Chloroquine-induced pruritus in malaria fever: contribution of malaria parasitaemia and the effects of prednisolone, niacin, and their combination, compared with antihistamine

R. A. Adebayo,[1] G. G. Sofowora,[1] O. Onayemi,[2] S. J. Udoh[3] & A. A. Ajayi[1]

[1]*Departments of Medicine,*[2]*Dermatology,* [3]*Microbiology and Parasitology, College of Health Sciences, Obafemi Awolowo University, Ile-Ife, Osun State, Nigeria*

Aims Chloroquine treatment of malaria fever, results in a generalized pruritus of unknown mechanism in up to 60% of adult Africans, by contrast pruritus is unusual in Caucasians following chloroquine use.

Methods We conducted a double-blind, randomized, parallel group study to examine and compare the antipruritic effects of promethazine, niacin, prednisolone and their combination on pruritus induced by chloroquine, in 28 historical itching patients with parasitologically proven malaria fever. We also evaluated the role of the antecedent malaria parasite density in the severity of chloroquine pruritus intensity.

Results The concurrent administration of chloroquine (2.1g base total dose) with prednisolone caused a statistically significant reduction in the pruritus AUC (0, 72 h) ($P<0.001$ ANOVA) compared with the antihistamine promethazine alone. The areas under the pruritus intensity-time curve were promethazine 105 ± 28 (units h), niacin 76 ± 22, prednisolone 28 ± 24, and prednisolone and niacin 34 ± 17 ($P<0.001$ ANOVA). The 95% confidence interval for the difference in the pruritus AUC between prednisolone and promethazine was 8.4 to 145.6 units h. There was a statistically significant and positive correlation between the pruritus intensity (AUC 0, 72 h) and the malaria parasite load in the itching subjects, not receiving prednisolone ($n=9$) ($r=0.73$, $P=0.026$ ANOVA).

Conclusion A single oral dose of prednisolone (10 mg) may be preferable to the antihistamine promethazine (25 mg) as an antipruritic agent for concurrent prescription with chloroquine in individuals predisposed to severe itching. Malaria parasite clearance and clinical amelioration were unaffected by any of the treatments.

Keywords: chloroquine, pruritus, malaria, prednisolone, malaria parasite density, antihistamines

Introduction

The antimalarial chloroquine is still the drug of choice for malarial chemosuppression and radical cure in hyperendemic areas with chloroquine sensitive plasmodium strains [1]. It is cheap, rapidly effective and orally active. Its clinical use is associated with significant adverse effects, however, which must be overcome in order to extend its utility. For example, up to 60% of adult Africans develop generalized and severe pruritus following chloroquine treatment of malaria [2].

The pruritogenic potential of chloroquine in historical itchers, hampers the effective control of malaria [3, 4], diminishes compliance with treatment regimens [5] and possibly contributes to the emergence of chloroquine-resistant strains of *Plasmodium falciparum* [5, 6].

The mechanism(s) underlying chloroquine-induced pruritus are poorly understood, but the role of histamine appears to be minor [7, 8]. Additionally, there is evidence for a pharmacogenetic basis for the pruritus, as it is extremely rare in Caucasians treated for malaria [9]. Further, there is a familial clustering of the tendency to chloroquine-induced itching in black Africans, but by contrast, a poor association between spouses [2, 10, 11].

We have reported previously the clinical utility and safety of prednisolone and niacin in the prophylaxis and palliation of chloroquine-induced pruritus in Nigerians with malaria fever [12]. In the present study, we further examined the possible mechanisms of chloroquine-induced pruritus by investigating the relationship between the antecedent malaria parasite density and the subsequent pruritus intensity. The study was also designed to compare the effects of prednisolone or niacin, or their combination with that of promethazine, an antihistamine usually prescribed as a standard antipruritic agent, with chloroquine, in patients with malaria fever predisposed to generalized itching.

