cycles of denaturation at 95°C for 15 seconds and annealing/extension at 60°C for 1 minute.

Study outcomes

The primary aim of the study was to assess the influence of genetic polymorphisms in CYP3A4, CYP3A5, CYP2C19, and CYP2C9 on plasma concentrations of PZQ and trans-4-OH-PZQ, and the metabolic ratio (trans-4-OH-PZQ/PZQ). Secondary outcomes included evaluating the effects of these genotypes on treatment effectiveness (measured by cure rates and changes in egg count) and the occurrence of adverse events.

The cure rate was determined by identifying the proportion of children who were initially S. mansoni egg-positive and subsequently became egg-negative at the 3-week post-treatment follow-up [11]. Egg count reduction was quantified by calculating the percent change in egg count per gram of stool between baseline and 3 weeks post-treatment. Adverse events were classified as any symptoms reported within 4 hours of PZQ administration, though these symptoms were not necessarily causally linked to the drug [22].

Statistical data analyses

All data were entered into Microsoft Excel and analyzed using SPSS software (version 20, IBM Corp., Armonk, NY, USA). Descriptive statistics were computed for both socio-demographic and clinical data. Categorical variables were expressed as frequencies and percentages, while continuous variables were summarized as mean ± standard deviation (SD) or median (range/interquartile range - IQR) based on the data distribution.

Treatment outcomes, such as cure rates and the occurrence of adverse events, were analyzed as proportions for different CYP genotype groups. The Chi-square test was used to examine genotype and allele distributions and to test Hardy-Weinberg equilibrium for each SNP. For categorical data, genotype categories for CYP2C19 were defined as follows: wild type (*1/*1), heterozygous carriers (*1/*17), and carriers of the *2/*3 variants (including homozygous and compound heterozygous forms such as *2/*2, *3/*3, etc.).

To evaluate differences in plasma drug concentrations (PZQ, trans-4-OH-PZQ, and the metabolic ratio), one-way analysis of variance (ANOVA) was performed on the log-transformed data, and geometric means were calculated by taking the antilog of the results. Associations between cure rates, adverse events, and CYP genotype groups were analyzed using Pearson's Chi-square or Fisher's exact tests, depending on the data distribution.

Univariate and multivariate logistic regression analyses were conducted to identify predictors of treatment success (cure rate) and the occurrence of adverse events. Variables with a p-value < 0.2 from the univariate analysis were included in the multivariate regression model. The effect of genetic variation on egg count reduction was assessed using a one-way ANOVA, while a negative binomial regression model was applied to identify predictors of egg count reduction at 3 weeks post-treatment. A p-value < 0.05 was considered statistically significant.

Participant baseline characteristics

The study included a total of 340 children, with a median age of 12 years, spanning an age range of 7 to 17 years. Of the participants, 53.2% were female. At the time of enrollment, the median egg count in stool samples was 222 eggs per gram (epg), with a range from 96 to 468 epg. Approximately 22.4% of participants were found to have

anaemia, indicated by hemoglobin levels below 11.5 g/dL. Regarding nutritional status, 34.1% of the children were classified as stunted, and 10.0% were categorized as wasted based on their height-for-age and BMI-for-age z-scores **(Table 1)**.

Table 1. Baseline characteristics of the studied population.

Variable	Value
Age (years)	
Mean ± SD	11.8 ± 1.7
≤12 years, n (%)	235 (69.1%)
>12 years, n (%)	105 (30.9%)
Sex, n (%)	
Male	159 (46.8%)
Female	181 (53.2%)
Baseline egg count (eggs/gram of stool)	
Median (IQR)	222 (96–468)
Baseline infection intensity, n (%)	
Light	87 (25.6%)
Moderate	152 (44.7%)
Heavy	101 (29.7%)
Weight (kg)	
Median (IQR)	30.2 (26.3–34.8)
Height (cm)	
Median (IQR)	138.5 (130.4–144.0)
Stunting status (HAZ), n (%)	
Stunted	116 (34.1%)
Not stunted	224 (65.9%)
Wasting status (BAZ), n (%)	
Wasted	34 (10.0%)
Not wasted	306 (90.0%)
Haemoglobin concentration (g/dL)	
Median (IQR)	12.7 (11.6–13.5)
Anaemia status, n (%)	
Anaemic	76 (22.4%)
Not anaemic	264 (77.6%)

