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Original

Factors associated with chloroquine induced pruritus during malaria treatment in Mozambican University students

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ABSTRACT

Introduction: It has been suggested that reductions in chloroquine use may be followed by a resurgence of chloroquine-susceptible falciparum malaria, and chloroquine might once again be an effective treatment choice, which renews the importance of aspects related to its use and misuse. Therefore, we aimed to estimate the prevalence of chloroquine-induced pruritus and to identify risk factors for its occurrence in Mozambican University students.

Methods: A cross-sectional study was conducted at a private University in Maputo. Students were approached in the classrooms to complete a self-administered questionnaire covering sociodemographic characteristics, number of previous malaria episodes, utilization of antimalarial drugs, and life prevalence of chloroquine induced pruritus.

Results: Among 795 respondents, 77.4% (601/777) reported at least one malaria episode and 73.2% (542/740) had used chloroquine before. The life-prevalence of chloroquine-induced pruritus was 30.1% (158/525). Pruritus tended to be more frequent when chloroquine was used for treatment compared with prophylaxis only (31.2% vs. 10.3%, $p<0.05$), and chloroquine use in the last malaria episode was less frequent in participants recalling chloroquine-induced pruritus (52.3% vs. 65.1%, $p<0.05$).

Conclusion: About one third of the black population using chloroquine experienced chloroquine-induced pruritus at least once. This adverse reaction tended to be less frequent when lower doses of chloroquine were used and to influence future anti-malarial therapeutic choices.

Factores asociados a la aparición de prurito por cloroquina durante el tratamiento de la malaria en estudiantes universitarios de Mozambique

Palabras clave:
Cloroquina
Prurito
Malaria
Prevalencia
Factores de riesgo

RESUMEN

Introducción: Se ha sugerido que la reducción en el uso de la cloroquina puede derivar en el resurgimiento de la malaria *falciparum* sensible a la cloroquina, por lo que ésta puede volver a ser un tratamiento efectivo de elección, renovando la importancia de aspectos relacionados con su uso y su mal uso. Se pretende estimar la prevalencia de prurito inducido por cloroquina e identificar los factores de riesgo asociados a su ocurrencia en estudiantes universitarios de Mozambique.

Métodos: Se realizó una encuesta transversal en una Universidad privada de Mozambique. Los estudiantes fueron abordados en las aulas para completar un cuestionario autoadministrado, que contenía datos sociodemográficos e información sobre el número de episodios previos de malaria, la utilización de fármacos antipalúdicos y la prevalencia de prurito inducido por cloroquina.

Resultados: De los 795 que respondieron, el 77,4% (601/777) reportó al menos un episodio de malaria y el 73,2% (542/740) utilizó la cloroquina anteriormente. La prevalencia del prurito inducido por cloroquina fue del 30,1% (158/525). El prurito tendió a ser más frecuente cuando la cloroquina era utilizada como tratamiento en comparación con su uso profiláctico (31,2% vs. 10,3%, $p<0,05$), y su empleo en el último episodio de malaria fue menos frecuente en los participantes que recordaban haber sufrido prurito inducido por cloroquina (52,3% vs. 65,1%, $p<0,05$).

Conclusión: Cerca de un tercio de la población de raza negra que usa cloroquina tuvo al menos un episodio de prurito inducido por este fármaco. Esta reacción adversa tendió a ser menos frecuente cuanto más bajas fueron las dosis de cloroquina utilizadas, e influenciaba las opciones futuras de fármacos antipalúdicos.

Introduction

There are promising new insights on the development of novel medicines for malaria therapeutics. Meanwhile, the choice between available anti-malarial agents is being determined by drug resistances, price, side effects, and adherence to treatment[1,2].

Chloroquine treatment has remained the most common single treatment for malaria chemo-suppression for many years.[3] However, since the 1980s, parasite resistance to this drug has emerged as a major challenge and chloroquine's effectiveness was lost in most parts of Africa.

Currently, the World Health Organization recommends artemisin-based combination treatments as first-line therapy for falciparum malaria in all endemic areas in Africa.[3] However, it has been suggested that reductions in chloroquine use may be followed by a resurgence of chloroquine-susceptible *falciparum* malaria throughout the African region,[4,5] and chloroquine might

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once again be an effective treatment choice, in combination with other antimalarial drugs.[5] Malawi was the first country in Sub-Saharan Africa to replace chloroquine as first-line treatment for malaria, and has recently experienced a resurgence of chloroquine susceptible falciparum malaria, 12 years after its withdrawal.[5]

Chloroquine is not associated with significant serious adverse events in antimalarial doses, but chloroquine-induced pruritus is known to affect a large proportion of black patients, contributing to poor compliance with anti-malarial treatment.[6–8] The role of the extensive use and misuse of antimalarial therapeutics for the emergence of drug resistances is particularly evident, for which the experience of adverse reactions could be a great contributor.[1,2,9]

In this study we estimated the prevalence of chloroquine-induced pruritus and identified risk factors for this condition, in a sample of Mozambican University students.