Methods

The study design was a double-blind, randomized, parallel group comparison of the prophylactic and palliative effects of prednisolone (10 mg), promethazine (25 mg), niacin (50 mg) and the combination of prednisolone (10 mg) and niacin (50 mg) on chloroquine-induced pruritus in patients with malaria fever.

Correspondence: Professor A. A. Ajayi, Department of Medicine, Faculty of Clinical Sciences, Obafemi Awolowo University, Ile-Ife, Nigeria.

The baseline clinical and demographic data of patients randomized to each of the four treatment groups is shown in Table 1. The study protocol and chloroquine dosing (2.1 g base total) schedule and entry and exclusion criteria are as described previously [12]. Pre-chloroquine blood samples and body temperature and pulse rate record were obtained at time 0 h and repeated at 72 h.

The severity of the pruritus was assessed at 0, 6, 12, 24, 48 and 72 h, using a questionnaire with a ranked ordinal scale thus: 0-none, 1-mild, 2-moderate, 3-severe, 4-worst possible pruritus.

Provision was made for the administration of a 'hydrocortisone rescue' dose of 250 mg intravenously in subjects who develop unbearable pruritus on any of the four treatments.

The malaria parasite density was quantified by Giemsa staining of thick and thin films of the blood samples at $\times 100$ magnification [13].

Statistical analysis

Data are mean $\pm$s.d., or mean $\pm$s.e. mean and median and ranges as stated.

The areas under the pruritus intensity time curve (AUC) reflecting itching severity was evaluated by Kruskal Wallis one way analysis of variance (ANOVA). Relationship between antecedent malaria parasitaemia and the subsequent pruritus was assessed by linear regression analysis. A 'parasite pruritogenic index' indicating the pruritus severity corrected for parasite load, under the four treatments was calculated in each individual by dividing the pruritus AUC (0, 72 h) by the malaria parasite density (μl^{-1}) of blood. Inter-group comparison was again by Kruskal Wallis one way analysis of variance (ANOVA) by ranks. 95% confidence limits have been quoted for the difference between pruritus AUC of prednisolone and antihistamine. The null hypothesis was rejected at $P<0.05$.

Results

Thirty-five pruritus reactors were recruited, of whom 28 patients completed the study per protocol. Two patients with chloroquine itching history presented with pyrexia and arthralgia but who had no demonstrable malaria parasites in the peripheral blood film were excluded from the study. Two patients who completed the study presented with mild itching prior to chloroquine dosing, and claimed it was their usual warning sign of malaria; seven patients were lost to follow-up or did not complete the study per protocol. In all the 28 patients who completed the study protocol, *Plasmodium falciparum* was the causal agent of the malaria.

Effects of promethazine, compared which niacin, prednisolone or their combination on chloroquine-induced pruritus

Prevention of itching and 'hydrocortisone rescue' The antihistamine, promethazine prevented the onset of itching in two out of seven patients. The prevention rates for prednisolone alone was six out of nine patients, niacin one out of six, and three out of six patients on prednisolone + niacin combination.

One patient each receiving prednisolone (malaria parasite density 80 μl) or niacin (parasite density 920 μl^{-1}) and promethazine (500 μl^{-1}) experienced severe pruritus requiring the 'parenteral hydrocortisone rescue'. Their pruritus was terminated within 2 h of hydrocortisone administration.

Time course of pruritus and pruritus intensity AUC

The mean time course of pruritus intensity in each treatment group, following chloroquine administration, is shown in Figure 1. The onset of pruritus was within 6 h, with a peak at 24–48 h, and was still apparent at 72 h in some patients, albeit of reduced severity.

There was a statistically significant difference in the pruritus intensity areas under the curve on the different treatments ($P<0.001$ ANOVA H-corrected for ties = 19.2). The values (mean $\pm$s.e. mean) were respectively for promethazine 105 ± 28 units h, (median 144, range 0–180 units h), for niacin 76 ± 22 units h, (median 84, range 0–153 units h), for prednisolone alone 28 ± 24 units h (median 0, range 0–204 units h) and 34 ± 17 units h (median 15, range 0–114 units h) for prednisolone and niacin in combination ($P<0.001$) (Figure 1).