SD-Standard deviation; IQR-Interquartile range: BAZ-Body Mass Index (BMI) for Age Z score; HAZ: Height for Age Z score

Frequencies of genotypes and alleles

The distribution of genotypes and alleles for the CYP3A4*1B, CYP3A5 (*3, *6, *7), CYP2C19 (*2, *3, *17), and CYP2C9 (*2, 3) variants among the Tanzanian children included in this study is presented in **Table 2**. There were no significant deviations from Hardy-Weinberg equilibrium in the observed genotype frequencies. The most common allele was CYP3A4 1B, occurring in 66.7% of the study population, followed by CYP3A56, which had a frequency of 24.4%. The least frequent allele was CYP2C92, found in just 0.4% of the participants **(Table 2)**. Previous studies on CYP3A haplotypes across various sub-Saharan African populations, including Tanzanians, have shown no significant linkage disequilibrium among the SNPs analyzed [19, 31, 32]. Similarly, no linkage disequilibrium was observed between the *2 and *3 alleles of CYP2C9 and CYP2C19 [31, 33, 34].

Table 2. Genotype and Allele Frequencies of Selected CYP Polymorphisms (N = 340 individuals)

Gene / Variant	Genotype	n (%)	Minor Allele	Minor Allele Frequency (%)
CYP3A4*1B (-392A>G)	*1/*1	42 (12.3)	*1B	66.7
	*1/*1B	143 (42.1)		

	*1B/*1B	155 (45.6)		
CYP3A5*3 (c.6986A>G)	*1/*1	244 (71.8)	*3	15.9
	*1/*3	84 (24.7)		
	*3/*3	12 (3.5)		
CYP3A5*6 (c.14690G>A)	*1/*1	192 (56.5)	*6	24.4
	*1/*6	130 (38.2)		
	*6/*6	18 (5.3)		
CYP3A5*7 (27,131_27132insT)	*1/*1	279 (82.1)	*7	9.7
	*1/*7	56 (16.40)		
	*7/*7	5 (1.5)		
CYP2C19*2	*1/*1	228 (67.1)	*2	17.8
	*1/*2	103 (30.3)		
	*2/*2	9 (2.6)		
CYP2C19*3	*1/*1	328 (96.5)	*3	1.7
	*1/*3	12 (3.5)		
	*3/*3	0 (0.0)		
CYP2C19*17	*1/*1	236 (69.4)	*17	17.1
	*1/*17	92 (27.1)		
	*17/*17	12 (3.5)		
CYP2C9*2	*1/*1	337 (99.1)	*2	0.4
	*1/*2	3 (0.9)		
	*2/*2	0 (0.0)		
CYP2C9*3	*1/*1	335 (98.5)	*3	0.7
	*1/*3	5 (1.5)		
	*3/*3	0 (0.0)		

Genotype categorization and analysis of PZQ metabolism

In our study cohort, the alleles associated with defective CYP variants occurred at relatively low frequencies, and very few participants were homozygous for these variants. To assess the influence of genotypes on PZQ metabolism **(Table 3)** and treatment outcomes **(Table 4)**, we grouped participants based on their genotype profiles. For the CYP3A4, CYP3A5, and CYP2C9 genes, individuals were classified into two broad categories: normal metabolizers (*1/*1) and those carrying at least one defective allele, who were considered intermediate or slow metabolizers. For CYP2C19, we focused on the *17 allele, known for its higher metabolic activity, and the loss-of-function alleles (*2 and *3). Participants were categorized into three groups: those with the *17 allele (classified as ultrarapid or rapid metabolizers, *17/*17 or *1/*17), those with normal metabolism (*1/*1), and those carrying the defective alleles (*2 or *3), considered intermediate or slow metabolizers. This classification scheme follows the recommendations outlined by the Clinical Pharmacogenetics Implementation Consortium (CPIC) for CYP2C19 [35].

Table 3. Comparison of the geometric means of PZQ, *trans*-4-OH-PZQ concentrations (ng/mL) and metabolic ratio (t*rans*-4-OH-PZQ/PZQ) between CYP450 genotypes using One-way ANOVA.