Methods

We conducted a cross-sectional study of students enrolled at a private University in Maputo, Mozambique, chosen in order to comprise a large number of students and a relatively wide range of degrees, encompassed in a single campus. The University had nearly 1500 students.

Students were asked to read a declaration of consent, in which the objectives of the study and the methods to be used for data collection were described, in agreement with the Helsinki Declaration. Only students who agreed to sign the informed consent document were considered participants and asked to fill in the questionnaire. Students who agreed to participate were asked to complete a self-administered questionnaire applied in the classes, with the consent of the teachers.

In March 2004, 47 of the 55 classes in the institution were systematically approached, comprising 829 students, distributed among all diurnal classes and 21 of 26 nocturnal classes. In order to shorten the period of data collection, a one week time frame was set in order to synchronize the period that responses referred to. During this time frame, absenteeism and schedule constraints accounted for the impossibility to approach all classes and all students in each class. Additionally, 32 students (3.9%) refused to participate. The above-mentioned losses and refusals accounted for the final number of 795 participants that represented approximately 50% of the total number of students in the institution.

The questionnaire covered sociodemographic information, number of previous malaria episodes, utilization of antimalarial drugs (including specific questions for the use of chloroquine), and life prevalence of chloroquine induced pruritus. The latter was assessed through the close-ended question: «Have you ever had intense pruritus, itching or scratching while using chloroquine?» The use of antimalarial drugs in the last malaria episode was assessed by a questionnaire where the malaria drugs were presented as answering options in the following order: chloroquine, quinine, sulfadoxine-pyrimethamine, amodiaquine, halofantrine, artemisinine/artesunate, mefloquine, lumefantrine+artemether, tetracyclines/doxycycline, clindamycin, other.

Proportions were compared using the χ^2 test. The association of sociodemographic factors and intended use of chloroquine (prophylaxis, treatment, or both) with the occurrence of chloroquine induced pruritus, and the association between sociodemographic factors and history of chloroquine induced pruritus and the use of chloroquine in the last malaria episode, was quantified through crude and age- and ethnicity-adjusted odds ratios (OR) with 95% confidence intervals (95%CI) computed by unconditional logistic regression. Data analysis was conducted with Stata®, version 9.2.

Results

Among 795 respondents the median age was 23 years (range: 18 to 51 years), 58.7% were females, and 18.4% were attending a health-related degree (pharmacy or dentistry).

70.7% (601/777) of the subjects had malaria at least once in their lives, from which 92.0% (553/601) described the treatment performed in the last episode. The most frequently used drugs were chloroquine (59.9%), followed by sulfadoxine-pyrimethamine (24.2%), quinine (17.9%), artemisinine/artesunate (4.5%), tetracyclines/doxycycline (4.2%), halofantrine (4.0%), and mefloquine (0.9%).

73.2% (542/740) subjects reported to have used chloroquine before, at least once, and the prevalence of chloroquine-induced pruritus was 30.1% (158/525), more frequent in blacks (35.6% vs. 13.4%, OR = 2.96, 95%CI: 1.65–5.28), and increased with age (from 22.0% in the age-group 18 to 25 years to 43.4% in those aged above 35 (OR = 2.28, 95%CI: 1.38–3.78). The recall of pruritus associated with the use of chloroquine increased with the number of malaria episodes during life, from 13.8% in those with one episode to 44.4% in subjects with 5 or more episodes (OR = 5.04, 95%CI: 2.49–10.20). Pruritus was more frequent when chloroquine was used for treatment compared with prophylaxis only (31.2% vs. 10.3%, OR = 2.74, 95% CI: 0.79–9.47) (Table 1).

In subjects having used chloroquine both for treatment and prophylaxis, 13 (34.2%) reported pruritus only during treatment, 3 (7.9%) during treatment and prophylaxis, and none during prophylaxis.

Among subjects reporting more than one malaria episode during their lives, chloroquine use in the last episode was more frequent in participants not recalling previous pruritus associated with its use (65.1% vs. 52.3%, OR = 1.57, 95%CI: 0.93–2.68), in those having had malaria less often (65.0% vs. 53.0%, OR = 1.65, 95%CI: 0.98–2.79), and in the younger subjects, compared with those aged above 35 (61.4% vs. 47.8%, OR = 1.97, 95%CI: 1.06–3.64) (Table 2).