The 95% confidence intervals for the difference in pruritus AUC between prednisolone alone and promethazine was from 8.4 to 145.6 units h.

Relationship between malaria parasite density and pruritus severity

There was a positive and statistically significant linear relationship between the malaria parasite density (μl^{-1}

Table 1 Baseline clinical and demographic data of the patients with malaria (mean $\pm$s.d.).

Parameter	*Promethazine*	*Niacin*	*Prednisolone*	*Prednisolone + niacin*
n	7	6	9	6
Age (years)	28 ± 9	29 ± 8	29 ± 8	23 ± 8
Male/Female	5/2	3/3	4/5	2/4
Malaria parasite density range (μl^{-1})	130–2,400	320–1360	120–1510	832–2,000
Mean $\pm$s.e. mean	1196 ± 825	737 ± 371	625 ± 494	1318 ± 425
Body temperature (°C)	37.2 ± 0.3	37.1 ± 0.8	37.6 ± 0.9	36.7 ± 0.4
Pulse rate (beats min^{-1})	81 ± 11	78 ± 7	85 ± 18	75 ± 4

No significant differences by ANOVA.

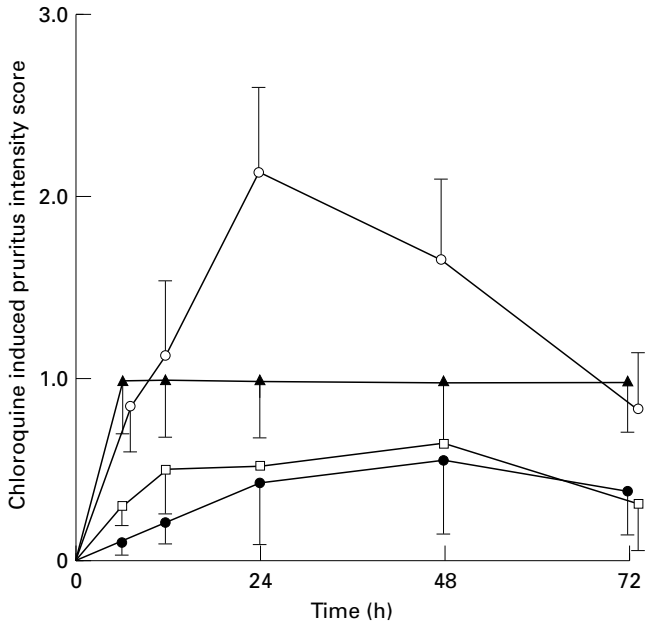

Figure 1 Time course of chloroquine-induced pruritus following, prednisolone 10 mg (●, $n=9$), niacin 50 mg (▲, $n=6$), the combination (□, $n=6$), and promethazine 25 mg (○, $n=7$). The pruritus AUC (0, 72 h), following prednisolone 10 mg alone or with niacin was significantly reduced compared with promethazine ($P<0.001$) Kruskal-Wallis ANOVA) values are mean ± s.e. mean.