Genotype		N	PZQ GM ± SD	p-value	Trans-4-OH-PZQ	p-value	trans-4-OH-PZQ/PZQ	p-value
CYP3A4	*1/*1	40	249.5 ± 3.3	0.88	9,299.7 ± 2.1	0.99	37.2 ± 3.0	0.86
	*1B carriers	247	258.2 ± 3.6		9,289.7 ± 1.9		36.0 ± 3.0	
CYP3A5	*1/*1	77	261.2 ± 3.5	0.89	9,462.4 ± 1.0	0.77	36.2 ± 2.8	1.00
	*3, *6, *7 carriers	210	255.3 ± 3.6		9,225.7 ± 1.9		36.1 ± 3.1	
CYP2C19	*17 carriers	79	191.9 ± 3.3	0.04	9,311.1 ± 1.8	0.92	48.5 ± 3.0	0.01
	*1/*1	109	267.9 ± 3.3		9,440.6 ± 1.9		35.2 ± 2.6	
	*2, *3 carriers	99	310.5 ± 4.0		9,099.1 ± 2.0		29.3 ± 3.3	
CYP2C9	*1/*1	279	258.2 ± 3.5	0.68	9,246.9 ± 1.9	0.37	35.7 ± 2.9	0.32
	*2, *3 carriers	8	214.3 ± 4.6		11,350.1 ± 1.6		52.9 ± 5.1	

Table 4. Association of genotype with praziquantel efficacy (cure rates) and treatment-associated adverse events.

Genotype		Cure rates		*p* Value	Adverse events		*p* Value
		Cured N (%)	Not Cured N (%)		Yes N (%)	No N (%)	
CYP3A4	*1/*1	33 (12.0)	9 (14.1)	0.39	12 (13.2)	30 (12.0)	0.85
	*1B carriers	243 (88.0)	55 (85.9)		79 (86.8)	219 (88.0)	
CYP3A5	*1/*1	69 (25.0)	16 (25.0)	0.57	30 (33.0)	55 (22.1)	0.048
	*3, *6, or *7 carriers	207 (75.0)	48 (75.0)		61 (67.0)	194 (77.9)	
CYP2C19	*17 carriers	68 (24.6)	19 (29.7)	0.26	21 (23.1)	56 (26.5)	0.64
	*1/*1	104 (37.7)	28 (43.8)		39 (42.9)	93 (37.3)	
	*2, or *3 carriers	104 (37.7)	17 (26.6)		31 (34.1)	90 (36.1)	
CYP2C9	*1/*1	269 (97.5)	63 (98.4)	0.54	89 (97.8)	243 (97.6)	1.00
	*2, or *3 carriers	7 (2.5)	1 (1.6)		2 (2.2)	6 (2.4)	

CYP genotypes and their effect on PZQ, trans-4-OH-PZQ levels, and metabolic ratios

The geometric averages of PZQ, trans-4-OH-PZQ, and their metabolic ratio (trans-4-OH-PZQ/PZQ) across the study group were 257.0 ± 3.6 ng/mL, 9,289.7 ± 1.9 ng/mL, and 36.1 ± 3.0, respectively. These values, as well as their relationships to various CYP450 genotypes, are detailed in **Table 3**. Significant differences were found between PZQ concentrations and the CYP2C19 genotype ($p < 0.05$). Specifically, individuals with the CYP2C19 *2 or *3 alleles showed notably higher PZQ levels compared to those with the *1/*1 wild-type genotype or *17 carriers. In contrast, the ratio of trans-4-OH-PZQ to PZQ was substantially greater among those with the CYP2C19 *17 allele compared to the *1/*1 and *2, *3 carriers. No significant impact was observed from the CYP3A4, CYP3A5, or CYP2C9 genotypes on PZQ or trans-4-OH-PZQ concentrations or the metabolic ratio ($p > 0.05$) **(Table 3)**.

CYP genotypes and treatment success

At the 3-week follow-up, 81.2% (276 out of 340) of the children had been successfully cured. However, no statistically significant association was identified between any of the CYP3A4, CYP3A5, CYP2C19, or CYP2C9 genotypes and cure rates ($p > 0.05$) **(Table 4)**. Logistic regression analysis, performed to explore potential predictors for treatment success, revealed that the CYP gene variants did not significantly predict the likelihood of cure at 3 weeks post-treatment. The model was well-calibrated, as shown by the Hosmer-Lemeshow test, which yielded a $\chi 2$ value of 6.40 and a p-value of 0.60 **(Table 5)**.