Discussion

Thirty percent of adult students in this sample reported having experienced pruritus while using chloroquine. Chloroquine-induced pruritus was more frequent in blacks, and increased with age with the number of previous malaria episodes and with chloroquine dose. Subjects experiencing chloroquine-induced pruritus were less keen to use chloroquine again than those not recalling this adverse event.

Although we approached students in all diurnal and most nocturnal classes and the proportion of refusals was low, information was obtained from only half the institution students. Females resulted overrepresented in our sample (58.7% vs. 50% enrolled in the university). Although women are more likely to use different types of medication,[10,11] namely in this specific population,[12,13] it is not expected that this could also happen with drugs used to treat acute life-threatening diseases such as malaria, and therefore we do not expect that this aspect could have biased our estimates. The population median age of 27 years in this University, as collected from University statistics, was higher than the observed in our sample. This could contribute to an underestimation of chloroquine induced pruritus prevalence, once we found it increased with age.

Table 1
Prevalence of chloroquine-induced pruritus in relation to age, ethnicity, number of malaria episodes, and intended use of chloroquine

	n[a]	Prevalence of chloroquine-induced pruritus, n (%)[a]	OR (95%CI)[b]	OR (95%CI)[c]
Gender				
Females	289	80 (27.7)	1	1
Males	232	77 (33.2)	1.22 (0.82–1.80)	1.00 (0.66–1.52)
Age (years)				
18–25	259	57 (22.0)	1	1
26–35	121	40 (33.0)	1.76 (1.09–2.85)	1.54 (0.93–2.53)
36 and over	106	46 (43.4)	2.73 (1.68–4.44)	2.28 (1.38–3.78)
Ethnicity				
Non-black	127	17 (13.4)	1	1
Black	390	139 (35.6)	3.46 (1.95–6.10)	2.96 (1.65–5.28)
Number of malaria episodes				
0–1[d]	123	17 (13.8)	1	1
2–4	182	52 (28.6)	2.22 (1.20–4.11)	1.96 (1.04–3.68)
5 or more	81	36 (44.4)	5.12 (2.58–10.14)	5.04 (2.49–10.20)
Use of chloroquine				
For treatment	480	149 (31.0)	1	1
Only for prophylaxis	29	3 (10.3)	2.31 (0.99–11.22)	2.74 (0.79–9.47)

OR (95%CI): Odds ratio (95% confidence interval).
[a] The sum of subjects may vary due to missing data.
[b] Crude OR, computed for participants with information available for age and ethnicity.
[c] OR adjusted for age and ethnicity.
[d] Includes subjects using chloroquine for prophylaxis.

Table 2
Use of chloroquine in the last malaria episode according to sex, age, ethnicity, number of malaria episodes and previous occurrence of chloroquine-induced pruritus, in subjects recalling two or more malaria episodes

	n	Use of chloroquine in the last malaria episode, n (%)[a]	OR (95%CI)[b]	OR (95%CI)[c]
Gender				
Males	161	87 (54.0)	1	1
Females	127	80 (63.0)	1.35 (0.82–2.22)	1.42 (0.86–2.36)
Age (years)				
18–25	145	89 (61.4)	1.93 (1.05–3.55)	1.97 (1.06–3.64)
26–35	61	35 (57.4)	1.46 (0.71–2.98)	1.33 (0.64–2.74)
36 and over	67	32 (47.8)	1	1
Ethnicity				
Non-black	68	40 (58.8)	1.21 (0.66–2.21)	1.27 (0.69–2.34)
Black	215	125 (58.1)	1	1
Number of malaria episodes				
2–4	186	121 (65.0)	1.65 (0.98–2.79)	–
5 or more	83	44 (53.0)	1	
Chloroquine-induced pruritus				
Never	170	110 (64.7)	1.67 (0.99–2.82)	1.57 (0.93–2.68)
At least once	88	46 (52.3)	1	1

OR (95%Cl): Odds ratio (95% confidence interval).
[a] The sum of subjects may vary due to missing data.
[b] Crude OR, computed for participants with information available for the number of malaria episodes.
[c] OR adjusted for the number of malaria episodes.

In the present methodological approach data was collected at the campus premises, leaving absent students unsampled. Therefore a sort of «healthy worker effect» could account for a selection bias as those less fit are more prone for a higher consumption of medicines and any type of adverse reaction to drugs, which would then also contribute to an underestimation of the frequency of chloroquine induced pruritus by our study, but it does not impair comparisons with studies conducted under similar conditions.