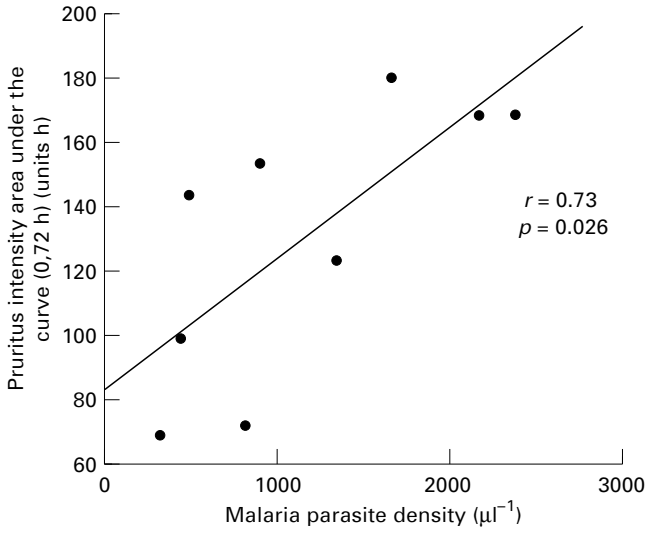

Figure 2 The correlation between malaria parasite density and pruritus severity AUC (0, 72 h), y = 0.04x ± 83.5, ($r=0.73$, $P=0.026$ ANOVA).

blood) prior to chloroquine and degree of chloroquine pruritus (pruritus AUC (0, 72 h units h) in subjects not receiving prednisolone. The correlation coefficent was $r=0.73$, $P=0.026$, ANOVA (Figure 2).

Parasite pruritogenic index

The pruritus severity measured as areas under the curve was corrected for parasite density in the individual patient. This provides an indication of the pruritogenic potential of a single parasite in the presence of each of the four treatments. The values ($\times 10^{-2}$) were for niacin (mean ± s.e. mean) 11.5 ± 3.6, (median 13, range 0–22), promethazine 9.0 ± 3.4 (median 7.6, range 0–29) but significantly lower with prednisolone 4.5 ± 3.8 (median 0, range 0–30) and lowest with the prednisolone + niacin combination, 2.6 ± 1.3 (median 0.5, range 0–9) ($P<0.001$ ANOVA, H-corrected for ties 22.8) (Figure 3).

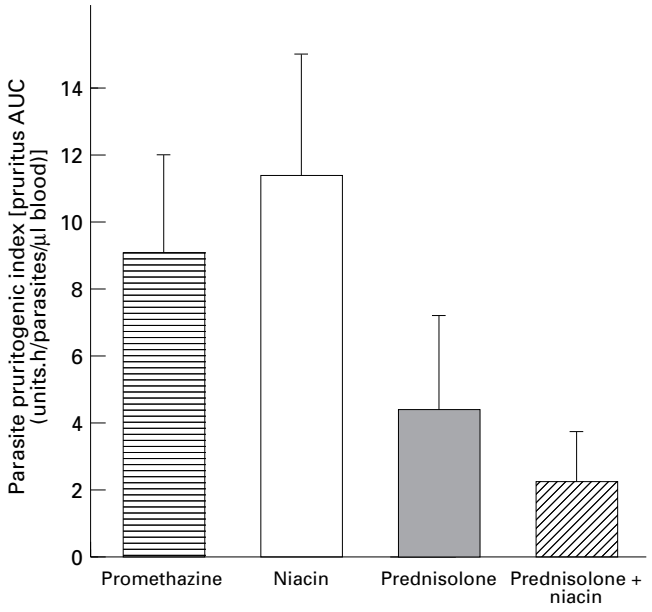

Figure 3 The parasite pruritogenic index: pruritus AUC corrected for parasite load. Prednisolone (▦), and niacin combined with prednisolone (▨) were significantly different from promethazine (▤) and niacin (□) ($P<0.001$ ANOVA mean ± s.e. mean).

Effects on malaria parasite clearance

Chloroquine treatment resulted in the eradication of the malaria parasites in all but two patients by 72 h. There was a reduction in parasitaemia in a patient on prednisolone combined with niacin from 1,240/μl to 200/μl and in another on promethazine from 820 to 160/μl by 72 h. No patient on prednisolone alone had persistent parasitaemia. All the patients exhibited clinical amelioration by 72 h and remained well on follow-up.