Table 5. Univariate and Multivariate logistic regression analysis for predictors of cure at 3 weeks' post-treatment.

Variable		Cured N (%)	Univariate analysis		Multivariate analysis	
			cOR (95%)	*p*-value	aOR (95%)	*p*-value
Age (years)	≤12	190 (80.9)	1	0.82		
	>12	86 (81.9)	1.07 (0.59–1.94)			
Sex	Male	127 (79.9)	1	0.57		
	Female	149 (82.3)	1.17 (0.68–2.02)			
Baseline infection intensity	Light	72 (82.8)	1			
	Moderate	126 (82.9)	0.71 (0.34–1.46)	0.35		
	Heavy	78 (77.2)	0.70 (0.37–1.31)	0.27		
Anaemia	Yes	67 (88.2)	0.51 (0.24–1.09)	0.08	0.51 (0.24–1.09)	0.08
	No	209 (79.2)	1		1	
Stunting (HAZ)	Yes	96 (83.6)	0.78 (0.43–1.41)	0.41		
	No	179 (79.9)	1			
Wasting (BAZ)	Yes	30 (88.2)	0.55 (0.19–1.61)	0.27		
	No	246 (80.4)	1			
CYP3A4	*1/*1	33 (78.6)	1	0.65		
	*1B carriers	243 (81.5)	0.83 (0.38–1.83)			
CYP3A5	*1/*1	69 (25.0)	1			
	*3,*6,*7 carriers	207 (75.0)	1.00 (0.53–1.87)	1.00		
CYP2C19	*17 carriers	68 (24.6)	1		1	

	*1/*1	104 (37.7)	0.59 (0.28–1.21)	0.15	0.58 (0.28–1.21)	0.15
	*2,*3 carriers	104 (37.7)	0.96 (0.49–1.86)	0.91	0.97 (0.49–1.88)	0.92
CYP2C9	*1/*1	269 (97.5)	1	0.65		
	*2,*3 carriers	7 (2.5)	0.61 (0.17–5.05)			

cOR- Crude odd ratio; aOR–Adjusted odd ratio.

Egg reduction and genetic influence

The mean reduction in egg counts at 3 weeks post-treatment was 101.6% with a standard deviation of 113.6%. However, there were no statistically significant associations between the genetic variations in CYP3A4, CYP3A5, CYP2C19, and CYP2C9 and the reduction in egg counts after treatment ($p > 0.05$) **(Table 1)**. Furthermore, when using negative binomial regression, these same CYP gene variants did not emerge as predictors for the degree of egg count reduction at 3 weeks post-treatment ($p > 0.05$) **(Table 2)**.

Adverse events and CYP genotypes

Approximately 26.8% (91 out of 340) of the children experienced treatment-related adverse events within 4 hours after receiving praziquantel. The most frequent side effects were abdominal pain (26.5%, 90/340) and vomiting (1.8%, 6/340). No significant associations were found between the CYP2C9, CYP2C19, CYP3A4, or CYP3A5 genotypes and the occurrence of adverse events **(Table 4)**. However, a notable increase in adverse events was observed in children with defective alleles of CYP3A5 (*3, *6, *7), compared to those with the wild-type CYP3A5 genotype (*1/*1), with statistical significance ($p = 0.048$) **(Tables 4 and 6)**.

Table 6. Univariate and Multivariate logistic regression analysis for predictors of adverse events.