The specific problem of recall bias or misclassification of the main variables for this investigation should not play an important role in this study, since malaria is a well-known disease, severe enough to warrant the accurate recall of previous episodes, chloroquine has been the drug more frequently used for its treatment for a long time, and the chloroquine induced pruritus is easily recognizable and recalled by patients. Itching lasts usually for 1–3 days, and can persist for up to 7 days. It is mainly generalized, but it can also affect only specific sites, like hands, legs and feet, or perineum/genitaliae.[14] The questionnaire was structured to make clear that the information regarding pruritus should refer only to «intense pruritus, itching or scratching while

using chloroquine», and the results from a previous investigation in this population yielded the unexpected result of an 18% prevalence of self-reported allergy to chloroquine in black subjects,[15] which may reflect the highly frequent itching produced by chloroquine in black patients and the recognition by the patients of its association with the antimalarial treatment. Regarding the accuracy of previous diagnoses of malaria, blood test for *Plasmodium* were performed in 94% of the most recent malaria episodes, and nearly half of the students had the last malaria episode diagnosed by a private doctor/clinic, as shown in a subsequent study conducted in the same population.[13]

University students do not seem to represent general Mozambican population namely due to education level attained, and social and cultural backgrounds. Moreover, the fact that our sample was drawn from a private University further limits representativeness regarding the country's university population. A previous study in this Mozambican population[16] suggests that these students have a pattern of utilization of medicines similar to the observed in university students from developed countries. Such an easy access could only account for preference for newer antimalarial drugs other than chloroquine and therefore, for a lower prevalence of chloroquine induced pruritus, compared with the general population. In an investigation conducted in the same setting[13] information was also obtained regarding the antimalarial treatment in the last episode, when applicable, as well as the date of the last episode. The proportion of subjects using chloroquine in the treatment of malaria was 57% when the last episode took place before 2004, and 42%, 18% and 12% in the episodes occurring respectively in 2004, 2005 and 2006. However, only one quarter of the treatments with chloroquine were done in association with other antimalarial drugs, and this proportion remained unchanged in the last years, showing that the inadequate use of chloroquine is still present in this highly educated population.

Chloroquine induced pruritus was shown to be frequent in African subjects under chloroquine treatment, with prevalence ranging from 16% to 64%.[5,8,17,18] The previous studies differ considerably in the characteristics of the populations and in the methods used, which makes a direct comparison difficult. In the present study a high prevalence of chloroquine-induced pruritus among black subjects was also noticed. A 1.9% prevalence has been observed in *Plasmodium vivax* malaria patients treated with chloroquine in Thailand,[19] which is in accordance with the lower prevalence observed in the non-black subjects in our study.

The etiology of chloroquine-induced pruritus appears to be multifactorial. Direct release of histamine does not appear to be its cause, nor other allergic mechanisms[9,20,21] but rather an interaction between the drug itself and the disease or the parasite, leading to development of pruritus.[9,20,21] Moreover, differences in hepatic metabolism of chloroquine caused by genetic polymorphisms may also explain different patterns of chloroquine-induced pruritus.[17,22] Finally, an involvement of endogenous opioid peptides in chloroquine induced itching modulation is possible.[23]

In our study life prevalence of chloroquine-induced pruritus increased with age and doses of chloroquine (assuming the intended use of chloroquine as a surrogate for dosage), which could be related with pharmacokinetic aspects. There is evidence suggesting an association between higher chloroquine levels and decreased metabolism in pruritus susceptible subjects. This could be affected either by age or by chloroquine dosage.[20,22]

In African countries where chloroquine has become ineffective against *Plasmodium falciparum*, artemisin-based combination treatments are now considered the best therapy for *falciparum* malaria.[24] Some authors suggest that reducing the use of chloroquine in a region could result in a reemergence of chloroquine sensitive *Plasmodium falciparum*, thus permitting reintroduction of this affordable drug in combination with other drugs, to prevent the reemergence of resistance,[5] while others think it is still too early to lay chloroquine to rest.[4]

Chloroquine-induced pruritus compromises compliance with treatment regimens and possible contributes to the emergence of chloroquine resistant strains of *Plasmodium falciparum*.[6–8] Returning or not to its primary place in antimalarial treatment, compliance will still be an important challenge in anti-infective therapy, in order to prevent the emergence of resistances.

In this study, a large proportion of responders recalled that this adverse event influenced future anti-malarial therapeutic choices. This observation may not apply to less educated subjects, with a more difficult access to less affordable drugs, but is similar in its nature to the generalized problem of non-adherence to therapy, one of the possible causes of growing parasite resistance in Africa.

About one third of the black population using chloroquine experienced chloroquine induced pruritus at least once. This adverse reaction tended to be less frequent when lower doses of chloroquine were used and to influence future anti-malarial therapeutic choices. Prevention of this effect could be achieved by identifying therapeutically effective drug levels that are not high enough to induce the reaction, or by restricting its use to less susceptible groups.

Competing interests

The authors declare no competing interests.

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