Discussion

Our findings show that a single 10 mg dose of prednisolone (alone or in combination with niacin) exerted a prophylactic effect on chloroquine-induced pruritus and attenuated itching severity as indicated by a statistically significant reduction in the pruritus AUC. The antihistamine, promethazine, usually prescribed as a standard prophylactic/palliative agent for chloroquine-induced pruritus in patients with malaria had no appreciable impact on the pruritus. These findings are consistent with our previous study in malaria patients, using 5 mg prednisolone [12] as well as reports in healthy volunteers [14]. They are also consistent with the concept that histaminergic mechanisms play a minor role in chloroquine pruritus [7, 8, 15]. Hence the poor antipruritic efficacy of promethazine at the clinically prescribed doses, seen in this study.

Three patients who experienced severe pruritus on the different antipruritic treatments, including prednisolone, had dramatic amelioration within 2 h, following parenteral hydrocortisone. This confirms the efficacy of corticosteroids in aborting chloroquine pruritus even after its onset.

Our results demonstrate a strong positive linear association between malaria parasite density and the subsequent pruritus intensity (AUC). The r^2 value (0.53) indicates that in the patients who itched to chloroquine, more than 50% of the intersubject variation in pruritus intensity is attributable to the density of parasitaemia. This finding is similar to the trend we observed in our earlier study [12]. Taken together, these findings strongly suggest a pathophysiologically important role for malaria parasites in chloroquine-induced itching. This notion is further strengthened by the absence of chloroquine-induced itching in two established pruritus reactors, who still self-administered chloroquine, despite absence of malaria parasitaemia. Further, the incidence of pruritus following chloroquine in historical itchers (without malaria) is about 10%, but is increased greatly during a malaria infection [16).

As a result of the dependence of itching severity on parasite load, we corrected the pruritus intensity AUC for malaria parasite density, to obtain a 'parasite pruritogenic index' (see Figure 3). Again, prednisolone in combination with niacin, has the lowest index, followed in rank order by prednisolone alone, and the values were statistically significantly different from niacin or promethazine alone. Thus, at a given parasite density, prednisolone combined with niacin, or prednisolone alone, had a significantly greater antipruritic action compared with niacin or the antihistamine, promethazine.

The antipruritic action of these agents was independent of the clinical or parasitological effects of chloroquine. Thus, prednisolone, even at a higher dose of 10 mg, appears safe in addition to its improved efficacy in chloroquine pruritus [12].

The report of mild, low grade itching antecedent to chloroquine ingestion, is consistent with anecodotal reports. In the two subjects, in whom it was confirmed this was claimed to be a warning symptom of imminent malaria fever. The mechanism is unclear, but we speculate that it results from residual chloroquine blood levels, from repeated chloroquine use and long half-life [17], and the onset of parasitaemia in the early phases of malaria fever.

This study provides a further insight into the possible mechanisms of the enigmatic chloroquine-induced pruritus, or, indeed, pruritus in general [18]. It is likely that chloroquine pruritus involves a multifactorial interplay, including host genetic susceptibility, malaria parasite load, and chloroquine or it metabolites. The efficacy of prednisolone, a phospholipase A_2 inhibitor [19], implies that it modifies a significant mechanism in chloroquine pruritus, possibly inhibition of cytokine and arachidonate release [20, 21].

Our findings also have important economic and clinical implications. The concurrent use of chloroquine in pruritus susceptible people with malaria is not only safe, but is much cheaper than newer, less pruritogenic alternatives. Moreover, the safety to the foetus of the new antimalarial agents is not established. In pregnant malarial patients with predisposition to pruritus, prednisolone will extend the use of the cheap and safe chloroquine treatment. Concurrent prednisolone increased the prescription of chloroquine and compliance with the regimen in a recent study [22].

In conclusion, a single 10 mg dose of prednisolone, exhibited superior efficacy to the antihistamine promethazine or niacin in chloroquine-induced pruritus in malaria fever. There was a positive and significant correlation between malaria parasite density and pruritus AUC. Further studies, to examine the role of cytokines in chloroquine pruritus and in parasitized red blood cells *in vitro* are required.

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