Variable		Adverse Events	Univariate analysis		Multivariate analysis	
		Yes N (%)	cOR (95%)	*p*-value	aOR (95%)	*p*-value
Age (years)	≤12	68 (28.9)	1.45 (0.85–2.49)	0.18	1.59 (0.90–2.80)	0.11
	>12	23 (21.9)	1		1	
Sex	Male	38 (23.9)	1	0.26		
	Female	53 (29.3)	0.76 (0.47–1.23)			
Baseline infection intensity	Light	11 (12.6)	1		1	
	Moderate	40 (26.3)	0.22 (0.11–0.47)	≤0.001	0.20 (0.09–0.43)	≤0.001
	Heavy	40 (39.6)	0.55 (0.32–0.93)	0.03	0.50 (0.29–0.87)	0.01
Anaemia	Yes	25 (32.9)	1.47 (0.85–2.56)	0.17	1.43 (0.80–2.57)	0.23
	No	66 (25.0)	1		1	
Stunting (HAZ)	Yes	28 (24.1)	0.81 (0.49–1.36)	0.43		
	No	63 (28.1)	1			
Wasting (BAZ)	Yes	8 (23.5)	0.83 (0.36–1.89)	0.65		
	No	83 (27.1)	1			
CYP3A4	*1/*1	12 (28.6)	1			
	*1B carriers	79 (26.5)	0.90 (0.44–1.85)	0.78		
CYP3A5	*1/*1	30 (33.0)	1		1	
	*3,*6,*7 Carriers	61 (67.0)	0.58 (0.34–0.98)	0.04	0.62 (0.36–1.07)	0.09
CYP2C19	*17 carriers	21 (23.1)	1			
	*1/*1	39 (42.9)	1.08 (0.57–2.05)	0.81		
	*2,*3 carriers	31 (34.1)	1.32 (0.71–2.44)	0.38		
CYP2C9	*1/*1	89 (97.8)	1			
	*2,*3 carriers	2 (2.2)	0.91 (0.18–4.59)	0.91		

cOR- Crude odd ratio; aOR–Adjusted odd ratio.

Adverse events and treatment response

In analyzing the role of genetic variations in CYP enzymes, the multivariate logistic regression revealed that none of the studied genotypes—CYP3A4, CYP3A5, CYP2C19, or CYP2C9—were statistically significant predictors of adverse treatment events. Interestingly, the baseline level of infection was found to be a critical factor influencing the likelihood of experiencing side effects, with children exhibiting higher infection intensity at baseline showing a significantly increased risk of treatment-associated adverse events. This relationship was well-

supported by the Hosmer-Lemeshow test for model fit, which indicated a good alignment ($\chi^2 = 4.43$, $p = 0.73$) **(Table 6)**.

Exploring pharmacogenetics in schistosomiasis treatment

In this investigation, we sought to better understand the influence of genetic differences on praziquantel (PZQ) pharmacokinetics and its clinical outcomes, focusing on efficacy and the occurrence of adverse events among school-aged children infected with Schistosoma mansoni. Our findings largely mirrored those from previous Tanzanian studies regarding the frequencies of CYP3A4*1B, CYP3A5 (*3, *6, *7), CYP2C19 (*2, *3, *17), and CYP2C9 (*2, *3) alleles [19, 36]. Specifically, our results demonstrated: (1) a notable link between CYP2C19 genetic variations and plasma PZQ concentrations, as well as the metabolic ratio (trans-4-OH-PZQ/PZQ), (2) no significant effect of any CYP450 genotypes on treatment efficacy at three weeks post-treatment, and (3) a borderline association between CYP3A5 variants and the incidence of adverse treatment events, particularly among carriers of *3, *6, and *7 alleles. To our knowledge, this is the first study to examine the pharmacogenetic influence on both plasma PZQ concentrations and clinical outcomes, including efficacy and safety in this context.

PZQ undergoes metabolic processing through cytochrome P450 enzymes, notably CYP3A4, CYP3A5, CYP2C19, and CYP2C9 [23]. Our results indicate that CYP2C19, rather than the other enzymes, plays a key role in PZQ metabolism, as evidenced by significantly higher plasma PZQ concentrations in children carrying *2 or *3 variants compared to the wild-type or ultra-rapid metabolizer (*17) alleles. In addition, the ratio of trans-4-OH-PZQ to PZQ was notably higher in *17 allele carriers, suggesting CYP2C19's pivotal involvement in forming the active metabolite. This supports earlier findings that highlighted CYP2C19's primary role in generating 4-OH-PZQ [37], while CYP3A was implicated in the formation of other metabolites like X-OH-PZQ [24].

Although our study did not identify any significant correlation between CYP450 genotypes and the effectiveness of the PZQ treatment, we observed a trend suggesting a higher cure rate in children with certain genotypic variations, particularly those with the CYP3A4*1B allele. While not statistically significant, this finding may be attributed to varying levels of CYP3A4 activity in the Tanzanian population, which could influence the drug's pharmacokinetics and efficacy [38, 39]. Moreover, the lack of a clear, statistically significant relationship between CYP3A4 genotype and treatment success could be due to the multifactorial nature of drug metabolism and response, which includes environmental factors and the disease stage itself.

Genetic variations and schistosomiasis treatment response

CYP3A5, an enzyme that plays a central role in the metabolism of many drugs, is notably more prevalent in African populations compared to others. This is particularly relevant in understanding how different genotypes can influence the metabolism of medications, such as praziquantel (PZQ), used to treat schistosomiasis [31, 32]. Previous research has shown that certain genetic variations in CYP3A5 (*3, *5, *7 alleles) lead to reduced enzyme activity, particularly in African cohorts, including Tanzanians [39]. In this study, while we observed differences in genotype frequencies, the link between CYP3A5 genetic variations and the therapeutic outcomes of PZQ treatment was not significant. However, it is worth noting that children with genetic variations in CYP3A5 (*3, *6, *7) exhibited slightly better cure rates compared to those with the wild-type genotype, though these differences were not statistically conclusive **(Tables 4 and 5)**.

Interestingly, although no significant relationship was found between CYP3A5 and the overall efficacy of PZQ treatment, the analysis did show that CYP2C19 genetic variants influenced PZQ plasma concentrations and the metabolic ratio of trans-4-OH-PZQ to PZQ. Specifically, individuals with the defective *2 or *3 alleles exhibited higher plasma PZQ concentrations compared to those with the *1/*1 or *17 genotypes. This suggests that CYP2C19 might be a major contributor to PZQ metabolism, particularly in the formation of its key metabolite, trans-4-OH-PZQ. These findings corroborate prior research that suggested CYP2C19 plays a critical role in PZQ metabolism [37]. However, the influence of CYP2C19 on treatment success was less clear in terms of efficacy, as no direct correlation was observed with cure rates **(Table 4)**.

The low prevalence of defective alleles in CYP2C9 (*2, *3) in the study cohort, coupled with a lack of significant findings related to treatment outcomes, aligns with previous reports from African populations [40]. This suggests that the clinical impact of CYP2C9 variations on PZQ efficacy may be minimal in sub-Saharan populations. Larger studies are needed to further explore the potential role of these variants in treatment response.

Impact of pharmacogenetics on adverse events

Several factors, including age, pre-treatment infection intensity, and pharmacogenetic variations, can influence the frequency and severity of adverse events following drug treatment [14, 15]. In our study, the primary predictor of treatment-related adverse events was baseline infection intensity, with children who had higher infection loads more likely to experience side effects following PZQ treatment. This finding aligns with previous work, which suggested that infection severity is a major determinant of adverse reactions to schistosomiasis treatment [11, 41]. In contrast to some other studies, we did not find significant correlations between age, anemia, or the CYP genotypes of CYP3A4, CYP2C19, or CYP2C9 with the incidence of adverse events. However, a notable observation was that children with the defective CYP3A5 alleles (*3, *6, *7) were more likely to experience adverse effects compared to those with the wild-type CYP3A5 *1/*1 genotype. This suggests that CYP3A5 genetic variations could influence the risk of side effects, although the exact mechanism remains unclear **(Tables 4 and 6)**. The role of S-PZQ, the non-active component of PZQ that causes nausea and vomiting, may be exacerbated by CYP3A5 activity, although this hypothesis was not fully tested in our study.

Limitations and further research

While this study provides valuable insights into the potential impact of pharmacogenetic factors on PZQ treatment, it also has some limitations. For example, we did not investigate all possible PZQ metabolites, particularly those linked to the non-active enantiomer, S-PZQ. Future research should focus on quantifying both R- and S-PZQ metabolites, as well as other metabolites that may contribute to adverse events. Additionally, exploring genetic variations in other CYP enzymes and their combined effects on PZQ metabolism could provide further understanding of treatment variability in African populations.

Conclusion

Our findings reveal that the CYP2C19 genotype plays a significant role in the plasma concentrations of praziquantel (PZQ) and its metabolic ratio (trans-4-OH-PZQ/PZQ) in children affected by schistosomiasis. While the genotypes for CYP3A4, CYP2C19, and CYP2C9 did not show a direct impact on the effectiveness of the treatment or the occurrence of side effects, there was a potential link between CYP3A5 gene variants and treatment-related adverse events that could benefit from further study. This research is the first to explore how genetic differences might influence both the pharmacokinetics of PZQ and treatment outcomes in children with schistosomiasis, offering important insights into the treatment of this widespread neglected disease in sub-Saharan Africa.

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Conflict of Interest: None

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